Epidemiology of medication use among patients prior to and following hospital admission

A retrospective, population-based cohort study

Freyja Jónsdóttir

Thesis for the degree of Philosophiae Doctor

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Faraldsfræði lyfjanotkunar meðal sjúklinga fyrir og eftir innlögn á sjúkrahús

Aftursýn, lýsandi gagnarannsókn

Freyja Jónsdóttir

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"Starting medications, they say, is like the bliss of marriage; stopping them is like the agony of divorce."

Doug Danforth

Ágrip

Hugtakið fjöllyfjameðferð er vel þekkt innan heilbrigðiskerfisins. Hugtakið vísar til samtímis notkun margra lyfjaflokka en sú skilgreining hugtaksins, sem nýtur hvað víðtækastrar viðurkenningar, vísar til notkunar á fimm eða fleiri lyfjum. Fjölveikindi og tilheyrandi fjöllyfjameðferð eru þekktur áhættuþættur sem getur haft neikvæð áhrif á heilsufar. Rannsóknir hafa sýnt að slík neikvæð áhrif geta falist í skertum lífsgæðum, skertri meðferðarheldni, auknum hrumleika og auknum líkum á spítalainnlögn. Í ljós hefur komið að fjöllyfjameðferð er helsti áhættuþátturinn, sem leitt getur til mögulegrar óviðeigandi lyfjameðferðar. Möguleg óviðeigandi lyfjameðferð tengist bæði neikvæðum útkomum í heilsufarslegu- og fjárhagslegu tilliti. Því er hægt að meta hvort lyfjameðferðir séu mögulega óviðeigandi og nýta það sem gæðavísi um lyfjaávísanir og lyfjaöryggi.

Markmiðið í þessari doktorverkefnis var að meta algengi og nýgengi fjöllyfjameðferðar meðal allra sjúklinga í tengslum við innlagnir á skurðdeildir og lyflæknisdeildir, bæði fyrir og eftir spítalainnlögn, auk þess að meta mögulega óviðeigandi lyfjameðferð í fyrir eldri sjúklinga (≥65) sjúklinga í tengslum við innlagnir á skurðdeildir og lyflæknisdeildir. Hannaðar voru fjórar rannsóknir og niðurstöðum þeirra gerð skil í fjórum greinum. Í fyrstu greininni var markmiðið að nota íslenska skurðgagnagrunninn til að meta algengi, nýgengi og breytingar á fjöllyfjanotkun, bæði fyrir innlögn og eftir útskrift, og tengda áhættuþætti og klínískar útkomur allra fullorðinna sjúklinga eftir útskrift á tímabilinu milli 2005 til 2018. Í annarri greininni var markmiðið að nýta íslenska lyflæknisgagnagrunninn til að meta algengi, nýgengi og breytingar í fjöllyfjanotkun, bæði fyrir innlögn og eftir útskrift, tengda áhættuþætti og klínískar útkomur allra fullorðinna sjúklinga eftir útskrift. Hvað varðar þriðju greinina, var markmiðið nýta íslenska lyflæknisgagnagrunninn til að meta algengi, nýgengi og breytingar á algengi mögulega óviðeigandi lyfjameðferðar á meðal sjúklinga ≥65 ára á tímabilinu milli 2010 til 2020 með því að nota Beers 2019 sérgreindar kríteríur. Auk þessa var tenging mögulegrar óviðeigandi lyfjanotkunar við fjöllyfjameðferð, sjúklingatengda þætti, lyfjaflokka og klínískar útkomur, rannsökuð. Loks var markmiðið í fjórðu greininni að nýta íslenska skurðgagnagrunninn til að meta algeng og nýgengi, auk breytingar á algengi, mögulega óviðeigandi lyfjanotkunar á meðal sjúklinga (≥65) á tímabilinu frá 2005 til 2018 með því að nota Beers 2019 sérgreindar kríteríur fyrir lyfjaávísanir. Jafnframt voru tengsl mögulega óviðeigandi lyfjanotkunar við fjöllyfjanotkun, sjúklingatengda þætti, lyfjaflokka og klínískar útkomur, rannsökuð.
Þessi doktorsritgerð byggir á fjórum aftursýnum lýsandi hóprannsóknum, þar sem nýtt voru gögn úr tveimur gagnagrunnum, þ.e. íslenska skurðgagnagrunninum og íslenska lyflæknisgagnagrunninum. Fyrsta og fjórða grein rannsóknarverkefnisins snerist um

íslenska skurðgagnagrunninn, sem var þegar til staðar fyrir þetta doktorsverkefni. Önnur og þriðja greinin leiddu af íslenska lyflæknisgagnagrunninum, sem varð til í tengslum við þetta doktorsverkefni en honum mun verða haldið við í kjölfarið. Hvor gagnagrunnurinn um sig inniheldur klínísk gögn úr sjúkraskrám sjúklinga frá Landspítala, Lyfjagagnagrunni Landlæknisembættisins og ICD-10 kóðum frá Landspítala og heilsugæslu. Báðum framangreindum gagnagrunnum verður haldið við fyrir framtíðarrannsóknarverkefni.

Fjöllyfjameðferð og möguleg óviðeigandi lyfjanotkun eru algeng á meðal sjúklinga sem leggjast inn á spítala, bæði vegna skurðaðgerða og til lyflæknismeðferðar. Ný lyfjameðferð, eftir útskrift af spítala, er algeng og að auki er ný mögulega óviðeigandi lyfjameðferð algeng á meðal eldri sjúklinga (>65) eftir innlögn á sjúkrahús. Þessi doktorsritgerð sýnir fram á að fjöllyfjanotkun á meðal skurðsjúklinga tengist skertum lífslíkum, bæði til skemmri og lengri tíma, lengdri spítalainnlögn og aukinni tíðni endurinnlagna. Jafnframt sýnir þessi doktorsritgerð fram á að mögulega óviðeigandi lyfjanotkun er algeng á meðal sjúklinga sem lagðir hafa verið inn á lyflæknisdeild og tengdir áhættuþættir eru meðal annars hækkandi aldur, kvenkyn, taka fleiri lyf og nýta lyfjaskömmtun.

Samfélagið er stöðugt að eldast. Þetta hefur í för með sér tilteknar áskoranir þar sem aukin fjölveikindi og tengd fjöllyfjanotkun verður sífellt meira áhyggjuefni varðandi heilsu almennings. Það eru engar algildar lausnir til að takast á við fjöllyfjanotkun og óviðeigandi lyfjameðferð. Markmið heilbrigðisstarfsfólks ætti að vera að hefja einungis lyfjameðferð þegar þess reynist þörf og hefja hana ekki ef meiri skaða leiðir af meðferðinni. Jafnvægið þarna á milli verður enn viðkvæmara eftir því sem hrumleiki sjúklinga eykst. Þess vegna er nauðsynlegt að beita fjölda úrræða, allt frá því að auka kennslu, valdefla sjúklinga og meðferðaraðila þeirra, taka upp þverfagleg inngrip, sem bæði eru almenn og sérmiðuð að tilteknum lyfjaflokkum og sjúklingahópum, auk þess að nýta rafrænar lausnir til að styðja við lyfjaávísanir, þar sem hægt er. Heilbrigðisstarfsfólk, og þá sérstaklega þeir sem ávísa lyfjum, og sjúklingar þurfa aukinn stuðning með áætlanir sem stuðla að öruggri og skilvirkri lyfjanotkun. Fjölga þarf verkfærum í verkfærakassa íslenskra heilbrigðisstarfsmanna og sjúklinga. Aukið samstarf milli heilbrigðisstétta og aukin tilfærsla á færni þeirra á milli, myndi þjóna þessu markmiði. Að lokum, er mikilvægt að heilbrigðisstarfsfólk sýni varfærna fyrirhyggju þegar ný lyfjameðferð er hafin og skipuleggja viðeigandi endurskoðanir.

Lykilorð:

Fjöllyfjameðferð, ofur-fjöllyfjameðferð, mögulega óviðeigandi lyfjameðferð, lyfjatengd vandamál, eldri einstaklingar, sjúkrahúsinnlögn.

Abstract

Polypharmacy is a well-known term within the healthcare setting. The term describes the usage of multiple medicines, and the most widely accepted definition of it refers to the usage of five or more medications. Living with multimorbidity and associated polypharmacy is a known risk factor for adverse health consequences, and research has shown that such consequences can be decreased quality of life, decreased medication adherence, increased frailty, and increased likelihood of hospitalisation. Polypharmacy has been identified as the leading risk for potentially inappropriate medication use, which is where harm exceeds the benefit of the medication. Potentially inappropriate medication use is associated with adverse health and economic outcomes. Therefore, it can be a helpful indicator of prescribing practice and medicine safety.

This thesis aimed to estimate the prevalence and incidence of polypharmacy among all adult surgical and internal medicine patients, both preceding and following hospital admission and assess potential inappropriate medication use among older (≥65) surgical and internal medicine patients. Four studies were designed and presented in four manuscripts. Manuscript I aimed to use the Icelandic perioperative database to estimate the prevalence, incidence, and changes of polypharmacy, pre-admission and post-discharge, and associated with patient factors and clinical outcomes of patients, post-discharge among all adults during the period between 2005 and 2018. The aim of manuscript II was to use the newly established Icelandic internal medicine database to estimate the prevalence, incidence, and changes of polypharmacy pre-admission and post-discharge, associated risk factors and clinical outcomes of patients' post-discharge among all adults during the period between 2010 and 2020. As regards manuscript III, the aim was to use the Icelandic internal medicine database to estimate the prevalence, incidence and changes of the prevalence of potentially inappropriate medication use amongst patients ≥65 years during the period between 2010 and 2020 by applying Beers 2019 explicit prescribing criteria. Additionally, the association of potentially inappropriate medication use with polypharmacy, patient-specific factors, drug classes, and outcomes was studied. Finally, manuscript IV aimed to use the Icelandic perioperative database to estimate the prevalence and incidence as well as changes in the prevalence of potentially inappropriate medication use amongst patients ≥65 years in Iceland during the period between 2005 and 2018 by applying Beers 2019 explicit prescribing criteria. Additionally, the association of potentially inappropriate medication use with polypharmacy, patient-specific factors, drug classes, and clinical outcomes was investigated.

This thesis is based on four retrospective, population-based cohort studies that used data from two separate databases for hospital settings: the Icelandic perioperative database and the Icelandic internal medicine Database. The first and fourth manuscripts of the research project revolved around the Icelandic perioperative database, which

was already established prior to this doctoral project. The second and third manuscripts were derived from the Icelandic internal medicine database generated for this doctoral project and will be maintained. Both databases include clinical data from the patient's medical record from the hospital, the national prescription database of the Directorate of Health, and the ICD-10 codes from hospital and primary care records. Both databases will be maintained for future research projects.

Polypharmacy and potentially inappropriate medication use are common among patients admitted to hospitals both for surgical and internal medicine care. New medication post-discharge for frequent, as well as new, new potentially inappropriate medication among older (>65) patients admitted by internal medicine speciality and due to surgical admission. This thesis demonstrates that polypharmacy among surgical patients was associated with decreased short-term and long-term survival, more extended hospital stays and readmission rates. On the contrary, this thesis also demonstrates that polypharmacy and internal medicine patients were not associated with decreased short-term and long-term survival, more extended hospital stays and readmission rates. This thesis also demonstrated that potentially inappropriate medication use is prevalent among patients admitted by internal medicine speciality and due to surgical admission and associated risk factors among increased ages, female gender, use higher number of medications and use multidose dispensing service.

The population is continously ageing. This presents certain challenges with multimorbidity and associated polypharmacy becoming an increasingly alarming factor concerning public health and there is no one-size-fits-all solution for addressing polypharmacy and inappropriate prescribing. The aim for healthcare providers should be to initiate medication treatment only when there is a need to do so and refrain from doing so when there is more harm associated with the treatment. This balance becomes more delicate as the patient becomes more frail. Therefore, multiple measures are required, ranging from upscaling educational activities, empowering patients and their carers, implementing multidisciplinary interventions that are both general and targeted at specific medication classes and patient groups, in addition to using computerised prescribing aids when possible. Healthcare providers and, especially, prescribers and patients need further support with strategies to facilitate safe and effective use of medications. Tools need to be added to the toolbox of Icelandic healthcare professionals and patients. Increased collaboration between healthcare professionals, as well as an increased skill shift between them, would serve this purpose. Finally, it is important that healthcare professionals apply cautious foresight when initiating new medication and planning appropriate revisions.

Keywords:

Polypharmacy, hyperpolypharmacy, potentially inappropriate medication, drug-related problems, aged, hospitalisation.

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Firstly, I would like to thank my supervisor, Martin Ingi Sigurðsson, whom I initially reached out to and met when he had recently published a manuscript on increased mortality among surgical patients who were on benzodiazepines and opioids, which I felt was very interesting. We have had a fruitful collaboration for numerous years in supervising pharmacy and medical students, and Martin has also been my main supervisor during this PhD project. I contacted Martin and asked him to be my supervisor after Kristín Ingólfsdóttir, former rector of the University of Iceland, encouraged me to do so. I am very grateful for her advice because Martin has been a fantastic supervisor, very accessible and reliable, and you can always ask him for good, honest and straightforward advice. Martin is a knowledgeable, experienced researcher, an excellent teacher and a dedicated and inspirational supervisor. His support and guidance through this journey have been exceptional, and I feel very grateful for having had the opportunity to develop as a researcher under his supervision. Martin is also a dear friend, who I highly appreciate.

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Table of contents

List of abbreviations

ADE	Adverse drug events
ADR	Adverse drug reactions
ATC	Anatomical Therapeutic Chemical
ICD	International Classification of Diseases
MAI	Medication Appropriateness Index
NICE	National Institute for Health and Care Excellence
NOMESCO	Nordic Medico-Statistical Committee Classification of Surgical Procedures
OECD	Organisation for Economic Corporation and Development
RPS	Royal Pharmaceutical Society
WHO	World Health Organization

List of tables

List of figures

List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Epidemiology and association with outcomes of polypharmacy in patients undergoing surgery: retrospective, population-based cohort study. BJS open. 2023 Jun;7(3): zrad041.

II. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. The association of degree of polypharmacy before and after among hospitalised internal medicine patients and clinical outcomes: a retrospective, population-based cohort study. BJM open. 2024 March; 14(3), e078890.

III. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Potentially inappropriate medication use before and after admission to internal medicine for older patients and association with polypharmacy. The American Journal of Medicine 2024 July.

IV. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Epidemiology of potentially inappropriate prescribing and association with polypharmacy among surgical inpatients: retrospective, population-based cohort study. Draft prepared. *Aimed for publication in the Surgery.*

In addition, some unpublished data are presented. All papers are reprinted with the kind permission of the publishers.

Declaration of contribution

The doctoral candidate designed the study with her supervisors, Martin Ingi Sigurðsson and Anna Bryndís Blöndal, and support from the doctoral committee. Freyja and Martin applied for ethical approval for the addition to the Perioperative database and the entire Internal Medicine database, which proved to be an extensive application process. Freyja and Martin gathered the data, and Martin was responsible for generating the new Internal medicine database. The doctoral candidate analysed the data with help from Martin and the doctoral committee. The doctoral candidate also wrote each manuscript's first draft, which Martin subsequently revised and then the doctoral committee.

1 Introduction

The primary challenge for governments and healthcare systems worldwide is the ageing of the global population, which leads to increased care needs due to multimorbidity, including the risk of polypharmacy. The current trend is for people living longer with more age-related chronic diseases, which frequently leads to polypharmacy and increased risk of medication-related harm. Studies have estimated that multimorbidity and polypharmacy will increase significantly in the coming years.[2, 3] In this thesis, the pharmacoepidemiology of polypharmacy, potentially inappropriate medication usage and medication-related harm among patients in relationship with an inpatient admission to the hospital in Iceland was explored.

1.1 Iceland

In recent years, there has been a heightened focus on the safety and quality of medication usage in Iceland. In 2020, the Medication Without Harm campaign was based on the global initiative previously initiated by WHO in 2017.[4] The Icelandic campaign has extensive organisational sponsorship from the Directorate of Health, the Ministry of Health, and the Icelandic Medicine Agency, as well as a partnership with the leading hospitals, primary care, and professional bodies of physicians, pharmacists, and nurses. The campaign has increased awareness among healthcare professionals of the importance of working towards increasing medication safety in Iceland. The need for high-quality research to address the topic of medication safety in Iceland was highlighted at a multi-disciplinary seminar focusing on medication safety during the Annual Meeting of The Icelandic Medical Association in 2021. There has been a lack of research on polypharmacy and appropriateness of medication usage in Iceland. However, in recent years, there has been a proliferation of studies focusing on medication utilisation. There have been a few retrospective studies focusing on medication use among hospitalised patients, like opioids,[5-7], proton pump inhibitors[8], benzodiazepines and Z-drugs[5], psychotropic medication [9] and medication adherence. [10] These studies have all shed light on the high medication usage of the Icelandic population and raised questions regarding the appropriateness of medication usage. One study focused on polypharmacy in general practice, where all adults (≥18) were included. This identified that during the study period between 2010-2019, the prevalence of polypharmacy (≥5) increased from 9.8% to 13.6%, and the prevalence of hyperpolypharmacy increased from 1.8% to 3.0%.[11] There has also been a lack of research on the appropriateness of medication prescribing in Iceland. In 2007, a retrospective study was done in Iceland's largest secondary care hospital, where medication appropriateness was assessed by applying quality indicators. The study,

which included 913 patients, concluded that the quality of the drug medication regime of older patients at admission was suboptimal.[12]

Icelandic health care is state-centred and mainly publicly funded, with some out-of-pocket payments. Healthcare services are run by an integrated purchaser-provider model of care provided by the government and private practitioners and organisations. Hospitals and general practitioners are publicly funded. However, in recent years, more general practitioners' settings have been run by private organisations. The Icelandic healthcare system is divided into seven health districts. There is only one university hospital in Iceland, located in the capital, which provides all tertiary care and the majority of secondary care for the whole country. Life expectancy in Iceland is high, at 83.5 years, in 2023.[13] The proportion of senior citizens is higher in Iceland compared to other Western countries as the fertility rate of Icelandic women remained higher than in other Western countries for a long time.[13]

1.2 Medication-related harm

Medicines are the most frequently used medical intervention to treat acute and chronic conditions.[14] Medications are effective interventions however, ensuring appropriate and safe usage can be difficult.[15] Research in 2020 has shown that medication usage is still increasing. The volume of medicines used globally is 4,5 trillion doses, with an annual cost of 1.4 trillion USD. Numerous factors may jeopardise medication safety and, consequently, the patient's safety. It is often a combination of risks associated with the medication, the healthcare provider, the patient, or the system's factors.[16]

Medication-related harm has been defined as "The harm caused by medication if taken incorrectly, monitored insufficiently or as the result of an error, accident or communication problem".[16] Harm to patients because of unsafe healthcare has been identified as the principal cause of mortality and disability globally, and the majority of the harm has been deemed avoidable.[17] The definition of preventable medication-related harm is not unanimous. However, most studies describe "patient harm as preventable if it occurs as a result of an identifiable and modifiable cause, and its future recurrence can be avoided by reasonable adaptation to a process or adherence to guidelines".[18] There is a variation in reported rates of medication-related harm, which might be due to the disparity in terminology and study design. Studies have reported harm due to medication, ranging from 3-35% and mortality due to medication, from 0.14-4.7%.[19] Among research articles on medication-related hospital admission, there is a variation rate from 1.3% to 41.3%, with an average rate of 15.4%.[20]

The terminology for adverse drug events and the link to medication errors is described in Figure 1. All medications can lead to adverse drug events (ADE), which has been defined as *"any injury resulting from medical interventions related to a drug"*. Adverse drug event may be due to medication error or be unpreventable and unpredictable. Adverse drug events that are neither preventable nor predictable are called adverse

drug reactions (ADR) and are defined as "*a response to a drug which is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis or therapy of diseases or for the modification of physiological function*".[21] If ADEs are deemed preventable, they are considered a medication error. They are defined as "*any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.*"[22]

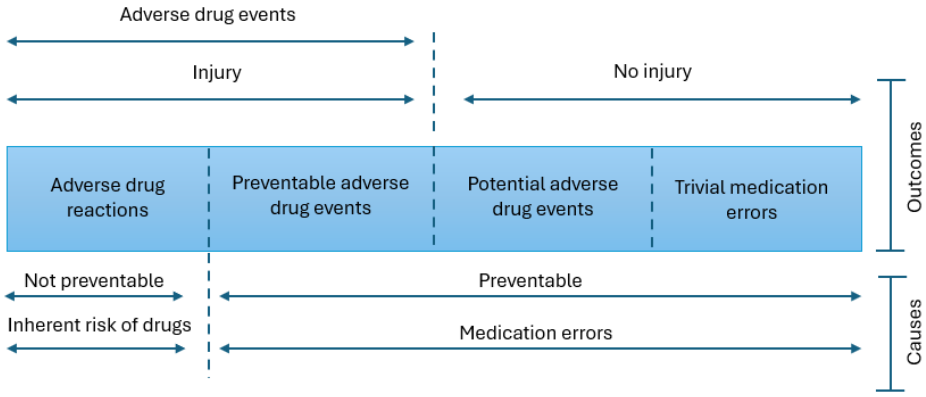

Figure 1 Relations between medication errors and adverse drug events [23]

A recent systematic review reported that 50% of preventable harm in health care is due to medication and therapeutic options, and the pooled prevalence globally was 5%.[23] The majority of the preventable medication-related harm was deemed to have moderate effects (44%), followed by mild effects (38%), and 23% were considered to have severe or potentially life-threatening effects.[18, 23] The systematic review showed an increasing prevalence of preventable medication-related harm, with a higher prevalence in 2020-2022 (5.9%) compared to 1.8% in 2000-2004.[23] The highest prevalence of preventable medication-related harm has been reported in geriatric settings (17%), followed by surgical wards (9%), and then in intensive care units (7%) and, finally, in emergency settings (6%). [23] Studies have evaluated the difference in patient populations in relation to the prevalence of preventable medication-related harm. No statistically significant difference has been observed between the genders. However, higher age (>80) is associated with increased risk.[23] Medication-related harm can cause patients' decreased quality of life in many ways, such as hospital admissions, a more extended stay in the hospital, and increased morbidity and mortality.[24, 25]

Medication-related harm can occur at all stages of the medication use process (prescribing, transcribing, dispensing, administering and monitoring). A systematic review has identified that the majority of medication-related harm occurs during the prescribing process (53%), followed by monitoring of the treatment (36%) and then administration of medicines (21%). Medication-related harm is most frequently associated with non-steroidal anti-inflammatory medication (20%), medication acting on the nerve system (18%) and then analgesics (17%) and hypnotics and sedatives (17%).[23]

Several studies have estimated the economic burden of medication errors and medication-related harm. In 2019, Elliott et al. published an analysis of England's annual clinical and economic burden of medication errors. The study reported that 237 million medication errors occurred annually, and more than a quarter was deemed potentially clinically significant.[26] Additionally, the Organisation for Economic Co-operation and Development recently published a report stating that 10% of hospitalisations were due to medication-related harm, and 20% of patients experienced medication-related harm during admission. Additionally, the estimated annual cost due to medication-related harm in the OECD is 54 million USD, accounting for 11% of the total medication cost across the OCED countries.[27]

Medication safety is defined as "*freedom from preventable harm with medication use*"[28] Additionally, WHO has described patient safety as " a *framework of organised activities that creates cultures, processes, procedures, behaviours, technologies and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make errors less likely and reduce the impact of harm when it does occur*".[29] Increasing patient safety by eliminating preventable harm in healthcare is the priority of the Global Patient Safety Action Plan for 2021-2030 because the lack thereof is the leading cause of death and incapacity.[30] This action plan follows the previous Global Patient Safety Challenge from the World Health Organization (WHO) in 2017, which focused on medication without harm. That action plan highlights three key areas to prevent avoidable medication-related harm: high-risk situations, polypharmacy, and transition of care.[16]

1.3 Aging and frailty

In recent decades, life expectancy has generally risen globally.[16] Longevity is increasing in the Western world, and the proportion of older people is steadily rising. In 1997, 10.7% of the population in Iceland was 65 years and older; in 2017, it was 13%, and Statistics Iceland forecasts that in 2039, it will reach 20% and further increase to 25% by 2057.[13] An ageing population is a diverse group affected by genetic, biological, environmental, and social factors.[31] Frailty has been used to describe diversity among older adults. There is a lack of consensus regarding an international definition of frailty. A description from WHO has been widely adopted, which describes frailty as: "*progressive age-related decline in physiological systems that results*

in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes".[32]

Multiple studies have described the biological changes that happen in relation to ageing. This development affects both the pharmacokinetics and pharmacodynamics among this older population.[33] The interindividual variability in the physiological responses widens in this age group.[34] Pharmacokinetics involves medication absorption, distribution, metabolism and excretion. Age-related changes to the absorption of medications have been reported as reduced gastric secretion,[35] delayed gastric emptying,[36] and reduced blood flow in the internal intestine in the abdomen. However, the studies are conflicting regarding the extent of change and whether it is clinically significant in affecting drug absorption.[34] Decreased metabolism by first-pass effect among older patients has been linked to reduced liver volume and blood flow.[37] Numerous studies have confirmed changes in first-pass metabolism in medication, which should, therefore, be considered when prescribing medication for older patients for medication undergoing extensive first-pass metabolism or having first-pass activation.[38, 39] Drug distribution is also affected by the changes in the body composition due to ageing. There is a decrease in total body water due to less body mass and increased fat composition.[40] Therefore, water-soluble medications, like digoxin, have a smaller volume of distribution, which may lead to higher concentrations in older adults.[41] On the contrary, fat-soluble medications, like diazepam and opioids, have a larger volume of distribution, leading to lower levels of medication concentration and extended half-lives.[42, 43] Decreased protein binding has also been studied, and theoretically, that could affect the concentration of free medication in plasma for highly protein-bound medication. However, studies have concluded that the effect is likely to be of little clinical relevance due to the fact the effect of protein binding on free medication in plasma is corrected by the clearance of the medication.[44] Drug elimination is mainly by the kidneys and the liver. Age-related changes in kidney excretion have been widely studied and are of clinical relevance, mainly due to a diminished glomerular filtration rate. The decrease in glomerular filtration rate affects water-soluble medication, such as digoxin, lithium, and nonsteroidal anti-inflammatory medication, and it is of increased importance if the medication has a narrow therapeutic index.[34] The medication clearance by the liver relies on the blood flow and the liver's ability to extract medications from the blood flowing through the liver. Numerous studies have revealed that age affects the liver clearance of medication by decreasing liver size and diminishing blood flow. However, age-related changes in liver structure and enzyme function are considered moderate.[42, 43] Pharmacodynamics is related to the biochemical and physiological effects of medications. Studies have generally identified increased sensitivity to medications with higher age. However, the generalisability of these studies is often difficult due to methodological differences. Psychotropic medications have been widely studied, and older patients seem to have increased vulnerability to their adverse drug reactions like delirium, extrapyramidal

effect and orthostatic hypotension.[45, 46] Anticoagulants, like warfarin, have increased sensitivity and are linked to an increasing inhibition of vitamin K-dependent clotting factor synthesis.[34] There is a heightened need to apply a cautious approach when prescribing medications for older patients, who often have increased frailty and are affected by age-related changes in the pharmacokinetics and pharmacodynamics processes of medications. Patients at a more advanced age should have their medication regularly reviewed, increased follow-up on adverse effects, and, especially for, those using multiple medications.[34]

1.4 Polypharmacy

Polypharmacy is a well-known term within the healthcare setting that describes the usage of multiple medicines.[24] The definition of polypharmacy has, however, proven to be disparate and has been changing over the years.[47] A global consensus on the definition of polypharmacy would support future research and use in clinical practice. For pharmacoepidemiology studies, a numerical threshold is frequently applied.[47] A systematic review indicated that it is defined in a wide range of quantitative and descriptive definitions in studies, including a shift towards integrating medication appropriateness into polypharmacy definitions. Some studies explored the use of "appropriate" versus "inappropriate" polypharmacy. The most widely accepted definition of polypharmacy refers to the usage of five or more medications.[2, 48, 49], and subsequent definitions describe hyper-polypharmacy as the usage of ten or more medications. Polypharmacy has mainly been studied in the older population[47, 50, 51], with only a few, including the younger adults.[52, 53] However, relying simply on a numeric count of medication and assuming polypharmacy is always unsafe is an oversimplification, as the medication treatment of individual patients should be evaluated in the context of their comorbidities.[54] Living with multimorbidity and associated polypharmacy is a known risk factor for adverse health consequences, for example, increased likelihood of experiencing adverse effects and drug interactions. Research has linked polypharmacy with decreased quality of life, decreased medication adherence, increased frailty, increased likelihood of hospitalisation, extended stay, increased risk of readmission, increased risk of dementia, falls, declining nutritional status, increased usage of healthcare resources and greater mortality.[16, 48, 50, 55-64]

Polypharmacy has been used as a quality indicator of prescribing practice, even though it may often be rational when patients live with multiple diseases. Nevertheless, medication appropriateness among patients with polypharmacy must be addressed regularly to ensure the treatment is safe and effective.[28, 65, 66] A prescribing cascade happens when a new medicine is prescribed to manage an adverse reaction to another drug in the mistaken belief that a new medical condition requiring treatment has developed, leading to harm for patients.[67] Polypharmacy has been identified as the leading risk for potentially inappropriate prescribing. Potentially inappropriate medication is associated with adverse health and economic outcomes. Therefore, it can

be a helpful indicator of prescribing practice and medicine safety. However, healthcare professionals must identify when polypharmacy is inappropriate, as it can lead to adverse effects and poorer health outcomes for patients.[2, 65, 66, 68] Inappropriate medication use and associated polypharmacy increase the risk of medication-specific adverse effects, drug-drug and drug-disease interactions and a range of other adverse outcomes (Table 1).[69]

Table 1 Examples of medication-related harm are associated with inappropriate medication use and polypharmacy.[69]

Medication-related harm	Reference
Cognitive impairment/delirium	70-73
Weight loss, malnutrition	59, 74
Falls	75-78
Fractures	76
Urinary incontinence	79
Functional impairment, immobility	80, 81
Hospitalisation	80, 82-88
Long-term care placement	83-87, 89
Decrease in quality of life.	89
Mortality	89
Lack of medication adherence	90
Increased healthcare utilisation and cost	80, 83-85, 87, 91-97

Multimorbidity is described as the coexistence of two or more chronic diseases. Studies have estimated the prevalence of multimorbidity ranging between 55-98% in the older population.[56] Research on the safety aspects of medicine usually excludes patients with multiple diseases, which may lead to limited knowledge of the potential risk of taking numerous medications to treat various diseases simultaneously.[48] Additionally, there has been a proliferation of clinical guidelines focusing on specific conditions, leading to a narrow focus rather than a broader scope to address multimorbid patients. Inevitably, this may lead to increased polypharmacy.[66, 98] Additionally, the biomarker and treatment goals that were researched among younger adults are less applicable to older adults, especially the oldest.[99, 100] In addition, patient-related risk factors for developing polypharmacy have been identified as being managed by multiple specialists, chronic mental health conditions, and living in long-term care housing. System-related risk factors have been identified as poorly updated medical records, automated re-prescribing of medications, and prescriptions to meet disease-specific quality metrics.[24]

The prevalence of polypharmacy has been assessed in various settings, and there is a wide range in the reported prevalence from 10-90%, depending on the setting, the studied population, and the definition of polypharmacy used.[48] A recent systematic review estimated the prevalence of polypharmacy across different settings to be 37% and that the lowest prevalence was in the general population (20%), followed by outpatient settings (37%) and then hospital settings (52%). The systematic review

included 106 studies, of which 49% defined polypharmacy as using five or more medications simultaneously. However, the review also included various definitions of polypharmacy, limiting the results.[101] Another recent extensive European cohort study reported that the prevalence of polypharmacy ranged from 26% to 40% across the studied countries.[102] The prevalence among older patients (≥65) in the United States of America has been reported to be around 65%.[103] Most studies elevating the prevalence of polypharmacy have focused on older patients among the general population. A Danish study focusing on that patient group reported the prevalence of polypharmacy to be 29.0% and hyperpolypharmacy (> 10 medications) at 5%.[104] Likewise, a Swedish study reported the prevalence of polypharmacy in the same patient group to be 44.0% and hyperpolypharmacy to be 11.7%.[105] . A Scottish study reported the prevalence of polypharmacy and hyperpolypharmacy to 16.3% and 5.8% among the general population (≥20). A study from Switzerland, among adults (≥18) in the general population, reported the prevalence of polypharmacy and hyperpolypharmacy to be 24.0%.[101] Only a few studies have focused on the prevalence in hospital settings. Canadian research reports the prevalence of polypharmacy and hyperpolypharmacy among older surgical patients (≥65) to be 54.8%.[106] Additionally, a Dutch study (≥70) reported the prevalence of polypharmacy and hyperpolypharmacy among surgical patients to be 67.0% and 26.0%.[107]

Concern is reported about the increasing prevalence of polypharmacy. A Swedish study of the whole population showed that the prevalence of polypharmacy rose from 16.9% in 2006 to 19.0% in 2014.[53] A similar study from the United Kingdom reported a change in the prevalence of polypharmacy from 11.2% in 1995 to 20.8% in 2010.[108] A Dutch study reported that the annual prevalence doubled among all adults from 1999 to 2014 in the Netherlands.[109]

1.5 High-risk medications and medication associated with harm

All medicines may lead to medication errors and associated harm. However, medication errors concerning some medications pose a higher risk, and those medications are referred to as "high-risk" (high-alert).[110] A list of medications has recently been updated, which represents the most common drug classes (Table 2). This systematic review evaluated the prevalence of medication error with high-risk medication. However, the prevalence among the studies varied widely, ranging from 0.24 to 89.6%. The highest prevalence observed in this systematic review was among the pediatric population, which warrants further study.[110] Several studies have also aimed to report the most common medication classes associated with medication-related harm. A recent systematic review identified that a larger proportion of medication-related harm was associated with non-steroidal anti-inflammatory drugs (20%), followed by medications that act on the central nervous system (18%), analgesics (17%), and hypnotics and sedatives (17%).[23]

Table 2 High-risk (high alert) medications associated with harm when used in error.[111]

High-risk medication groups	Reasoning
Anticancer medicine	Complex treatment regime, narrow therapeutic index and associated risk of acute or delayed toxicities
Anticoagulants	Extensive use, narrow therapeutic index, high risk of adverse drug events
HYDROmorphone	Potent opioid, 5-7 times more potent than morphine, with variation in strength and formulation. High risk of errors.
Insulin	Error in relation to insulin common
Methotrexate (oral)	Unusual treatment regime, once a week, errors common
Neuromuscular blocking agents	If used inadvertently in patients without skilled staff to support the airway, it may lead to serious harm like respiratory arrest.
Opioid analgesic	Frequently used, various strengths and formulations. It can cause, for example, respiratory depression, sedation and risk of dependency.
Paracetamol	High-risk medication for patient groups at risk of hepatotoxicity
Potassium (intravenous)	Potassium given inadvertently or incorrectly administered may lead to mortality
Vina alkaloids	High-risk medication due to the fact, if given via intrathecal accidentally, leads to mortality

1.6 Transfer of care

The transition of care is one of WHO's priorities in the Third Global Patient Safety Challenge: Medication Without Harm.[16] Studies have focused, to a great extent, on challenges in medication safety during hospital admission, where unintended medication discrepancies often lead to patient harm. However, a recent systematic review sheds light on what can happen after hospital discharge. The review concluded that medication errors and adverse reactions are common following hospital discharge. Another systematic review, which focused on medication-related harm in older adults after hospital discharge, also reported that it was common, and there is increased risk during the first 30 days post-discharge.[112, 113] Frequent changes in medication regime during hospital admission and lack of or poor communication during the transition of care are among the contributing factors to medication-related harm.[114] A recent multicentered study in the United Kingdom (PRIME Study) developed the first prediction model to identify patients at risk of experiencing medication-related harm after discharge from the hospital. This can support healthcare professionals identify patients who need to be supported. The tool consists of eight variables drawn from clinical, medication, and psychosocial domains. Applied at the point of discharge, it provides the absolute risk of an individual, an older adult, experiencing medication-related harm

during the eight weeks after discharge from acute hospital admission. This stratification is important in order to deliver targeted interventions in resource-limited healthcare settings.[115] National Institute for Health and Care Excellence (NICE) guideline 2015 suggests that 30-70% of patients may experience a medication error during transitions of care. [116] Therefore, continuity of care has been emphasised as a vital factor in increasing patient safety. Continuity of care has three dimensions (Table 3).[117] Numerous studies have evaluated the effectiveness of continuity of care, and they have identified continuity of care as leading to reduced mortality, decreased hospitalisation and emergency hospitalisation, fewer healthcare cases and increased patient satisfaction. A recent systematic review concluded that incorporating pharmacists in community pharmacies into continuity of care is associated with improved medication adherence, improved medication appropriateness and decreased healthcare-associated costs.[118] Additionally, a systematic review evaluated the relationship between polypharmacy, medication appropriateness and continuity of care. The study indicates that less continuity of care has a negative effect on the development of polypharmacy and inappropriate medication use. [119]

Table 3 Continuity of care, descriptions of three dimensions [117]

Continuity of care -three dimensions	
Relational continuity	Ongoing therapeutic relationship between a patient and one or more providers
Informational continuity	Use of information on past events and personal circumstances to make current care appropriate for each individual,
Management continuity	Consistent and coherent approach to the management of a health condition that is responsive to a patient's changing needs

1.7 Interventions

Recently, polypharmacy has been greatly studied, and interventions targeted towards polypharmacy have been widely published. The interventions range from deprescribing interventions to screening tools to identify potentially inappropriate medication use [120-123] and comprehensive multifactorial strategies. [124-126] However, most interventions apply a medication review as the basis of the intervention.[103] Polypharmacy intervention studies have a wide range of elements, including criteria to identify potentially inappropriate prescribing, physician- or patient-focused educational programmes, multidisciplinary teams, computerised prescribing aids, home care checklists and geriatric assessments.[103] The studied interventions are mainly provided by a general practitioner, pharmacist, or a collaborative approach from both professions.[120-122, 127] However, pharmacists most often review the medications and provide feedback to the prescribers.[103] Additionally, some studies, including older patients, highlight the importance of involving geriatricians[81] , and others emphasise the benefits of implementing interventions through interdisciplinary teams, which might include professions like doctors, nurses, pharmacists, social workers, and physical and occupational therapists to provide a comprehensive geriatric assessment.[128] As

mentioned earlier, most interventions are targeted at general practitioner settings; however, some are implemented in hospital settings and nursing homes.[124, 129-133] Studies have highlighted the importance of empowering patients and the importance of their role in addressing polypharmacy.[134] There are limited recommendations for the frequency of applying interventions targeted at polypharmacy. However, a published report on medication safety among patients with polypharmacy recommends that the appropriateness of medication use should be evaluated when a new medication therapy is initiated or during a transfer of care between healthcare settings.[135] NICE guidelines have also recommended that medication used among nursing home residents should be reviewed at least yearly.[136]

Even though polypharmacy interventions have been extensively studied, few have reported a subsequent decrease in clinical outcomes and healthcare utilisation.[137] However, the pooled analysis of a recent systematic review of systematic reviews suggests a significant decrease in potentially inappropriate medication use, potential medication omissions, an improvement in medication appropriateness and a decrease in the number of medications used.[137] The majority of studies explore interventions to address polypharmacy. However, ways to hinder the development of polypharmacy remain understudied and underdeveloped, and there seems to be a lack of strategies to prevent inappropriate polypharmacy from developing.[138] A position paper from Mangin et al., in 2018, on recommendations for action to reduce polypharmacy and associated inappropriate medication use. The recommendation includes actions directed at research and clinical practice (Table 4).[69]

Table 4 Recommendations of the International Group for Reducing Inappropriate Medication Use & Polypharmacy.[69]

Actions	Research
Review medications of all older adults with a focus on deprescribing, especially those at increased risk.	Evaluate the risks and benefits of interventions to address polypharmacy by applying patient-relevant outcomes such as mortality, morbidity, cognitive function and healthcare cost and utilisation.
Evaluate the appropriateness of medications before initiating, and consider the evidence and applicability to each patient's characteristics and preferences.	Aim to identify subgroups that benefit the most.
Consider medications for deprescribing beyond the criteria for potentially inappropriate medications.	Aim to determine the reversibility of worse health outcomes from inappropriate medication use and polypharmacy.
Apply a combination of explicit and implicit criteria to address polypharmacy.	Evaluate the effect of stopping medications used for a long time.
Consider the underrepresentation of older adults in clinical trials	Evaluate the different funding models for clinical care models on intervention to address polypharmacy
Acknowledge and address commercial influences on polypharmacy. Research data for older patients should be available prior to licencing indications.	Aim to define core important outcomes in clinical trials for medications used for patients with multimorbidity that evaluated the risk and benefit based on patient- and system-relevant domains.
Education and training need increased focus on inappropriate medication use and polypharmacy. Improve clinicians' understanding of best-applying care to vulnerable older adults with multimorbidity. Awareness of strengths and weaknesses of evidence	Research, synthesise and review the relative risks and benefits of specific treatments for patients with chronic diseases, including non-pharmaceutical therapies.
Medical training should incorporate methods of deprescription, and equal attention should be given to benefits and side effects.	Research, synthesise, and review how and in whom specific medications should be deprescribed.
For patients with multimorbidity, a single disease model should be questioned.	Aim to develop tools to assess the burden and capacity of medication treatment in patients with multimorbidity.
Decisions for older patients with multimorbidity, survival and quality of life should be prioritised in partnership with patient/family preferences.	Aim to develop tools to manage and detect adverse effects of medication.
	Evaluate ways to incorporate patients' prioritisation, such as cognitive function.
	Research optimal dosage regimen for older adults

1.7.1 Potentially inappropriate prescribing

Several studies have reported that polypharmacy is an independent factor for potentially inappropriate medication use. The majority of the studies have evaluated potentially inappropriate medication use among general practice settings.[125, 139, 140] Weir et al.

investigated the prevalence and incidence of potentially inappropriate medication use among hospitalised patients by applying the Beers criteria, STOPP criteria and Choosing Wisely statements among older (≥65) and concluded that 2/3 of patients were prescribed a potentially inappropriate medication at discharge.[141] Another study also studied older inpatients who applied the Beers and STOPP criteria and reported prevalence and incidence to be around 70% at admission and discharge.[142] The causes of potentially inappropriate polypharmacy are multifaceted.[143] Potentially inappropriate prescriptions, where harm exceeds the benefit of the medication, have been reported with a wide-ranging prevalence between 11.5%-85.1% among the older population.[52, 140] Potentially inappropriate prescribing has become a public health concern.[120] Older patients are vulnerable to adverse drug events due to potentially inappropriate medication use like falls, delirium, decreased quality of life and increased mortality.[144-148] A recent systematic review evaluated the link between potentially inappropriate prescribing and readmission to the hospital. Further studies are needed on the topic as the link remains unclear and dependent on the assessment tool applied to evaluate potentially inappropriate medication use.[149] Only two studies showed an association between potentially inappropriate medication use and hospital readmission. Those studies use STOPP and START or a combination of STOPP and START and the Beers criteria.[150] The prevalence of potentially inappropriate medication use varies among published studies, depending on the tool applied to detect potential inappropriate medication use, setting and studied populations. Increased age and the female gender are associated with increased risk, as well as having multiple prescribers and multidose dispensing services. There is a lack of studies on medication appropriateness among patients admitted to hospital.

Several criteria-based strategies to identify inappropriate medication have been published. The most frequently used are summarised in Table 5. Criteria-based strategies are either implicit (judgement-based), explicit (criterion-based), or a combination thereof.[120] Implicit criteria are based on the clinical judgment of clinicians, patient-specific, and take into account the entire medication regime of patients. Implicit criteria rely on the applicant's knowledge, experience, and even patients' preferences and are often time-consuming and have low reliability. An example of implicit criteria is the Medication Appropriateness Index. Explicit criteria are developed by literature reviews, expert opinions, or consensus techniques. Explicit criteria are mostly medication or disease-oriented, not considering the inter variability of patients or their medication regime and application requires limited clinical knowledge. They need to be frequently updated and adapted to each country. Several explicit assessment methods have emerged over the past three decades, like the Beers criteria.[151] and The Screening Tool for Older Person's Potentially Inappropriate Prescriptions (START and STOPP).[152] However, evidence of improved outcomes, such as reduced hospitalisation and mortality, remains unclear.[123]

Most of the prescriber's aid tools to identify potentially inappropriate medication use have been developed for older patients in the general population, and only a few target individuals living in nursing homes or hospitalised patients.[122, 153] Additionally, there are tools specifically designed for use in community pharmacies[154] Many national or local prescribing tools have been developed and adapted to local needs based on the previously published list. The Beers criteria are most commonly used (58.3%), followed by STOPP criteria (27.8%) as a base for developing new lists. The development of prescribing aids to identify potentially inappropriate medication use among older individuals proves difficult because older patients are frequently omitted or underrepresented in clinical trials evaluating the safety and efficacy of medications.[155]

Beers criteria were first developed by a geriatrician named Mark H. Beers in 1991 to identify potentially inappropriate medication use among older adults.[156] The Beers criteria is now the most widely used prescription aid and has been updated regularly by the American Geriatric Society. The list has developed over the years and is updated by an international panel of experts. In the 2019 update, medications that should be used with caution, medicines that have potential medication interactions that are likely to cause harm, and medications that are affected due to decreased renal function were added to the criteria.[157] The latest version, published in 2023, included notable updates, such as categorising aspirin and rivaroxaban as medications to be avoided. Most other changes involved strengthening existing criteria with new evidence or clarifying language.[158]

Beers criteria identify potentially inappropriate prescribing, which has been linked to an increased risk of developing adverse drug reactions, hospitalisation, and falls. These include several common medications used for cardiovascular, gastrointestinal and endocrine disorders, as well as medications used to treat pain, insomnia and anxiety. The disadvantages of Beers criteria are it does not address under-prescribing and duplication of medications. The Beers list is not as relevant for all countries as not all the included drugs are available.[159]

The Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (START and STOPP) criteria are alternative criteria developed in 2008 by an Irish geriatrician leading a European consensus group. The criteria identify potentially inappropriate medication use among older adults (≥65) as part of the STOPP criteria and additionally address potential prescribing omission as part of the START criteria. The list has also developed since its first publication in 2008. The START/STOPP criteria were recently updated.[152]

The MAI was developed in 1992 in the United States of America by a collaboration between a clinical pharmacist and a geriatrician.[160] The MAI is based on impliced criteria consisting of questions assessing the appropriateness of the medication on a three-point scale (appropriate, marginally appropriate, and inappropriate medication), and the score of the medication appropriateness is calculated. The disadvantage of the

MAI is that it is time-consuming and, therefore, challenging to apply in clinical practice. It also provides no guidance on optimising medication treatment.[161]

Studies comparing Beers and STOPP criteria have identified only a modest difference between the two explicit outcome measures. A study concluded the tools could be used in a complementary fashion to increase the sensitivity to adverse drug events. A systematic review concluded that having a national list of inappropriate medications for the older population is crucial to monitoring appropriate prescribing. Including the list of inappropriate prescribing in the national formulary could promote appropriate prescribing.[162]

The use of inappropriate medication is associated with economic burden due to the occurrence of adverse drug events and with increased healthcare costs and contributes to avoidable costs.[163] Additionally, Heider et. al concluded that inappropriate medication use increases healthcare costs and is linked to the number of medications used.

Drugs with high cholinergic activity are known to cause medication-related harm. Their anticholinergic activity can also lead to a cumulative effect, referred to as the anticholinergic burden. Among the adverse effects which they are associated with are cardiovascular events, falls, cognitive impairment in older people, and increased mortality.[162, 164-167] Various scales have been developed to evaluate the anticholinergic burden. However, there is no agreement on which is optimal. These tools list commonly prescribed medicines, ranked according to their potential anticholinergic burden. Validation of the scales differs in study design, settings, and age population. The ranges were established from studies primarily in the older population.[162] Nevertheless, it has been recognised that the anticholinergic burden may also affect younger adults, at least those with multimorbidity and associated polypharmacy. A recent study concluded that the anticholinergic burden was related to various adverse effects in a younger and relatively healthier population than previously studied. The frailty status has also been explored as an indicator of medication appropriateness and the likelihood of developing medication-related harm. The relationship between polypharmacy and frailty is, however, not fully understood. A recent review concluded that more studies are needed to explore the benefit of reducing polypharmacy to delay or reverse frailty.[48] A study from 2016 showed a significant correlation between a patient's frailty status and medication-related harm.[168, 169]

Table 5 Examples of prescribers' aid tools. Criteria to assess the appropriateness of prescriptions. Potentially inappropriate medications (PIM), potentially omitted drugs (POM)

Tool name	Beers criteria	START/STOPP	Medication Appropriateness Index (MAI)	FORTA (Fit fOR The Aged)
Target population	≥65	≥65	≥65	≥65
First published	1991	2007-2008	1992	2009
Last update	2023	2024	2012	2021
Description	Consists of medications and medication classes to avoid and use with caution	Indicators to identify prescribing omission and identifying medication potentially inappropriate	Questions to assess medication appropriateness linked to the rating of appropriateness	Grades medication into four groups concerning appropriateness for older patients
Category	PIM Drug-oriented listing approaches	PIM POM Patient-in-focus listing	PIM	PIM POM Patient-in-focus listing
Tools	Explicit	Explicit	Implicit	Explicit
Origin	USA	UK	USA	German
Reference	170	152	160	171

1.7.2 Deprescribing

The term deprescribing was first described in the literature in 2003.[172] There has been an an increased focus on the process of deprescribing medication to combat the increase of of polypharmacy and associated inappropriate medication use. Deprescribing has been described as "*the process of withdrawal of an inappropriate medication, supervised by a health a health care professional with the goal of managing polypharmacy and improving outcomes*". *outcomes*". Changing to a safer medication or reducing a dose is also considered deprescribing deprescribing (

1.7.3 Description of the Icelandic internal medicine database

The Icelandic internal medicine database was generated similarly to the Icelandic perioperative database. The Internal Medicine database includes all patients hospitalised in internal medicine wards at Landspitali – The National University Hospital of Iceland during the study period, between the 1st of January 2010 and the 31st of December 2022, with a follow-up of clinical outcomes through the 17th of March 2022. All of the patients' admissions were included in the analysis for this project. The hospital is the primary hospital for 75% of the Icelandic population and the tertiary for the whole nation. Figure 6 Describes the databases linked together in establishing the Icelandic internal medicine database.

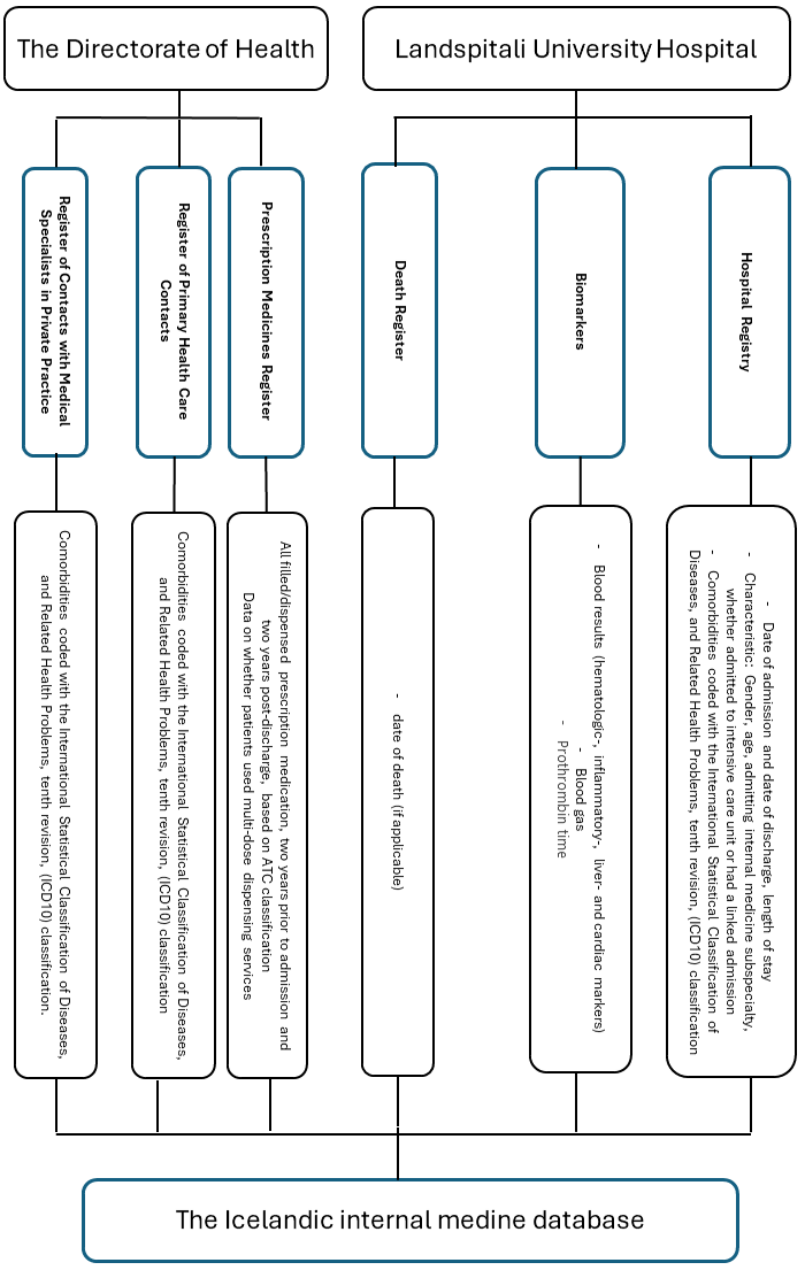

Figure 6 A schematic description of the Icelandic internal medicine database.

1.8 Exposure variable definition and follow-up period

1.8.1 Calculation of medication use categories

For all manuscripts, variables that described polypharmacy were generated. The primary exposure was the extent of medication use, defined as the number of different medications filled in the year preceding (pre-admission) and the year following discharge (post-discharge). Patients were separated into three groups based on the medication use categories they fulfilled (non-polypharmacy (<5), polypharmacy (5-9), and hyperpolypharmacy (≥10)) based on their pre-admission and post-discharge medication filling in the year prior to admission and post-discharge (Figure 7). Information was gathered to identify whether patients were using multidose dispensing services. In the Icelandic internal medicine database, a linked admission to the intensive care unit when patients have been admitted to the intensive care unit during an acute admission. Linked admission to palliative care, rehabilitation and geriatrics generally follows an acute admission to the internal medicine ward.

Figure 7 The timeline for allowing for medication filling pre-admission (-365 days until admission) and post-discharge (+ 365 days after discharge).

All regular and as-required medications were included; non-prescribed (over-the-counter), topical, and herbal/homoeopathic medications were not included. The number of medications were counted within different anatomical/pharmacological groups (ATC 1st level) and pharmacological/therapeutical subgroups (ATC 2nd level) filled in the year preceding and following surgical and internal medicine admissions Table 11.

Table 11 The Anatomical Therapeutic Chemical (ATC) classification system used for determining medication filled by prescription.

Medication Group	**ATC code**
Cardiovascular medications	C (entire category)
Beta-blockers	C07
Calcium Channel Blockers	C08
ACE inhibitors and Angiotensin II Receptor Blockers	C09
Statins	C10AA
Anticoagulant	B01A
Antiplatelet	B01AC
Proton Pump Inhibitors	A02BC
Anti-diabetics	A10B
Urinary	G04
Hormones	G03 ATH
Corticosteroids	H02AB
Respiratory	R (entire category)
Antibiotics	J01
Paracetamol/orphenadrine combinations	N02BE01
Opioids	N02A
Nonsteroidal anti-inflammatory medications	M01AE
Selective cox-2 inhibitors	M01AH
Antidepressants	N06A
Benzodiazepines	N05BA
Antipsychotic medications	N05A
Z-medications	N05CF
Anti-dementia medications	N06D
Antihistamines	R06

1.8.2 Calculation of potential inappropriate medication use

The American Geriatric Society 2019 Beers criteria are explicit criteria to identify inappropriate prescribing validated among ≥65 years. The Beers criteria provide a list of medications that have been identified as potentially inappropriate medication use for ≥65 years, which has been linked to an increased risk of developing adverse drug reactions, hospitalisation, and falls .[157] For the purpose of these studies, all prescription

medications filled in the year prior to admission and post-discharge were assessed for potentially inappropriate medication use by comparing them to the list of medications in the Beers criteria that are potentially inappropriate in most ≥65 older adults, which should typically be avoided. The Beers Criteria include individual criteria and medications or medication classes generally best avoided by older adults or under specific circumstances, such as certain diseases or conditions .[157]

For manuscripts III and IV, the primary exposure was the prevalence of potentially inappropriate medication use prior to admission and the incidence of new potentially inappropriate medication use post-discharge. The prevalence of filling a medication for subcategories of Beers criteria was also evaluated. The prevalence of medication use within different Beers categories was calculated, and the total number of criteria met was calculated based on the 2019 Beers criteria and the medication filled in the year preceding and the year following discharge from the hospital.

1.9 Baseline patient characteristics

Information on all baseline patient characteristics, such as age and gender were gatherd from hospital data. Information on comorbidities was gathered using the International Statistical Classification of Diseases and Related Health Problems (ICD) coding. The ICD 10 codes were used from both hospital, primary care, and private practice data to report on comorbidities prior to and post-discharge.

1.9.1 Elixhauser comorbidity index on admission

Elixhauser comorbidity Index is a comorbidity measurement and can be used to describe and compare patients' populations and used for an adjustment for confounding when comorbidity is correlating with an outcome. The Elixhause comorbidity Index was developed by Elixhause In 1998 and was calculated to estimate the overall severity of comorbidities segregated from the primary reason for hospitalisation. The index was based on 30 comorbidities, and each score ranges from -7-12. The final Elixhauser score ranges from -19 to 89. Elixhauser et al. developed the Elixhauser comorbidity index for large-scale inpatient administrative databases.[216] In 2009, Walraven et al. modified the Elixhasuer comorbidity Index to provide a single numeric score summarising the comorbidity burden.[217] The purpose of using the Elixhauser comorbidity Index for this study was to estimate the comorbidity burden among the study cohort and use the measurement to allow comparison and adjustment for confounding. For the purpose of this study, the Elixhauser comorbidity index was categorised as (<1), (1-4), (5-8), and (>8).

1.9.2 Hospital frailty risk index classification

Frailty has been used to describe diversity among older adults. There is a lack of consensus regarding an international definition of frailty. A description from WHO has

been widely adopted: 'progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes. [218] Frailty refers to a state where individuals are particularly vulnerable, facing an elevated risk of adverse health consequences or mortality when exposed to stressors.[219] Measurement of frailty risk can be applied to describe and compare patients' populations and used to adjust for confounding when comorbidity is correlating with an outcome. A specific hospital facility risk stratification tool was recently developed and validated for older (≥65 years) in acute care settings, relying on administrative data.[220] The frailty risk assessment Is derived from ICD-10 codes from electronic hospital records. The risk stratification tool was developed and evaluated using a three-step approach. First, it was analysed by cluster analysis, which evaluated patients admitted with signs of frailty and whether they could be identified by using ICD-10 codes. Secondly, the hospital facility risk scoring was developed by using ICD-10 codes that were overly represented. The cohort was evaluated. Thirdly, the newly established Hospital facility Risk Scoring was validated in two separate validation cohorts. The score Is categorised into low risk (<5), intermediate risk (5–15) and high risk (>15). The Hospital Frailty Risk Score has also been validated for older (≥65 years) surgical patients.

1.9.3 Anticholinergic Cognitive Burden Scale

The use of medication with anticholinergic effects has been linked to worse clinical outcomes. Studies evaluating the impact of increased anticholinergic burden have revealed that the anticholinergic effect is linked to an increase in the likelihood of cognitive impairment by 45% over six years. The decline of cognitive functions was evaluated using the mini-mental state examination assessment, and mortality risk was increased. Several tools have been developed to identify medication with anticholinergic burden. Boustani et al. developed the anticholinergic cognitive burden scale as a practical tool to identify and country the anticholinergic effect of medications.[221] The anticholinergic cognitive burden scale can additionally be used in research to quantify the anticholinergic burden of medication, Table 12. For the purpose of this study, the anticholinergic burden was quantified based on filled in both prior and post-discharge. A literature review established the tool to identify medications with an anticholinergic cognitive burden. An expert panel was then consulted to categorise the medication into minor (score=1), moderate (score=2), and major (score =3). [221] The quantification of the Anticholinergic burden refers to possible effect (score=1) and definite effect (score= 2 or 3)(Table 12).[221]

Table 12 Anticholinergic cognitive burden scale. Criteria for Categorisation: Score of 1: In vitro data shows that the chemical entity has antagonist activity at the muscarinic receptor. A score of 2: Evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect. A score of 3: Evidence from literature, expert opinion, or prescriber information that medication may cause delirium. The list has been adapted to the accessibility of medications in the Icelandic healthcare settings adapted to Icelandic healthcare settings. [221]

Drugs with ACB Score of 1	Drugs with ACB Score of 2	Drugs with ACB Score of 3
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Carbamazepine	Atropine
Aripiprazole	Cyproheptadine	Chlorpheniramine
Atenolol	Oxcarbazepine	Chlorpromazine
Bupropion	Pimozide	Clemastine
Captopril		Clomipramine
Cetirizine		Clozapine
Cimetidine		Diphenhydramine
Clidinium		Doxepin
Codeine		Doxylamine
Colchicine		Fesoterodine
Desloratadine		Hydroxyzine
Diazepam		Hyoscyamine
Digoxin		Imipramine
Dipyridamole		Nortriptyline
Fentanyl		Olanzapine
Furosemide		Orphenadrine
Fluvoxamine		Oxybutynin
Fluvoxamine		Paroxetine
Haloperidol		Perphenazine
Hydralazine		Promethazine
Hydrocortisone		Propantheline
Isosorbide		Quetiapine
Loperamide		Scopolamine
Loratadine		Solifenacin
Metoprolol		Tolterodine
Morphine		Trifluoperazine
Nifedipine		Trihexyphenidyl
Paliperidone		Trimipramine
Prednisone		
Risperidone		
Theophylline		
Trazodone		
Venlafaxine		
Warfarin		

1.9.4 Medication-related Harm Risk Stratification

Medication-related harm is known to cause morbidity among older patients. Parekh et al. developed a risk prediction tool to Identify older patients at Increased risk of medication-related harm post-discharge from the hospital. The tool was developed in a multicenter prospective study in the UK between 2013 and 2015. In the study, participants were ≥65 years old, followed up for 8 weeks post-discharge and medication-related harm was identified by an experienced pharmacist. Two systematic reviews were done to identify characteristics and clinical variables to be evaluated, and patients' views and an expert panel of clinicians were gathered. The tool was then developed by multivariable logistic regression with backward elimination. The PRIME tool, a risk prediction tool, was designed to Identify patients at heightened risks of medication-related harm in the post-discharge period. The tool predicts the absolute patient risk of older patients (≥65 years) experiencing medication-related harm post-discharge. The calculated score is based on clinical, medication, and psychosocial variables to determine the likelihood of medication-related harm. The risk score is based on gender, age, sodium level, number of medicines, and whether the patient uses antiplatelet or diabetic medication (Figure 8). The risk assessment tool was developed by Parekh et al. to identify older patients at risk of medication-related harm post-discharge. The validation was undertaken in a multicenter study 8 weeks post-discharge in the United Kingdom.[112, 115]

Model equation for risk score = -2.384 + 0.5x (0.025(age-81) – 0.398(gender) + 0.515(antiplatelet drug) – 0.042(sodium -137) + 0.591(antidiabetic drug) + 0.477(past adverse drug reaction) + 0.056(number of medications) + 0.397(living alon)

Induvidual estimated risk of medication related harm (%) = $(1/1+e^{\text{-risk score}})*100$

Figure 8 Equation to calculate patients' risk of experiencing medication-related harm requiring the use of health care services within 8 weeks of hospitalisation based on the PRIME risk stratification tool developed by Parekh et al.[112]

1.10 Definition of study clinical outcomes

For all manuscripts, the primary clinical outcomes were mortality (short-term, < 30 days, and long-term mortality) (censored on the 17th of March 2022 for the Internal of medicine database and the 19th of April 2021 for the Perioperative database), length of hospital stay (number of days, ≥ ten days), and readmission (number of days until readmission, readmission <30 days). The prevalence and incidence of diagnosis of an adverse drug reaction and falls were evaluated both before admission and post-discharge.

1.11 Statistical analysis

All Data visualisation and statistical analysis data for this study for all four manuscripts were conducted using R (The R Foundation for Statistical Computing R, Vienna, Austria) version 4.0.3 and 4.2.2, via R studio (RStudio PBC, USA), version 2022.12.0.

1.11.1 Descriptive statistics

Descriptive statistics were applied to describe the demographic and clinical characteristics of the patient populations in all four manuscripts. Descriptive statistics were also used to exhibit the number of medications filled in the year prior to admission (either a surgical or internal medicine) and the medication use category (non-polypharmacy, polypharmacy and hyperpolypharmacy). Descriptive statistics were also applied for paper III to describe potentially inappropriate medication use based on the Beers criteria. The number of medications was described for all papers as median and interquartile range. The prevalence and incidence were described as percentages, and the distribution of the medication use into categories of varying polypharmacy pre- and post-discharge was described as a percentage with a 95% confidence interval calculated using the Pearson-Klopper method to obtain binomial probability in the binom package in R.

In manuscript I and II, the comparison between the demographics, patient characteristics and clinical outcomes were made between groups of non-polypharmacy (< 5 medications), polypharmacy (5-9) and hyperpolypharmacy (≥10) frailty using ANOVA for continuous variables and chi-square tests for categorical variables. In manuscripts III and IV, the demographics, patient characteristics, and clinical outcomes were compared between groups that did not fill a potentially inappropriate medication and those that filled a potentially inappropriate medication using ANOVA for continuous variables and chi-square tests for categorical variables.

1.11.2 Multivariable analysis

For manuscript I, a multivariable logistic regression was used to compare multivaritate patient and procedural variables between groups of varying preoperative and postoperative medication use. No multivariable analysis was done in Manuscript II; for manuscript III, multivariable logistic regression models were used to evaluate patient- and admission-related risk factors of receiving a new potentially Inappropriate medication use post-discharge to identify independent risk factors using the covariates: age, sex, admitting speciality, Elixhauser comorbidity index, comorbidities, multidose dispensing service, category of medication usage (polypharmacy and hyperpolypharmacy) prior to admission and a diagnosis of fall or adverse drug reaction diagnosis prior to admission.

1.11.3 Survival

For manuscripts I and II, the long-term survival was visualised on a Kaplan-Meier plot between different medication use categories (non-polypharmacy = <5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications). For manuscript III, the long-term survival was visualised on a Kaplan-Meier plot between different medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) and modelled with cox proportional hazard risk model. The proportionality assumption was assessed using the cox.zph function in R with adjusting for number of medications used prior to admission, gender, age, hypertension, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, liver disease, kidney disease, malignant neoplasm, benign neoplasm, Elixhauser comorbidity index and admitting speciality and quantifying changes in Schoenfeld residuals against time.

1.11.4 Risk of Outcomes

Clinical outcomes were compared (short long-term mortality, primary hospitalisation length of stay, and risk of readmission) by applying descriptive statistics.

For manuscripts I and II, a restricted cubic spline were used to visualise the relationship between the medication use categories (non-polypharmacy, polypharmacy and hyperpolypharmacy) and the ratio of following clinical outcomes, short-term mortality (<30 days), extended hospital stay (>10 days), and risk of readmission (<30 days) a restricted cubic spline analysis was performed, with prespecified knots at the cut-off for the medication use categories (non-polypharmacy=0,polypharmacy=5, and hyperpolypharmacy=10 medications).

For manuscripts III and IV, a restricted cubic spline was used to visualise the relationship between the medication use categories (non-polypharmacy, polypharmacy and hyperpolypharmacy) and the ratio of potentially inappropriate medication use based on Beers criteria 2019; a restricted cubic spline analysis was performed, with prespecified knots at the cut-off for the medication use categories (non-polypharmacy=0,polypharmacy=5, and hyperpolypharmacy=10 medications).

1.11.5 Missing data

All four manuscripts were observational cohort studies based on retrospective data, which relies on accurate documentation of healthcare professionals. Therefore, the absence of documentation of a condition (diagnosis) might lead to underreporting, which is an assumption. No imputation for missing data was made.

1.11.6 Sensitivity analyses

A sensitivity analysis was performed to assess whether reclassification of the time frame allowed for filling medication prior to admission and post-discharge for the study definition of including medications filled in the 12 months preceding surgery would affect the prevalence of polypharmacy or hyperpolypharmacy groups. A sensitivity analysis was also performed in order to assess whether including antibiotics from the medication database to estimate the burden of polypharmacy without antibiotics would overstate the number of medications filled in the year prior and post-admission.

2 Results

This thesis is based on four manuscripts evaluating the epidemiology of polypharmacy, potentially inappropriate prescribing patterns, and its association with clinical outcomes among inpatients, both surgical and internal medicine patients. Manuscript I assessed the prevalence of preoperative polypharmacy, the incidence of postoperative polypharmacy/hyperpolypharmacy, and their association with patient- and procedural variables. Furthermore, the association between preoperative polypharmacy and postoperative outcomes was assessed. Similarly, manuscript II evaluated the prevalence of pre-admission polypharmacy and incidence of post-discharge polypharmacy/ hyperpolypharmacy among internal medicine patients admitted to hospital and their association with patient factors, admitting subspeciality, and clinical outcomes. In manuscript III, the prevalence and incidence of potentially inappropriate prescribing were described as associated with the burden of polypharmacy among internal medicine patients. Furthermore, the potentially inappropriate prescribing, association with the patient- and internal medicine subspecialties, and associated variables were reported. Similarly, in manuscript IV, the prevalence and incidence of potentially inappropriate prescribing and the association with the burden of polypharmacy among surgical patients were determined. Furthermore, the potentially inappropriate prescribing and the association with the patients- and associated variables in this population were studied.

2.1 Paper I – Epidemiology of polypharmacy and medication use among patients undergoing surgery and association with clinical outcomes

2.1.1 Clinical characteristics of the patient cohort

In total, 84,009 surgeries were performed at Landspitali hospital during the study period 2005-2018. Of those, 28,012 were reoperations or subsequent operations during the study period. Reoperations were excluded; therefore, the final study population included 55,997 patients undergoing their first surgery during the study period (Figure 9). Table 13 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). Of the whole cohort, 57.4% were female, and the median age [IQR] was 55 [39, 69]. They used a median [IQR] of 6 [2, 10] medications in the year preceding the surgery and 6.00 [3, 11] in the year after the surgery. Multidose

dispensing service was used by 13.7% of the cohort in the year preceding the surgery. The majority of the cohort had a low (<5) hospital frailty risk score class, 60.2%, 34.8% had a medium score (5-15), and 5.0% had a high score (>15). The most common comorbidity of the whole cohort was hypertension, 30.5%, malignant neoplasm, 16.2%, and chronic obstructive pulmonary disease, 16.0%. The majority of the surgeries, 65.8%, were elective surgeries. Of the cohort, 34.2% had an emergency operation. The most frequent types of surgeries were orthopaedic 28.1%, abdominal 18.9%, and gynaecology 15.9%.

2.1.2 Prevalence and incidence of different medication use categories (non-polypharmacy, polypharmacy and hyperpolypharamacy)

Figure 9 presents the prevalence of preoperative non-polypharmacy (<5 medications), which was (42.2%, 95% CI 41.7-42.6), polypharmacy (5-9 medications) which was (32.3%, 95% CI 33.5-34.3) and hyper–polypharmacy (≥10 medications), which was (25.5%, 95% CI 25.2-25.9).

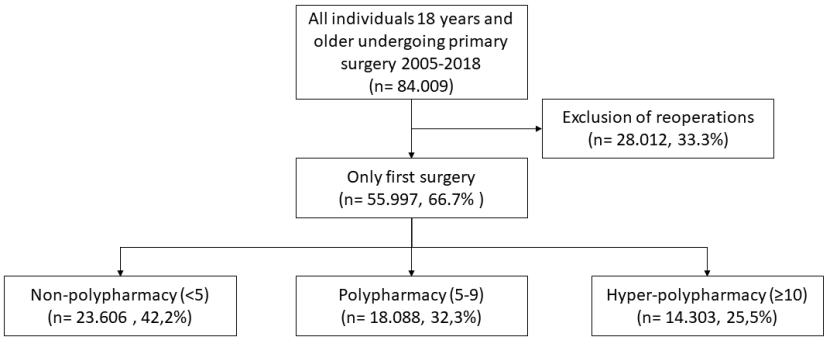

Figure 9 A consort diagram of participant inclusion and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy) based on a number of different medications filled in the year preceding surgery.

A total of 23,606 patients who underwent surgical procedures had not been exposed to polypharmacy in the year prior to the surgery. The incidence of new postoperative polypharmacy was (33.4%, 95% CI 32.4-34.0) and the incidence of new hyperpolypharmacy was (16.3%, 95% CI 16.0-16.7) hyper polypharmacy was (33.4%, 95% CI 32.4-34.0).

Figure 10 presents the distribution of patients into medication use categories of non-polypharmacy, polypharmacy and hyperpolypharmacy by year of surgery over the study period 2005-2018. The prevalence among the different medication use categories (non-polypharmacy vs polypharmacy vs hyperpolypharmacy) over the study period were similar, with a slightly higher prevalence of hyperpolypharmacy in 2006, 2009 and 2014.

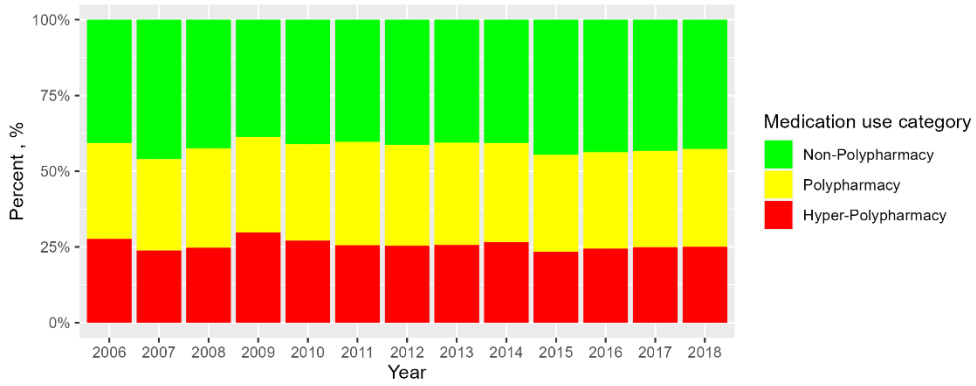

Figure 10 The distribution of patients into medication use categories over the study period 2005-2018 (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) based on the medication filled in the year preceding admission by internal medicine.

A sensitivity analysis was done to estimate whether the timeframe allowed for filling of medications in order to fulfil the requirement of the medication use categories (polypharmacy, 5-9 medications vs hyperpolypharmacy, ≥10 medications). The reclassification of polypharmacy classification if a shorter window of time to fill prior to admission was considered (Figure 11). This revealed that, for example, if only the last six months before admission were considered to classify polypharmacy, roughly 60% of the patients would remain within their medication use category compared with a 12-month filling window.

The prevalence was also estimated after eliminating antibiotics from the medication database to estimate the burden of the medication use categories (polypharmacy and hyperpolypharmacy) without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification. If antibiotics were removed from the list of medications, 80.2% of patients with polypharmacy and 79.9% with hyperpolypharmacy would have remained within their medication use category. This sub-analysis was performed due to the fact that antibiotics are most often short-term use (Table 13).

2.1.3 Clinical characteristics of the patient cohort of different medication use categories (non-polypharmacy, polypharmacy and hyperpolypharamacy)

Table 14 also presents the study cohort characteristics, categorised by their medication use category (non-polypharmacy (<5 medications), polypharmacy (5-9 medications), and hyperpolypharmacy (≥10 medications)). Patients were more likely to be female in all medication use categories: 63.1% for hyperpolypharmacy, 59.7% for polypharmacy, and 52.1% for non-polypharmacy. Those with hyperpolypharmacy also had higher median [IQR] age 67 [55, 76] years, compared to polypharmacy 58 [43, 69] and non-polypharmacy 45 [32, 59]. Patients with hyperpolypharmacy were also more likely to use multidose dispensing service preoperatively, 32.3% vs 11.9% for polypharmacy and 3.9% for non-polypharmacy. Additionally, patients with hyperpolypharmacy were more likely to have a high hospital frailty risk score class 13.1% vs. 3.4% for polypharmacy

and 1.3% for non-polypharmacy. Hypertension was the most common comorbidity for all medication categories, 55.8% for hyperpolypharmacy, 35.0% for polypharmacy, and 11.8% for patients with non-polypharmacy. The second most common comorbidity was chronic obstructive pulmonary disease, 30.2% for hyperpolypharmacy, but malignant neoplasm for polypharmacy, 17.1% and non-polypharmacy, 11.1%. Patients with hyperpolypharmacy were less likely to undergo an emergency operation, 26.9% compared to 28.0% for patients with polypharmacy and 43.3% for patients with non-polypharmacy. The most common surgical procedure for patients with all medication use categories was orthopaedic surgery, 29.5% for patients with hyperpolypharmacy, 24.9% for patients with polypharmacy and 29.6% for patients with non-polypharmacy. The second most common surgical procedure among the study cohort was abdominal surgery, 17.1%) for patients with hyperpolypharmacy, 18.9%) for patients with polypharmacy and 20.3% for patients with non-polypharmacy.

For patients exposed to polypharmacy prior to the surgery, the incidence of new postoperative hyperpolypharmacy was 28.9%, 95% CI 28.3-29. Table 15 presents the characteristics, including the comorbidity of patients moving to a higher medication use category, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Surgical patients moving to higher medication use category had higher median[IQR] age 57 [42, 68] vs 55 [38, 69], but they had a lower hospital frailty risk index classification with 63.1% with low risk vs 59.3% of patients not moving to a higher polypharmacy category. They were also more likely to have a diagnosis of malignant neoplasm (23.3% vs 14.0%) and longer median hospital stay (median [IQR]) 2 [1, 5] vs 1 [0, 3]. Finally, they were more often undergoing cardiac procedures (6.4% vs. 2.3%) or vascular procedures (10.9% vs. 5%).

2.1.4 Medication use and multidose dispensing services

In Table 14 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding surgery. The most frequent medications were filled in preoperatively for the whole study cohort and additionally arranged by the medication use categories. For the entire cohort, the most frequently used medications in the year prior to admission were antibiotics (49.0%), cardiac medications (42.4%), and opioids (42.2%). For patients with hyperpolypharmacy in the year prior to surgery, the most frequent medication classes were cardiac medications (77.8%), followed by antibiotics (75.0%) and opioids (67.0%). For patients with polypharmacy in the year prior to the surgery. The medication most commonly added were antibiotics (56.4%), followed by cardiac medications (50.9%) and opioids (46.8%). Finally, patients with non-polypharmacy most often filled antibiotics (27.7%), followed by opioids (23.6%) and paracetamol/orphenadrine combinations (20.7%) in the year preceding surgery.

For the whole cohort, the most frequently added medications were opioids (26.9%), paracetamol (20.1%), antibiotics (20.0%), anticoagulants (10.0%), respiratory medications (9.7%), proton pump inhibitors (9.6%), corticosteroids (8.0%), musculoskeletal (8.0%), urinary medications (8.0%), benzodiazepines (5.9%) and anti-diabetic medications (5.9%).

Multidose dispensing service was used in the year prior to surgery in the whole study cohort by 13.7% of patients. Those patients were more likely to have higher median [IQR] ages 76 [65, 83] vs 52 [37, 65], a higher number of medications filled median [IQR] 1 [0, 3] vs 3 [0, 9]. They have a higher Elixhauser comorbidity Index median [IQR] 0 [0, 4] vs 4 [0, 10] and higher frailty risk classification score with 66.3% of patients using multidose dispensing service having medium or high-risk score classification compared to 34.7% of those not using multidose dispensing service. Patients using multi-dose dispensing service were more likely to have a diagnosis associated with cognitive function like delirium (13.5% vs 2.3%), dementia (5.0% vs 0.2%), and psychiatric diagnosis (29.9% vs 9.5%). They were also more likely to undergo orthopaedic (43% vs 25.7%) and cardiac surgery (5.4% vs 2.9%). Finally, they were more likely to have a diagnosis of an adverse drug reaction (21.1% vs 9.2%). Patients with a higher medication use category were more likely to use multidose dispensing services, patients with hyperpolypharmacy (32.3%), hyperpolypharmacy, polypharmacy (11.9%) and non-polypharmacy (3.9%)(Table 16).

2.1.5 Clinical outcomes and survival post-discharge

To visualise the ratio of patients experiencing clinical outcomes of interest compared with a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications), the year pre-prior to a surgical admission were evaluated by using an unadjusted restricted cubic spline analysis. The analysis revealed a relationship between the absolute number of medications filled in the year before the surgery and the incidence of mortality (< 30 days). Readmission (< 30 days) and an extended hospital stay (≥ ten days) (Figure 12, Figure 14 and Figure 13).

Patients with hyperpolypharmacy prior to the surgery had higher 30-day mortality, 2.3%, compared to those with polypharmacy, 0.8%, and non-polypharmacy, 0.6% ($p < 0.001$). Additionally, patients with hyperpolypharmacy had a higher incidence of extended hospital stay, 11.3%, compared with those with polypharmacy, 6.3%, and non-polypharmacy, 4.1% ($p < 0.001$). Finally, patients with hyperpolypharmacy prior to the surgery had a higher incidence of readmission, 10.2%, compared with those with polypharmacy, 6.1%, and non-polypharmacy, 4.8% ($p < 0.001$).

Patients (≥65) with polypharmacy and hyperpolypharmacy were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm

post-discharge compared to non-polypharmacy, with a median [IQR] of 10.4% vs. 14.7% vs. 24.7%).

The long-term survival of patients with different medication use categories was visualised on a Kaplan-Meier plot. Figure 15 shows the long-term survival of patients with medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) based on filled medications in the year preceding hospital admission. A trend over time was observed with increased mortality among patients with polypharmacy and hyperpolypharmacy.

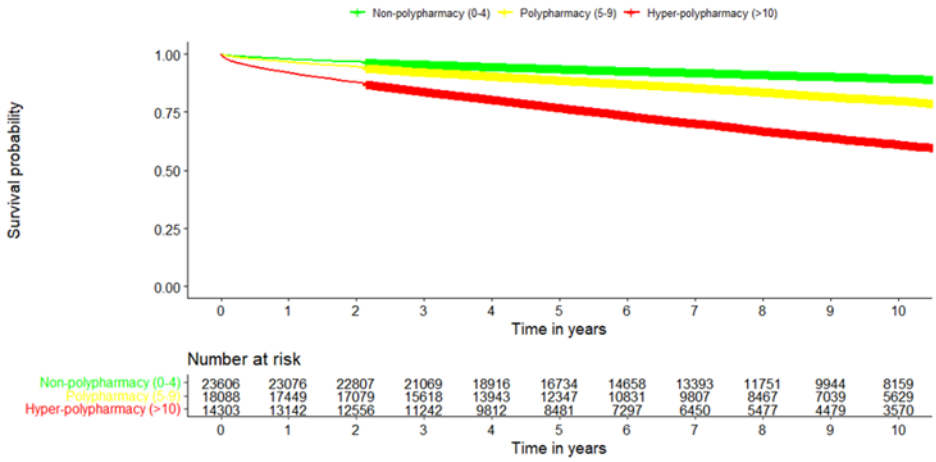

Figure 15 A Kaplan–Meier survival curve of long-term survival of patients compared based on the number of medications before surgery (green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10). Thicker lines represent 95% confidence intervals.

Table 13 Patient characteristics of cohorts based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR).

	Non-Polypharmacy	Polypharmacy	Hyper-polypharmacy	All patients	P-value
Total number of patients	23606 (42.2)	18088 (32.3)	14303 (25.5)	55997	
Sex (male)	12310 (52.1)	10806 (59.7)	9020 (63.1)	32136 (57.4)	<0.001
Age (median [IQR]), years	45 [32, 59]	58 [43, 69]	67 [55, 76]	55 [39, 69]	<0.001
Multidose dispensing services preoperatively	916 (3.9)	2148 (11.9)	4616 (32.3)	7680 (13.7)	<0.001
Number of preoperative medications (median [IQR])	2 [1, 3]	7 [6, 8]	13 [11, 16]	6 [2, 10]	<0.001
Number of postoperative medications (median [IQR])	3 [1, 5]	7 [5, 10]	13 [9, 17]	6 [3, 11]	<0.001
Elixhauser Comorbidity Index [IQR])	0 [0, 3]	0 [0, 4]	3 [0, 8]	0 [0, 4]	<0.001
Hospital Frailty Risk Score Class					
Low (< 5)	18096 (76.7)	10586 (58.5)	5034 (35.2)	33716 (60.2)	
Med (5-15)	5201 (22.0)	6894 (38.1)	7402 (51.8)	19497 (34.8)	
High (> 15)	309 (1.3)	608 (3.4)	1867 (13.0)	2784 (5.0)	
Comorbidities					<0.001
Ischemic heart disease	952 (4)	2416 (13.4)	4248 (29.7)	7616 (13.6)	
Congestive heart failure	220 (0.9)	425 (2.3)	1358 (9.5)	2003 (3.6)	
Hypertension	2787 (11.8)	6330 (35.0)	7976 (55.8)	17093 (30.5)	
Diabetes Mellitus	334 (1.6)	1026 (5.7)	2360 (16,5)	4381 (7.8)	
Chronic obstructive pulmonary disease	1814 (7.7)	2839 (15.7)	4323 (30.2)	8976 (16.0)	
Liver disease	147 (0.6)	223 (1.2)	361 (2.5)	731 (2.5)	
Chronic kidney disease	128 (0.5)	316 (1,2)	961 (6.7)	1405 (2.5)	
Malignant neoplasm	2632 (11.1)	3093 (17.1)	3343 (23.4)	9068 (16.2)	
Benign neoplasm	4444 (18.8)	5007 (27.7)	5657 (39.6)	15108 (27.0)	
Psychiatric	1759 (7.5)	2139 (11.8)	3003 (21,0)	6901 (12.3)	
Delerium	449 (1.9)	674 (3.7)	1020 (7.1)	2143 (3.8)	
Surgery Location and Classification					<0.001
Emergency operation	10247 (43.4)	5072 (28.0)	3841 (26.9)	19160 (34.2)	

Abdominal	4781 (20.3)	3415 (18.9)	2439 (17.1)	10635 (18.9)	
Cardiac	499 (2.1)	726 (4.0)	596 (4.2)	1821 (3.3)	
Endocrine	464 (2.0)	340 (1.9)	238 (1.7)	1042 (1.9)	
Gynaecology	4450 (18.8)	2978 (16.5)	1469 (10.3)	8897 (15.9)	
Neurosurgery	2309 (9.8)	2335 (12.9)	1770 (12.4)	6414 (11.4)	
Orthopaedic	6983 (29.6)	4490 (24.9)	4221 (29.5)	15694 (28.1)	
Thoracic	417 (1.8)	306 (1.6)	386 (2.7)	1109 (2.0)	
Urology	1397 (5.9)	1468 (8.1)	1307 (9.1)	4172 (7.4)	
Vascular	1335 (5.6)	1243 (6.9)	1142 (8.0)	3720 (6.7)	
Outcomes					
Number of pre-surgery medications (median [IQR])	2[1, 3]	7[6, 8]	13 [11, 16]	6 [2, 10]	
Number of post-discharge medications (median [IQR])	3 [1, 5]	7 [5, 10]	13 [9, 17]	6 [3, 11]	
Diagnosis of adverse drug reaction pre-admission (%)	698 (3.0)	1059 (5.9)	1660 (11.6)	3417 (6.1)	
Diagnosis of adverse drug reaction post admission (%)	562 (2.4)	876 (4.8)	1235 (8.6)	2673 (4.8)	
Length of stay (median [IQR])	1[0, 2]	1 [0, 4]	2 [1, 5]	1 [0, 3]	

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 14 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%).

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	p
Total number of patients	23606	18088	14303	55997	
Pre-operative medication					
Proton Pump Inhibitors	1720 (7.3)	4390 (24.3)	7368 (51.5)	13478 (24.1)	<0.001
Anti-diabetics	198 (0.8)	975 (5.4)	2216 (15.5)	3389 (6.1)	<0.001
Anticoagulants	377 (1.6)	1966 (10.9)	4004 (28.0)	6347 (11.3)	<0.001
Antiplatelet	204 (0.9)	1231 (6.8)	2685 (18.8)	4120 (7.4)	<0.001
Cardiac	3417 (14.5)	9198 (50.9)	11126 (77.8)	23741 (42.4)	<0.001
Beta-blockers	1211 (5.1)	4378 (24.2)	6386 (44.6)	11975 (21.4)	<0.001
Calcium Channel Blockers	395 (1.7)	2006 (11.1)	3552 (24.8)	5953 (10.6)	<0.001
ACE inhibitors and Angiotensin II Receptor Blockers	1566 (6.6)	4737 (26.2)	6305 (44.1)	13156 (23.4)	<0.001
Statins	885 (3.7)	3595 (19.9)	5677 (39.7)	10157 (18.1)	<0.001
Urinary	4007 (17.0)	6449 (35.7)	6606 (46.2)	17062 (30.5)	<0.001
Hormones	1247 (5.3)	3783 (20.9)	6566 (45.9)	11596 (20.7)	<0.001
Corticosteroids	640 (2.7)	2444 (13.5)	5024 (35.1)	8108 (14.5)	<0.001
Antibiotics	6530 (27.7)	10202 (56.4)	10724 (75.0)	27456 (49.0)	<0.001
Opioids	5568 (23.6)	8469 (46.8)	9582 (67.0)	23619 (42.2)	<0.001
Paracetamol/orphenadrine combinations	4877 (20.7)	7930 (43.8)	7570 (52.9)	20377 (36.4)	<0.001
Nonsteroidal anti-inflammatory drugs	4609 (19.5)	7263 (40.2)	6547 (45.8)	18419 (32.9)	<0.001
Selective cox-2 inhibitors	316 (1.3)	1037 (5.7)	1821 (12.7)	3174 (5.7)	<0.001
Antipsychotic	259 (1.1)	988 (5.5)	2052 (14.3)	3299 (5.9)	<0.001
Benzodiazepines	723 (3.1)	2586 (14.3)	4952 (34.6)	8261 (14.8)	<0.001
Antidepressants	1617 (6.8)	4112 (22.7)	6317 (44.2)	12046 (21.5)	<0.001
Anti-dementia	40 (0.2)	162 (0.9)	284 (2.0)	486 (0.9)	<0.001
Respiratory	2180 (9.2)	5317 (29.4)	7401 (51.7)	14898 (26.6)	<0.001
Antihistamin	591 (2.5)	1529 (8.5)	2522 (17.6)	4642 (8.3)	<0.001

Table 15 Patient characteristics of cohorts based on whether they changed to a higher polypharmacy category. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No change in polypharmacy category	Shift to higher polypharmacy category	p
Total number of patients	42872	13125	
Sex (female)	24744 (57.7)	7392 (56.3)	0.005
Age (median [IQR]), years	55 [38, 69]	57 [42, 68]	<0.001
Length of stay (days)(median [IQR])	1 [0, 3]	2 [1, 5]	<0.001
Number of preoperative medications (median [IQR])	6 [2, 11]	4 [2, 7]	<0.001
Number of postoperative medications (median [IQR])	5 [2, 9]	1 [6, 12]	<0.001
Elixhauser Comorbidity Index [IQR])	0 [0, 4]	0 [0, 4]	0.936
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	25428 (59.3)	8288 (63.1)	
Med (5-15)	14994 (35.0)	4503 (34.3)	
High (> 15)	2450 (5.7)	334 (2.5)	
Surgery Location and Classification			<0.001
Emergency operation	15131 (35.3)	4029 (30.7)	<0.001
Abdominal	8369 (19.5)	2266 (17.3)	
Cardiac	976 (2.3)	845 (6.4)	
Endocrine surgery	751 (1.8)	291 (2.2)	
Gynaecology	7015 (16.4)	1882 (14.4)	
Neurosurgery	5331 (12.4)	1083 (8.3)	
Orthopaedic	12245 (28.6)	3449 (26.2)	
Thoracic	757 (1.8)	352 (2.7)	
Urology	3225 (7.5)	947 (7.2)	
Vascular	2285 (5.5)	1435 (10.9)	
Comorbidities			
Congestive heart failure	1674 (3.9)	329 (2.5)	<0.001
Ischemic heart disease	5891 (13.7)	1725 (13.1)	0.083
Hypertension	13124 (30.6)	3969 (30.2)	0.424
Diabetes Mellitus	3098 (7.2)	622 (4.7)	<0.001
Chronic obstructive pulmonary disease	7177 (16.7)	1799 (13.7)	<0.001
Liver disease	582 (1.4)	149 (1.1)	0.055
Chronic kidney disease	1190 (2.8)	215 (1.6)	<0.001
Malignant neoplasm	6009 (14.0)	3059 (23.3)	<0.001
Benign neoplasm	11728 (27.4)	3380 (25.8)	<0.001
Psychiatric	5564 (13.0)	1337 (10.2)	<0.001
Delirium	1750 (4.1)	393 (3.0)	<0.001
Adverse drug reaction	2774 (6.5)	643 (4.9)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 16 Patient characteristics of cohorts based on whether they used multidose dispensing services in the year preceding the surgery. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No multidose dispensing	Multidose dispensing	P-value
Total number of patients	48317(86.3)	7680(13.7)	
Sex (male)	27785 (57.5)	4351 (56.7)	<0.001
Age (median [IQR]), years	52 [37, 65]	76 [65, 83]	<0.001
Number of pre-admission medications (median [IQR])	5 [2, 8]	11 [7, 16]	
Number of post-discharge medications (median [IQR])	6 [3, 10]	12 [8, 17]	
Elixhauser Comorbidity Index [IQR])	0 [0, 4]	4 [0, 10]	<0.001
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	31535 (65.3)	2181 (28.4)	
Med (5-15)	15652 (32.4)	3845 (50.1)	
High (> 15)	1130 (2.3)	1654 (21.5)	
Comorbidities			<0.001
Ischemic heart disease	4980 (10.3)	2636 (34.3)	
Congestive heart failure	932 (1.9)	1071 (13.9)	
Hypertension	12641 (26.2)	4452 (58.0)	
Diabetes Mellitus	2378 (4.9)	1342 (17.5)	
Chronic obstructive pulmonary disease	6896 (14.3)	2080 (27.1)	
Liver disease	515 (1.1)	216 (2.8)	
Chronic kidney disease	689 (1.4)	716 (9.3)	
Malignant neoplasm	7314 (15.1)	1754 (22.8)	
Benign neoplasm	12191 (25.2)	2917 (38.0)	
Psychiatric	4601 (9.5)	2300 (29.9)	
Delerium	1108 (2.3)	1035 (13.5)	
Dementia	94 (0.2)	387 (5.0)	
Surgery Location and Classification			<0.001
Emergency operation	15722 (32.5)	3438 (44.8)	
Abdominal	1875 (19.9)	1014 (13.2)	
Cardiac	1409 (2.9)	412 (5.4)	
Endocrine	950 (2.0)	92 (1.2)	
Gynaecology	8557 (17.8)	340 (4.5)	
Neurosurgery	5690 (11.8)	724 (9.4)	
Orthopaedic	12397 (25.7)	3297 (43.0)	

Thoracic	954 (2.0)	155 (1.7)	
Urology	3476 (7.2)	696 (9.0)	
Vascular	3130 (6.5)	590 (7.7)	
Outcomes			
Diagnosis of adverse drug reaction pre-admission (%)	2486 (5.1)	931 (12.1)	
Diagnosis of adverse drug reaction post admission (%)	1985 (4.1)	688 (9.0)	
Length of stay (median [IQR])	1 [0, 3]	3 [1, 9]	

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

2.2 Paper II - Epidemiology of polypharmacy and medication use among internal medicine patients and association with clinical outcomes

2.2.1 Clinical characteristics of the patient cohort

In total, the cohort included 85,942 admissions of 38,338 individuals to internal medicine at Landspitali Hospital during the study period 2010-2020. Table 17 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). Of the whole cohort, 51.1 % were male, and the median age [IQR] was 73 [60, 82]. They used a median [IQR] of 12 [7,18] medications in the year preceding the admission and 12 [7, 17] in the year after the admission. Multidose dispensing service was used by 46992 (54.7%) of the cohort in the year preceding the admission. The majority of the cohort had a medium (5-15) hospital frailty risk score class: 45.1%, 37.5% had a low score (<5), and 17.4% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 54.1%, followed by chronic obstructive pulmonary disease 32.3%, and then ischemic heart disease, 30.8%. The most frequent admissions were by the following internal medicine specialities: cardiology 21.7%, general internal medicine 13.5%, and pulmonology 10.6%. A portion of the cohort (11.2%) had a linked admission after being admitted by an internal medicine speciality either to intensive care 5.6%, geriatrics 3.7%, palliative care 1.0% or rehabilitation 1.0%. The median number of admissions per patient [IQR] for the whole cohort was 1 [1-3] admission per individual, ranging from 1-40 admissions.

2.2.2 Prevalence and incidence of new post-discharge polypharmacy/hyperpolypharmacy

Figure 16 presents the prevalence of pre-admission non-polypharmacy (<5 medications), which was 15.1%, 95% CI 14.9-15.4, polypharmacy (5-9 medications), which was 22.9%, 95% CI 22.6-23.2 and hyper-polypharmacy (≥10 medications), which was 62.5%, 95% CI 62.2-62.9.

Figure 16 A consort diagram of participant inclusion based on the number of different medications filled in the year preceding admission by internal medicine speciality. Medicaiton use categories = (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy, and ≥ 10 medications = hyper-polypharmacy.

Table 17 presents the study cohort characteristics, categorised by their medication use category (non-polypharmacy, polypharmacy, and non-polypharmacy). Patients were more likely to be male in all categories: 50.9% for hyperpolypharmacy, 51.4% for polypharmacy, and 51.6% for non-polypharmacy. Patients within all medication use categories had similar median [IQR] age 73 [60, 82], 73 [60, 82], and 72 [60, 83] for hyperpolypharmacy, polypharmacy, and non-polypharmacy. Patients with hyperpolypharmacy were more likely to use multidose dispensing service prior to admission, 65.9% vs. 45.6% for polypharmacy and 22.0% for non-polypharmacy. Patients within all medication use categories had a similar Elixhauser Comorbidity Index [IQR]) and Hospital Frailty Risk Score Class. The prevalence of all comorbidities was similar within all three medication use categories, with hypertension most common (54.0-54.8), followed by chronic obstructive pulmonary disease (32.3-32.6) and then ischemic heart disease (30.5-31.1). The same pattern was seen in the prevalence of admission to internal medicine specialities among the three medication use categories. Cardiology (21.2-21.8) was the most common admitting speciality, followed by general medicine (13.5-13.7) and pulmonology (10.5-10.6). The prevalence of linked admissions was also similar between the medication use categories, with admission intensive care most common (5.5-5.8), followed by geriatrics (3.5-3.8), followed by palliative care (0.9-1.0) and rehabilitation wards (1.0-1.1).

Figure 17 presents the distribution of patients into categories of non-polypharmacy (<5 medications), polypharmacy (5-9 medications) and, hyperpolypharmacy (>10 medications), polypharmacy by year of surgery over the study period 2010-2020. The prevalence among the different medication categories (non-polypharmacy vs polypharmacy vs hyperpolypharmacy) over the study period were similar.

A total of 15,847 patients, 18.4% (95% CI 18.2% to 18.7%) who were admitted by internal medicine speciality had an increase in medication use, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Table 18 presents the characteristics, including the comorbidity of patients moving to a higher medication use category, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Internal medicine patients moving to the higher medication use category had similar characteristics, including their comorbidity, except they were less likely to use multi-dose dispensing service prior to admission (40.6% vs. 57.9%). Additionally, they were less likely to have had a diagnosis of an adverse drug reaction both prior to admission (12.0% vs. 5.8%) or after discharge (6.2% vs. 15.0%) than those with no change.

A sensitivity analysis was done to estimate whether the timeframe allowed for filling of medications In order to fulfil the requirement of the medication use categories (polypharmacy, 5-9 medications vs hyperpolypharamcy, >10 medications. The reclassification of polypharmacy classification if a shorter window of time to fill prior to admission by internal medicine speciality was considered (Figure 18). This revealed that, for example, if only the last six months before admission were considered to classify polypharmacy and hyperpolypharmacy, roughly 75-85% of the patients would remain within their medication use category compared with a 12-month filling window.

Figure 18 Proportion of classification agreement (Y-axis) for patients classified into polypharmacy or hyper-polypharmacy groups when the study definition of including medications filled in the 12 months preceding the admission by internal medicine speciality was compared against reclassification using a shorter duration of filling (1-11 months (X-axis)).

The prevalence was also estimated after eliminating antibiotics from the medication database to estimate the burden of the medication use categories (polypharmacy and hyperpolypharmacy) without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification if antibiotics were removed from the list of medications, 89.5% of patients with polypharmacy and 92.7% with hyperpolypharmacy would have remained within their medication use category.

2.2.3 Medication use and multidose dispensing services

In Table 19, the most frequent medications were filled in the year prior to admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). For the entire cohort, the most frequently used medications were medications acting on the nervous system (80.6%), including opioids (51.0%), Z-drugs (43%), antidepressants (37.9%), and benzodiazepines (29.0%). The second highest category was cardiac medications (74.5%), followed by antibiotics (60.7%). The order was the same for all three medication use categories, with medication acting on the nervous system, cardiac medications and antibiotics.

For the whole cohort the most commonly added medications for the entire cohort were anticoagulants (15.6%), antibiotics (14.9%), opioids (14.2%), proton pump inhibitors (13.2%), antiplatelets (12.0%), corticosteroids (10.3%), respiratory medications (9.6%) and medication acting on the central nervous system (8.9%), with Z-drugs (8.4%).

Multidose dispensing service was used in the year prior to admission in the whole study cohort by 46992 (54.7%) patients. Those patients were more likely to have higher median [IQR] ages 78 [73, 84] vs 72 [69, 77] and a higher number of medications filled prior to admission median [IQR] 13 [9, 18] vs 9 [6, 13]. They had similar Elixhauser comorbidity Index and higher frailty risk classification. Patients using multi-dose dispensing service had a similar prevalence of a diagnosis associated with cognitive function like (delirium (9.2% vs 8.8%), dementia (2.0% vs 2.1%), and psychiatric diagnosis (16.4% vs 16.7%). They also had a similar distribution between the different internal medicine specialities (Table 20).

2.2.4 Clinical outcomes and survival post-discharge

An analysis using an unadjusted restricted cubic spline analysis revealed no relationship between the absolute number of medications filled in the year before the surgery and the incidence of mortality (< 30 days). Readmission (< 30 days) and an extended hospital stay (≥ ten days) (Figure 19). Patients with hyperpolypharmacy prior to the surgery had higher 30-day mortality, 2.3%, compared to those with polypharmacy, 0.8%, and non-polypharmacy, 0.6% ($p < 0.001$).

Patients (≥65) with polypharmacy and hyperpolypharmacy were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge compared to non-polypharmacy, with a median [IQR] of 9.0% vs. 12.8% vs. 23.3%).

The long-term survival of patients with different medication use categories was visualised on a Kaplan-Meier plot. Figure 20 shows the long-term survival of patients with medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) based on filled medications in the year preceding hospital admission (Figure 20). No difference in mortality was observed over time with polypharmacy and hyperpolypharmacy compared to non-polypharmacy.

Table 17 Patient characteristics of the patient cohorts are based on the number of medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy, and ≥ 10 medications = hyper- polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR). Linked admissions refers to whether the admission was linked to rehabilitation, geriatric, or palliative care services following discharge from the acute service.

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P-value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	
Sex (male)	6664 (51.6)	10052 (51.4)	27198 (50.9)	43914 (51.1)	0.250
Age (median [IQR]), years	72[60, 83]	73[60, 82]	73 [60, 82]	73 [60, 82]	0.877
[15,25)	227 (1.8)	351 (1.8)	960 (1.8)	1538	0.558
[25,35)	475 (3.7)	708 (3.7)	1875 (3.5)	3058	
[35,45)	598 (4.7)	936 (4.8)	2501 (4.7)	4035	
[45,55)	1024 (8.0)	1590 (8.2)	4360 (8.2)	6974	
[55,65)	1923 (15.0)	2968 (15.3)	7996 (15.1)	12887	
[65,75)	2838 (22.1)	4067 (21.0)	11534 (21.7)	18439	
[75,85)	3360 (26.2)	5207 (26.9)	13879 (26.2)	22446	
[85,95.)	2384 (18.6)	3563 (18.4)	9954 (18.8)	15901	
Multi-dose dispensing services	2838 (22.0)	8919 (45.6)	35235 (65.9)	46992 (54.7)	<0.001
Number of pre-admission medications (median [IQR])	2 [1, 3]	7 [6, 8]	16 [13, 21]	12 [7, 18]	<0.001
Number of post-discharge medications (median [IQR])	5 [2, 8]	9 [6, 12]	15 [10, 20]	12 [7, 17]	<0.001
Number of pre-admission medications without antibiotics (median [IQR])	2 [0, 3]	6 [5, 8]	14 [11, 19]	11 [6, 16]	<0.001
Elixhauser Comorbidity Index [IQR])	6 [0, 12]	6 [0, 13]	6[0, 12]	6[0, 12]	0.804
(<1]	3492 (27.0)	5245 (26.8)	14523 (27.2)	23260 (27.1)	0.791
(1-4]	1911 (14.8)	2963 (15.2)	8039 (15.0)	12913 (15.0)	
(4-5]	860 (6.7)	1355 (6.9)	3608 (6.7)	5823 (6.8)	
(5-8]	1618 (12.5)	2351 (12.0)	6421 (12.0)	10390 (12.1)	
(>8]	5045 (39.0)	7640 (39.1)	20871 (39.0)	33556 (39.0)	

Hospital Frailty Risk Score Class					0.976
Low (< 5)	4823 (37.3)	7334 (37.5)	20111 (37.6)	32268 (37.5)	
Med (5-15)	5844 (45.2)	8828 (45.1)	24070 (45.0)	38742 (45.1)	
High (> 15)	2259 (17.5)	3392 (17.3)	9281 (17.4)	14932 (17.4)	
Comorbidities					
Ischemic heart disease	4017 (31.1)	5967 (30.5)	16477 (30.8)	26461 (30.8)	0.545
Congestive heart failure	2644 (20.5)	3952 (20.2)	10734 (20.1)	17330 (20.2)	0.621
Hypertension	7081 (54.8)	10554 (54.0)	28855 (54.0)	46490 (54.1)	0.236
Diabetes Mellitus	2108 (16.3)	3143 (16.1)	8804 (16.5)	14055 (16.4)	0.438
Chronic obstructive pulmonary disease	4118 (31.9)	6379 (32.6)	17288 (32.3)	27785 (32.3)	0.353
Liver disease	405 (3.1)	658 (3.4)	1635 (3.1)	2698 (3.1)	0.109
Chronic kidney disease	1311 (10.1)	2054 (10.5)	5268 (9.9)	8633 (10.0)	0.032
Malignant neoplasm	3265 (25.3)	4821 (24.7)	13376 (25.0)	21462 (25.0)	0.431
Psychiatric	2094 (16.2)	3284 (16.8)	8812 (16.5)	14190 (16.5)	0.354
Dementia	253 (2.0)	402 (2.1)	1139 (2.1)	1794 (2.1)	0.438
Delerium	1183 (9.2)	1715 (8.8)	4800 (9.0)	7698 (9.0)	0.480
Internal Medicine Sepciality					0.129
General internal medicine	1741 (13.5)	2671 (13.7)	7205 (13.5)	11617 (13.5)	
Geriatrics	1072 (8.3)	1611 (8.2)	4602 (8.6)	7285 (8.5)	
Cardiology	2746 (21.2)	4269 (21.8)	11646 (21.8)	18661 (21.7)	
Endocrine	198 (1.5)	315 (1.6)	864 (1.6)	1377 (1.6)	
Gastroenterology	1112 (8.6)	1598 (8.2)	4293 (8.0)	7003 (8.1)	
Infectious diseases	733 (5.7)	1111 (5.7)	2901 (5.4)	4745 (5.5)	
Haematology	665 (5.1)	958 (4.9)	2783 (5.2)	4406 (5.1)	
Nephrology	302 (2.3)	479 (2.4)	1299 (2.4)	2080 (2.4)	
Neurology	1107 (8.6)	1699 (8.7)	4316 (8.1)	7122 (8.3)	
Oncology	853 (6.6)	1218 (6.2)	3391 (6.3)	5462 (6.4)	
Dermatology	79 (0.6)	106 (0.5)	257 (0.5)	442 (0.5)	
Pulmonology	1352 (10.5)	2054 (10.5)	5674 (10.6)	9080 (10.6)	
Rheumatology	588 (4.5)	923 (4.7)	2699 (5.0)	4210 (4.9)	
Rehabilitation	144 (1.1)	207 (1.1)	597 (1.1)	948 (1.1)	
Palliative care	234 (1.8)	335 (1.7)	935 (1.7)	1504 (1.8)	

Admissions linked with primary admission					
Geriatrics	467 (3.6)	687 (3.5)	2007 (3.8)	3161 (3.7)	0.283
Palliative care	127 (1.0)	173 (0.9)	534 (1.0)	834 (1.0)	0.375
Rehabilitation	125 (1.0)	215 (1.1)	530 (1.0)	870 (1.0)	0.371
Intensive care unit admission	715 (5.5)	1127 (5.8)	2937 (5.5)	4779 (5.6)	0.366
Outcomes					
Diagnosis of adverse drug reaction pre-admission (%)	506 (3.9)	1436 (7.3)	7393 (13.8)	9335 (10.9)	<0.001
Diagnosis of adverse drug reaction post discharge (%)	388 (3.0)	946 (4.8)	3793 (7.1)	5127 (6.0)	<0.001
Next admission (median [IQR])	118 [26, 438]	124 [26, 463]	128[27, 468]	125 [27, 462]	0.031
Mortality < 30 days (%)	853 (6.6)	1266 (6.5)	3519 (6.6)	5638 (6.6)	0.857
Readmission within 30 days (%)	1961 (15.2)	2946 (15.1)	7973 (14.9)	12880 (15.0)	0.717
Length of stay (median [IQR])	6 [3, 12]	6 [3, 12]	6[3, 12]	6 [3, 12]	0.630

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 18 Patient characteristics of cohorts based on whether they changed to a higher polypharmacy category. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No shift to higher polypharmacy category	Shift to higher polypharmacy category	P-value
Total number of patients	70095	15847	
Sex (male)	35816 (51.1)	8098 (51.1)	0.642
Age (median [IQR]), years	73.00 [60.00, 82.00]	73.00 [60.00, 83.00]	0.622
Number of pre-admission medications (median [IQR])	14.00 [10.00, 19.00]	5.00 [3.00, 8.00]	<0.001
Number of post-discharge medications (median [IQR])	12.00 [6.00, 18.00]	11.00 [8.00, 13.00]	<0.001
Multidose dispensing services	40559 (57.9)	6433 (40.6)	<0.001
Internal Medicine Sepciality			0.425
Cardiology	15175 (21.6)	3486 (22.0)	
Dermatology	350 (0.5)	92 (0.6)	
Endocrinology	1124 (1.6)	253 (1.6)	
Gastroenterology	5687 (8.1)	1316 (8.3)	
General internal medicine	9518 (13.6)	2099 (13.2)	
Geriatrics	5944 (8.5)	1341 (8.5)	
Haematology	3617 (5.2)	789 (5.0)	
Infectious_Disease	3846 (5.5)	899 (5.7)	
Nephrology	1726 (2.5)	354 (2.2)	
Neurology	5772 (8.2)	1350 (8.5)	
Oncology	4449 (6.3)	1013 (6.4)	
Palliative_Care	1229 (1.8)	275 (1.7)	
Pulmonology	7397 (10.6)	1683 (10.6)	
Rehabilitation	774 (1.1)	174 (1.1)	
Rheumatology	3487 (5.0)	723 (4.6)	
Linked admissions			
Geriatrics	2621 (3.7)	540 (3.4)	0.048
Palliative care	681 (1.0)	153 (1.0)	0.980
Rehabilitation	706 (1.0)	164 (1.0)	0.787
Intensive care unit admission	3899 (5.6)	880 (5.6)	0.978
Elixhauser Comorbidity Index [IQR])			0.599
(<1]	18967 (27.1)	4293 (27.1)	
(1-4]	10527 (15.0)	2386 (15.1)	
(4-5]	4770 (6.8)	1053 (6.6)	
(5-8]	8523 (12.2)	1867 (11.8)	
(>8]	27308 (39.0)	6248 (39.4)	

Hospital Frailty Risk Score Class			0.138
Low (< 5)	26264 (37.5)	6004 (37.9)	
Med (5-15)	31707 (45.2)	7035 (44.4)	
High (> 15)	12124 (17.3)	2808 (17.7)	
Comorbidities			
Congestive heart failure	14078 (20.1)	3252 (20.5)	0.220
Diabetes Mellitus	11469 (16.4)	2586 (16.3)	0.903
Hypertension			
Chronic obstructive pulmonary disease	22701 (32.4)	5084 (32.1)	0.465
Ischemic heart disease	21610 (30.8)	4851 (30.6)	0.598
Liver disease	2185 (3.1)	513 (3.2)	0.449
Chronic kidney disease	7006 (10.0)	1627 (10.3)	0.311
Malignant neoplasm	17520 (25.0)	3942 (24.9)	0.762
Benign neoplasm	27819 (39.7)	6301 (39.8)	0.871
Delirium	6239 (8.9)	1459 (9.2)	0.229
Dementia	1462 (2.1)	332 (2.1)	0.966
Psychiatric	11536 (16.5)	2654 (16.7)	0.381
Outcomes			
Fall pre-admission	201 (0.3)	18 (0.1)	<0.001
Fall post admission	71 (0.1)	21 (0.1)	0.342
Diagnosis of adverse drug reaction pre-admission (%)	8423 (12.0)	912 (5.8)	<0.001
Diagnosis of adverse drug reaction post-discharge (%)	4332 (6.2)	795 (5.0)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 19 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding admission to internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%).

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P-value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	<0.001
Pre-admission medication					
Proton Pump Inhibitors	1163 (9.0)	5352 (27.4)	33063 (61.8)	39578 (46.1)	
Anti-diabetics	281 (2.2)	1632 (8.3)	10481 (19.6)	12394 (14.4)	
Anticoagulants	729 (5.6)	5303 (27.1)	27087 (50.7)	33119 (38.5)	
Antiplatelets	365 (2.8)	3023 (15.5)	16125 (30.2)	19513 (22.7)	
Cardio-vascular	3578 (27.7)	13660 (69.9)	46748 (87.4)	63986 (74.5)	
Beta-blockers	1434 (11.1)	7386 (37.8)	29415 (55.0)	38235 (44.5)	
Calcium Channel Blockers	550 (4.3)	3198 (16.4)	15536 (29.1)	19284 (22.4)	
ACE inhibitors and Angiotensin II Receptor Blockers	1582 (12.2)	7057 (36.1)	27140 (50.7)	35779 (41.6)	
Statins	997 (7.7)	5660 (28.9)	24057 (45.0)	30714 (35.7)	
Urinary	1241 (9.6)	4399 (22.5)	20449 (38.2)	26089 (30.4)	
Hormones	874 (6.8)	4464 (22.8)	29318 (54.8)	34656 (40.3)	
Corticosteroids	461 (3.6)	2896 (14.8)	23863 (44.6)	27220 (31.7)	
Medication acting on the nervous system	4330 (33.5)	14485 (74.1)	50477 (94.4)	69292 (80.6)	
Antibiotics	2906 (22.5)	9120 (46.6)	40158 (75.1)	52184 (60.7)	
Opioids	1911 (14.8)	6766 (34.6)	35120 (65.7)	43797 (51.0)	
Paracetamol/orphenadrine combinations	1524 (11.8)	4188 (21.4)	16400 (30.7)	22112 (25.7)	
Nonsteroidal anti-inflammatory drugs	1352 (10.5)	3389 (17.3)	11921 (22.3)	16662 (19.4)	
Selective cox-2 inhibitors	200 (1.5)	940 (4.8)	6236 (11.7)	7376 (8.6)	
Antipsychotic	362 (2.8)	1815 (9.3)	10011 (18.7)	12188 (14.2)	
Z-drugs	9281 (19.0)	11613 (23.7)	28060 (57.3)	48954 (57.0)	
Benzodiazepines	522 (4.0)	2914 (14.9)	21473 (40.2)	24909 (29.0)	
Antidepressants	935 (7.2)	4804 (24.6)	26832 (50.2)	32571 (37.9)	
Anti-dementia	147 (1.1)	902 (4.6)	2269 (4.2)	3318 (3.9)	
Respiratory	1229 (9.5)	5147 (26.3)	27612 (51.6)	33988 (39.5)	
Antihistamin	281 (2.2)	1180 (6.0)	7725 (14.4)	9186 (10.7)	

Table 20 Patient characteristics of cohorts based on whether they used multidose dispensing services in the year preceding admission by internal medicine. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No multidose dispensing	Multidose dispensing	p
Total number of patients	38,950	46,992	
Sex (male)	19,876 (51.0)	24,038 (51.2)	0.786
Age (median [IQR]), years	72[69, 77]	78 [73, 84]	<0.001
Number of pre-admission medications (median [IQR])	9 [6, 13]	13 [9, 18]	<0.001
Number of pre-admission medications (median [IQR])	9 [5, 13]	14 [9, 18]	<0.001
Elixhauser Comorbidity Index [IQR])			0.503
(<1]	10578 (27.2)	12682 (27.0)	
(1-4]	5932 (15.2)	6981 (14.9)	
(4-5]	2632 (6.8)	3191 (6.8)	
(5-8]	4685 (12.0)	5705 (12.1)	
(>8]	15123 (38.8)	18433 (39.2)	
Hospital Frailty Risk Score Class			0.384
Low (< 5)	14533 (37.3)	17735 (37.7)	
Med (5-15)	17650 (45.3)	21092 (44.9)	
High (> 15)	6767 (17.4)	8165 (17.4)	
Internal Medicine Sepciality			0.710
Cardiology	8405 (21.6)	10256 (21.8)	
Dermatology	200 (0.5)	242 (0.5)	
Endocrinology	613 (1.6)	764 (1.6)	
Gastroenterology	3215 (8.3)	3788 (8.1)	
General Medicine	5255 (13.5)	6362 (13.5)	
Geriatrics	3353 (8.6)	3932 (8.4)	
Haematology	2015 (5.2)	2391 (5.1)	
Infectious Disease	2203 (5.7)	2542 (5.4)	
Nephrology	920 (2.4)	1160 (2.5)	
Neurology	3230 (8.3)	3892 (8.3)	
Oncology	2484 (6.4)	2978 (6.3)	
Palliative Care	679 (1.7)	825 (1.8)	
Pulmonology	4099 (10.5)	4981 (10.6)	
Rehabilitation	407 (1.0)	541 (1.2)	
Rheumatology	1872 (4.8)	2338 (5.0)	
Admissions linked with primary admission			
Geriatrics	1447 (3.7)	1714 (3.6)	0.613
Palliative care	378 (1.0)	456 (1.0)	1.000

Rehabilitation	407 (1.0)	463 (1.0)	0.403
General internal medicine	820 (2.1)	994 (2.1)	0.938
Intensive care unit admission	2181 (5.6)	2598 (5.5)	0.662
Body mass index			0.405
Underweight	462 (4.0)	502 (3.7)	
Normal Weight	3625 (31.4)	4379 (32.1)	
Overweight	4014 (34.8)	4768 (34.9)	
Obese	3435 (29.8)	4014 (29.4)	
Comorbidities			
Hypertension	21093 (54.2)	25397 (54.0)	0.756
Diabetes Mellitus	6275 (16.1)	7780 (16.6)	0.080
Chronic obstructive pulmonary disease	12596 (32.3)	15189 (32.3)	0.965
Ischemic heart disease	11898 (30.5)	14563 (31.0)	0.163
Liver disease	1281 (3.3)	1417 (3.0)	0.023
Chronic kidney disease	3874 (9.9)	4759 (10.1)	0.385
Malignant neoplasm	9668 (24.8)	11794 (25.1)	0.356
Benign neoplasm	15442 (39.6)	18678 (39.7)	0.767
Delerium	3568 (9.2)	4130 (8.8)	0.059
Dementia	834 (2.1)	960 (2.0)	0.327
Psychiatric	6503 (16.7)	7687 (16.4)	0.188
Outcomes			
Fall pre-admission	49 (0.1)	170 (0.4)	<0.001
Fall post discharge	34 (0.1)	58 (0.1)	0.132
Diagnosis of adverse drug reaction pre-admission (%)	2713 (7.0)	6622 (14.1)	<0.001
Diagnosis of adverse drug reaction post discharge (%)	1847 (4.7)	3280 (7.0)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

2.3 Paper III – Potentially inappropriate medication use before and after admission to internal medicine for older patients and association with polypharmacy

2.3.1 Clinical characteristics of the patient cohort

In total, the cohort included 55,859 individual admissions of ≥65 years to internal medicine at Landspitali Hospital during the study period 2010-2020. Table 21 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on whether the patients had potentially inappropriate medication use prior to admission based on the 2019 Beers criteria or not). Of the whole cohort, 48.5% were male, and the median age [IQR] was 80 [73, 86]. They used a median [IQR] of 12 [7,17] medications in the year preceding the admission and in the year after the admission. Multidose dispensing service was used by 54.6% of the cohort in the year preceding the admission. The majority of the cohort had a medium (5-15) hospital frailty risk score class, 49.0%, 28.0% had a low score (<5), and 23.1% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 65.8%, ischemic heart disease 40.8%, chronic obstructive pulmonary disease 36.8%, and malignant neoplasm 27.7%. The most frequent admissions were by the following internal medicine specialities: cardiology 22.6%, general internal medicine 13.5%, and then geriatrics 12.9%. A portion of the cohort (11.5%) had a linked admission after being admitted by an internal medicine speciality either to intensive care 4.2%, geriatrics 5.6%, palliative care 1.0% or rehabilitation 0.7%. For the whole cohort, the median number of admissions per patient [IQR] was 2 [1-3] per individual, ranging from 1-39.

2.3.2 Prevalence and incidence of potentially inappropriate medication use

Figure 21 presents the prevalence of potentially inappropriate prescribing in the whole cohort based on the Beers criteria 2019, which was 46,201, 82,7% 95% CI 82.4-83.0. Figure 21 also presents the prevalence of potentially inappropriate medication use by varying levels of medication use categories non-polypharmacy (<5 medications), which was 34.0%, 95% CI 33.1-35.0, polypharmacy (5-9 medications), which was 77.7%, 95% Cl 76.9-78.4 and hyper-polypharmacy (≥10 medications), which was 96.4%, 95% Cl 96.2-96.6.

Figure 21 A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medications based on 2019 Beers criteria.

Table 21 presents the study cohort characteristics, categorised by whether they fulfilled criteria for potentially inappropriate prescribing based on the 2019 Beers criteria in the year preceding the admission. Patients with potentially inappropriate medication use were more likely to be female, 51.7% and use more medications in the year prior to admission median [IQR]) 13 [9-19] vs. 4 [1-7]. Patients, irrespective of whether they had potentially inappropriate medication use, had similar median [IQR] ages of 80 [73, 86] and 80 [73, 85]. Patients with potentially inappropriate medication use were more likely to use multidose dispensing service prior to admission, 59.1% vs. 33.0%. Patients, irrespective of whether they had potentially inappropriate medication use, had a similar Elixhauser Comorbidity Index [IQR]) and Hospital Frailty Risk Score Class. The prevalence of all comorbidities was similar irrespective of whether they had potentially inappropriate medication use, with hypertension most common (65.8-66.2), followed by Ischemic heart disease (40.8-41.1) and then chronic obstructive pulmonary disease (36.0-37.0). The same pattern was seen in the prevalence of admission to internal medicine specialities irrespective of whether they had potentially inappropriate medication use. Cardiology (22.5-23.2) was the most common admitting speciality, followed by General internal medicine (13.1-13.5) and geriatrics (12.1-13.1). The prevalence of linked admissions was also similar, with admission to geriatrics most common (5.6-5.8), followed by intensive care (4.2-4.3), followed by palliative care (1.0-1.1) and rehabilitation wards (0.7-0.8).

Figure 22 shows the development of potentially inappropriate prescribing use based on 2019 Beers criteria according to the medications filled in the year preceding the admission by internal medicine speciality over the study period 2010-2020. The prevalence was similar over the study period. Figure 23 shows the incidence of new potentially inappropriate medication use among the study cohort over the study period. The results indicate that there is a decrease in new potentially inappropriate medication use from the year 2018.

Figure 22 The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding admission by internal medicine (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).

Figure 23 Incidence of new potentially inappropriate medication use among those patient who did not fulfil a Beers criteria preceding the admission by internal medicine speciality over the study period 2010-2020.

2.3.3 Potentially inappropriate medication use

In Table 22, the most frequent Beers criteria and Beers criteria subgroups were met in the year prior to admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper polypharmacy). For the entire cohort, the median [IQR] number of criteria fulfilled was 3 [1, 4]. The most frequently fulfilled Beers criteria medication were medications acting on the nervous system (59.2%), predominantly Z-drugs (43.1%), and benzodiazepines (31.2%), followed by medication acting on the gastrointestinal system (48.4%), most frequently proton pump inhibitors (45.8%) and pain medications (21.5%) most often, none-selective NSAIDs (19.5%). Patients with hyperpolypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 4 [2, 5], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (76.4%), followed by medication acting on the gastrointestinal system (64.9%) and medication acting on the endocrine system (25.8%). Patients with polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (42.7%), followed by medication acting on the gastrointestinal system (29.0%) and pain medications (18.8%). Patients with non-polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (13.1%), followed by pain medications (11.0%) and medication acting on the gastrointestinal system (9.1%).

A total of 4452 patients, 53.4% (95% CI 52.4% to 54.4%), who were admitted by the internal medicine specialities and did not fill a potentially inappropriate medication in the year preceding admission were prescribed a new potentially inappropriate medication use following discharge. Table 23 compares the patient characteristics, admitting speciality, comorbidity, and clinical outcomes between cohorts, between patients prescribed a new potentially inappropriate medication use following discharge and those who continued without filling a potentially inappropriate prescription. Patients prescribed a new, potentially inappropriate medication use following discharge compared to those who continued without filling a potentially inappropriate prescription had comparable characteristics, including their age, gender and comorbidity. The distribution between admitting internal medicine sub-specialities was similar except for patients admitted to a geriatric ward, where patients were less likely to be prescribed new potentially inappropriate medication (6.3% vs 5.1%).

Patients prescribed a new potentially inappropriate medication use following discharge were less likely to use multi-dose dispensing service prior to admission (36.9% vs 41.3%) and used a higher median [IQR] number of medication both prior to admission 4 [2,7] vs 3 [0,6] and post-discharge 9 [6,13] vs 4 [1,7]. Additionally, they were more likely to have higher median [IQR] risk scores for the likelihood of experiencing medication-related harm post-discharge, 10.70[7.17,14.54] vs. 10.20 [7.44,15.30].

Figure 24 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related risk factors, after adjustment for comorbidities

and admission information, of receiving a new potentially inappropriate medication use following discharge was associated with higher odds of using multi-dose dispensing service (OR 1.26,95% CI 1.15-1.39), dementia (OR 1.29, 95% CI 1.01-1.65), polypharmacy (OR 1.45,95% CI 1.32-1.60) and hyper-polypharmacy (OR 1.38,95% CI 1.22-1.59) but admission to internal medicine followed by transfer to geriatrics was associated with lower odds (OR 0.80, 95% CI 0.67-1.39) after adjustment for comorbidities and admission information.

The association of potentially inappropriate medication use and a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications) the year prior to admission were evaluated by using an unadjusted restricted cubic spline analysis. An unadjusted restricted cubic spline analysis revealed a strong non-linear relationship between the absolute number of different medications filled in the year preceding admission and the prevalence of potentially inappropriate medication usage based on the Beers criteria. Figure 25 shows the relationship between an absolute number of filled medications and the prevalence of potentially inappropriate medication by different organ systems based on the Beers criteria. The most frequent medication category to be prescribed as potentially inappropriate were medications acting on the central nervous and gastrointestinal systems. Further analyses were done for these subcategories and revealed a strong relationship between the increased burden of polypharmacy and the likelihood of having potentially inappropriate prescribing of benzodiazepines and Z-drugs among the medications acting on the central nervous system (Figure 26) and among medications acting on the gastrointestinal system for proton pump inhibitors (Figure 27). For the whole cohort, the most frequently added Beers criteria post-discharge were proton pump inhibitors (15.3%), Z-drugs (9.2%), benzodiazepines (8.9%), anti-psychotics (6.6%), anti-cholinergic (5.4%), cardiovascular (5.2.%) and antihistamine (5.0%) medications.

2.3.4 Clinical outcomes and survival post-discharge

The ratio of patients experiencing clinical outcomes of interest were compared based on whether the patients had potentially inappropriate medication use in the year prior to admission based on the 2019 Beers criteria. No statistical difference was observed for readmission (< 30 days) and an extended hospital stay (≥ ten days) in using (Table 23). In the whole cohort, 30-day mortality was 4.3%, prolonged admission was 10.2%, 30-day re-admission rate was 15.5%, and the median (IQR) length of stay was 7 [3, 15] (Table 23).

Patients with potentially inappropriate medication use were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge, with a median [IQR] of 19.58 vs. 10.48). Finally, they were also more likely

to have been diagnosed with an adverse drug reaction both prior to admission (12.3% vs. 4.5%) and post-discharge (6.7% vs. 3.2%) (Table 23).

The long-term survival of patients based on whether they had filled a potentially inappropriate medication in the year preceding hospital admission was visualised on a Kaplan-Meier plot. No difference in mortality was observed over time among patients who filled a potentially inappropriate medication compared to patients who did not fill a potentially inappropriate medication in the year preceding the admission to the hospital based on the 2019 Beers criteria (Figure 28).

Figure 24 The results of a multivariable regression model of the odds of filling new potentially inappropriate medication use in the year following admission to internal medicine, for patients without a potentially inappropriate medication before admission.

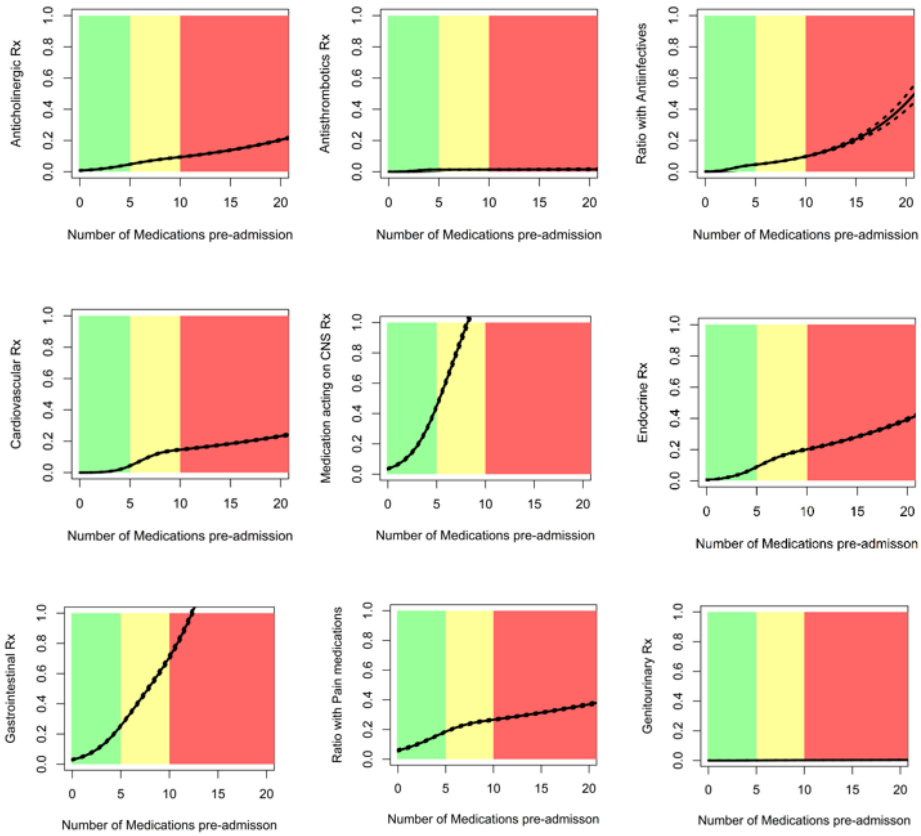

Figure 25 The association between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria. The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the polypharmacy category based on the different medications filled in the year preceding admission by internal medicine. (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy).

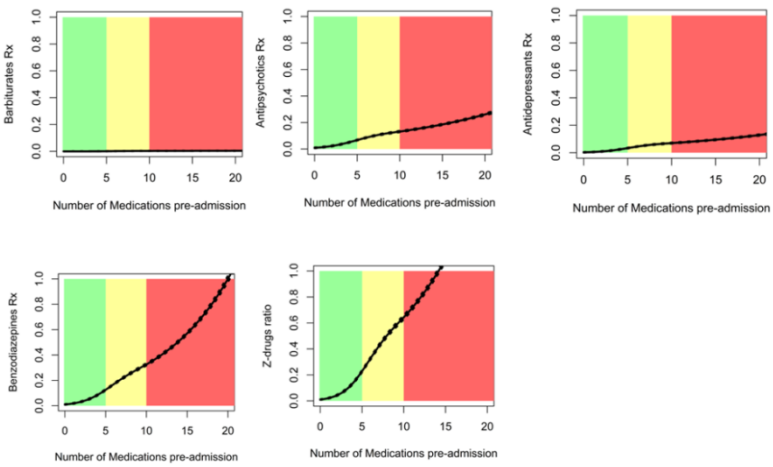

Figure 26 The association between the number of medications pre-admission and risk of potentially inappropriate medication use based on the 2019 Beers criteria for specific medications acting on the central nervous system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.

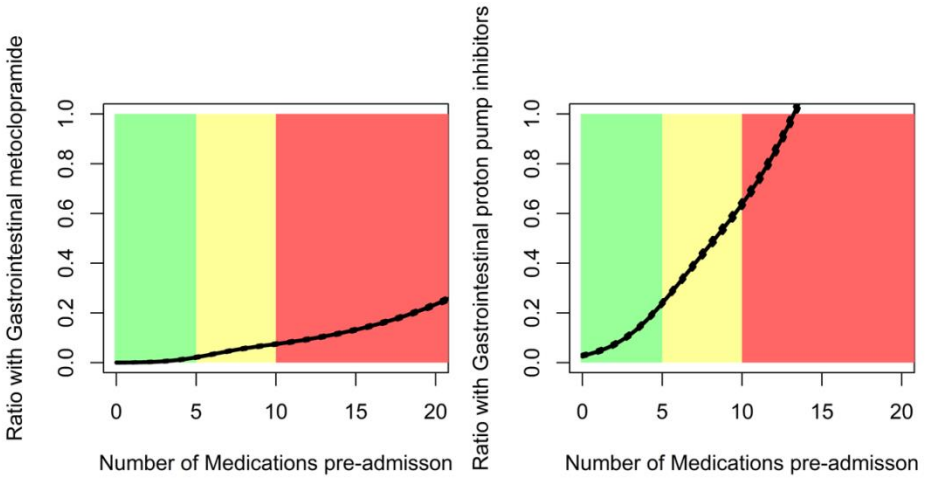

Figure 27 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine

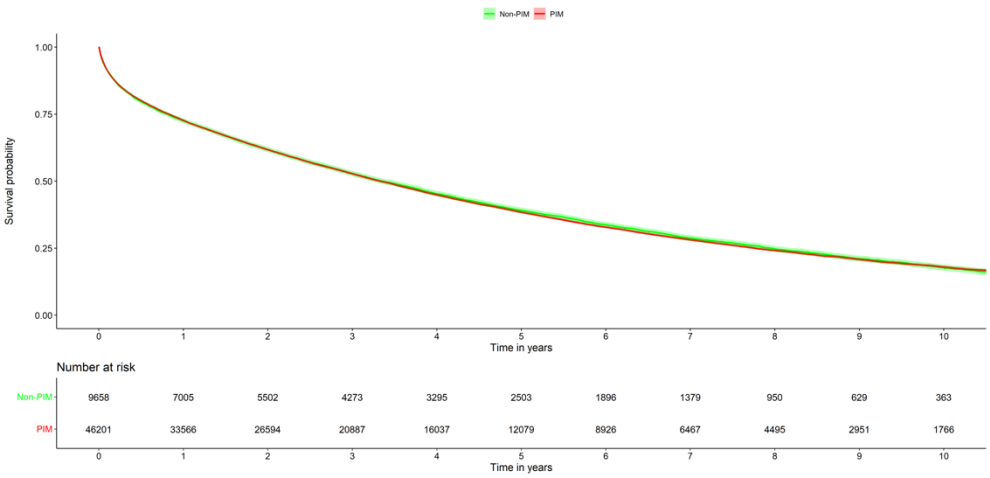

Figure 28 Kaplan–Meier survival curve of long-term survival of patients compared based on whether they had filled a with potentially inappropriate medication before admission (green = No potentially inappropriate medication use (No PIM), and red = potentially inappropriate medication use.

Table 21 Patient characteristics for patients who filled a prescription for a potentially inappropriate medication based on the 2019 Beers criteria pre-admission. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No potentially inappropriate medication use pre-admission	Potentially inappropriate medication use pre-admission	All patients	p
Total number of patients	9546 (17.1%)	46313 (82.9%)	55859	
Sex (male)	4748 (49.7)	22371 (48.3)	27119 (48.5)	0.044
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	0.055
Multi-dose dispensing services	3129 (32.8)	27376 (59.1)	30505 (54.6)	<0.001
Number of pre-admission medications (median [IQR])	4.00 [1.00, 7.00]	13.00 [9.00, 19.00]	12.00 [7.00, 17.00]	<0.001
Number of post-discharge medications (median [IQR])	6.00 [3.00, 10.00]	13.00 [8.00, 18.00]	12.00 [7.00, 17.00]	<0.001
Elixhauser Comorbidity Index [IQR])	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	0.305
(<1]	1882 (19.7)	9079 (19.6)	10961 (19.6)	0.495
(1-4]	1351 (14.2)	6298 (13.6)	7649 (13.7)	
(4-5]	700 (7.3)	3467 (7.5)	4167 (7.5)	
(5-8]	1229 (12.9)	5785 (12.5)	7014 (12.6)	
(>8]	4384 (45.9)	21684 (46.8)	26068 (46.7)	
Hospital Frailty Risk Score Class				0.749
Low (< 5)	2707 (28.4)	12910 (27.9)	15617 (28.0)	
Med (5-15)	4654 (48.8)	22690 (49.0)	27344 (49.0)	
High (> 15)	2185 (22.9)	10713 (23.1)	12898 (23.1)	
Individual comorbidities				
Ischemic heart disease	3927 (41.1)	18879 (40.8)	22806 (40.8)	0.506
Congestive heart failure	2687 (28.1)	12793 (27.6)	15480 (27.7)	0.075
Hypertension	6307 (66.1)	30467 (65.8)	36774 (65.8)	0.602
Diabetes Mellitus	1754 (18.4)	8766 (18.9)	10520 (18.8)	0.213
Chronic obstructive pulmonary disease	3439 (36.0)	17135 (37.0)	20574 (36.8)	0.075
Liver disease	198 (2.1)	1171 (2.5)	1369 (2.5)	0.010
Chronic kidney disease	1261 (13.2)	6240 (13.5)	7501 (13.4)	0.502
Malignant neoplasm	2675 (28.0)	12605 (27.2)	15280 (27.4)	0.111
Psychiatric	1606 (16.8)	7604 (16.4)	9210 (16.5)	0.339
Dementia	280 (2.9)	1431 (3.1)	1711 (3.1)	0.438
Delerium	1213 (12.7)	5742 (12.4)	6955 (12.5)	0.415
Internal Medicine Specialty				0.025
Cardiology	2216 (23.2)	10413 (22.5)	12629 (22.6)	
Dermatology	30 (0.3)	152 (0.3)	182 (0.3)	
Endocrinology	147 (1.5)	701 (1.5)	848 (1.5)	

Gastroenterology	634 (6.6)	3164 (6.8)	3798 (6.8)	
General internal medicine	1247 (13.1)	6275 (13.5)	7522 (13.5)	
Geriatrics	1157 (12.1)	6062 (13.1)	7219 (12.9)	
Hematology	411 (4.3)	1938 (4.2)	2349 (4.2)	
Infectious diseases	454 (4.8)	2155 (4.7)	2609 (4.7)	
Nephrology	235 (2.5)	1107 (2.4)	1342 (2.4)	
Neurology	707 (7.4)	3041 (6.6)	3748 (6.7)	
Oncology	496 (5.2)	2362 (5.1)	2858 (5.1)	
Palliative care	162 (1.7)	836 (1.8)	998 (1.8)	
Pulmonology	1111 (11.6)	5219 (11.3)	6330 (11.3)	
Rehabilitation	43 (0.5)	282 (0.6)	325 (0.6)	
Rheumatology	496 (5.2)	2606 (5.6)	3102 (5.6)	
Admissions linked with primary admission				
Geriatrics	551 (5.8)	2590 (5.6)	3141 (5.6)	0.454
Palliative care	103 (1.1)	467 (1.0)	570 (1.0)	0.660
Rehabilitation	73 (0.8)	301 (0.7)	374 (0.7)	0.282
Intensive care unit admission	410 (4.3)	1928 (4.2)	2338 (4.2)	0.566
Clinical Outcomes				
Fall diagnosis post-discharge	16 (0.2)	128 (0.3)	144 (0.3)	0.064
Fall diagnosis post-discharge	6 (0.1)	57 (0.1)	63 (0.1)	0.153
Length of hospital stay (days)	7 [3, 15]	7 [3, 15]	7 [3, 15]	0.244
Diagnosis of adverse drug reaction pre-admission (%)	431 (4.5)	5684 (12.3)	6115 (10.9)	<0.001
Diagnosis of adverse drug reaction post-discharge (%)	305 (3.2)	3100 (6.7)	3405 (6.1)	<0.001
Next admission (median [IQR]	131 [29, 463]	132 [29, 455]	132 [29, 456]	0.609
Mortality 30 days (%)	392 (4.1)	2033 (4.4)	4354 (7.8)	0.227
Readmission within 30 days (%)	1486 (15.6)	7146 (15.4)	8632 (15.5)	0.748
PRIME score (median [IQR])	10.42 [7.30, 14.98]	19.58 [12.86, 29.76]	17.55 [11.25, 27.50]	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 22 The table shows the subcategories of Beers Criteria filled, based on 2019 Beers criteria based on the patient's pre-admission polypharmacy burden estimated by the number of different medications filled in the year preceding admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR).

	Non-Polypharmacy pre-admission	Polypharmacy pre-admission	Hyper-Polypharmacy pre-admission	All patients pre-admission	P-value
Total number of patients	8435 (15.1)	12658 (22.7)	34766 (62.2)	55859	
Age (median [IQR]), years	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	0.089
[65,75)	2594 (31.1)	3724 (29.8)	10530 (30.6)	16848 (30.5)	
[75,85)	3360 (40.3)	5207 (41.7)	13879 (40.4)	22446 (40.7)	
[85,95.)	2384 (28.6)	3563 (28.5)	9954 (29.0)	15901 (28.8)	
PRIME score (median [IQR])	9.02 [6.57, 12.44]	12.78 [9.20, 17.77]	23.29 [16.01, 33.77]	17.55 [11.25, 27.50]	<0.001
Diagnosis of adverse drug reaction pre-admission (%)	327 (3.9)	951 (7.5)	4837 (13.9)	6115 (10.9)	<0.001
Diagnosis of adverse drug reaction post admission (%)	263 (3.1)	636 (5.0)	2506 (7.2)	3405 (6.1)	<0.001
Beers criteria total score pre-admission (median [IQR])	0 [0, 1]	1 [1, 2]	4.[2, 5]	3 [1, 4]	<0.001
Beers criteria anticholinergics (%)	199 (2.4)	794 (6.3)	5302 (15.3)	6295 (11.3)	<0.001
Beers criteria Anticholinergics (antihistamines) (%)	179 (2.1)	730 (5.8)	4981 (14.3)	5890 (10.5)	<0.001
Beers criteria Anticholinergics (antiparkinsonian) (%)	15 (0.2)	45 (0.4)	198 (0.6)	258 (0.5)	0.017
Beers criteria Anticholinergics (antispasmodics) (%)	5 (0.1)	24 (0.2)	232 (0.7)	261 (0.5)	<0.001
Beers criteria antithrombotic (%)	14 (0.2)	123 (1.0)	485 (1.4)	622 (1.1)	<0.001
Beers criteria anti-infective (%)	46 (0.5)	342 (2.7)	2880 (8.3)	3268 (5.9)	<0.001
Beers criteria cardiovascular (%)	75 (0.9)	859 (6.8)	6336 (18.2)	7270 (13.0)	<0.001
Beers criteria (cardiovascular peripheral alpha) (%)	9 (0.1)	103 (0.8)	802 (2.3)	914 (1.6)	<0.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	1 (0.0)	9 (0.0)	10 (0.0)	0.178
Beers criteria (cardiovascular disopyramide) (%)	6 (0.1)	32 (0.3)	110 (0.3)	148 (0.3)	<0.001
Beers criteria (cardiovascular dronedarone) (%)	2 (0.0)	38 (0.3)	148 (0.4)	188 (0.3)	<0.001
Beers criteria (cardiovascular digoxin) (%)	29 (0.3)	369 (2.9)	3152 (9.1)	3550 (6.4)	<0.001
Beers criteria (cardiovascular nifedipine) (%)	10 (0.1)	95 (0.8)	486 (1.4)	591 (1.1)	<0.001

Beers criteria (cardiovascular amiodarone) (%)	21 (0.2)	261 (2.1)	2411 (6.9)	2693 (4.8)	<0.001
Beers criteria central nervous system (%)	1102 (13.1)	5406 (42.7)	26550 (76.4)	33058 (59.2)	<0.001
Beers criteria (central nervous system antidepressant) (%)	105 (1.2)	575 (4.5)	3668 (10.6)	4348 (7.8)	<0.001
Beers criteria (central nervous system antipsychotics) (%)	243 (2.9)	1131 (8.9)	6503 (18.7)	7877 (14.1)	<0.001
Beers criteria (central nervous system barbiturates) (%)	1 (0.0)	36 (0.3)	136 (0.4)	173 (0.3)	<0.001
Beers criteria (central nervous system benzodiazepines) (%)	369 (4.4)	2088 (16.5)	14965 (43.0)	17422 (31.2)	<0.001
Beers criteria (central nervous system z-drugs) (%)	539 (6.4)	3338 (26.4)	20183 (58.1)	24060 (43.1)	<0.001
Beers criteria endocrine (%)	250 (3.0)	1450 (11.5)	8974 (25.8)	10674 (19.1)	<0.001
Beers criteria (endocrine androgens) (%)	24 (0.3)	114 (0.9)	713 (2.1)	851 (1.5)	<0.001
Beers criteria (endocrine desiccated thyroid) (%)	1 (0.0)	0 (0.0)	11 (0.0)	12 (0.0)	0.093
Beers criteria (endocrine estrogens) (%)	112 (1.3)	591 (4.7)	4082 (11.7)	4785 (8.6)	<0.001
Beers (endocrine growth hormone) (%)	1 (0.0)	9 (0.1)	21 (0.1)	31 (0.1)	0.165
Beers criteria (endocrine megestrol) (%)	1 (0.0)	2 (0.0)	12 (0.0)	15 (0.0)	0.360
Beers criteria (endocrine sulfonylurea) (%)	113 (1.3)	769 (6.1)	4665 (13.4)	5547 (9.9)	<0.001
Beers criteria gastrointestinal (%)	770 (9.1)	3669 (29.0)	22579 (64.9)	27018 (48.4)	<0.001
Beers criteria (gastrointestinal metoclopramide) (%)	46 (0.5)	455 (3.6)	5936 (17.1)	6437 (11.5)	<0.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	735 (8.7)	3418 (27.0)	21448 (61.7)	25601 (45.8)	<0.001
Beers criteria Pain medications (%)	929 (11.0)	2384 (18.8)	8694 (25.0)	12007 (21.5)	<0.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	3 (0.0)	3 (0.0)	0.402
Beers criteria pain medications nonselective NSAID (%)	875 (10.4)	2230 (17.6)	7713 (22.2)	10818 (19.4)	<0.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	81 (1.0)	266 (2.1)	1577 (4.5)	1924 (3.4)	<0.001
Beers criteria (genitourinary) (%)	2 (0.0)	21 (0.2)	129 (0.4)	152 (0.3)	<0.001

Table 23 Comparison of patients with no potentially inappropriate medication use pre-admission or post-discharge to patients with no potentially inappropriate medication use pre-admission but new potentially inappropriate medication use post-discharge. Unless specified otherwise, values are presented as count (%) or median (IQR)

	No potentially inappropriate medication use pre-admission nor new potentially inappropriate medication use post-discharge	New potentially inappropriate medication use post-discharge and but not pre-admission	p
Total number of patients	5094	4452	
Sex (male)	2516 (49.4)	2232 (50.1)	0.481
Age median [IQR]), years	80 [73, 85]	80 [73, 85]	0.526
Multi-dose dispensing services	2690 (41.3)	1643 (36.9)	<0.001
Number of pre-admission medications (median [IQR])	3[0, 6]	4 [2, 7]	<0.001
Number of post-discharge medications (median [IQR])	4 [1, 7]	9 [6, 13]	<0.001
Number of pre-admission medications without antibiotics (median [IQR])	2[0, 6]	4 [1, 6]	<0.001
Elixhauser Comorbidity Index [IQR])			
(<1]	987 (19.4)	895 (20.1)	0.328
(1-4]	722 (14.2)	629 (14.1)	
(4-5]	388 (7.6)	312 (7.0)	
(5-8]	682 (13.4)	547 (12.3)	
(>8]	2315 (45.4)	2069 (46.5)	
Hospital Frailty Risk Score Class			0.659
Low (< 5)	1427 (28.0)	1280 (28.8)	
Med (5-15)	2504 (49.2)	2150 (48.3)	
High (> 15)	1163 (22.8)	1022 (23.0)	
Comorbidities			
Ischemic heart disease	2140 (42.0)	1787 (40.1)	0.067
Congestive heart failure	1432 (28.1)	1255 (28.2)	0.951
Hypertension	3392 (66.6)	2915 (65.5)	0.261
Diabetes Mellitus	1841 (36.1	822 (18.5)	0.854
Chronic obstructive pulmonary disease	18976 (36.9)	1598 (35.9)	0.819
Liver disease	101 (2.0)	97 (2.2)	0.549
Chronic kidney disease	669 (13.1)	592 (13.3)	0.837
Malignant neoplasm	1407 (27.6)	1268 (28.5)	0.362
Psychiatric	836 (16.4)	770 (17.3)	0.261
Dementia	133 (2.6)	147 (3.3)	0.053

Delerium	643 (12.6)	570 (12.8)	0.815
Internal Medicine Specialty			0.747
Cardiology	1189 (23.3)	1027 (23.1)	
Dermatology	15 (0.3)	15 (0.3)	
Endocrinology	76 (1.5)	71 (1.6)	
Gastroenterology	327 (6.4)	307 (6.9)	
General internal medicine	666 (13.1)	581 (13.1)	
Geriatrics	633 (12.4)	524 (11.8)	
Haematology	226 (4.4)	185 (4.2)	
Infectious diseases	248 (4.9)	206 (4.6)	
Nephrology	120 (2.4)	115 (2.6)	
Neurology	365 (7.2)	342 (7.7)	
Oncology	254 (5.0)	242 (5.4)	
Palliative care	80 (1.6)	82 (1.8)	
Pulmonology	592 (11.6)	519 (11.7)	
Rehabilitation	29 (0.6)	14 (0.3)	
Rheumatology	274 (5.4)	222 (5.0)	
Admissions linked with primary admission			
Geriatrics	323 (6.3)	228 (5.1)	0.012
Palliative care	49 (1.0)	54 (1.2)	0.278
Rehabilitation	40 (0.8)	33 (0.7)	0.898
Intensive care unit admission	113 (2.2)	192 (4.3)	0.977
Outcomes			
Length of hospital stay (days)	7 [3, 15]	7 [3, 14]	0.024
Diagnosis of adverse drug reaction pre-admission (%)	223 (4.4)	208 (4.7)	0.521
Diagnosis of adverse drug reaction post-discharge (%)	114 (2.2)	191 (4.3)	<0.001
Next admission (median [IQR]	133 [29, 461]	125 [28, 461]	0.994
Mortality 30 days (%)	388 (7.6)	360 (8.1)	0.416
Readmission within 30 days (%)	796 (15.6)	690 (15.5)	0.947

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

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2.3.5 Clinical characteristics of the patient cohort

In total, the cohort included 30 082 individual admissions of ≥65 years to surgical care at Landspitali Hospital during the study period 2005-2018. Of those, 12 884 were reoperations or subsequent operations during the study period. Reoperations were excluded; therefore, the final study population included 17 198 patients undergoing their first surgery during the study period (Figure 29). Table 24 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on whether the patients had potentially inappropriate medication use prior to a surgical admission based on the 2019 Beers criteria or not). Of the whole cohort, 9252 (53.8%) were female, and the median age [IQR] was 75 [70, 81]. They used a median [IQR] of 9 [5,13] medications in the year preceding the admission and 9 [6,14] in the year after the admission. Multidose dispensing service was used by 32.8% of the cohort in the year preceding the admission. The majority of the cohort had a low (<5) hospital frailty risk score class, 71.4%, 24.6% had a medium score (5-15), and 4.0% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 57.0%, ischemic heart disease 32.1%, malignant neoplasm 27.7% and chronic obstructive pulmonary disease 23.5%. The majority of the surgeries were elective surgeries, 67.3%. Of the cohort, 32.7% had an emergency operation. The most frequent types of surgeries were orthopaedic 37.5%, abdominal 14.4%, and urology 11.4%.

2.3.6 Prevalence and incidence of potentially inappropriate medication use

Figure 29 presents the prevalence of potentially inappropriate prescribing in the whole cohort based on the Beers criteria 2019, which was 13.386, 77.8% 95% CI 77.2-78.5 and also presents the prevalence of potentially inappropriate medication use by varying levels of medication use categories non-polypharmacy (<5 medications), which was 36.6%, 95% CI 35.1-38.2, polypharmacy (5-9 medications), which was 80.2%, 95% CI 79.2-81.2) and hyper-polypharmacy (≥10 medications), which was 95.8%, 95% CI 95.3-96.2.

Figure 29 A consort diagram of participant inclusion level of polypharmacy based on the number of different medications filled in the year preceding surgical admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medication based on 2019 Beers criteria.

Table 24 presents the study cohort characteristics, categorised by whether they fulfilled criteria for potentially inappropriate prescribing based on the 2019 Beers criteria in the year preceding the surgical admission. Patients with potentially inappropriate medication use were more likely to be female, 57.0% and use more medications both in the year prior to admission median [IQR]) 10 [4,14] vs. 3 [1,6] and the year following discharge 11 [7,15] vs. 5 [2,9]. Patients, irrespective of whether they had potentially inappropriate medication use, had similar median [IQR] ages of 75 [70, 81] and 75 [70, 82]. Patients with potentially inappropriate medication use were more likely to use multidose dispensing service prior to admission, 36.0% vs. 21.3%. Patients with potentially inappropriate medication use had increased comorbidity based on the Elixhauser Comorbidity Index median [IQR]) 2 [2,5] vs 0 [0,5] and also slightly higher Hospital Frailty Risk Score Class. The prevalence of all comorbidities was higher for those with potentially inappropriate medication use, except for dementia (2.5% vs. 3.4%). The most common comorbidities for those with and without potentially inappropriate medication use was hypertension (60.1% vs 45.9%), followed by Ischemic heart disease (33.7% vs 26.5%) and then malignant neoplasm (27.7% vs 24.5%). Patients with potentially inappropriate medication use were more likely to undergo elective surgery (70.0% vs 57.9%). The majority of the surgeries, 67.3%, were elective surgeries. Of the cohort, 32.7% had an emergency operation. The most frequent types of surgeries for those with and without potentially inappropriate medication use he most were orthopaedic 36.8% vs 40.1%, abdominal 14.9% vs 12.8%, and urology 10.6% vs 14.0%.

Figure 30 shows the development of potentially inappropriate prescribing use based on 2019 Beers criteria according to the medications filled in the year preceding a surgical admission speciality over the study period 2006-2018. The prevalence was similar over the study period. This shows the prevalence of new potentially inappropriate medication use among the study cohort over the study period. The results indicate a decrease in new potentially inappropriate medication use since 2011, with an exception in 2017.

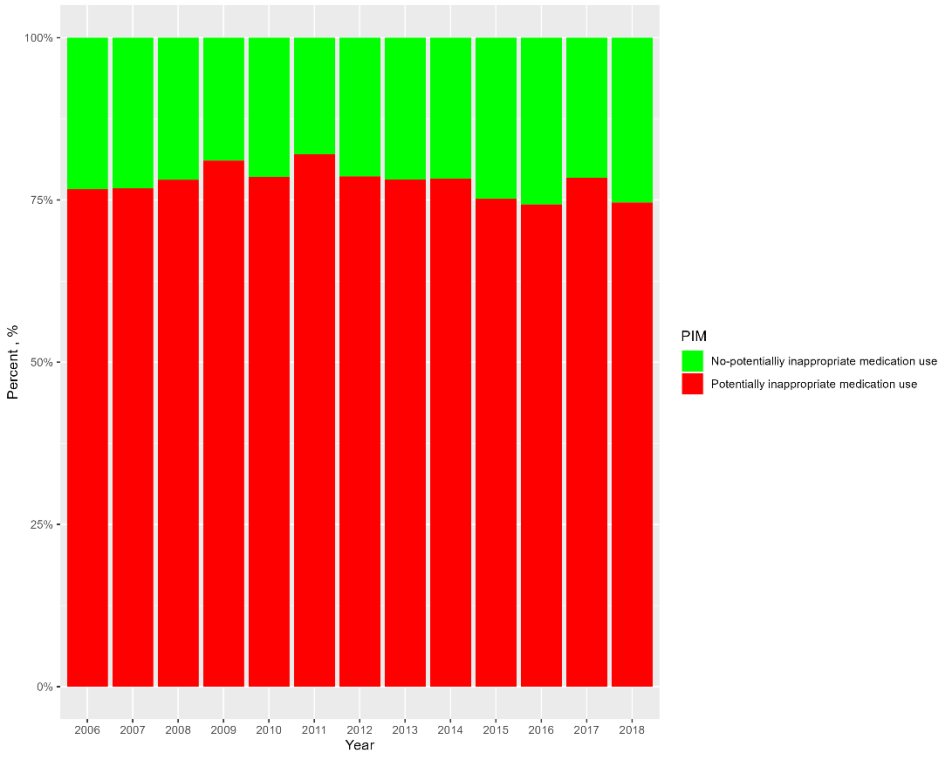

Figure 30 The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding surgical admission (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).

2.3.7 Potentially inappropriate medication use

In (Table 25) the most frequent Beers criteria and Beers criteria subgroups were met in the year prior to a surgical admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper polypharmacy). The median [IQR] number of criteria fulfilled for the entire cohort was 3 [1, 4]. The most frequently fulfilled Beers criteria medication were medications acting on the nervous system (50.0%), predominantly Z-drugs (36.2%), and benzodiazepines (22.7%), followed by medication acting on the gastrointestinal system (35.2%), most frequently proton pump inhibitors (34.0%) and pain medications (28.9%) most often, none-selective NSAIDs (27.7%). Patients with hyperpolypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 4 [2, 5], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (72.3%), followed by medication acting on the gastrointestinal system (54.4%) and pain medication (37.6%). Patients with polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria

were medications acting on the nervous system (42.9%), followed by pain medications (27.7%) and medication acting on the gastrointestinal system (27.3%). Patients with non-polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 0 [0,1], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (15.3%), followed by pain medications (12.9%) and medication acting on the gastrointestinal system (8.5%).

A total of 1481 patients, 38.5% (95% CI 37.0-40.1), who were admitted for surgical admissions and did not fill a potentially inappropriate medication in the year preceding admission were prescribed a new potentially inappropriate medication use following discharge. Table 26 compares the patient characteristics, admitting speciality, comorbidity, and clinical outcomes between cohorts, between patients prescribed a new potentially inappropriate medication use following discharge and those who continued without filling a potentially inappropriate prescription. Patients prescribed a new, potentially inappropriate medication use following discharge compared to those who continued without filling a potentially inappropriate prescription were more likely to be female (60.0% vs 56.5%) and have increased comorbidity. Patients prescribed a new potentially inappropriate medication use following discharge were more likely to use multi-dose dispensing service prior to admission (28.4% vs 17.1%) and used a higher median [IQR] number of medications both prior to admission 5 [2,7] vs 3 [0,6] and post-discharge 9 [6,12] vs 3 [0,6]. Patients prescribed a new, potentially inappropriate medication were more likely to have malignant neoplasm (29.2% vs 19.4%), Ischemic heart disease (29.6% vs 20.3%) and hypertension (18.5% vs 15.4%) and less likely to have a diagnosis of mental illness (6.2% vs 11.4%) and dementia (1.8% vs 4.4%) and delirium (2.6% vs 3.9%). Patients prescribed a new, potentially inappropriate medication post-discharge were more likely to undergo cardiac surgery (14.9% vs 4.4%), vascular surgery (11.1% vs 8.2%) and gynaecology surgery (4.3% vs 1.7%) and less likely to undergo orthopedic surgery (28.6% vs 47.0%). They were also less likely to undergo emergency surgery (31.9% vs 48.3%).

Additionally, they were more likely to have higher median [IQR] risk scores for the likelihood of experiencing medication-related harm post-discharge, 12.57 [9.29,17.24] vs 11.33 [8.46,16.37] and have increased 30-days mortality (5.2% vs 0.3%).

Figure 31 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related risk factors. After adjustment for comorbidities and admission information, receiving a new potentially inappropriate medication use following discharge was associated with higher odds of using multi-dose dispensing service (OR 2.52, 95% CI2.11-3.02), hyper-polypharmacy (OR 2.40,95% C 1.3.10), polypharmacy (OR 1.76,95% CI 1.51-2.05) and malignant neoplasm (OR 1.83, 95% CI 1.55-2.16), and having a diagnosis of dementia was associated with lower odds (OR 0.47, 95% CI 0.29-0.73) after adjustment for comorbidities and admission information.

Figure 31 The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), Elixhauser comorbidity index class (compared with <1), individual comorbidities, multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of an adverse drug reaction diagnosis prior to a surgical admission, as covariates.

The association of potentially inappropriate medication use and a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications) the year prior to admission were evaluated by using an unadjusted restricted cubic spline analysis. An unadjusted restricted cubic spline analysis revealed a strong non-linear relationship between the absolute number of different medications filled in the year preceding a surgical admission and the prevalence of potentially inappropriate medication usage based on the Beers criteria. **Error! Reference source not found.** shows the relationship between an absolute number of filled medications and the prevalence of potentially inappropriate medication by different organ systems based on the Beers criteria. The most frequent medication category to be prescribed as potentially inappropriate were medications acting on the central nervous and gastrointestinal systems. (**Error! Reference source not found.**) Further analyses were done for these subcategories and revealed a strong relationship between the increased burden of polypharmacy and the likelihood of having potentially inappropriate prescribing of benzodiazepines and Z-drugs among the medications acting on the central nervous system (Figure 33) and among medications acting on the gastrointestinal system for proton pump inhibitors (Figure 34). For the whole cohort, the most frequently added Beers criteria post-discharge were proton pump inhibitors (11.3%), Z-drugs (9.7%), benzodiazepines (6.4%), anti-psychotics (3.3%), anti-cholinergic (3.8 %) and cardiovascular (3.5%).

Figure 34 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system.).[173] Deprescribing studies generally focus either on interventions to address polypharmacy or potentially inappropriate medication use or target a specific medication or medication class considered inappropriate. Recent research evaluated the possibility of using a family conference to facilitate the deprescribing process through shared-decision making. The intervention included the medications reviewed by a pharmacist before three family conferences, where shared making was applied to evaluate the patient's preferences, deprescribing decisions and the possibility of non-pharmacologic measures and then follow-up. The result did not affect number of hospitalisations within 12 months. However, there was a decrease in inappropriate medication use after 6 months. The authors concluded that family conferences might be helpful to initiate deprescribing.[174]

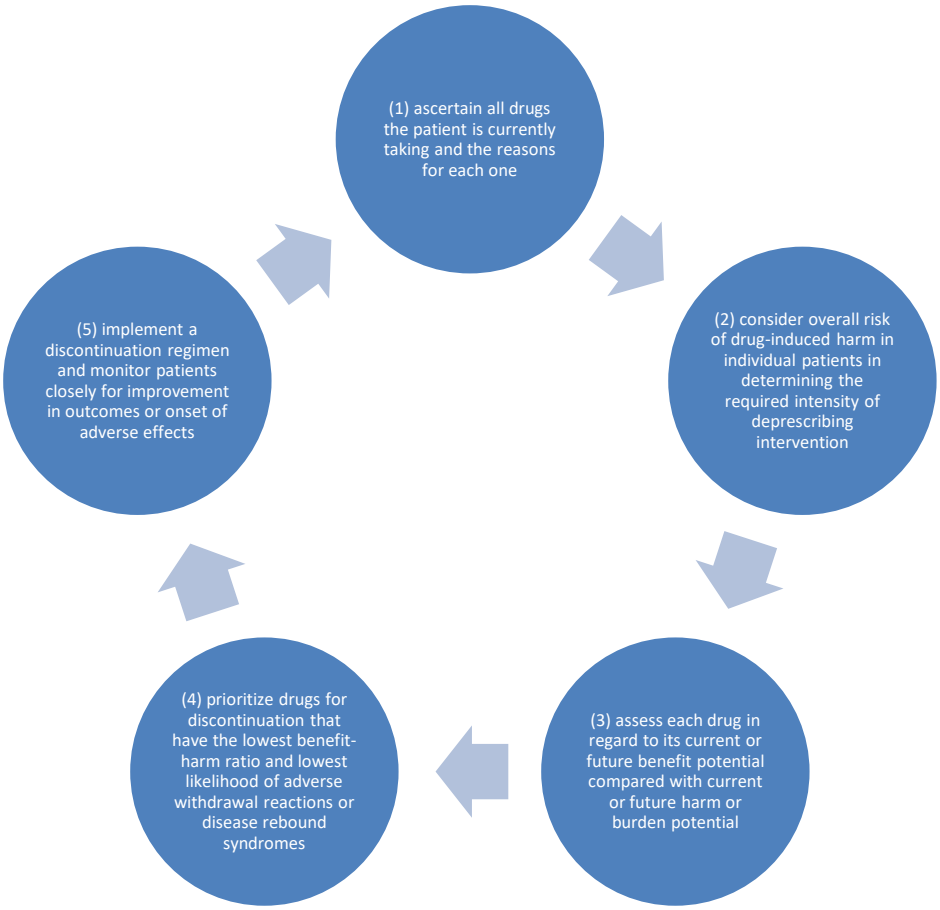

Figure 2 The process of deprescribing as proposed by Scott et. all in Jama Internal Medicine [1]

A recent systematic review studied the facilitators and barriers to applying deprescribing interventions in clinical practice from the view of patients/carers.[175] The study identified the barrier to deprescribing among older patients as their perception of the older adult that their medications are necessary for their health. This leads to their reluctance to deprescribe medications and fear of risking a balance if medications are discontinued. Additionally, a lack of communication, especially during transfer of care, negatively impacts older patient and affects their willingness to deprescribe medications. Having multiple healthcare providers was additionally identified as a barrier to deprescribing, and older patients were reluctant to have someone other than the initial prescriber deprescribing their medications. Additionally, patients described the current welling and relief of symptoms, making them hesitant to deprescribe. Among the enablers for deprescribing was the belief or perceived appropriateness of medication withdrawal. Patients' experience of adverse drug effects or the awareness of the possibility of adverse drug effects has been identified as an enabler for deprescribing. The fear of medications causing dependence was also a facilitator, as well as drug interactions. The patient and prescriber relationship was identified as a key enabler. Additionally, a clear strategy for deprescribing and an appropriate follow-up were identified as enablers for deprescribing from the view of patients/carers[175] Several strategies have been developed to support the deprescribing process[153, 176] Examples include PrescQIPP's Polypharmacy and deprescribing webkit[177] , NO TEARS tool[178] , MedStopper tool[179] , Australian ten-step discontinuation guide[180] and the Polypharmacy guidance[181]

2.3.8 [182] Comprehensive Strategies

Comprehensive strategies have also been researched. Bergert et al. described a comprehensive strategy developed for general practitioners and targeted for adults with polypharmacy. The strategy involved eight steps, with the second step involving several explicit criteria, including MAI and STOPP/START.[183] Another comprehensive strategy is polypharmacy guidance, which was developed by a pan-European project called "Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly" (SIMPATHY). This guideline is likely the most comprehensive approach available. It was first introduced in 2012 and has been regularly updated, with the newest version from 2018. The guideline has been applied learning from tools like Beers, STOPP/START and MAI.[184] The comprehensive strategy offers a holistic patient-centred approach where 7 steps guide healthcare professionals to optimise polypharmacy.[181] The process involves the assessment of treatment goals in partnership with the patient (step 1), reviewing the need for essential medications (step 2) and reviewing the need for unessential medication, considering deprescribing (step 3), and then the effectiveness is assessed and an evaluation made as to whether treatment goals are being met (step 4), then the safety of the medication treatment is evaluated (step 5), followed by a cost-effectiveness evaluation (step 6) and finally adherence is assessed (step 7) (Figure 3). The advantages of the polypharmacy guidance are its comprehensive evidence base

and practicality. The disadvantage of the tool is that the process is time-consuming. Pharmacists have been employed to support general practitioners in providing polypharmacy services to overcome these disadvantages.[184]

A recent publication reported on a prospective longitudinal cohort study applying a poly-de-prescribing intervention using the Garfinkel algorithm, where the appropriateness of all medications is evaluated in partnership with patients and/or carers. The study included patients (≥65) in primary care using more than six medications. The patients received a comprehensive geriatric assessment for deprescribing. Their approach differs from other interventions as they seek to deprescribe not potentially inappropriate medication but as many non-life-saving medications as possible in collaboration with patients and carers. This method aims to combat the prescribing cascade which may happen as multiple clinical guidelines are applied to the heterogeneous patient group of older patients. The study reported no change in hospitalisation and mortality rate between the groups and improvements in some outcomes among the intervention group. However, these results should be interpreted cautiously as this small study lacks randomisation and an inappropriate comparison group. This study, therefore, should only be interpreted as an innovative way of addressing the challenges of polypharmacy.[185]

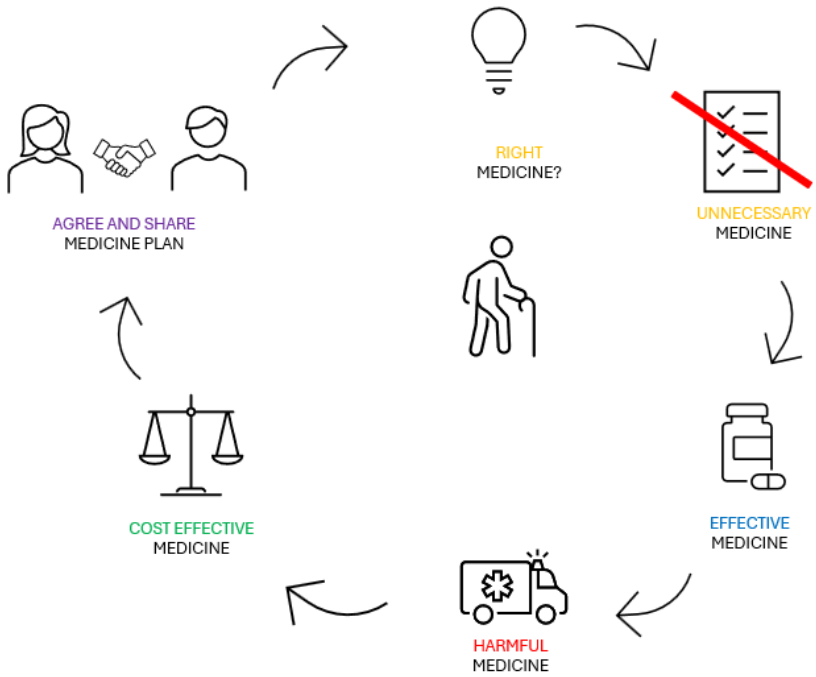

Figure 3 7 Steps to approprite polypharmacy, NSH Scotland

NICE guidelines on medication optimisation have encouraged the review of medications for all adults and children who are taking multiple medications, everyone

with chronic disease and all older patients.[186] However, several studies have aimed to identify sub-groups of patients who might benefit most from having their medications reviewed [187-190] and few developing clinical pharmacy priority scores.[191-193]

A recent European benchmarking survey for polypharmacy management across Europe included most European countries (Table 6). However, Iceland was omitted. The study's conclusion can guide the implementation of a polypharmacy management programme for older patients. A formal polypharmacy management programme exists in more than half of the countries. In the majority of the countries, the programmes are delivered in primary care (50%), hospitals (23%) and community pharmacies (21%). Pharmacists were most frequently identified as the programme provider (32%), and general practitioners were most commonly mentioned (36%). The polypharmacy programmes in Europe are often provided in collaboration between pharmacists and physicians (30%), followed by pharmacists, physicians and nurses (22%). In 18% of the polypharmacy programmes, a financial incentive was applied. Even though only 1/5 of programmes were financially supported, there is evidence that a financial incentive can motivate providers. The survey identified enablers such as having a regional or national body responsible for the programme and technology support for applicability. Factors identified to facilitate the scalability were disseminating guidelines for providing the programme.[134]

Table 6 Lessons for the benchmarking survey of polypharmacy management programs in older patients across European countries.[134]

Most EU countries have polypharmacy management programmes for older patients.
The majority of polypharmacy management programmes are provided in primary care.
Polypharmacy management programmes for older patients are known by healthcare workers
Polypharmacy management for older patients combines the benefits of the patient and a comprehensive strategy that integrates efforts to reduce an organisation's existing costs and control current and future costs
Current use of information and communications technology does not provide sufficient for polypharmacy management for older patients
Training regarding polypharmacy management programmes must be better incorporated among undergraduates and postgraduates.
Evidence is for the effectiveness of polypharmacy management programmes. However, the evidence for cost-effectiveness is scarce.
Indicators for effectiveness and cost-effectiveness is advisable.
Funding for the up-scaling of polypharmacy management programmes is not widespread.
Targeted activities with change management indicators should be used in order to increase the number of polypharmacy management programmes for older patients in Europe

2.4 Clinical pharmacy

Clinical pharmacy as a discipline has been developing since around 1950 and developed out of the need for a healthcare professional with comprehensive knowledge of the therapeutic use of medications.[194] An updated definition of clinical pharmacy was recently introduced by the European Society of Clinical Pharmacy in 2022. The core definition is *"Clinical pharmacy aims to optimise the utilisation of medicines through practice and research in order to achieve person-centred goals"* (Figure 4).[195]

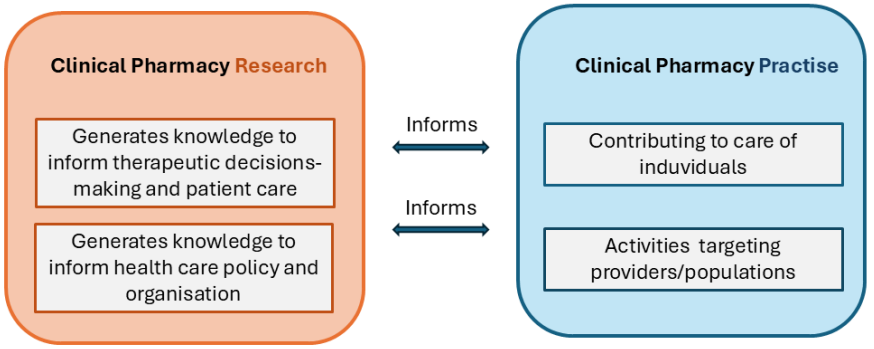

Figure 4 Defention of Clinical Pharmacy by European Society of Clinical Pharmacy (1)

The utility of clinical pharmacists' services has been researched in a range of healthcare settings, such as hospital settings, general practice, and community pharmacies. Clinical pharmacists' activities vary widely between countries and range from medication reconciliation, medication review, therapeutic drug monitoring, deprescribing interventions, and medication counselling to more advanced roles such as prescribing.[182, 196-198] The value of having clinical pharmacists as members of multidisciplinary teams has been highlighted in numerous studies. Increased levels of clinical services and pharmacist-led reviews in community service have been shown to affect clinical outcomes and economic impact positively. A recent systematic summarised available clinical pharmacy practice guidelines.[182] The majority of guidelines were from Australia, Ireland, the USA and the UK (Table 7). There is a need to develop international practice guidelines for clinical pharmacy practices.

Table 7 Examples of clinical pharmacy practice guidelines

Aim/scope	Organisation and country	Year	Target audience and settings	Reference
Inpatient, outpatient, and dispensary-based pharmacy consultations	London NW University, hospital, UK	2020		[199]
In practice: Guidance for pharmacist prescribers	General Pharmaceutical Council, UK	2019	All pharmacists are competent in prescribing. All settings.	[200]
Medicines optimisation guidelines to help patients make the most of medicines	Royal Pharmaceutical Society, UK	2013	All healthcare professionals. All settings.	[201]

Clinical pharmacists in Iceland have increased their services significantly during the last decade. The profession's development dates back to the nineties; however, due to the lack of access to educational programmes in Iceland, there was a limited increase in the service level in the first decades. In 2016, a new postgraduate education programme was established in Iceland in collaboration with the University of Iceland and Landspitali University Hospital.[202] The training programme was developed in partnership with the Royal Pharmaceutical Society and the University College London School of Pharmacy. Increased access to education programmes in Iceland has accelerated the profession's development. The postgraduate training is a 90 ECTS three-year master's degree work-based educational programme.[203]

Clinical services provided by pharmacists in primary care have developed over the last decade. A doctoral thesis focusing on implementing pharmaceutical care in primary care initiated the development [204, 205], which has been supported by the increase in the number of qualified clinical pharmacists in Iceland after implementing a national educational programme. Additionally, in 2018, two studies were conducted to evaluate the feasibility of increasing the clinical roles of community pharmacies.[206, 207] The studies were introduced to the minister of health. In recent years, there has been an increased focus on facilitating ways to utilise the community pharmacists' knowledge and improve their accessibility to support the safe and effective use of medications in Iceland. A few initiatives have already been started based on established services in the United Kingdom and Norway, like new medicine services, deprescribing opioids, and vaccinations.[208-210]

2.5 Summary

WHO has called attention to the pressing need for solid leadership globally, nationally, and locally to foster a culture around medication safety and quality.[16] It is crucial to minimise medication-related harm globally and nationally as it has risen as the population ages, with multimorbidity and increasing polypharmacy.[47, 50, 55, 57] Even though older patients are most affected by this development, there is a grave need also to address this matter in younger adults, as it is essential to find ways to prevent polypharmacy at an early stage and reduce medication-related harm. Studies and reports about medication usage among the Icelandic population have reported high consumption in general and also in specific medication categories like opioids.[211, 212] and hypnotics and sedative medication.[213, 214] Additionally, a small study shed light on the lack of medication appropriateness among older patients.[215] There is a lack of studies in Iceland focusing on patients admitted to the hospital. Additionally, there is a need for studies distinguishing between surgical patients and internal medicine patients. The characteristics of surgical and internal medicine patients are likely to be very different. With the ageing of the global population, patients at more advanced ages and increased frailty are likely to undergo surgeries. With limited resources within the healthcare settings, it is important to identify subgroups that might need increased

attention and different approaches in care, both prior to admission and post-discharge. Improved emphasis has been put on a perioperative continuum that maximises patient benefit and minimises risk; there is an increased focus on preoperative medication optimisation. This requires identifying medication classes associated with elevated risk in the correct patient populations/surgeries; therefore, it is important to identify those sub-groups.

Additionally, internal medicine patients are often older, with multimorbidity and increased frailty; therefore, it is important to identify those who might need increased follow-up after hospital admission or may benefit from a medication option during a hospital stay.

Understanding the prevalence incidence and risk factors of pre-admission and post-discharge polypharmacy and inappropriate medication usage can assist in identifying sub-groups of patients, both among the surgical population and the internal medicine population at risk, that might be useful in designing a medication optimisation intervention to reduce polypharmacy, inappropriate medication usage and hinder medication-related harm. With accumulating age, comorbidity burden and frailty, the therapeutic index of many commonly used medications narrows, making their risk/benefit ratio less favourable to justify treatment in these sensitive patient cohorts. By applying the Beers criteria to evaluate the potentially inappropriate medication use among patients admitted to hospitals in Iceland, it is possible to identify certain medication classes suggested to be potentially harmful to all older adults and have an increased potency for harm, particularly in patients with increased frailty. This information will be able to direct limited resources of the healthcare system towards those patient groups or specific medication classes to hinder associated harm.

WHO has highlighted the period of transfer of care as one of the high-risk situations. Therefore, it is essential to study hospitalised patients better and identify sub-groups of patients at increased risk of medication-related harm. These groups might need increased attention in the form of healthcare professionals in relation to their medications.

In recent years, clinical services have been rapidly developed in hospital settings in Iceland, which is in line with the development in other countries. Clinical pharmacy services aim to ensure effective, safe, and cost-effective medication use. The services provided have already started to develop in general practice settings. However, the resources of clinical pharmacists are still limited, so it is important to gather data to prioritise clinical pharmacists' services. This study can, therefore, support and prioritise strategies to promote the safe and appropriate use of medication, especially for older adults and patient groups at heightened risk of medication-related harm in Iceland. as it can result in greater tangible clinical benefits and better translation of research on medication safety into clinical practice.

3 Aims

This doctoral thesis aimed to estimate the prevalence and incidence of polypharmacy among patients preceding and following hospital admission and assess potential inappropriate prescribing among the study population. The aim of each paper is listed below:

Paper I - to use the Icelandic perioperative database to estimate the prevalence, incidence, and changes of polypharmacy pre-admission and post-discharge and associated with patient factors and clinical outcomes of patients' post-discharge.

The hypothesis was that pre- and post-operative polypharmacy and potentially inappropriate prescribing is common, especially among older patients, patients with a high comorbidity and frailty burden, and patients undergoing more complicated surgery. Our hypothesis is additionally that preoperative polypharmacy is associated with a higher short- and long-term mortality, a longer primary hospitalisation length of stay, and a higher risk of readmission.

Paper II - to use the Icelandic internal medicine database to estimate the prevalence, incidence, and changes of polypharmacy pre-admission and post-discharge, associated risk factors and clinical outcomes of patients' post-discharge.

The hypothesis was that pre-admission and post-discharge internal medicine polypharmacy is common, especially among older patients, patients with a high comorbidity and frailty burden, and patients undergoing more frequent internal medicine admission. Our hypothesis is additionally that polypharmacy prior to internal medicine admission are associated with a higher short- and long-term mortality, a longer primary hospitalization length of stay, and a higher risk of readmission.

Paper III - to use the Icelandic internal medicine database to estimate the prevalence and incidence and changes of the prevalence of potentially inappropriate prescribing amongst patients ≥65 years in Iceland over the period 2010-2020 by applying Beers 2019 explicit prescribing criteria. Additionally, it investigates the association of potentially inappropriate prescribing with polypharmacy, patient-specific factors, drug classes, and outcomes.

The hypothesis was that pre-admission and post-discharge internal medicine potentially inappropriate prescribing is common among older patients, patients with a high comorbidity and frailty burden, and patients undergoing more frequent internal medicine admission. Our hypothesis is additionally that potentially inappropriate prescribing prior to internal medicine admission are associated with a higher short- and long-term mortality, a longer primary hospitalisation length of stay, and a higher risk of readmission

Paper IV - to use the Icelandic perioperative database to estimate the prevalence and incidence and changes of the prevalence of potentially inappropriate prescribing amongst patients ≥65 years in Iceland over the period 2005-2018 by applying Beers 2019 explicit prescribing criteria. Additionally, it investigates the association of potentially inappropriate prescribing with polypharmacy, patient-specific factors, drug classes, and outcomes.

3 Materials and Methods

3.1 Study design

This thesis is based on four retrospective, population-based cohort studies that used data from two separate databases for hospital settings: the Icelandic perioperative database and the Icelandic internal medicine Database. The first and fourth manuscripts of the research project revolved around the Icelandic perioperative database, which was already established prior to this doctoral project. However, some additional variables were added for the purpose of this project. An extended ethical approval for the additional data was established (appendix). The perioperative database includes clinical data from the patient's medical record from the hospital, the national prescription database of the Directorate of Health, and the ICD-10 codes from hospital and primary care records (Table 8).

The study period was between December 2005 and December 2018, with a follow-up of clinical outcomes through the 11th of March 2021. Ethical approval was obtained from the National Bioethics Committee of Iceland (VSN-14-139-V1) (appendix). The study protocol was published on clinicaltrials.gov before analysis (NCT04805151).

Table 8 The International Classification of Diseases Tenth (ICD-10) codes used for determining comorbid conditions and complications.

Comorbidity	**ICD-10 code**
Hypertension	I10-I15
Congestive heart failure	I50
Ischemic heart disease	I20-I25
Diabetes mellitus	E10-E14
Chronic obstructive pulmonary disease	J40-J44
Chronic kidney disease	N18-N19
Liver disease	K70-K76
Malignant neoplasm	C00-C97
Benign neoplasm	D00-D97
Psychiatric	F00-F99
Dementia	F00-F02
Delirium	F05
Clinical outcomes and complications	
Falls	falls_dx=c("W00","W01","W02","W03","W04","W05","W06","W07","W08","W09","W10","W11","W12","W13","W14","W15","W16","W17","W18","W19","E880","E881","E882","E883","E884","E885","E886","E887","E888")
Mortality	Died during follow-up
Adverse drug effect	Y40-59, X40-59, T36-59

The second and third manuscripts were derived from the Icelandic internal medicine database that was generated for this doctoral project. The Internal Medicine database also includes clinical data from the patient's medical record from the hospital, the national prescription database of the Directorate of Health, and the ICD-10 codes from primary care and hospital records. The study period was between December 2010 and December 2020, with a follow-up of clinical outcomes through the 17th of March 2022. Ethical approval was obtained from the National Bioethics Committee of Iceland (VSN-21-179) (appendix). The study protocol was published on clinicaltrials.gov before analysis (NCT05756400). The Icelandic Internal Medicine database will be further maintained and has already been utilised for numerous multidisciplinary research projects. Table 9 demonstrates a summary of the included cohorts, as the four manuscripts are based on separate cohorts with some overlap between I and IV and II and III.

Table 9 Summary of study populations and exposure of interest.

	Paper I	Paper II	Paper III	Paper IV
Study population	Surgical patients	Internal medicine patients	Internal medicine patients	Surgical patients
Study period	2005-2018	2010-2020	2010-2020	2005-2018
Age (years)	≥18	≥18	≥65	≥65
Number of admissions	55,997	85,942	55,859	27,541
Exposure of interest	Medication use category	Medication use category	Potentially inappropriate prescribing	Potentially inappropriate prescribing

3.2 Study population

The two previously mentioned databases were established by connecting data from various sources and databases described in the following subsections. The data was connected to each patient by their personal identification number, which all individuals in Iceland have. The two databases included all patients ≥18 years hospitalised in either surgical or internal medicine wards at Landspitali – The National University Hospital of Iceland. Landspitali – The National University Hospital was the basis for the study´s population for both databases. The hospital is the secondary care hospital for approximately 75% of the nation and the tertiary hospital for the whole country. The Ministry of Health funds the hospital and provides general and specialised care. The hospital's capacity is approximately 700 beds.

3.2.1 Description of the Icelandic perioperative database

The Icelandic perioperative database contains information on all surgeries performed from 2005-2018, with a follow-up of clinical outcomes through 11th March 2021. The data sources are from six databases in Landspitali and two from the Directorate of Health. The first surgery for each patient was included in the analysis for this project for the reason that the following admissions could be due to reoperations, and the subsequent surgeries would allow less timeframe prior to the surgery and less follow-up time afterwards. The hospital performs all tertiary surgeries and serves as the primary hospital for all surgeries for most of the nation. Figure 5 describes the databases linked together in establishing the Icelandic perioperative database. Information on all surgical procedures was collected from Orbit, the surgical database at Landspitali. Surgical codes were based on the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (Table 10). This classification system is based on three characters to delineate the surgery's anatomical location and two digits that further specify the surgical procedure. All surgeries were split into emergency or elective for further evaluation.

Table 10 Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO) classification codes are used to categorise surgical procedures into subgroups. [210] The classification system is based on a three-character group of surgical procedures. The surgical groups included all subgroups; the subgroups (numbers) are not presented in the table

	NOMESCO surgical procedure code
Surgical procedures	
Abdominal	J
Cardiac	F
Endocrine	B
Gynaecology	L
Neurosurgery	A
Orthopaedic	N
Thoracic	G
Urology	K
Vascular	P

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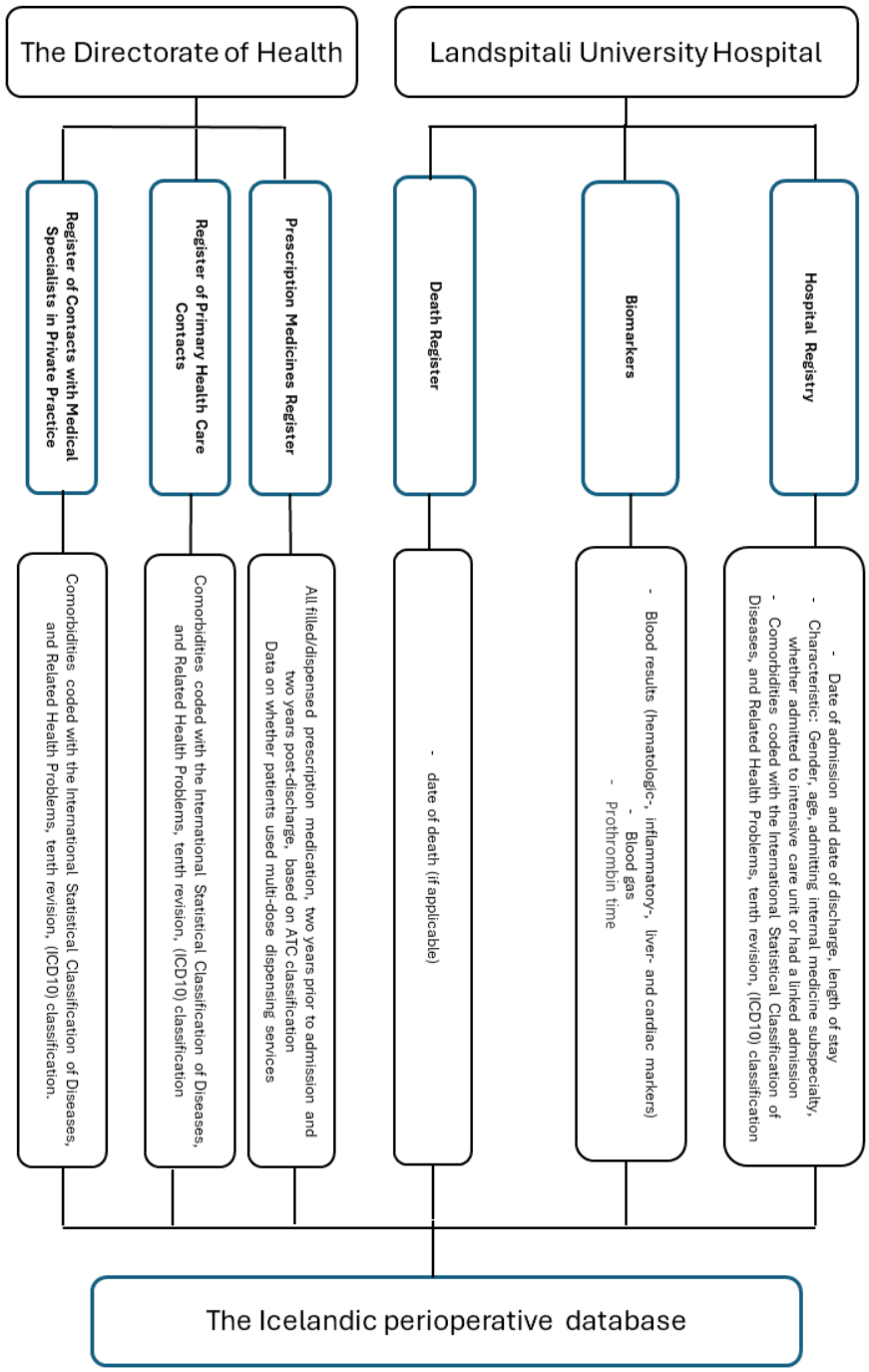

Figure 5 A schematic description of the Icelandic perioperative database.

3.2.2 Description of the Icelandic internal medicine database

The Icelandic internal medicine database was generated similarly to the Icelandic perioperative database. The Internal Medicine database includes all patients hospitalised in internal medicine wards at Landspitali – The National University Hospital of Iceland during the study period, between the 1st of January 2010 and the 31st of December 2022, with a follow-up of clinical outcomes through the 17th of March 2022. All of the patients' admissions were included in the analysis for this project. The hospital is the primary hospital for 75% of the Icelandic population and the tertiary for the whole nation. Figure 6 Describes the databases linked together in establishing the Icelandic internal medicine database.

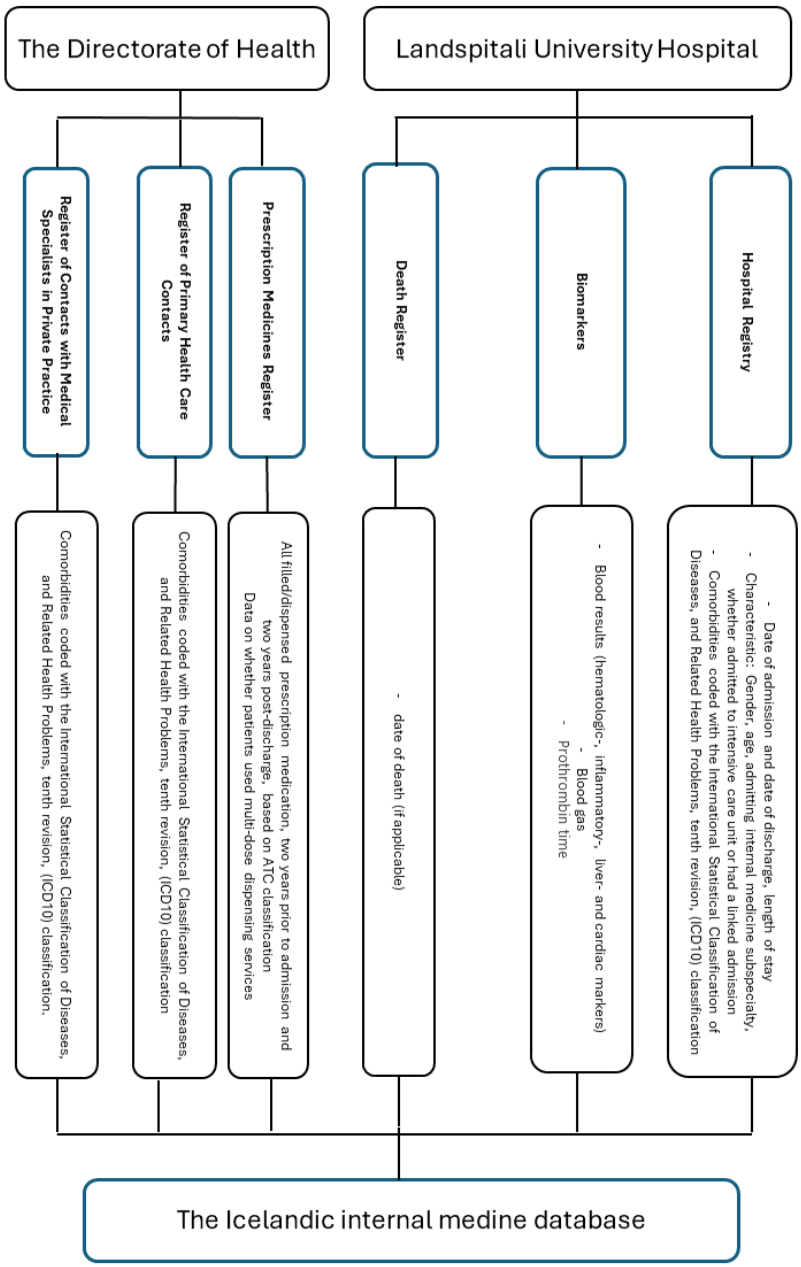

Figure 6 A schematic description of the Icelandic internal medicine database.

3.3 Exposure variable definition and follow-up period

3.3.1 Calculation of medication use categories

For all manuscripts, variables that described polypharmacy were generated. The primary exposure was the extent of medication use, defined as the number of different medications filled in the year preceding (pre-admission) and the year following discharge (post-discharge). Patients were separated into three groups based on the medication use categories they fulfilled (non-polypharmacy (<5), polypharmacy (5-9), and hyperpolypharmacy (≥10)) based on their pre-admission and post-discharge medication filling in the year prior to admission and post-discharge (Figure 7). Information was gathered to identify whether patients were using multidose dispensing services. In the Icelandic internal medicine database, a linked admission to the intensive care unit when patients have been admitted to the intensive care unit during an acute admission. Linked admission to palliative care, rehabilitation and geriatrics generally follows an acute admission to the internal medicine ward.

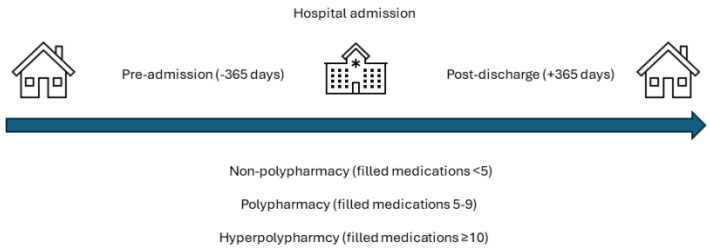

Figure 7 The timeline for allowing for medication filling pre-admission (-365 days until admission) and post-discharge (+ 365 days after discharge).

All regular and as-required medications were included; non-prescribed (over-the-counter), topical, and herbal/homoeopathic medications were not included. The number of medications were counted within different anatomical/pharmacological groups (ATC 1st level) and pharmacological/therapeutical subgroups (ATC 2nd level) filled in the year preceding and following surgical and internal medicine admissions Table 11.

Table 11 The Anatomical Therapeutic Chemical (ATC) classification system used for determining medication filled by prescription.

Medication Group	**ATC code**
Cardiovascular medications	C (entire category)
Beta-blockers	C07
Calcium Channel Blockers	C08
ACE inhibitors and Angiotensin II Receptor Blockers	C09
Statins	C10AA
Anticoagulant	B01A
Antiplatelet	B01AC
Proton Pump Inhibitors	A02BC
Anti-diabetics	A10B
Urinary	G04
Hormones	G03 ATH
Corticosteroids	H02AB
Respiratory	R (entire category)
Antibiotics	J01
Paracetamol/orphenadrine combinations	N02BE01
Opioids	N02A
Nonsteroidal anti-inflammatory medications	M01AE
Selective cox-2 inhibitors	M01AH
Antidepressants	N06A
Benzodiazepines	N05BA
Antipsychotic medications	N05A
Z-medications	N05CF
Anti-dementia medications	N06D
Antihistamines	R06

3.3.2 Calculation of potential inappropriate medication use

The American Geriatric Society 2019 Beers criteria are explicit criteria to identify inappropriate prescribing validated among ≥65 years. The Beers criteria provide a list of medications that have been identified as potentially inappropriate medication use for ≥65 years, which has been linked to an increased risk of developing adverse drug reactions, hospitalisation, and falls .[157] For the purpose of these studies, all prescription

medications filled in the year prior to admission and post-discharge were assessed for potentially inappropriate medication use by comparing them to the list of medications in the Beers criteria that are potentially inappropriate in most ≥65 older adults, which should typically be avoided. The Beers Criteria include individual criteria and medications or medication classes generally best avoided by older adults or under specific circumstances, such as certain diseases or conditions .[157]

For manuscripts III and IV, the primary exposure was the prevalence of potentially inappropriate medication use prior to admission and the incidence of new potentially inappropriate medication use post-discharge. The prevalence of filling a medication for subcategories of Beers criteria was also evaluated. The prevalence of medication use within different Beers categories was calculated, and the total number of criteria met was calculated based on the 2019 Beers criteria and the medication filled in the year preceding and the year following discharge from the hospital.

3.4 Baseline patient characteristics

Information on all baseline patient characteristics, such as age and gender were gatherd from hospital data. Information on comorbidities was gathered using the International Statistical Classification of Diseases and Related Health Problems (ICD) coding. The ICD 10 codes were used from both hospital, primary care, and private practice data to report on comorbidities prior to and post-discharge.

3.4.1 Elixhauser comorbidity index on admission

Elixhauser comorbidity Index is a comorbidity measurement and can be used to describe and compare patients' populations and used for an adjustment for confounding when comorbidity is correlating with an outcome. The Elixhause comorbidity Index was developed by Elixhause In 1998 and was calculated to estimate the overall severity of comorbidities segregated from the primary reason for hospitalisation. The index was based on 30 comorbidities, and each score ranges from -7-12. The final Elixhauser score ranges from -19 to 89. Elixhauser et al. developed the Elixhauser comorbidity index for large-scale inpatient administrative databases.[216] In 2009, Walraven et al. modified the Elixhasuer comorbidity Index to provide a single numeric score summarising the comorbidity burden.[217] The purpose of using the Elixhauser comorbidity Index for this study was to estimate the comorbidity burden among the study cohort and use the measurement to allow comparison and adjustment for confounding. For the purpose of this study, the Elixhauser comorbidity index was categorised as (<1), (1-4), (5-8), and (>8).

3.4.2 Hospital frailty risk index classification

Frailty has been used to describe diversity among older adults. There is a lack of consensus regarding an international definition of frailty. A description from WHO has

been widely adopted: 'progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes. [218] Frailty refers to a state where individuals are particularly vulnerable, facing an elevated risk of adverse health consequences or mortality when exposed to stressors.[219] Measurement of frailty risk can be applied to describe and compare patients' populations and used to adjust for confounding when comorbidity is correlating with an outcome. A specific hospital facility risk stratification tool was recently developed and validated for older (≥65 years) in acute care settings, relying on administrative data.[220] The frailty risk assessment Is derived from ICD-10 codes from electronic hospital records. The risk stratification tool was developed and evaluated using a three-step approach. First, it was analysed by cluster analysis, which evaluated patients admitted with signs of frailty and whether they could be identified by using ICD-10 codes. Secondly, the hospital facility risk scoring was developed by using ICD-10 codes that were overly represented. The cohort was evaluated. Thirdly, the newly established Hospital facility Risk Scoring was validated in two separate validation cohorts. The score Is categorised into low risk (<5), intermediate risk (5–15) and high risk (>15). The Hospital Frailty Risk Score has also been validated for older (≥65 years) surgical patients.

3.4.3 Anticholinergic Cognitive Burden Scale

The use of medication with anticholinergic effects has been linked to worse clinical outcomes. Studies evaluating the impact of increased anticholinergic burden have revealed that the anticholinergic effect is linked to an increase in the likelihood of cognitive impairment by 45% over six years. The decline of cognitive functions was evaluated using the mini-mental state examination assessment, and mortality risk was increased. Several tools have been developed to identify medication with anticholinergic burden. Boustani et al. developed the anticholinergic cognitive burden scale as a practical tool to identify and country the anticholinergic effect of medications.[221] The anticholinergic cognitive burden scale can additionally be used in research to quantify the anticholinergic burden of medication, Table 12. For the purpose of this study, the anticholinergic burden was quantified based on filled in both prior and post-discharge. A literature review established the tool to identify medications with an anticholinergic cognitive burden. An expert panel was then consulted to categorise the medication into minor (score=1), moderate (score=2), and major (score =3). [221] The quantification of the Anticholinergic burden refers to possible effect (score=1) and definite effect (score= 2 or 3)(Table 12).[221]

Table 12 Anticholinergic cognitive burden scale. Criteria for Categorisation: Score of 1: In vitro data shows that the chemical entity has antagonist activity at the muscarinic receptor. A score of 2: Evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect. A score of 3: Evidence from literature, expert opinion, or prescriber information that medication may cause delirium. The list has been adapted to the accessibility of medications in the Icelandic healthcare settings adapted to Icelandic healthcare settings. [221]

Drugs with ACB Score of 1	Drugs with ACB Score of 2	Drugs with ACB Score of 3
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Carbamazepine	Atropine
Aripiprazole	Cyproheptadine	Chlorpheniramine
Atenolol	Oxcarbazepine	Chlorpromazine
Bupropion	Pimozide	Clemastine
Captopril		Clomipramine
Cetirizine		Clozapine
Cimetidine		Diphenhydramine
Clidinium		Doxepin
Codeine		Doxylamine
Colchicine		Fesoterodine
Desloratadine		Hydroxyzine
Diazepam		Hyoscyamine
Digoxin		Imipramine
Dipyridamole		Nortriptyline
Fentanyl		Olanzapine
Furosemide		Orphenadrine
Fluvoxamine		Oxybutynin
Fluvoxamine		Paroxetine
Haloperidol		Perphenazine
Hydralazine		Promethazine
Hydrocortisone		Propantheline
Isosorbide		Quetiapine
Loperamide		Scopolamine
Loratadine		Solifenacin
Metoprolol		Tolterodine
Morphine		Trifluoperazine
Nifedipine		Trihexyphenidyl
Paliperidone		Trimipramine
Prednisone		
Risperidone		
Theophylline		
Trazodone		
Venlafaxine		
Warfarin		

3.4.4 Medication-related Harm Risk Stratification

Medication-related harm is known to cause morbidity among older patients. Parekh et al. developed a risk prediction tool to Identify older patients at Increased risk of medication-related harm post-discharge from the hospital. The tool was developed in a multicenter prospective study in the UK between 2013 and 2015. In the study, participants were ≥65 years old, followed up for 8 weeks post-discharge and medication-related harm was identified by an experienced pharmacist. Two systematic reviews were done to identify characteristics and clinical variables to be evaluated, and patients' views and an expert panel of clinicians were gathered. The tool was then developed by multivariable logistic regression with backward elimination. The PRIME tool, a risk prediction tool, was designed to Identify patients at heightened risks of medication-related harm in the post-discharge period. The tool predicts the absolute patient risk of older patients (≥65 years) experiencing medication-related harm post-discharge. The calculated score is based on clinical, medication, and psychosocial variables to determine the likelihood of medication-related harm. The risk score is based on gender, age, sodium level, number of medicines, and whether the patient uses antiplatelet or diabetic medication (Figure 8). The risk assessment tool was developed by Parekh et al. to identify older patients at risk of medication-related harm post-discharge. The validation was undertaken in a multicenter study 8 weeks post-discharge in the United Kingdom.[112, 115]

Model equation for risk score = -2.384 + 0.5x (0.025(age-81) – 0.398(gender) + 0.515(antiplatelet drug) – 0.042(sodium -137) + 0.591(antidiabetic drug) + 0.477(past adverse drug reaction) + 0.056(number of medications) + 0.397(living alon)

Induvidual estimated risk of medication related harm (%) = $(1/1+e^{-\text{risk score}})*100$

Figure 8 Equation to calculate patients' risk of experiencing medication-related harm requiring the use of health care services within 8 weeks of hospitalisation based on the PRIME risk stratification tool developed by Parekh et al.[112]

3.5 Definition of study clinical outcomes

For all manuscripts, the primary clinical outcomes were mortality (short-term, < 30 days, and long-term mortality) (censored on the 17th of March 2022 for the Internal of medicine database and the 19th of April 2021 for the Perioperative database), length of hospital stay (number of days, ≥ ten days), and readmission (number of days until readmission, readmission <30 days). The prevalence and incidence of diagnosis of an adverse drug reaction and falls were evaluated both before admission and post-discharge.

3.6 Statistical analysis

All Data visualisation and statistical analysis data for this study for all four manuscripts were conducted using R (The R Foundation for Statistical Computing R, Vienna, Austria) version 4.0.3 and 4.2.2, via R studio (RStudio PBC, USA), version 2022.12.0.

3.6.1 Descriptive statistics

Descriptive statistics were applied to describe the demographic and clinical characteristics of the patient populations in all four manuscripts. Descriptive statistics were also used to exhibit the number of medications filled in the year prior to admission (either a surgical or internal medicine) and the medication use category (non-polypharmacy, polypharmacy and hyperpolypharmacy). Descriptive statistics were also applied for paper III to describe potentially inappropriate medication use based on the Beers criteria. The number of medications was described for all papers as median and interquartile range. The prevalence and incidence were described as percentages, and the distribution of the medication use into categories of varying polypharmacy pre- and post-discharge was described as a percentage with a 95% confidence interval calculated using the Pearson-Klopper method to obtain binomial probability in the binom package in R.

In manuscript I and II, the comparison between the demographics, patient characteristics and clinical outcomes were made between groups of non-polypharmacy (< 5 medications), polypharmacy (5-9) and hyperpolypharmacy (≥10) frailty using ANOVA for continuous variables and chi-square tests for categorical variables. In manuscripts III and IV, the demographics, patient characteristics, and clinical outcomes were compared between groups that did not fill a potentially inappropriate medication and those that filled a potentially inappropriate medication using ANOVA for continuous variables and chi-square tests for categorical variables.

3.6.2 Multivariable analysis

For manuscript I, a multivariable logistic regression was used to compare multivaritate patient and procedural variables between groups of varying preoperative and postoperative medication use. No multivariable analysis was done in Manuscript II; for manuscript III, multivariable logistic regression models were used to evaluate patient- and admission-related risk factors of receiving a new potentially Inappropriate medication use post-discharge to identify independent risk factors using the covariates: age, sex, admitting speciality, Elixhauser comorbidity index, comorbidities, multidose dispensing service, category of medication usage (polypharmacy and hyperpolypharmacy) prior to admission and a diagnosis of fall or adverse drug reaction diagnosis prior to admission.

3.6.3 Survival

For manuscripts I and II, the long-term survival was visualised on a Kaplan-Meier plot between different medication use categories (non-polypharmacy = <5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications). For manuscript III, the long-term survival was visualised on a Kaplan-Meier plot between different medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) and modelled with cox proportional hazard risk model. The proportionality assumption was assessed using the cox.zph function in R with adjusting for number of medications used prior to admission, gender, age, hypertension, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, liver disease, kidney disease, malignant neoplasm, benign neoplasm, Elixhauser comorbidity index and admitting speciality and quantifying changes in Schoenfeld residuals against time.

3.6.4 Risk of Outcomes

Clinical outcomes were compared (short long-term mortality, primary hospitalisation length of stay, and risk of readmission) by applying descriptive statistics.

For manuscripts I and II, a restricted cubic spline were used to visualise the relationship between the medication use categories (non-polypharmacy, polypharmacy and hyperpolypharmacy) and the ratio of following clinical outcomes, short-term mortality (<30 days), extended hospital stay (>10 days), and risk of readmission (<30 days) a restricted cubic spline analysis was performed, with prespecified knots at the cut-off for the medication use categories (non-polypharmacy=0,polypharmacy=5, and hyperpolypharmacy=10 medications).

For manuscripts III and IV, a restricted cubic spline was used to visualise the relationship between the medication use categories (non-polypharmacy, polypharmacy and hyperpolypharmacy) and the ratio of potentially inappropriate medication use based on Beers criteria 2019; a restricted cubic spline analysis was performed, with prespecified knots at the cut-off for the medication use categories (non-polypharmacy=0,polypharmacy=5, and hyperpolypharmacy=10 medications).

3.6.5 Missing data

All four manuscripts were observational cohort studies based on retrospective data, which relies on accurate documentation of healthcare professionals. Therefore, the absence of documentation of a condition (diagnosis) might lead to underreporting, which is an assumption. No imputation for missing data was made.

3.6.6 Sensitivity analyses

A sensitivity analysis was performed to assess whether reclassification of the time frame allowed for filling medication prior to admission and post-discharge for the study definition of including medications filled in the 12 months preceding surgery would affect the prevalence of polypharmacy or hyperpolypharmacy groups. A sensitivity analysis was also performed in order to assess whether including antibiotics from the medication database to estimate the burden of polypharmacy without antibiotics would overstate the number of medications filled in the year prior and post-admission.

4 Results

This thesis is based on four manuscripts evaluating the epidemiology of polypharmacy, potentially inappropriate prescribing patterns, and its association with clinical outcomes among inpatients, both surgical and internal medicine patients. Manuscript I assessed the prevalence of preoperative polypharmacy, the incidence of postoperative polypharmacy/hyperpolypharmacy, and their association with patient- and procedural variables. Furthermore, the association between preoperative polypharmacy and postoperative outcomes was assessed. Similarly, manuscript II evaluated the prevalence of pre-admission polypharmacy and incidence of post-discharge polypharmacy/ hyperpolypharmacy among internal medicine patients admitted to hospital and their association with patient factors, admitting subspeciality, and clinical outcomes. In manuscript III, the prevalence and incidence of potentially inappropriate prescribing were described as associated with the burden of polypharmacy among internal medicine patients. Furthermore, the potentially inappropriate prescribing, association with the patient- and internal medicine subspecialties, and associated variables were reported. Similarly, in manuscript IV, the prevalence and incidence of potentially inappropriate prescribing and the association with the burden of polypharmacy among surgical patients were determined. Furthermore, the potentially inappropriate prescribing and the association with the patients- and associated variables in this population were studied.

4.1 Paper I – Epidemiology of polypharmacy and medication use among patients undergoing surgery and association with clinical outcomes

4.1.1 Clinical characteristics of the patient cohort

In total, 84,009 surgeries were performed at Landspitali hospital during the study period 2005-2018. Of those, 28,012 were reoperations or subsequent operations during the study period. Reoperations were excluded; therefore, the final study population included 55,997 patients undergoing their first surgery during the study period (Figure 9). Table 13 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). Of the whole cohort, 57.4% were female, and the median age [IQR] was 55 [39, 69]. They used a median [IQR] of 6 [2, 10] medications in the year preceding the surgery and 6.00 [3, 11] in the year after the surgery. Multidose

dispensing service was used by 13.7% of the cohort in the year preceding the surgery. The majority of the cohort had a low (<5) hospital frailty risk score class, 60.2%, 34.8% had a medium score (5-15), and 5.0% had a high score (>15). The most common comorbidity of the whole cohort was hypertension, 30.5%, malignant neoplasm, 16.2%, and chronic obstructive pulmonary disease, 16.0%. The majority of the surgeries, 65.8%, were elective surgeries. Of the cohort, 34.2% had an emergency operation. The most frequent types of surgeries were orthopaedic 28.1%, abdominal 18.9%, and gynaecology 15.9%.

4.1.2 Prevalence and incidence of different medication use categories (non-polypharmacy, polypharmacy and hyperpolypharamacy)

Figure 9 presents the prevalence of preoperative non-polypharmacy (<5 medications), which was (42.2%, 95% CI 41.7-42.6), polypharmacy (5-9 medications) which was (32.3%, 95% CI 33.5-34.3) and hyper–polypharmacy (≥10 medications), which was (25.5%, 95% CI 25.2-25.9).

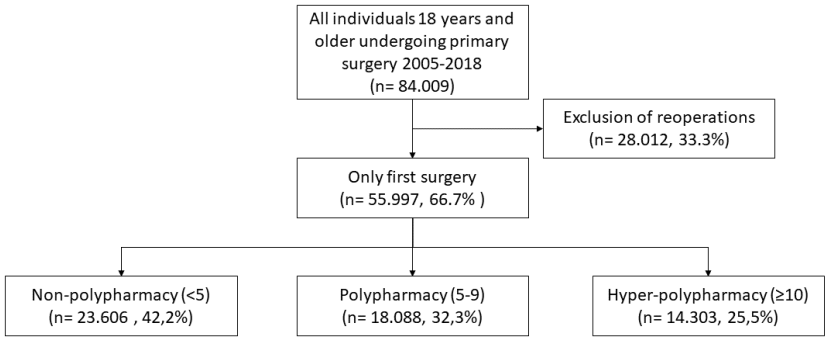

Figure 9 A consort diagram of participant inclusion and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy) based on a number of different medications filled in the year preceding surgery.

A total of 23,606 patients who underwent surgical procedures had not been exposed to polypharmacy in the year prior to the surgery. The incidence of new postoperative polypharmacy was (33.4%, 95% CI 32.4-34.0) and the incidence of new hyperpolypharmacy was (16.3%, 95% CI 16.0-16.7) hyper polypharmacy was (33.4%, 95% CI 32.4-34.0).

Figure 10 presents the distribution of patients into medication use categories of non-polypharmacy, polypharmacy and hyperpolypharmacy by year of surgery over the study period 2005-2018. The prevalence among the different medication use categories (non-polypharmacy vs polypharmacy vs hyperpolypharmacy) over the study period were similar, with a slightly higher prevalence of hyperpolypharmacy in 2006, 2009 and 2014.

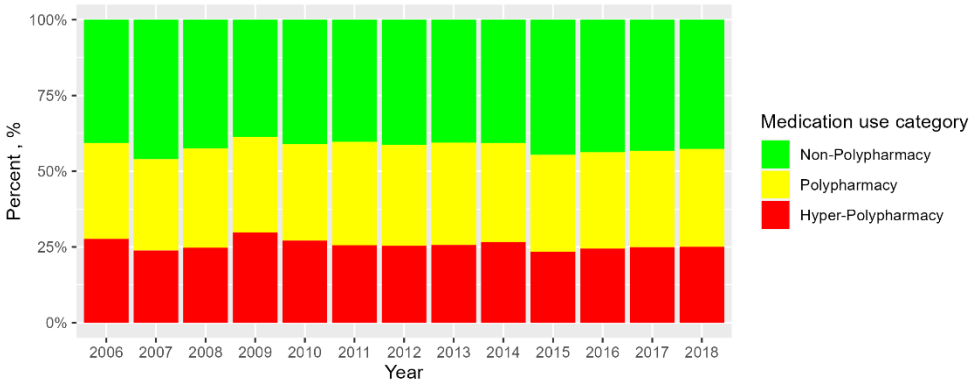

Figure 10 The distribution of patients into medication use categories over the study period 2005-2018 (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) based on the medication filled in the year preceding admission by internal medicine.

A sensitivity analysis was done to estimate whether the timeframe allowed for filling of medications in order to fulfil the requirement of the medication use categories (polypharmacy, 5-9 medications vs hyperpolypharmacy, ≥10 medications). The reclassification of polypharmacy classification if a shorter window of time to fill prior to admission was considered (Figure 11). This revealed that, for example, if only the last six months before admission were considered to classify polypharmacy, roughly 60% of the patients would remain within their medication use category compared with a 12-month filling window.

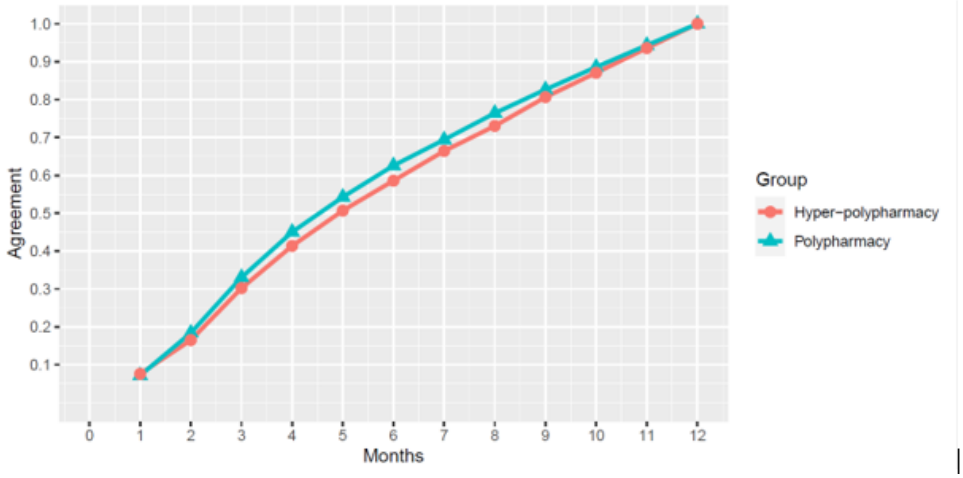

Figure 11 The proportion of classification agreement (Y-axis) for patients classified into polypharmacy or hyper-polypharmacy groups when the study definition of including medications filled in the 12 months preceding surgery was compared against reclassification using a shorter duration of filling (1-11 months (X-axis)).duration of filling

The prevalence was also estimated after eliminating antibiotics from the medication database to estimate the burden of the medication use categories (polypharmacy and hyperpolypharmacy) without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification. If antibiotics were removed from the list of medications, 80.2% of patients with polypharmacy and 79.9% with hyperpolypharmacy would have remained within their medication use category. This sub-analysis was performed due to the fact that antibiotics are most often short-term use (Table 13).

4.1.3 Clinical characteristics of the patient cohort of different medication use categories (non-polypharmacy, polypharmacy and hyperpolypharamacy)

Table 14 also presents the study cohort characteristics, categorised by their medication use category (non-polypharmacy (<5 medications), polypharmacy (5-9 medications), and hyperpolypharmacy (≥10 medications)). Patients were more likely to be female in all medication use categories: 63.1% for hyperpolypharmacy, 59.7% for polypharmacy, and 52.1% for non-polypharmacy. Those with hyperpolypharmacy also had higher median [IQR] age 67 [55, 76] years, compared to polypharmacy 58 [43, 69] and non-polypharmacy 45 [32, 59]. Patients with hyperpolypharmacy were also more likely to use multidose dispensing service preoperatively, 32.3% vs 11.9% for polypharmacy and 3.9% for non-polypharmacy. Additionally, patients with hyperpolypharmacy were more

likely to have a high hospital frailty risk score class 13.1% vs. 3.4% for polypharmacy and 1.3% for non-polypharmacy. Hypertension was the most common comorbidity for all medication categories, 55.8% for hyperpolypharmacy, 35.0% for polypharmacy, and 11.8% for patients with non-polypharmacy. The second most common comorbidity was chronic obstructive pulmonary disease, 30.2% for hyperpolypharmacy, but malignant neoplasm for polypharmacy, 17.1% and non-polypharmacy, 11.1%. Patients with hyperpolypharmacy were less likely to undergo an emergency operation, 26.9% compared to 28.0% for patients with polypharmacy and 43.3% for patients with non-polypharmacy. The most common surgical procedure for patients with all medication use categories was orthopaedic surgery, 29.5% for patients with hyperpolypharmacy, 24.9% for patients with polypharmacy and 29.6% for patients with non-polypharmacy. The second most common surgical procedure among the study cohort was abdominal surgery, 17.1%) for patients with hyperpolypharmacy, 18.9%) for patients with polypharmacy and 20.3% for patients with non-polypharmacy.

For patients exposed to polypharmacy prior to the surgery, the incidence of new postoperative hyperpolypharmacy was 28.9%, 95% CI 28.3-29. Table 15 presents the characteristics, including the comorbidity of patients moving to a higher medication use category, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Surgical patients moving to higher medication use category had higher median[IQR] age 57 [42, 68] vs 55 [38, 69], but they had a lower hospital frailty risk index classification with 63.1% with low risk vs 59.3% of patients not moving to a higher polypharmacy category. They were also more likely to have a diagnosis of malignant neoplasm (23.3% vs 14.0%) and longer median hospital stay (median [IQR]) 2 [1, 5] vs 1 [0, 3]. Finally, they were more often undergoing cardiac procedures (6.4% vs. 2.3%) or vascular procedures (10.9% vs. 5%).

4.1.4 Medication use and multidose dispensing services

In Table 14 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding surgery. The most frequent medications were filled in preoperatively for the whole study cohort and additionally arranged by the medication use categories. For the entire cohort, the most frequently used medications in the year prior to admission were antibiotics (49.0%), cardiac medications (42.4%), and opioids (42.2%). For patients with hyperpolypharmacy in the year prior to surgery, the most frequent medication classes were cardiac medications (77.8%), followed by antibiotics (75.0%) and opioids (67.0%). For patients with polypharmacy in the year prior to the surgery. The medication most commonly added were antibiotics (56.4%), followed by cardiac medications (50.9%) and opioids (46.8%). Finally, patients with non-polypharmacy most often filled antibiotics (27.7%),

followed by opioids (23.6%) and paracetamol/orphenadrine combinations (20.7%) in the year preceding surgery.

For the whole cohort, the most frequently added medications were opioids (26.9%), paracetamol (20.1%), antibiotics (20.0%), anticoagulants (10.0%), respiratory medications (9.7%), proton pump inhibitors (9.6%), corticosteroids (8.0%), musculoskeletal (8.0%), urinary medications (8.0%), benzodiazepines (5.9%) and anti-diabetic medications (5.9%).

Multidose dispensing service was used in the year prior to surgery in the whole study cohort by 13.7% of patients. Those patients were more likely to have higher median [IQR] ages 76 [65, 83] vs 52 [37, 65], a higher number of medications filled median [IQR] 1 [0, 3] vs 3 [0, 9]. They have a higher Elixhauser comorbidity Index median [IQR] 0 [0, 4] vs 4 [0, 10] and higher frailty risk classification score with 66.3% of patients using multidose dispensing service having medium or high-risk score classification compared to 34.7% of those not using multidose dispensing service. Patients using multi-dose dispensing service were more likely to have a diagnosis associated with cognitive function like delirium (13.5% vs 2.3%), dementia (5.0% vs 0.2%), and psychiatric diagnosis (29.9% vs 9.5%). They were also more likely to undergo orthopaedic (43% vs 25.7%) and cardiac surgery (5.4% vs 2.9%). Finally, they were more likely to have a diagnosis of an adverse drug reaction (21.1% vs 9.2%). Patients with a higher medication use category were more likely to use multidose dispensing services, patients with hyperpolypharmacy (32.3%), hyperpolypharmacy, polypharmacy (11.9%) and non-polypharmacy (3.9%)(Table 16).

4.1.5 Clinical outcomes and survival post-discharge

To visualise the ratio of patients experiencing clinical outcomes of interest compared with a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications), the year pre-prior to a surgical admission were evaluated by using an unadjusted restricted cubic spline analysis. The analysis revealed a relationship between the absolute number of medications filled in the year before the surgery and the incidence of mortality (< 30 days). Readmission (< 30 days) and an extended hospital stay (≥ ten days) (Figure 12, Figure 14 and Figure 13).

Patients with hyperpolypharmacy prior to the surgery had higher 30-day mortality, 2.3%, compared to those with polypharmacy, 0.8%, and non-polypharmacy, 0.6% ($p < 0.001$). Additionally, patients with hyperpolypharmacy had a higher incidence of extended hospital stay, 11.3%, compared with those with polypharmacy, 6.3%, and non-polypharmacy, 4.1% ($p < 0.001$). Finally, patients with hyperpolypharmacy prior to the surgery had a higher incidence of readmission, 10.2%, compared with those with polypharmacy, 6.1%, and non-polypharmacy, 4.8% ($p < 0.001$).

Patients (≥65) with polypharmacy and hyperpolypharmacy were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge compared to non-polypharmacy, with a median [IQR] of 10.4% vs. 14.7% vs. 24.7%).

The long-term survival of patients with different medication use categories was visualised on a Kaplan-Meier plot. Figure 15 shows the long-term survival of patients with medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) based on filled medications in the year preceding hospital admission. A trend over time was observed with increased mortality among patients with polypharmacy and hyperpolypharmacy.

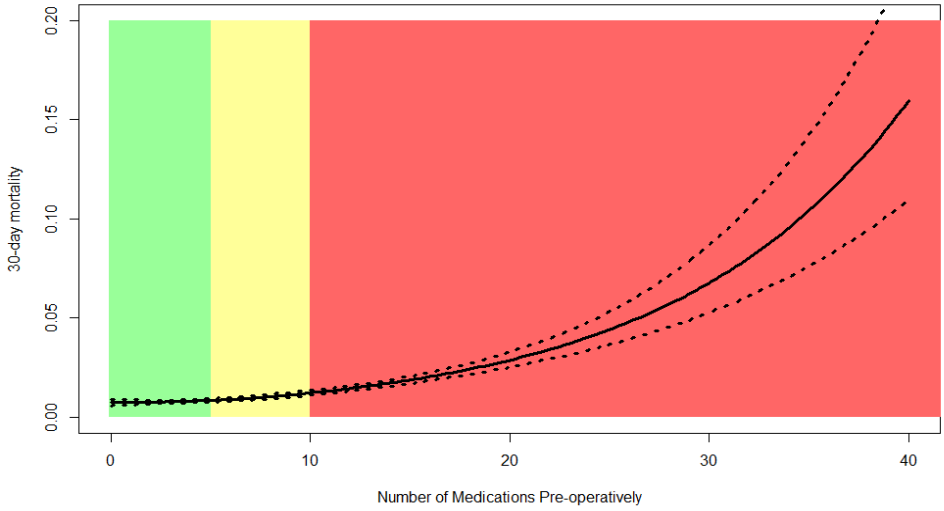

Figure 12 The association between the number of medications pre-surgery and 30-day mortality fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = p polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy. Dotted line represents a 95% confidence interval

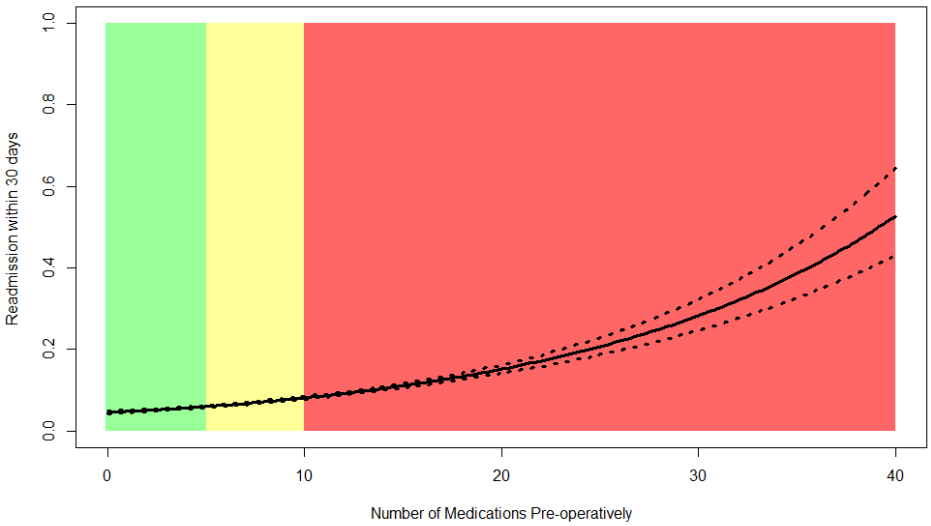

Figure 13 The association between the number of medications pre-surgery and 30-day readmission, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = p polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy. Dotted line represents a 95% confidence interval

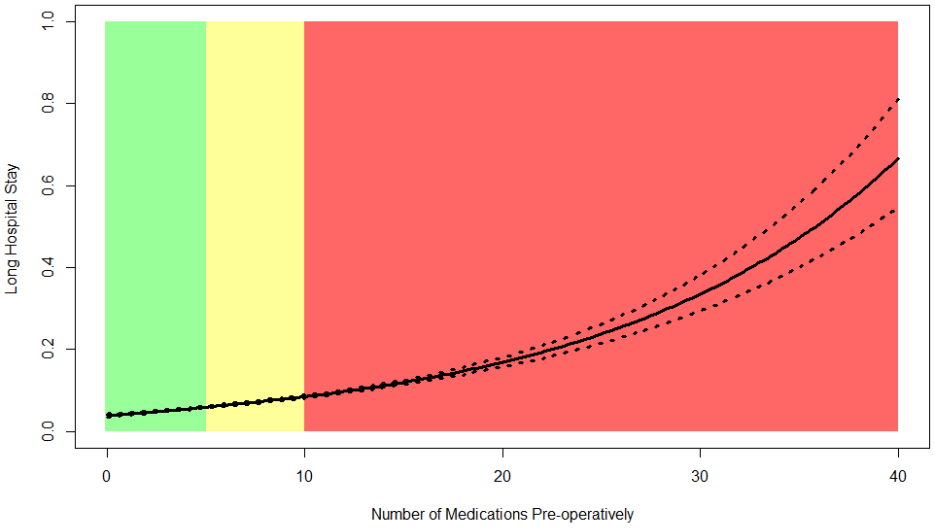

Figure 14 The association between the number of medications pre-surgery and long hospital stay >10 day, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = p polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy. Dotted line represents a 95% confidence interval

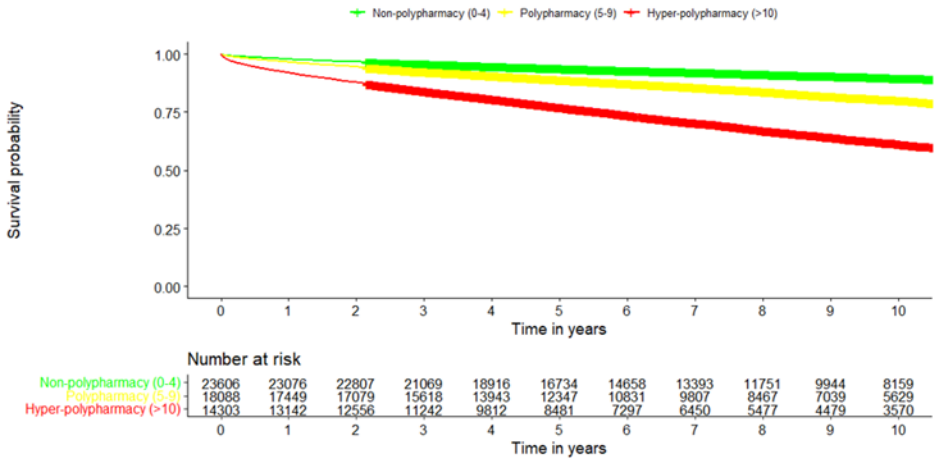

Figure 15 A Kaplan–Meier survival curve of long-term survival of patients compared based on the number of medications before surgery (green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10). Thicker lines represent 95% confidence intervals.

Table 13 Patient characteristics of cohorts based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR).

	Non-Polypharmacy	Polypharmacy	Hyper-polypharmacy	All patients	P-value
Total number of patients	23606 (42.2)	18088 (32.3)	14303 (25.5)	55997	
Sex (male)	12310 (52.1)	10806 (59.7)	9020 (63.1)	32136 (57.4)	<0.001
Age (median [IQR]), years	45 [32, 59]	58 [43, 69]	67 [55, 76]	55 [39, 69]	<0.001
Multidose dispensing services preoperatively	916 (3.9)	2148 (11.9)	4616 (32.3)	7680 (13.7)	<0.001
Number of preoperative medications (median [IQR])	2 [1, 3]	7 [6, 8]	13 [11, 16]	6 [2, 10]	<0.001
Number of postoperative medications (median [IQR])	3 [1, 5]	7 [5, 10]	13 [9, 17]	6 [3, 11]	<0.001
Elixhauser Comorbidity Index [IQR])	0 [0, 3]	0 [0, 4]	3 [0, 8]	0 [0, 4]	<0.001
Hospital Frailty Risk Score Class					
Low (< 5)	18096 (76.7)	10586 (58.5)	5034 (35.2)	33716 (60.2)	
Med (5-15)	5201 (22.0)	6894 (38.1)	7402 (51.8)	19497 (34.8)	
High (> 15)	309 (1.3)	608 (3.4)	1867 (13.0)	2784 (5.0)	
Comorbidities					<0.001
Ischemic heart disease	952 (4)	2416 (13.4)	4248 (29.7)	7616 (13.6)	
Congestive heart failure	220 (0.9)	425 (2.3)	1358 (9.5)	2003 (3.6)	
Hypertension	2787 (11.8)	6330 (35.0)	7976 (55.8)	17093 (30.5)	
Diabetes Mellitus	334 (1.6)	1026 (5.7)	2360 (16,5)	4381 (7.8)	
Chronic obstructive pulmonary disease	1814 (7.7)	2839 (15.7)	4323 (30.2)	8976 (16.0)	
Liver disease	147 (0.6)	223 (1.2)	361 (2.5)	731 (2.5)	
Chronic kidney disease	128 (0.5)	316 (1,2)	961 (6.7)	1405 (2.5)	
Malignant neoplasm	2632 (11.1)	3093 (17.1)	3343 (23.4)	9068 (16.2)	
Benign neoplasm	4444 (18.8)	5007 (27.7)	5657 (39.6)	15108 (27.0)	
Psychiatric	1759 (7.5)	2139 (11.8)	3003 (21,0)	6901 (12.3)	
Delerium	449 (1.9)	674 (3.7)	1020 (7.1)	2143 (3.8)	
Surgery Location and Classification					<0.001

Emergency operation	10247 (43.4)	5072 (28.0)	3841 (26.9)	19160 (34.2)	
Abdominal	4781 (20.3)	3415 (18.9)	2439 (17.1)	10635 (18.9)	
Cardiac	499 (2.1)	726 (4.0)	596 (4.2)	1821 (3.3)	
Endocrine	464 (2.0)	340 (1.9)	238 (1.7)	1042 (1.9)	
Gynaecology	4450 (18.8)	2978 (16.5)	1469 (10.3)	8897 (15.9)	
Neurosurgery	2309 (9.8)	2335 (12.9)	1770 (12.4)	6414 (11.4)	
Orthopaedic	6983 (29.6)	4490 (24.9)	4221 (29.5)	15694 (28.1)	
Thoracic	417 (1.8)	306 (1.6)	386 (2.7)	1109 (2.0)	
Urology	1397 (5.9)	1468 (8.1)	1307 (9.1)	4172 (7.4)	
Vascular	1335 (5.6)	1243 (6.9)	1142 (8.0)	3720 (6.7)	
Outcomes					
Number of pre-surgery medications (median [IQR])	2[1, 3]	7[6, 8]	13 [11, 16]	6 [2, 10]	
Number of post-discharge medications (median [IQR])	3 [1, 5]	7 [5, 10]	13 [9, 17]	6 [3, 11]	
Diagnosis of adverse drug reaction pre-admission (%)	698 (3.0)	1059 (5.9)	1660 (11.6)	3417 (6.1)	
Diagnosis of adverse drug reaction post admission (%)	562 (2.4)	876 (4.8)	1235 (8.6)	2673 (4.8)	
Length of stay (median [IQR])	1[0, 2]	1 [0, 4]	2 [1, 5]	1 [0, 3]	

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 14 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%).

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	p
Total number of patients	23606	18088	14303	55997	
Pre-operative medication					
Proton Pump Inhibitors	1720 (7.3)	4390 (24.3)	7368 (51.5)	13478 (24.1)	<0.001
Anti-diabetics	198 (0.8)	975 (5.4)	2216 (15.5)	3389 (6.1)	<0.001
Anticoagulants	377 (1.6)	1966 (10.9)	4004 (28.0)	6347 (11.3)	<0.001
Antiplatelet	204 (0.9)	1231 (6.8)	2685 (18.8)	4120 (7.4)	<0.001
Cardiac	3417 (14.5)	9198 (50.9)	11126 (77.8)	23741 (42.4)	<0.001
Beta-blockers	1211 (5.1)	4378 (24.2)	6386 (44.6)	11975 (21.4)	<0.001
Calcium Channel Blockers	395 (1.7)	2006 (11.1)	3552 (24.8)	5953 (10.6)	<0.001
ACE inhibitors and Angiotensin II Receptor Blockers	1566 (6.6)	4737 (26.2)	6305 (44.1)	13156 (23.4)	<0.001
Statins	885 (3.7)	3595 (19.9)	5677 (39.7)	10157 (18.1)	<0.001
Urinary	4007 (17.0)	6449 (35.7)	6606 (46.2)	17062 (30.5)	<0.001
Hormones	1247 (5.3)	3783 (20.9)	6566 (45.9)	11596 (20.7)	<0.001
Corticosteroids	640 (2.7)	2444 (13.5)	5024 (35.1)	8108 (14.5)	<0.001
Antibiotics	6530 (27.7)	10202 (56.4)	10724 (75.0)	27456 (49.0)	<0.001
Opioids	5568 (23.6)	8469 (46.8)	9582 (67.0)	23619 (42.2)	<0.001
Paracetamol/orphenadrine combinations	4877 (20.7)	7930 (43.8)	7570 (52.9)	20377 (36.4)	<0.001
Nonsteroidal anti-inflammatory drugs	4609 (19.5)	7263 (40.2)	6547 (45.8)	18419 (32.9)	<0.001
Selective cox-2 inhibitors	316 (1.3)	1037 (5.7)	1821 (12.7)	3174 (5.7)	<0.001
Antipsychotic	259 (1.1)	988 (5.5)	2052 (14.3)	3299 (5.9)	<0.001
Benzodiazepines	723 (3.1)	2586 (14.3)	4952 (34.6)	8261 (14.8)	<0.001
Antidepressants	1617 (6.8)	4112 (22.7)	6317 (44.2)	12046 (21.5)	<0.001
Anti-dementia	40 (0.2)	162 (0.9)	284 (2.0)	486 (0.9)	<0.001
Respiratory	2180 (9.2)	5317 (29.4)	7401 (51.7)	14898 (26.6)	<0.001
Antihistamin	591 (2.5)	1529 (8.5)	2522 (17.6)	4642 (8.3)	<0.001

Table 15 Patient characteristics of cohorts based on whether they changed to a higher polypharmacy category. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No change in polypharmacy category	Shift to higher polypharmacy category	p
Total number of patients	42872	13125	
Sex (female)	24744 (57.7)	7392 (56.3)	0.005
Age (median [IQR]), years	55 [38, 69]	57 [42, 68]	<0.001
Length of stay (days)(median [IQR])	1 [0, 3]	2 [1, 5]	<0.001
Number of preoperative medications (median [IQR])	6 [2, 11]	4 [2, 7]	<0.001
Number of postoperative medications (median [IQR])	5 [2, 9]	1 [6, 12]	<0.001
Elixhauser Comorbidity Index [IQR])	0 [0, 4]	0 [0, 4]	0.936
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	25428 (59.3)	8288 (63.1)	
Med (5-15)	14994 (35.0)	4503 (34.3)	
High (> 15)	2450 (5.7)	334 (2.5)	
Surgery Location and Classification			<0.001
Emergency operation	15131 (35.3)	4029 (30.7)	<0.001
Abdominal	8369 (19.5)	2266 (17.3)	
Cardiac	976 (2.3)	845 (6.4)	
Endocrine surgery	751 (1.8)	291 (2.2)	
Gynaecology	7015 (16.4)	1882 (14.4)	
Neurosurgery	5331 (12.4)	1083 (8.3)	
Orthopaedic	12245 (28.6)	3449 (26.2)	
Thoracic	757 (1.8)	352 (2.7)	
Urology	3225 (7.5)	947 (7.2)	
Vascular	2285 (5.5)	1435 (10.9)	
Comorbidities			
Congestive heart failure	1674 (3.9)	329 (2.5)	<0.001
Ischemic heart disease	5891 (13.7)	1725 (13.1)	0.083
Hypertension	13124 (30.6)	3969 (30.2)	0.424
Diabetes Mellitus	3098 (7.2)	622 (4.7)	<0.001
Chronic obstructive pulmonary disease	7177 (16.7)	1799 (13.7)	<0.001
Liver disease	582 (1.4)	149 (1.1)	0.055
Chronic kidney disease	1190 (2.8)	215 (1.6)	<0.001
Malignant neoplasm	6009 (14.0)	3059 (23.3)	<0.001
Benign neoplasm	11728 (27.4)	3380 (25.8)	<0.001
Psychiatric	5564 (13.0)	1337 (10.2)	<0.001
Delirium	1750 (4.1)	393 (3.0)	<0.001
Adverse drug reaction	2774 (6.5)	643 (4.9)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 16 Patient characteristics of cohorts based on whether they used multidose dispensing services in the year preceding the surgery. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No multidose dispensing	Multidose dispensing	P-value
Total number of patients	48317(86.3)	7680(13.7)	
Sex (male)	27785 (57.5)	4351 (56.7)	<0.001
Age (median [IQR]), years	52 [37, 65]	76 [65, 83]	<0.001
Number of pre-admission medications (median [IQR])	5 [2, 8]	11 [7, 16]	
Number of post-discharge medications (median [IQR])	6 [3, 10]	12 [8, 17]	
Elixhauser Comorbidity Index [IQR])	0 [0, 4]	4 [0, 10]	<0.001
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	31535 (65.3)	2181 (28.4)	
Med (5-15)	15652 (32.4)	3845 (50.1)	
High (> 15)	1130 (2.3)	1654 (21.5)	
Comorbidities			<0.001
Ischemic heart disease	4980 (10.3)	2636 (34.3)	
Congestive heart failure	932 (1.9)	1071 (13.9)	
Hypertension	12641 (26.2)	4452 (58.0)	
Diabetes Mellitus	2378 (4.9)	1342 (17.5)	
Chronic obstructive pulmonary disease	6896 (14.3)	2080 (27.1)	
Liver disease	515 (1.1)	216 (2.8)	
Chronic kidney disease	689 (1.4)	716 (9.3)	
Malignant neoplasm	7314 (15.1)	1754 (22.8)	
Benign neoplasm	12191 (25.2)	2917 (38.0)	
Psychiatric	4601 (9.5)	2300 (29.9)	
Delerium	1108 (2.3)	1035 (13.5)	
Dementia	94 (0.2)	387 (5.0)	
Surgery Location and Classification			<0.001
Emergency operation	15722 (32.5)	3438 (44.8)	
Abdominal	1875 (19.9)	1014 (13.2)	
Cardiac	1409 (2.9)	412 (5.4)	
Endocrine	950 (2.0)	92 (1.2)	
Gynaecology	8557 (17.8)	340 (4.5)	
Neurosurgery	5690 (11.8)	724 (9.4)	
Orthopaedic	12397 (25.7)	3297 (43.0)	

Thoracic	954 (2.0)	155 (1.7)	
Urology	3476 (7.2)	696 (9.0)	
Vascular	3130 (6.5)	590 (7.7)	
Outcomes			
Diagnosis of adverse drug reaction pre-admission (%)	2486 (5.1)	931 (12.1)	
Diagnosis of adverse drug reaction post admission (%)	1985 (4.1)	688 (9.0)	
Length of stay (median [IQR])	1 [0, 3]	3 [1, 9]	

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

4.2 Paper II - Epidemiology of polypharmacy and medication use among internal medicine patients and association with clinical outcomes

4.2.1 Clinical characteristics of the patient cohort

In total, the cohort included 85,942 admissions of 38,338 individuals to internal medicine at Landspitali Hospital during the study period 2010-2020. Table 17 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on the number of different medications filled in the year preceding surgery (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). Of the whole cohort, 51.1 % were male, and the median age [IQR] was 73 [60, 82]. They used a median [IQR] of 12 [7,18] medications in the year preceding the admission and 12 [7, 17] in the year after the admission. Multidose dispensing service was used by 46992 (54.7%) of the cohort in the year preceding the admission. The majority of the cohort had a medium (5-15) hospital frailty risk score class: 45.1%, 37.5% had a low score (<5), and 17.4% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 54.1%, followed by chronic obstructive pulmonary disease 32.3%, and then ischemic heart disease, 30.8%. The most frequent admissions were by the following internal medicine specialities: cardiology 21.7%, general internal medicine 13.5%, and pulmonology 10.6%. A portion of the cohort (11.2%) had a linked admission after being admitted by an internal medicine speciality either to intensive care 5.6%, geriatrics 3.7%, palliative care 1.0% or rehabilitation 1.0%. The median number of admissions per patient [IQR] for the whole cohort was 1 [1-3] admission per individual, ranging from 1-40 admissions.

4.2.2 Prevalence and incidence of new post-discharge polypharmacy/hyperpolypharmacy

Figure 16 presents the prevalence of pre-admission non-polypharmacy (<5 medications), which was 15.1%, 95% CI 14.9-15.4, polypharmacy (5-9 medications), which was 22.9%, 95% CI 22.6-23.2 and hyper-polypharmacy (≥10 medications), which was 62.5%, 95% CI 62.2-62.9.

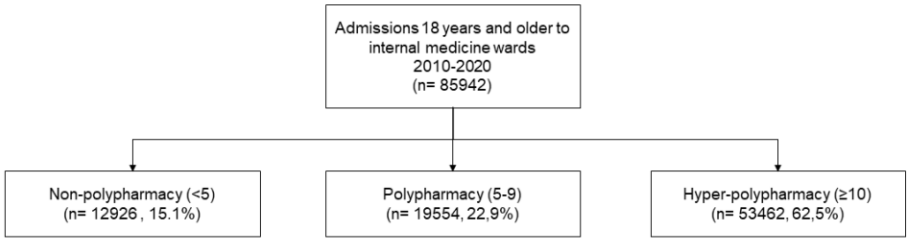

Figure 16 A consort diagram of participant inclusion based on the number of different medications filled in the year preceding admission by internal medicine speciality. Medicaiton use categories = (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy, and ≥ 10 medications = hyper-polypharmacy.

Table 17 presents the study cohort characteristics, categorised by their medication use category (non-polypharmacy, polypharmacy, and non-polypharmacy). Patients were more likely to be male in all categories: 50.9% for hyperpolypharmacy, 51.4% for polypharmacy, and 51.6% for non-polypharmacy. Patients within all medication use categories had similar median [IQR] age 73 [60, 82], 73 [60, 82], and 72 [60, 83] for hyperpolypharmacy, polypharmacy, and non-polypharmacy. Patients with hyperpolypharmacy were more likely to use multidose dispensing service prior to admission, 65.9% vs. 45.6% for polypharmacy and 22.0% for non-polypharmacy. Patients within all medication use categories had a similar Elixhauser Comorbidity Index [IQR]) and Hospital Frailty Risk Score Class. The prevalence of all comorbidities was similar within all three medication use categories, with hypertension most common (54.0-54.8), followed by chronic obstructive pulmonary disease (32.3-32.6) and then ischemic heart disease (30.5-31.1). The same pattern was seen in the prevalence of admission to internal medicine specialities among the three medication use categories. Cardiology (21.2-21.8) was the most common admitting speciality, followed by general medicine (13.5-13.7) and pulmonology (10.5-10.6). The prevalence of linked admissions was also similar between the medication use categories, with admission intensive care most common (5.5-5.8), followed by geriatrics (3.5-3.8), followed by palliative care (0.9-1.0) and rehabilitation wards (1.0-1.1).

Figure 17 presents the distribution of patients into categories of non-polypharmacy (<5 medications), polypharmacy (5-9 medications) and, hyperpolypharmacy (>10 medications), polypharmacy by year of surgery over the study period 2010-2020. The prevalence among the different medication categories (non-polypharmacy vs polypharmacy vs hyperpolypharmacy) over the study period were similar.

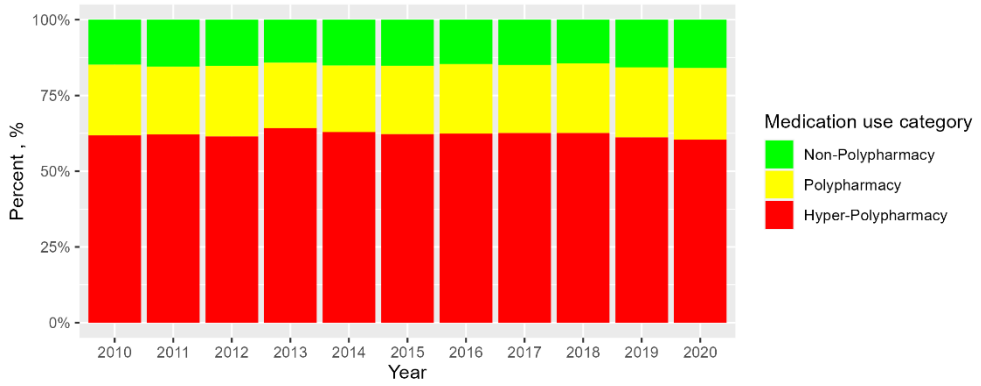

Figure 17 The distribution of patients into medication use categories over the study period 2010-2020(green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) based on the medication filled in the year preceding admission by internal medicine.

A total of 15,847 patients, 18.4% (95% CI 18.2% to 18.7%) who were admitted by internal medicine speciality had an increase in medication use, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Table 18 presents the characteristics, including the comorbidity of patients moving to a higher medication use category, either moving from non-polypharmacy to polypharmacy or polypharmacy to hyperpolypharmacy. Internal medicine patients moving to the higher medication use category had similar characteristics, including their comorbidity, except they were less likely to use multi-dose dispensing service prior to admission (40.6% vs. 57.9%). Additionally, they were less likely to have had a diagnosis of an adverse drug reaction both prior to admission (12.0% vs. 5.8%) or after discharge (6.2% vs. 15.0%) than those with no change.

A sensitivity analysis was done to estimate whether the timeframe allowed for filling of medications In order to fulfil the requirement of the medication use categories (polypharmacy, 5-9 medications vs hyperpolypharamcy, >10 medications. The reclassification of polypharmacy classification if a shorter window of time to fill prior to admission by internal medicine speciality was considered (Figure 18). This revealed that, for example, if only the last six months before admission were considered to classify polypharmacy and hyperpolypharmacy, roughly 75-85% of the patients would remain within their medication use category compared with a 12-month filling window.

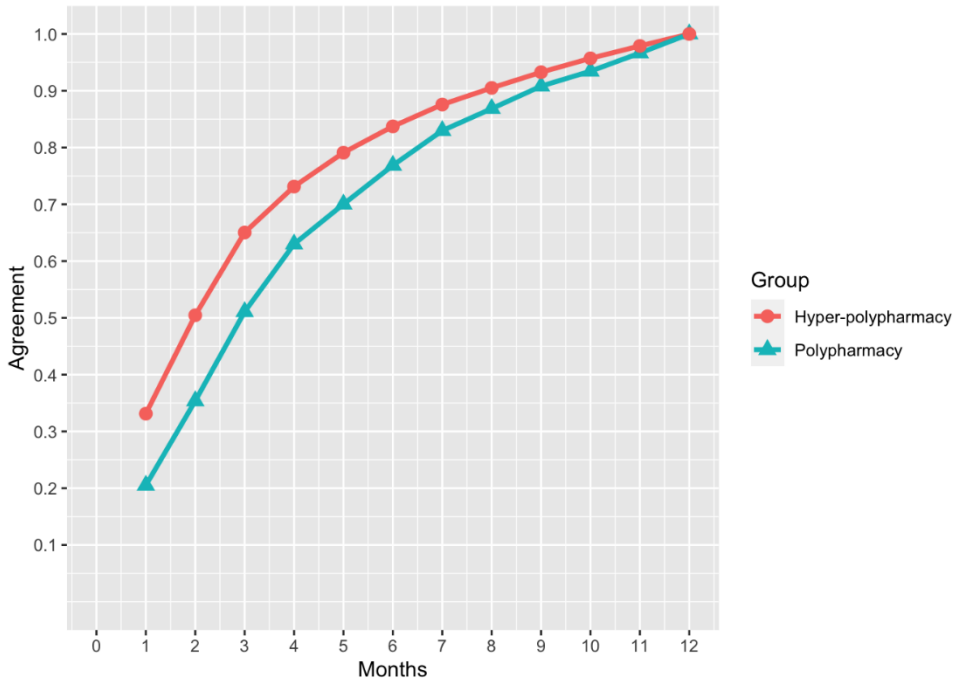

Figure 18 Proportion of classification agreement (Y-axis) for patients classified into polypharmacy or hyper-polypharmacy groups when the study definition of including medications filled in the 12 months preceding the admission by internal medicine speciality was compared against reclassification using a shorter duration of filling (1-11 months (X-axis)).

The prevalence was also estimated after eliminating antibiotics from the medication database to estimate the burden of the medication use categories (polypharmacy and hyperpolypharmacy) without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification if antibiotics were removed from the list of medications, 89.5% of patients with polypharmacy and 92.7% with hyperpolypharmacy would have remained within their medication use category.

4.2.3 Medication use and multidose dispensing services

In Table 19, the most frequent medications were filled in the year prior to admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyperpolypharmacy). For the entire cohort, the most frequently used medications were medications acting on the nervous system (80.6%), including opioids (51.0%), Z-drugs (43%), antidepressants (37.9%), and benzodiazepines (29.0%). The second highest category was cardiac medications (74.5%), followed by antibiotics

(60.7%). The order was the same for all three medication use categories, with medication acting on the nervous system, cardiac medications and antibiotics.

For the whole cohort the most commonly added medications for the entire cohort were anticoagulants (15.6%), antibiotics (14.9%), opioids (14.2%), proton pump inhibitors (13.2%), antiplatelets (12.0%), corticosteroids (10.3%), respiratory medications (9.6%) and medication acting on the central nervous system (8.9%), with Z-drugs (8.4%).

Multidose dispensing service was used in the year prior to admission in the whole study cohort by 46992 (54.7%) patients. Those patients were more likely to have higher median [IQR] ages 78 [73, 84] vs 72 [69, 77] and a higher number of medications filled prior to admission median [IQR] 13 [9, 18] vs 9 [6, 13]. They had similar Elixhauser comorbidity Index and higher frailty risk classification. Patients using multi-dose dispensing service had a similar prevalence of a diagnosis associated with cognitive function like (delirium (9.2% vs 8.8%), dementia (2.0% vs 2.1%), and psychiatric diagnosis (16.4% vs 16.7%). They also had a similar distribution between the different internal medicine specialities (Table 20).

4.2.4 Clinical outcomes and survival post-discharge

An analysis using an unadjusted restricted cubic spline analysis revealed no relationship between the absolute number of medications filled in the year before the surgery and the incidence of mortality (< 30 days). Readmission (< 30 days) and an extended hospital stay (≥ ten days) (Figure 19). Patients with hyperpolypharmacy prior to the surgery had higher 30-day mortality, 2.3%, compared to those with polypharmacy, 0.8%, and non-polypharmacy, 0.6% ($p < 0.001$).

Patients (≥65) with polypharmacy and hyperpolypharmacy were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge compared to non-polypharmacy, with a median [IQR] of 9.0% vs. 12.8% vs. 23.3%).

The long-term survival of patients with different medication use categories was visualised on a Kaplan-Meier plot. Figure 20 shows the long-term survival of patients with medication use categories (non-polypharmacy = >5 medications, polypharmacy =5-9 medications and hyperpolypharmacy ≥ 10 medications) based on filled medications in the year preceding hospital admission (Figure 20). No difference in mortality was observed over time with polypharmacy and hyperpolypharmacy compared to non-polypharmacy.

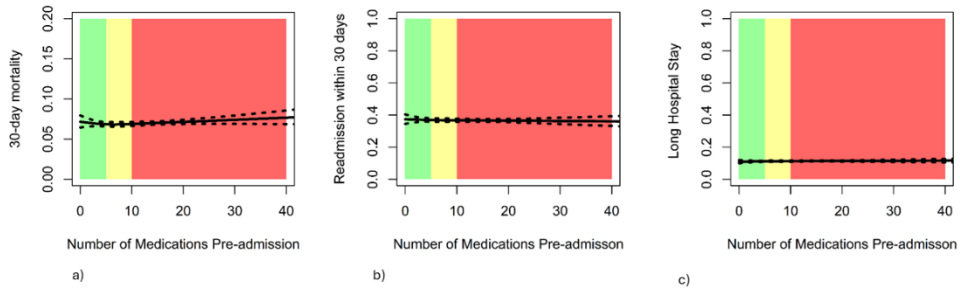

Figure 19 The association between the number of medications pre-admission and a) 30-day mortality, b) readmission within 30 day and c) Long stay >10 days. Dotted line represents a 95% confidence interval

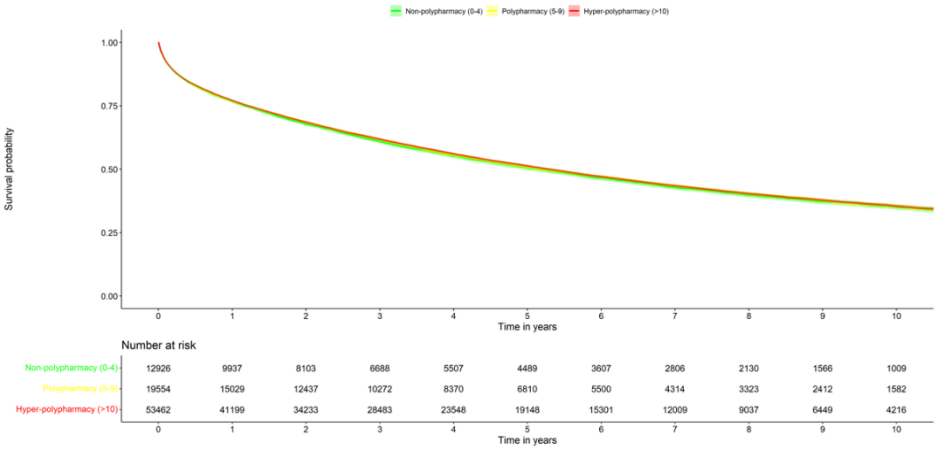

Figure 20 A Kaplan–Meier survival curve of long-term survival of patients compared based on the number of medications before admission by internal medicine (green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10.

Table 17 Patient characteristics of the patient cohorts are based on the number of medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy, and ≥ 10 medications = hyper- polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR). Linked admissions refers to whether the admission was linked to rehabilitation, geriatric, or palliative care services following discharge from the acute service.

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P-value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	
Sex (male)	6664 (51.6)	10052 (51.4)	27198 (50.9)	43914 (51.1)	0.250
Age (median [IQR]), years	72[60, 83]	73[60, 82]	73 [60, 82]	73 [60, 82]	0.877
[15,25)	227 (1.8)	351 (1.8)	960 (1.8)	1538	0.558
[25,35)	475 (3.7)	708 (3.7)	1875 (3.5)	3058	
[35,45)	598 (4.7)	936 (4.8)	2501 (4.7)	4035	
[45,55)	1024 (8.0)	1590 (8.2)	4360 (8.2)	6974	
[55,65)	1923 (15.0)	2968 (15.3)	7996 (15.1)	12887	
[65,75)	2838 (22.1)	4067 (21.0)	11534 (21.7)	18439	
[75,85)	3360 (26.2)	5207 (26.9)	13879 (26.2)	22446	
[85,95.)	2384 (18.6)	3563 (18.4)	9954 (18.8)	15901	
Multi-dose dispensing services	2838 (22.0)	8919 (45.6)	35235 (65.9)	46992 (54.7)	<0.001
Number of pre-admission medications (median [IQR])	2 [1, 3]	7 [6, 8]	16 [13, 21]	12 [7, 18]	<0.001
Number of post-discharge medications (median [IQR])	5 [2, 8]	9 [6, 12]	15 [10, 20]	12 [7, 17]	<0.001
Number of pre-admission medications without antibiotics (median [IQR])	2 [0, 3]	6 [5, 8]	14 [11, 19]	11 [6, 16]	<0.001
Elixhauser Comorbidity Index [IQR])	6 [0, 12]	6 [0, 13]	6[0, 12]	6[0, 12]	0.804
(<1]	3492 (27.0)	5245 (26.8)	14523 (27.2)	23260 (27.1)	0.791
(1-4]	1911 (14.8)	2963 (15.2)	8039 (15.0)	12913 (15.0)	
(4-5]	860 (6.7)	1355 (6.9)	3608 (6.7)	5823 (6.8)	
(5-8]	1618 (12.5)	2351 (12.0)	6421 (12.0)	10390 (12.1)	
(>8]	5045 (39.0)	7640 (39.1)	20871 (39.0)	33556 (39.0)	

Hospital Frailty Risk Score Class					0.976
Low (< 5)	4823 (37.3)	7334 (37.5)	20111 (37.6)	32268 (37.5)	
Med (5-15)	5844 (45.2)	8828 (45.1)	24070 (45.0)	38742 (45.1)	
High (> 15)	2259 (17.5)	3392 (17.3)	9281 (17.4)	14932 (17.4)	
Comorbidities					
Ischemic heart disease	4017 (31.1)	5967 (30.5)	16477 (30.8)	26461 (30.8)	0.545
Congestive heart failure	2644 (20.5)	3952 (20.2)	10734 (20.1)	17330 (20.2)	0.621
Hypertension	7081 (54.8)	10554 (54.0)	28855 (54.0)	46490 (54.1)	0.236
Diabetes Mellitus	2108 (16.3)	3143 (16.1)	8804 (16.5)	14055 (16.4)	0.438
Chronic obstructive pulmonary disease	4118 (31.9)	6379 (32.6)	17288 (32.3)	27785 (32.3)	0.353
Liver disease	405 (3.1)	658 (3.4)	1635 (3.1)	2698 (3.1)	0.109
Chronic kidney disease	1311 (10.1)	2054 (10.5)	5268 (9.9)	8633 (10.0)	0.032
Malignant neoplasm	3265 (25.3)	4821 (24.7)	13376 (25.0)	21462 (25.0)	0.431
Psychiatric	2094 (16.2)	3284 (16.8)	8812 (16.5)	14190 (16.5)	0.354
Dementia	253 (2.0)	402 (2.1)	1139 (2.1)	1794 (2.1)	0.438
Delerium	1183 (9.2)	1715 (8.8)	4800 (9.0)	7698 (9.0)	0.480
Internal Medicine Sepciality					0.129
General internal medicine	1741 (13.5)	2671 (13.7)	7205 (13.5)	11617 (13.5)	
Geriatrics	1072 (8.3)	1611 (8.2)	4602 (8.6)	7285 (8.5)	
Cardiology	2746 (21.2)	4269 (21.8)	11646 (21.8)	18661 (21.7)	
Endocrine	198 (1.5)	315 (1.6)	864 (1.6)	1377 (1.6)	
Gastroenterology	1112 (8.6)	1598 (8.2)	4293 (8.0)	7003 (8.1)	
Infectious diseases	733 (5.7)	1111 (5.7)	2901 (5.4)	4745 (5.5)	
Haematology	665 (5.1)	958 (4.9)	2783 (5.2)	4406 (5.1)	
Nephrology	302 (2.3)	479 (2.4)	1299 (2.4)	2080 (2.4)	
Neurology	1107 (8.6)	1699 (8.7)	4316 (8.1)	7122 (8.3)	
Oncology	853 (6.6)	1218 (6.2)	3391 (6.3)	5462 (6.4)	
Dermatology	79 (0.6)	106 (0.5)	257 (0.5)	442 (0.5)	
Pulmonology	1352 (10.5)	2054 (10.5)	5674 (10.6)	9080 (10.6)	
Rheumatology	588 (4.5)	923 (4.7)	2699 (5.0)	4210 (4.9)	
Rehabilitation	144 (1.1)	207 (1.1)	597 (1.1)	948 (1.1)	
Palliative care	234 (1.8)	335 (1.7)	935 (1.7)	1504 (1.8)	

Admissions linked with primary admission					
Geriatrics	467 (3.6)	687 (3.5)	2007 (3.8)	3161 (3.7)	0.283
Palliative care	127 (1.0)	173 (0.9)	534 (1.0)	834 (1.0)	0.375
Rehabilitation	125 (1.0)	215 (1.1)	530 (1.0)	870 (1.0)	0.371
Intensive care unit admission	715 (5.5)	1127 (5.8)	2937 (5.5)	4779 (5.6)	0.366
Outcomes					
Diagnosis of adverse drug reaction pre-admission (%)	506 (3.9)	1436 (7.3)	7393 (13.8)	9335 (10.9)	<0.001
Diagnosis of adverse drug reaction post discharge (%)	388 (3.0)	946 (4.8)	3793 (7.1)	5127 (6.0)	<0.001
Next admission (median [IQR])	118 [26, 438]	124 [26, 463]	128[27, 468]	125 [27, 462]	0.031
Mortality < 30 days (%)	853 (6.6)	1266 (6.5)	3519 (6.6)	5638 (6.6)	0.857
Readmission within 30 days (%)	1961 (15.2)	2946 (15.1)	7973 (14.9)	12880 (15.0)	0.717
Length of stay (median [IQR])	6 [3, 12]	6 [3, 12]	6[3, 12]	6 [3, 12]	0.630

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 18 Patient characteristics of cohorts based on whether they changed to a higher polypharmacy category. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No shift to higher polypharmacy category	Shift to higher polypharmacy category	P-value
Total number of patients	70095	15847	
Sex (male)	35816 (51.1)	8098 (51.1)	0.642
Age (median [IQR]), years	73.00 [60.00, 82.00]	73.00 [60.00, 83.00]	0.622
Number of pre-admission medications (median [IQR])	14.00 [10.00, 19.00]	5.00 [3.00, 8.00]	<0.001
Number of post-discharge medications (median [IQR])	12.00 [6.00, 18.00]	11.00 [8.00, 13.00]	<0.001
Multidose dispensing services	40559 (57.9)	6433 (40.6)	<0.001
Internal Medicine Sepciality			0.425
Cardiology	15175 (21.6)	3486 (22.0)	
Dermatology	350 (0.5)	92 (0.6)	
Endocrinology	1124 (1.6)	253 (1.6)	
Gastroenterology	5687 (8.1)	1316 (8.3)	
General internal medicine	9518 (13.6)	2099 (13.2)	
Geriatrics	5944 (8.5)	1341 (8.5)	
Haematology	3617 (5.2)	789 (5.0)	
Infectious_Disease	3846 (5.5)	899 (5.7)	
Nephrology	1726 (2.5)	354 (2.2)	
Neurology	5772 (8.2)	1350 (8.5)	
Oncology	4449 (6.3)	1013 (6.4)	
Palliative_Care	1229 (1.8)	275 (1.7)	
Pulmonology	7397 (10.6)	1683 (10.6)	
Rehabilitation	774 (1.1)	174 (1.1)	
Rheumatology	3487 (5.0)	723 (4.6)	
Linked admissions			
Geriatrics	2621 (3.7)	540 (3.4)	0.048
Palliative care	681 (1.0)	153 (1.0)	0.980
Rehabilitation	706 (1.0)	164 (1.0)	0.787
Intensive care unit admission	3899 (5.6)	880 (5.6)	0.978
Elixhauser Comorbidity Index [IQR])			0.599
(<1]	18967 (27.1)	4293 (27.1)	
(1-4]	10527 (15.0)	2386 (15.1)	
(4-5]	4770 (6.8)	1053 (6.6)	
(5-8]	8523 (12.2)	1867 (11.8)	
(>8]	27308 (39.0)	6248 (39.4)	

Hospital Frailty Risk Score Class			0.138
Low (< 5)	26264 (37.5)	6004 (37.9)	
Med (5-15)	31707 (45.2)	7035 (44.4)	
High (> 15)	12124 (17.3)	2808 (17.7)	
Comorbidities			
Congestive heart failure	14078 (20.1)	3252 (20.5)	0.220
Diabetes Mellitus	11469 (16.4)	2586 (16.3)	0.903
Hypertension			
Chronic obstructive pulmonary disease	22701 (32.4)	5084 (32.1)	0.465
Ischemic heart disease	21610 (30.8)	4851 (30.6)	0.598
Liver disease	2185 (3.1)	513 (3.2)	0.449
Chronic kidney disease	7006 (10.0)	1627 (10.3)	0.311
Malignant neoplasm	17520 (25.0)	3942 (24.9)	0.762
Benign neoplasm	27819 (39.7)	6301 (39.8)	0.871
Delirium	6239 (8.9)	1459 (9.2)	0.229
Dementia	1462 (2.1)	332 (2.1)	0.966
Psychiatric	11536 (16.5)	2654 (16.7)	0.381
Outcomes			
Fall pre-admission	201 (0.3)	18 (0.1)	<0.001
Fall post admission	71 (0.1)	21 (0.1)	0.342
Diagnosis of adverse drug reaction pre-admission (%)	8423 (12.0)	912 (5.8)	<0.001
Diagnosis of adverse drug reaction post-discharge (%)	4332 (6.2)	795 (5.0)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 19 Prescribed medications within different polypharmacy classes based on the number of different medications filled in the year preceding admission to internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%).

	Non-Polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P-value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	<0.001
Pre-admission medication					
Proton Pump Inhibitors	1163 (9.0)	5352 (27.4)	33063 (61.8)	39578 (46.1)	
Anti-diabetics	281 (2.2)	1632 (8.3)	10481 (19.6)	12394 (14.4)	
Anticoagulants	729 (5.6)	5303 (27.1)	27087 (50.7)	33119 (38.5)	
Antiplatelets	365 (2.8)	3023 (15.5)	16125 (30.2)	19513 (22.7)	
Cardio-vascular	3578 (27.7)	13660 (69.9)	46748 (87.4)	63986 (74.5)	
Beta-blockers	1434 (11.1)	7386 (37.8)	29415 (55.0)	38235 (44.5)	
Calcium Channel Blockers	550 (4.3)	3198 (16.4)	15536 (29.1)	19284 (22.4)	
ACE inhibitors and Angiotensin II Receptor Blockers	1582 (12.2)	7057 (36.1)	27140 (50.7)	35779 (41.6)	
Statins	997 (7.7)	5660 (28.9)	24057 (45.0)	30714 (35.7)	
Urinary	1241 (9.6)	4399 (22.5)	20449 (38.2)	26089 (30.4)	
Hormones	874 (6.8)	4464 (22.8)	29318 (54.8)	34656 (40.3)	
Corticosteroids	461 (3.6)	2896 (14.8)	23863 (44.6)	27220 (31.7)	
Medication acting on the nervous system	4330 (33.5)	14485 (74.1)	50477 (94.4)	69292 (80.6)	
Antibiotics	2906 (22.5)	9120 (46.6)	40158 (75.1)	52184 (60.7)	
Opioids	1911 (14.8)	6766 (34.6)	35120 (65.7)	43797 (51.0)	
Paracetamol/orphenadrine combinations	1524 (11.8)	4188 (21.4)	16400 (30.7)	22112 (25.7)	
Nonsteroidal anti-inflammatory drugs	1352 (10.5)	3389 (17.3)	11921 (22.3)	16662 (19.4)	
Selective cox-2 inhibitors	200 (1.5)	940 (4.8)	6236 (11.7)	7376 (8.6)	
Antipsychotic	362 (2.8)	1815 (9.3)	10011 (18.7)	12188 (14.2)	
Z-drugs	9281 (19.0)	11613 (23.7)	28060 (57.3)	48954 (57.0)	
Benzodiazepines	522 (4.0)	2914 (14.9)	21473 (40.2)	24909 (29.0)	
Antidepressants	935 (7.2)	4804 (24.6)	26832 (50.2)	32571 (37.9)	
Anti-dementia	147 (1.1)	902 (4.6)	2269 (4.2)	3318 (3.9)	
Respiratory	1229 (9.5)	5147 (26.3)	27612 (51.6)	33988 (39.5)	
Antihistamin	281 (2.2)	1180 (6.0)	7725 (14.4)	9186 (10.7)	

Table 20 Patient characteristics of cohorts based on whether they used multidose dispensing services in the year preceding admission by internal medicine. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No multidose dispensing	Multidose dispensing	p
Total number of patients	38,950	46,992	
Sex (male)	19,876 (51.0)	24,038 (51.2)	0.786
Age (median [IQR]), years	72[69, 77]	78 [73, 84]	<0.001
Number of pre-admission medications (median [IQR])	9 [6, 13]	13 [9, 18]	<0.001
Number of pre-admission medications (median [IQR])	9 [5, 13]	14 [9, 18]	<0.001
Elixhauser Comorbidity Index [IQR])			0.503
(<1]	10578 (27.2)	12682 (27.0)	
(1-4]	5932 (15.2)	6981 (14.9)	
(4-5]	2632 (6.8)	3191 (6.8)	
(5-8]	4685 (12.0)	5705 (12.1)	
(>8]	15123 (38.8)	18433 (39.2)	
Hospital Frailty Risk Score Class			0.384
Low (< 5)	14533 (37.3)	17735 (37.7)	
Med (5-15)	17650 (45.3)	21092 (44.9)	
High (> 15)	6767 (17.4)	8165 (17.4)	
Internal Medicine Sepciality			0.710
Cardiology	8405 (21.6)	10256 (21.8)	
Dermatology	200 (0.5)	242 (0.5)	
Endocrinology	613 (1.6)	764 (1.6)	
Gastroenterology	3215 (8.3)	3788 (8.1)	
General Medicine	5255 (13.5)	6362 (13.5)	
Geriatrics	3353 (8.6)	3932 (8.4)	
Haematology	2015 (5.2)	2391 (5.1)	
Infectious Disease	2203 (5.7)	2542 (5.4)	
Nephrology	920 (2.4)	1160 (2.5)	
Neurology	3230 (8.3)	3892 (8.3)	
Oncology	2484 (6.4)	2978 (6.3)	
Palliative Care	679 (1.7)	825 (1.8)	
Pulmonology	4099 (10.5)	4981 (10.6)	
Rehabilitation	407 (1.0)	541 (1.2)	
Rheumatology	1872 (4.8)	2338 (5.0)	
Admissions linked with primary admission			
Geriatrics	1447 (3.7)	1714 (3.6)	0.613
Palliative care	378 (1.0)	456 (1.0)	1.000

Rehabilitation	407 (1.0)	463 (1.0)	0.403
General internal medicine	820 (2.1)	994 (2.1)	0.938
Intensive care unit admission	2181 (5.6)	2598 (5.5)	0.662
Body mass index			0.405
Underweight	462 (4.0)	502 (3.7)	
Normal Weight	3625 (31.4)	4379 (32.1)	
Overweight	4014 (34.8)	4768 (34.9)	
Obese	3435 (29.8)	4014 (29.4)	
Comorbidities			
Hypertension	21093 (54.2)	25397 (54.0)	0.756
Diabetes Mellitus	6275 (16.1)	7780 (16.6)	0.080
Chronic obstructive pulmonary disease	12596 (32.3)	15189 (32.3)	0.965
Ischemic heart disease	11898 (30.5)	14563 (31.0)	0.163
Liver disease	1281 (3.3)	1417 (3.0)	0.023
Chronic kidney disease	3874 (9.9)	4759 (10.1)	0.385
Malignant neoplasm	9668 (24.8)	11794 (25.1)	0.356
Benign neoplasm	15442 (39.6)	18678 (39.7)	0.767
Delerium	3568 (9.2)	4130 (8.8)	0.059
Dementia	834 (2.1)	960 (2.0)	0.327
Psychiatric	6503 (16.7)	7687 (16.4)	0.188
Outcomes			
Fall pre-admission	49 (0.1)	170 (0.4)	<0.001
Fall post discharge	34 (0.1)	58 (0.1)	0.132
Diagnosis of adverse drug reaction pre-admission (%)	2713 (7.0)	6622 (14.1)	<0.001
Diagnosis of adverse drug reaction post discharge (%)	1847 (4.7)	3280 (7.0)	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

4.3 Paper III – Potentially inappropriate medication use before and after admission to internal medicine for older patients and association with polypharmacy

4.3.1 Clinical characteristics of the patient cohort

In total, the cohort included 55,859 individual admissions of ≥65 years to internal medicine at Landspitali Hospital during the study period 2010-2020. Table 21 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on whether the patients had potentially inappropriate medication use prior to admission based on the 2019 Beers criteria or not). Of the whole cohort, 48.5% were male, and the median age [IQR] was 80 [73, 86]. They used a median [IQR] of 12 [7,17] medications in the year preceding the admission and in the year after the admission. Multidose dispensing service was used by 54.6% of the cohort in the year preceding the admission. The majority of the cohort had a medium (5-15) hospital frailty risk score class, 49.0%, 28.0% had a low score (<5), and 23.1% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 65.8%, ischemic heart disease 40.8%, chronic obstructive pulmonary disease 36.8%, and malignant neoplasm 27.7%. The most frequent admissions were by the following internal medicine specialities: cardiology 22.6%, general internal medicine 13.5%, and then geriatrics 12.9%. A portion of the cohort (11.5%) had a linked admission after being admitted by an internal medicine speciality either to intensive care 4.2%, geriatrics 5.6%, palliative care 1.0% or rehabilitation 0.7%. For the whole cohort, the median number of admissions per patient [IQR] was 2 [1-3] per individual, ranging from 1-39.

4.3.2 Prevalence and incidence of potentially inappropriate medication use

Figure 21 presents the prevalence of potentially inappropriate prescribing in the whole cohort based on the Beers criteria 2019, which was 46,201, 82,7% 95% CI 82.4-83.0. Figure 21 also presents the prevalence of potentially inappropriate medication use by varying levels of medication use categories non-polypharmacy (<5 medications), which was 34.0%, 95% CI 33.1-35.0, polypharmacy (5-9 medications), which was 77.7%, 95% CI 76.9-78.4 and hyper-polypharmacy (≥10 medications), which was 96.4%, 95% CI 96.2-96.6.

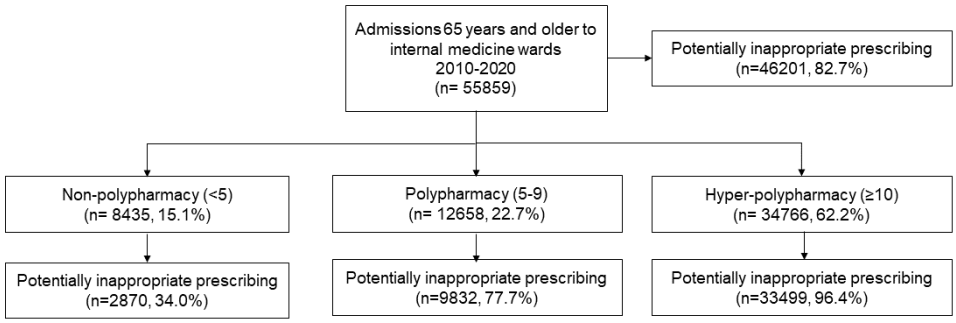

Figure 21 A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medications based on 2019 Beers criteria.

Table 21 presents the study cohort characteristics, categorised by whether they fulfilled criteria for potentially inappropriate prescribing based on the 2019 Beers criteria in the year preceding the admission. Patients with potentially inappropriate medication use were more likely to be female, 51.7% and use more medications in the year prior to admission median [IQR]) 13 [9-19] vs. 4 [1-7]. Patients, irrespective of whether they had potentially inappropriate medication use, had similar median [IQR] ages of 80 [73, 86] and 80 [73, 85]. Patients with potentially inappropriate medication use were more likely to use multidose dispensing service prior to admission, 59.1% vs. 33.0%. Patients, irrespective of whether they had potentially inappropriate medication use, had a similar Elixhauser Comorbidity Index [IQR]) and Hospital Frailty Risk Score Class. The prevalence of all comorbidities was similar irrespective of whether they had potentially inappropriate medication use, with hypertension most common (65.8-66.2), followed by Ischemic heart disease (40.8-41.1) and then chronic obstructive pulmonary disease (36.0-37.0). The same pattern was seen in the prevalence of admission to internal medicine specialities irrespective of whether they had potentially inappropriate medication use. Cardiology (22.5-23.2) was the most common admitting speciality, followed by General internal medicine (13.1-13.5) and geriatrics (12.1-13.1). The prevalence of linked admissions was also similar, with admission to geriatrics most common (5.6-5.8), followed by intensive care (4.2-4.3), followed by palliative care (1.0-1.1) and rehabilitation wards (0.7-0.8).

Figure 22 shows the development of potentially inappropriate prescribing use based on 2019 Beers criteria according to the medications filled in the year preceding the admission by internal medicine speciality over the study period 2010-2020. The prevalence was similar over the study period. Figure 23 shows the incidence of new potentially inappropriate medication use among the study cohort over the study period. The results indicate that there is a decrease in new potentially inappropriate medication use from the year 2018.

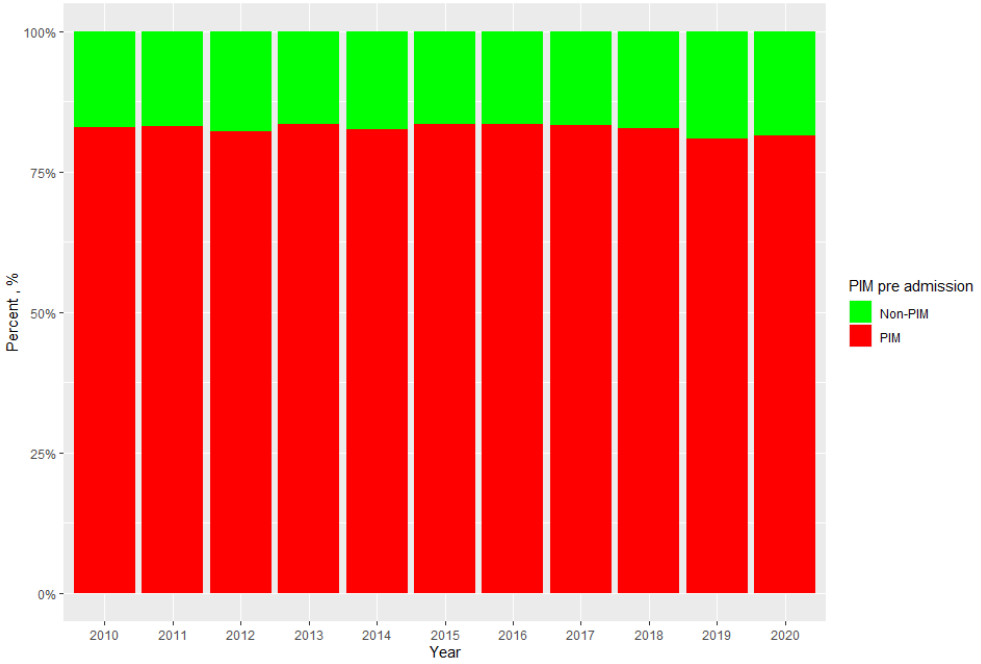

Figure 22 The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding admission by internal medicine (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).

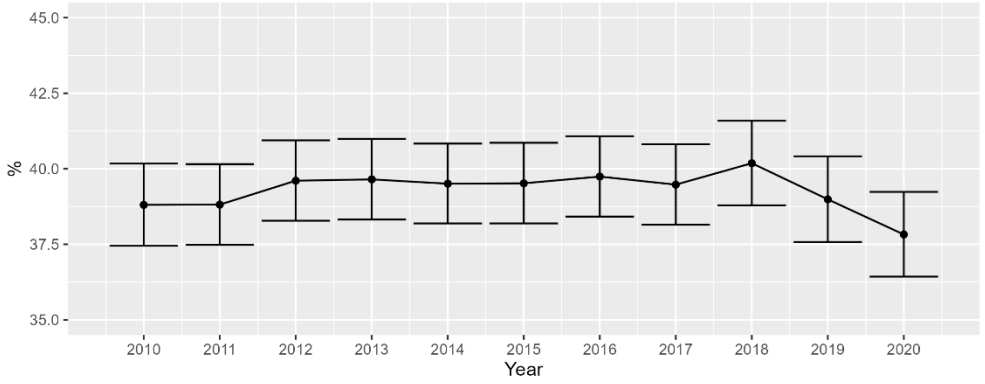

Figure 23 Incidence of new potentially inappropriate medication use among those patient who did not fulfil a Beers criteria preceding the admission by internal medicine speciality over the study period 2010-2020.

4.3.3 Potentially inappropriate medication use

In Table 22, the most frequent Beers criteria and Beers criteria subgroups were met in the year prior to admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper polypharmacy). For the entire cohort, the median [IQR] number of criteria fulfilled was 3 [1, 4]. The most frequently fulfilled Beers criteria medication were medications acting on the nervous system (59.2%), predominantly Z-drugs (43.1%), and benzodiazepines (31.2%), followed by medication acting on the gastrointestinal system (48.4%), most frequently proton pump inhibitors (45.8%) and pain medications (21.5%) most often, none-selective NSAIDs (19.5%). Patients with hyperpolypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 4 [2, 5], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (76.4%), followed by medication acting on the gastrointestinal system (64.9%) and medication acting on the endocrine system (25.8%). Patients with polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (42.7%), followed by medication acting on the gastrointestinal system (29.0%) and pain medications (18.8%). Patients with non-polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (13.1%), followed by pain medications (11.0%) and medication acting on the gastrointestinal system (9.1%).

A total of 4452 patients, 53.4% (95% CI 52.4% to 54.4%), who were admitted by the internal medicine specialities and did not fill a potentially inappropriate medication in the year preceding admission were prescribed a new potentially inappropriate medication use following discharge. Table 23 compares the patient characteristics, admitting speciality, comorbidity, and clinical outcomes between cohorts, between patients prescribed a new potentially inappropriate medication use following discharge and those who continued without filling a potentially inappropriate prescription. Patients prescribed a new, potentially inappropriate medication use following discharge compared to those who continued without filling a potentially inappropriate prescription had comparable characteristics, including their age, gender and comorbidity. The distribution between admitting internal medicine sub-specialities was similar except for patients admitted to a geriatric ward, where patients were less likely to be prescribed new potentially inappropriate medication (6.3% vs 5.1%).

Patients prescribed a new potentially inappropriate medication use following discharge were less likely to use multi-dose dispensing service prior to admission (36.9% vs 41.3%) and used a higher median [IQR] number of medication both prior to admission 4 [2,7] vs 3 [0,6] and post-discharge 9 [6,13] vs 4 [1,7]. Additionally, they were more likely to have higher median [IQR] risk scores for the likelihood of experiencing medication-related harm post-discharge, 10.70[7.17,14.54] vs. 10.20 [7.44,15.30].

Figure 24 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related risk factors, after adjustment for comorbidities

and admission information, of receiving a new potentially inappropriate medication use following discharge was associated with higher odds of using multi-dose dispensing service (OR 1.26,95% CI 1.15-1.39), dementia (OR 1.29, 95% CI 1.01-1.65), polypharmacy (OR 1.45,95% CI 1.32-1.60) and hyper-polypharmacy (OR 1.38,95% CI 1.22-1.59) but admission to internal medicine followed by transfer to geriatrics was associated with lower odds (OR 0.80, 95% CI 0.67-1.39) after adjustment for comorbidities and admission information.

The association of potentially inappropriate medication use and a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications) the year prior to admission were evaluated by using an unadjusted restricted cubic spline analysis. An unadjusted restricted cubic spline analysis revealed a strong non-linear relationship between the absolute number of different medications filled in the year preceding admission and the prevalence of potentially inappropriate medication usage based on the Beers criteria. Figure 25 shows the relationship between an absolute number of filled medications and the prevalence of potentially inappropriate medication by different organ systems based on the Beers criteria. The most frequent medication category to be prescribed as potentially inappropriate were medications acting on the central nervous and gastrointestinal systems. Further analyses were done for these subcategories and revealed a strong relationship between the increased burden of polypharmacy and the likelihood of having potentially inappropriate prescribing of benzodiazepines and Z-drugs among the medications acting on the central nervous system (Figure 26) and among medications acting on the gastrointestinal system for proton pump inhibitors (Figure 27). For the whole cohort, the most frequently added Beers criteria post-discharge were proton pump inhibitors (15.3%), Z-drugs (9.2%), benzodiazepines (8.9%), anti-psychotics (6.6%), anti-cholinergic (5.4%), cardiovascular (5.2.%) and antihistamine (5.0%) medications.

4.3.4 Clinical outcomes and survival post-discharge

The ratio of patients experiencing clinical outcomes of interest were compared based on whether the patients had potentially inappropriate medication use in the year prior to admission based on the 2019 Beers criteria. No statistical difference was observed for readmission (< 30 days) and an extended hospital stay (≥ ten days) in using (Table 23). In the whole cohort, 30-day mortality was 4.3%, prolonged admission was 10.2%, 30-day re-admission rate was 15.5%, and the median (IQR) length of stay was 7 [3, 15] (Table 23).

Patients with potentially inappropriate medication use were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge, with a median [IQR] of 19.58 vs. 10.48). Finally, they were also more likely

to have been diagnosed with an adverse drug reaction both prior to admission (12.3% vs. 4.5%) and post-discharge (6.7% vs. 3.2%) (Table 23).

The long-term survival of patients based on whether they had filled a potentially inappropriate medication in the year preceding hospital admission was visualised on a Kaplan-Meier plot. No difference in mortality was observed over time among patients who filled a potentially inappropriate medication compared to patients who did not fill a potentially inappropriate medication in the year preceding the admission to the hospital based on the 2019 Beers criteria (Figure 28).

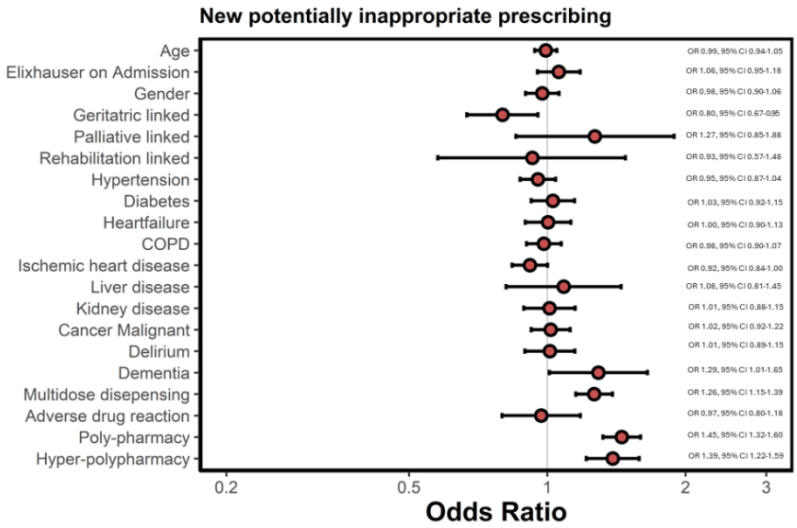

Figure 24 The results of a multivariable regression model of the odds of filling new potentially inappropriate medication use in the year following admission to internal medicine, for patients without a potentially inappropriate medication before admission.

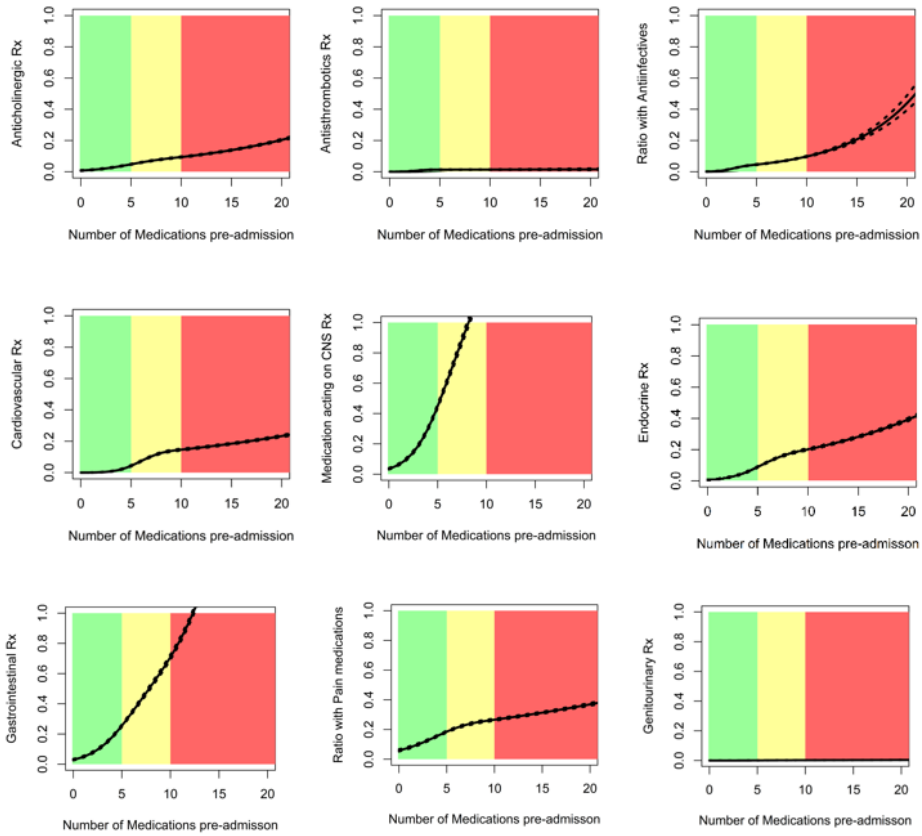

Figure 25 The association between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria. The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the polypharmacy category based on the different medications filled in the year preceding admission by internal medicine. (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy).

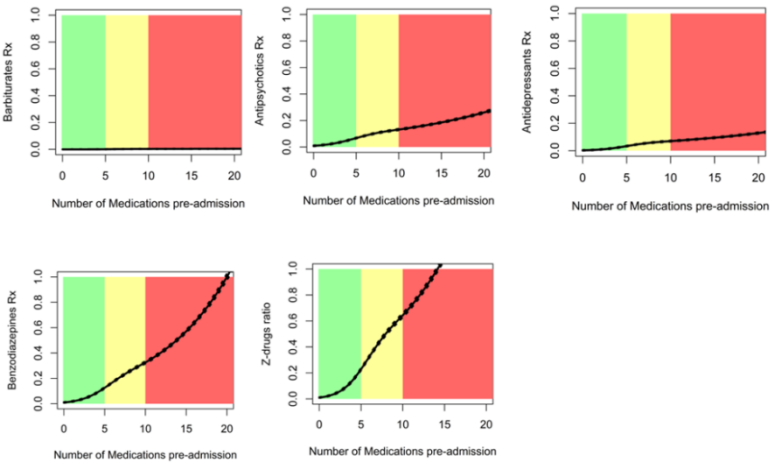

Figure 26 The association between the number of medications pre-admission and risk of potentially inappropriate medication use based on the 2019 Beers criteria for specific medications acting on the central nervous system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.

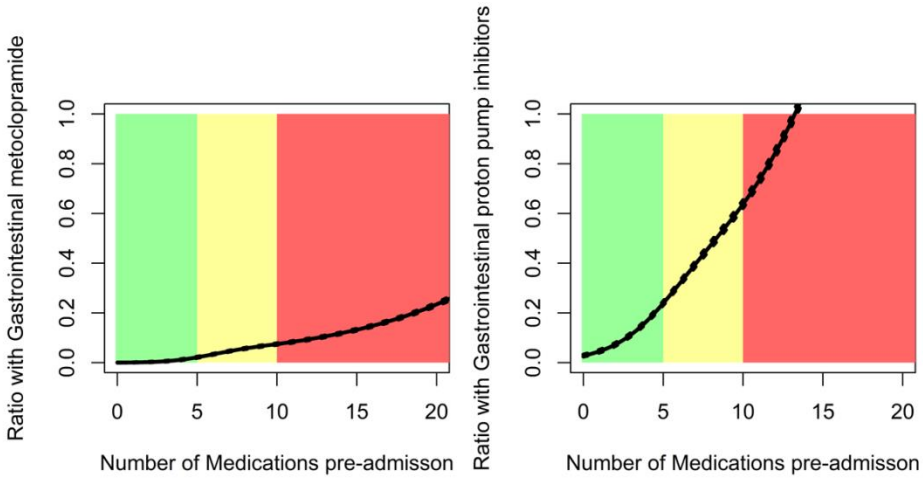

Figure 27 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine

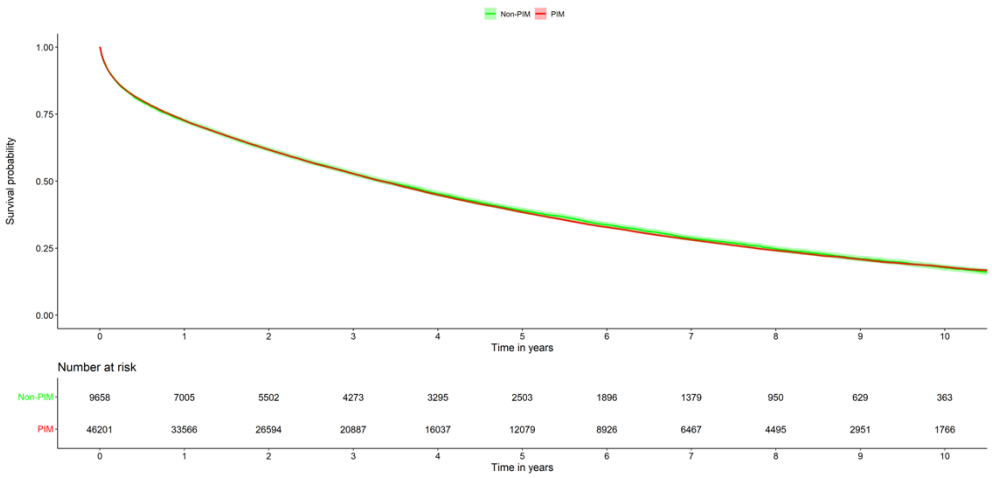

Figure 28 Kaplan–Meier survival curve of long-term survival of patients compared based on whether they had filled a with potentially inappropriate medication before admission (green = No potentially inappropriate medication use (No PIM), and red = potentially inappropriate medication use.

Table 21 Patient characteristics for patients who filled a prescription for a potentially inappropriate medication based on the 2019 Beers criteria pre-admission. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No potentially inappropriate medication use pre-admission	Potentially inappropriate medication use pre-admission	All patients	p
Total number of patients	9546 (17.1%)	46313 (82.9%)	55859	
Sex (male)	4748 (49.7)	22371 (48.3)	27119 (48.5)	0.044
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	0.055
Multi-dose dispensing services	3129 (32.8)	27376 (59.1)	30505 (54.6)	<0.001
Number of pre-admission medications (median [IQR])	4.00 [1.00, 7.00]	13.00 [9.00, 19.00]	12.00 [7.00, 17.00]	<0.001
Number of post-discharge medications (median [IQR])	6.00 [3.00, 10.00]	13.00 [8.00, 18.00]	12.00 [7.00, 17.00]	<0.001
Elixhauser Comorbidity Index [IQR])	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	0.305
(<1]	1882 (19.7)	9079 (19.6)	10961 (19.6)	0.495
(1-4]	1351 (14.2)	6298 (13.6)	7649 (13.7)	
(4-5]	700 (7.3)	3467 (7.5)	4167 (7.5)	
(5-8]	1229 (12.9)	5785 (12.5)	7014 (12.6)	
(>8]	4384 (45.9)	21684 (46.8)	26068 (46.7)	
Hospital Frailty Risk Score Class				0.749
Low (< 5)	2707 (28.4)	12910 (27.9)	15617 (28.0)	
Med (5-15)	4654 (48.8)	22690 (49.0)	27344 (49.0)	
High (> 15)	2185 (22.9)	10713 (23.1)	12898 (23.1)	
Individual comorbidities				
Ischemic heart disease	3927 (41.1)	18879 (40.8)	22806 (40.8)	0.506
Congestive heart failure	2687 (28.1)	12793 (27.6)	15480 (27.7)	0.075
Hypertension	6307 (66.1)	30467 (65.8)	36774 (65.8)	0.602
Diabetes Mellitus	1754 (18.4)	8766 (18.9)	10520 (18.8)	0.213
Chronic obstructive pulmonary disease	3439 (36.0)	17135 (37.0)	20574 (36.8)	0.075
Liver disease	198 (2.1)	1171 (2.5)	1369 (2.5)	0.010
Chronic kidney disease	1261 (13.2)	6240 (13.5)	7501 (13.4)	0.502
Malignant neoplasm	2675 (28.0)	12605 (27.2)	15280 (27.4)	0.111
Psychiatric	1606 (16.8)	7604 (16.4)	9210 (16.5)	0.339
Dementia	280 (2.9)	1431 (3.1)	1711 (3.1)	0.438
Delerium	1213 (12.7)	5742 (12.4)	6955 (12.5)	0.415
Internal Medicine Specialty				0.025
Cardiology	2216 (23.2)	10413 (22.5)	12629 (22.6)	
Dermatology	30 (0.3)	152 (0.3)	182 (0.3)	
Endocrinology	147 (1.5)	701 (1.5)	848 (1.5)	

Gastroenterology	634 (6.6)	3164 (6.8)	3798 (6.8)	
General internal medicine	1247 (13.1)	6275 (13.5)	7522 (13.5)	
Geriatrics	1157 (12.1)	6062 (13.1)	7219 (12.9)	
Hematology	411 (4.3)	1938 (4.2)	2349 (4.2)	
Infectious diseases	454 (4.8)	2155 (4.7)	2609 (4.7)	
Nephrology	235 (2.5)	1107 (2.4)	1342 (2.4)	
Neurology	707 (7.4)	3041 (6.6)	3748 (6.7)	
Oncology	496 (5.2)	2362 (5.1)	2858 (5.1)	
Palliative care	162 (1.7)	836 (1.8)	998 (1.8)	
Pulmonology	1111 (11.6)	5219 (11.3)	6330 (11.3)	
Rehabilitation	43 (0.5)	282 (0.6)	325 (0.6)	
Rheumatology	496 (5.2)	2606 (5.6)	3102 (5.6)	
Admissions linked with primary admission				
Geriatrics	551 (5.8)	2590 (5.6)	3141 (5.6)	0.454
Palliative care	103 (1.1)	467 (1.0)	570 (1.0)	0.660
Rehabilitation	73 (0.8)	301 (0.7)	374 (0.7)	0.282
Intensive care unit admission	410 (4.3)	1928 (4.2)	2338 (4.2)	0.566
Clinical Outcomes				
Fall diagnosis post-discharge	16 (0.2)	128 (0.3)	144 (0.3)	0.064
Fall diagnosis post-discharge	6 (0.1)	57 (0.1)	63 (0.1)	0.153
Length of hospital stay (days)	7 [3, 15]	7 [3, 15]	7 [3, 15]	0.244
Diagnosis of adverse drug reaction pre-admission (%)	431 (4.5)	5684 (12.3)	6115 (10.9)	<0.001
Diagnosis of adverse drug reaction post-discharge (%)	305 (3.2)	3100 (6.7)	3405 (6.1)	<0.001
Next admission (median [IQR]	131 [29, 463]	132 [29, 455]	132 [29, 456]	0.609
Mortality 30 days (%)	392 (4.1)	2033 (4.4)	4354 (7.8)	0.227
Readmission within 30 days (%)	1486 (15.6)	7146 (15.4)	8632 (15.5)	0.748
PRIME score (median [IQR])	10.42 [7.30, 14.98]	19.58 [12.86, 29.76]	17.55 [11.25, 27.50]	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 22 The table shows the subcategories of Beers Criteria filled, based on 2019 Beers criteria based on the patient's pre-admission polypharmacy burden estimated by the number of different medications filled in the year preceding admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR).

	Non-Polypharmacy pre-admission	Polypharmacy pre-admission	Hyper-Polypharmacy pre-admission	All patients pre-admission	P-value
Total number of patients	8435 (15.1)	12658 (22.7)	34766 (62.2)	55859	
Age (median [IQR]), years	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	0.089
[65,75)	2594 (31.1)	3724 (29.8)	10530 (30.6)	16848 (30.5)	
[75,85)	3360 (40.3)	5207 (41.7)	13879 (40.4)	22446 (40.7)	
[85,95.)	2384 (28.6)	3563 (28.5)	9954 (29.0)	15901 (28.8)	
PRIME score (median [IQR])	9.02 [6.57, 12.44]	12.78 [9.20, 17.77]	23.29 [16.01, 33.77]	17.55 [11.25, 27.50]	<0.001
Diagnosis of adverse drug reaction pre-admission (%)	327 (3.9)	951 (7.5)	4837 (13.9)	6115 (10.9)	<0.001
Diagnosis of adverse drug reaction post admission (%)	263 (3.1)	636 (5.0)	2506 (7.2)	3405 (6.1)	<0.001
Beers criteria total score pre-admission (median [IQR])	0 [0, 1]	1 [1, 2]	4.[2, 5]	3 [1, 4]	<0.001
Beers criteria anticholinergics (%)	199 (2.4)	794 (6.3)	5302 (15.3)	6295 (11.3)	<0.001
Beers criteria Anticholinergics (antihistamines) (%)	179 (2.1)	730 (5.8)	4981 (14.3)	5890 (10.5)	<0.001
Beers criteria Anticholinergics (antiparkinsonian) (%)	15 (0.2)	45 (0.4)	198 (0.6)	258 (0.5)	0.017
Beers criteria Anticholinergics (antispasmodics) (%)	5 (0.1)	24 (0.2)	232 (0.7)	261 (0.5)	<0.001
Beers criteria antithrombotic (%)	14 (0.2)	123 (1.0)	485 (1.4)	622 (1.1)	<0.001
Beers criteria anti-infective (%)	46 (0.5)	342 (2.7)	2880 (8.3)	3268 (5.9)	<0.001
Beers criteria cardiovascular (%)	75 (0.9)	859 (6.8)	6336 (18.2)	7270 (13.0)	<0.001
Beers criteria (cardiovascular peripheral alpha) (%)	9 (0.1)	103 (0.8)	802 (2.3)	914 (1.6)	<0.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	1 (0.0)	9 (0.0)	10 (0.0)	0.178
Beers criteria (cardiovascular disopyramide) (%)	6 (0.1)	32 (0.3)	110 (0.3)	148 (0.3)	<0.001
Beers criteria (cardiovascular dronedarone) (%)	2 (0.0)	38 (0.3)	148 (0.4)	188 (0.3)	<0.001
Beers criteria (cardiovascular digoxin) (%)	29 (0.3)	369 (2.9)	3152 (9.1)	3550 (6.4)	<0.001
Beers criteria (cardiovascular nifedipine) (%)	10 (0.1)	95 (0.8)	486 (1.4)	591 (1.1)	<0.001

Beers criteria (cardiovascular amiodarone) (%)	21 (0.2)	261 (2.1)	2411 (6.9)	2693 (4.8)	<0.001
Beers criteria central nervous system (%)	1102 (13.1)	5406 (42.7)	26550 (76.4)	33058 (59.2)	<0.001
Beers criteria (central nervous system antidepressant) (%)	105 (1.2)	575 (4.5)	3668 (10.6)	4348 (7.8)	<0.001
Beers criteria (central nervous system antipsychotics) (%)	243 (2.9)	1131 (8.9)	6503 (18.7)	7877 (14.1)	<0.001
Beers criteria (central nervous system barbiturates) (%)	1 (0.0)	36 (0.3)	136 (0.4)	173 (0.3)	<0.001
Beers criteria (central nervous system benzodiazepines) (%)	369 (4.4)	2088 (16.5)	14965 (43.0)	17422 (31.2)	<0.001
Beers criteria (central nervous system z-drugs) (%)	539 (6.4)	3338 (26.4)	20183 (58.1)	24060 (43.1)	<0.001
Beers criteria endocrine (%)	250 (3.0)	1450 (11.5)	8974 (25.8)	10674 (19.1)	<0.001
Beers criteria (endocrine androgens) (%)	24 (0.3)	114 (0.9)	713 (2.1)	851 (1.5)	<0.001
Beers criteria (endocrine desiccated thyroid) (%)	1 (0.0)	0 (0.0)	11 (0.0)	12 (0.0)	0.093
Beers criteria (endocrine estrogens) (%)	112 (1.3)	591 (4.7)	4082 (11.7)	4785 (8.6)	<0.001
Beers (endocrine growth hormone) (%)	1 (0.0)	9 (0.1)	21 (0.1)	31 (0.1)	0.165
Beers criteria (endocrine megestrol) (%)	1 (0.0)	2 (0.0)	12 (0.0)	15 (0.0)	0.360
Beers criteria (endocrine sulfonylurea) (%)	113 (1.3)	769 (6.1)	4665 (13.4)	5547 (9.9)	<0.001
Beers criteria gastrointestinal (%)	770 (9.1)	3669 (29.0)	22579 (64.9)	27018 (48.4)	<0.001
Beers criteria (gastrointestinal metoclopramide) (%)	46 (0.5)	455 (3.6)	5936 (17.1)	6437 (11.5)	<0.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	735 (8.7)	3418 (27.0)	21448 (61.7)	25601 (45.8)	<0.001
Beers criteria Pain medications (%)	929 (11.0)	2384 (18.8)	8694 (25.0)	12007 (21.5)	<0.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	3 (0.0)	3 (0.0)	0.402
Beers criteria pain medications nonselective NSAID (%)	875 (10.4)	2230 (17.6)	7713 (22.2)	10818 (19.4)	<0.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	81 (1.0)	266 (2.1)	1577 (4.5)	1924 (3.4)	<0.001
Beers criteria (genitourinary) (%)	2 (0.0)	21 (0.2)	129 (0.4)	152 (0.3)	<0.001

Table 23 Comparison of patients with no potentially inappropriate medication use pre-admission or post-discharge to patients with no potentially inappropriate medication use pre-admission but new potentially inappropriate medication use post-discharge. Unless specified otherwise, values are presented as count (%) or median (IQR)

	No potentially inappropriate medication use pre-admission nor new potentially inappropriate medication use post-discharge	New potentially inappropriate medication use post-discharge and but not pre-admission	p
Total number of patients	5094	4452	
Sex (male)	2516 (49.4)	2232 (50.1)	0.481
Age median [IQR]), years	80 [73, 85]	80 [73, 85]	0.526
Multi-dose dispensing services	2690 (41.3)	1643 (36.9)	<0.001
Number of pre-admission medications (median [IQR])	3[0, 6]	4 [2, 7]	<0.001
Number of post-discharge medications (median [IQR])	4 [1, 7]	9 [6, 13]	<0.001
Number of pre-admission medications without antibiotics (median [IQR])	2[0, 6]	4 [1, 6]	<0.001
Elixhauser Comorbidity Index [IQR])			
(<1]	987 (19.4)	895 (20.1)	0.328
(1-4]	722 (14.2)	629 (14.1)	
(4-5]	388 (7.6)	312 (7.0)	
(5-8]	682 (13.4)	547 (12.3)	
(>8]	2315 (45.4)	2069 (46.5)	
Hospital Frailty Risk Score Class			0.659
Low (< 5)	1427 (28.0)	1280 (28.8)	
Med (5-15)	2504 (49.2)	2150 (48.3)	
High (> 15)	1163 (22.8)	1022 (23.0)	
Comorbidities			
Ischemic heart disease	2140 (42.0)	1787 (40.1)	0.067
Congestive heart failure	1432 (28.1)	1255 (28.2)	0.951
Hypertension	3392 (66.6)	2915 (65.5)	0.261
Diabetes Mellitus	1841 (36.1	822 (18.5)	0.854
Chronic obstructive pulmonary disease	18976 (36.9)	1598 (35.9)	0.819
Liver disease	101 (2.0)	97 (2.2)	0.549
Chronic kidney disease	669 (13.1)	592 (13.3)	0.837
Malignant neoplasm	1407 (27.6)	1268 (28.5)	0.362
Psychiatric	836 (16.4)	770 (17.3)	0.261
Dementia	133 (2.6)	147 (3.3)	0.053

Delerium	643 (12.6)	570 (12.8)	0.815
Internal Medicine Specialty			0.747
Cardiology	1189 (23.3)	1027 (23.1)	
Dermatology	15 (0.3)	15 (0.3)	
Endocrinology	76 (1.5)	71 (1.6)	
Gastroenterology	327 (6.4)	307 (6.9)	
General internal medicine	666 (13.1)	581 (13.1)	
Geriatrics	633 (12.4)	524 (11.8)	
Haematology	226 (4.4)	185 (4.2)	
Infectious diseases	248 (4.9)	206 (4.6)	
Nephrology	120 (2.4)	115 (2.6)	
Neurology	365 (7.2)	342 (7.7)	
Oncology	254 (5.0)	242 (5.4)	
Palliative care	80 (1.6)	82 (1.8)	
Pulmonology	592 (11.6)	519 (11.7)	
Rehabilitation	29 (0.6)	14 (0.3)	
Rheumatology	274 (5.4)	222 (5.0)	
Admissions linked with primary admission			
Geriatrics	323 (6.3)	228 (5.1)	0.012
Palliative care	49 (1.0)	54 (1.2)	0.278
Rehabilitation	40 (0.8)	33 (0.7)	0.898
Intensive care unit admission	113 (2.2)	192 (4.3)	0.977
Outcomes			
Length of hospital stay (days)	7 [3, 15]	7 [3, 14]	0.024
Diagnosis of adverse drug reaction pre-admission (%)	223 (4.4)	208 (4.7)	0.521
Diagnosis of adverse drug reaction post-discharge (%)	114 (2.2)	191 (4.3)	<0.001
Next admission (median [IQR]	133 [29, 461]	125 [28, 461]	0.994
Mortality 30 days (%)	388 (7.6)	360 (8.1)	0.416
Readmission within 30 days (%)	796 (15.6)	690 (15.5)	0.947

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

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4.3.5 Clinical characteristics of the patient cohort

In total, the cohort included 30 082 individual admissions of ≥65 years to surgical care at Landspitali Hospital during the study period 2005-2018. Of those, 12 884 were reoperations or subsequent operations during the study period. Reoperations were excluded; therefore, the final study population included 17 198 patients undergoing their first surgery during the study period (Figure 29). Table 24 presents the study cohort characteristics, including their comorbidity and medication use for the whole cohort and based on whether the patients had potentially inappropriate medication use prior to a surgical admission based on the 2019 Beers criteria or not). Of the whole cohort, 9252 (53.8%) were female, and the median age [IQR] was 75 [70, 81]. They used a median [IQR] of 9 [5,13] medications in the year preceding the admission and 9 [6,14] in the year after the admission. Multidose dispensing service was used by 32.8% of the cohort in the year preceding the admission. The majority of the cohort had a low (<5) hospital frailty risk score class, 71.4%, 24.6% had a medium score (5-15), and 4.0% had a high score (>15). The most common comorbidity of the whole cohort was hypertension 57.0%, ischemic heart disease 32.1%, malignant neoplasm 27.7% and chronic obstructive pulmonary disease 23.5%. The majority of the surgeries were elective surgeries, 67.3%. Of the cohort, 32.7% had an emergency operation. The most frequent types of surgeries were orthopaedic 37.5%, abdominal 14.4%, and urology 11.4%.

4.3.6 Prevalence and incidence of potentially inappropriate medication use

Figure 29 presents the prevalence of potentially inappropriate prescribing in the whole cohort based on the Beers criteria 2019, which was 13.386, 77.8% 95% CI 77.2-78.5 and also presents the prevalence of potentially inappropriate medication use by varying levels of medication use categories non-polypharmacy (<5 medications), which was 36.6%, 95% CI 35.1-38.2, polypharmacy (5-9 medications), which was 80.2%, 95% CI 79.2-81.2) and hyper-polypharmacy (≥10 medications), which was 95.8%, 95% CI 95.3-96.2.

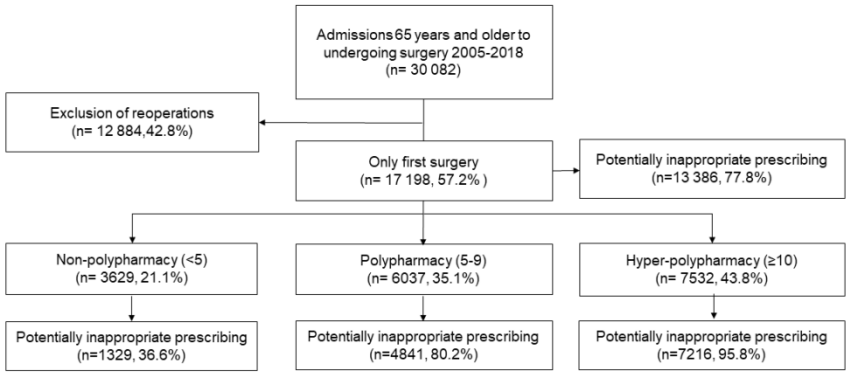

Figure 29 A consort diagram of participant inclusion level of polypharmacy based on the number of different medications filled in the year preceding surgical admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medication based on 2019 Beers criteria.

Table 24 presents the study cohort characteristics, categorised by whether they fulfilled criteria for potentially inappropriate prescribing based on the 2019 Beers criteria in the year preceding the surgical admission. Patients with potentially inappropriate medication use were more likely to be female, 57.0% and use more medications both in the year prior to admission median [IQR]) 10 [4,14] vs. 3 [1,6] and the year following discharge 11 [7,15] vs. 5 [2,9]. Patients, irrespective of whether they had potentially inappropriate medication use, had similar median [IQR] ages of 75 [70, 81] and 75 [70, 82]. Patients with potentially inappropriate medication use were more likely to use multidose dispensing service prior to admission, 36.0% vs. 21.3%. Patients with potentially inappropriate medication use had increased comorbidity based on the Elixhauser Comorbidity Index median [IQR]) 2 [2,5] vs 0 [0,5] and also slightly higher Hospital Frailty Risk Score Class. The prevalence of all comorbidities was higher for those with potentially inappropriate medication use, except for dementia (2.5% vs. 3.4%). The most common comorbidities for those with and without potentially inappropriate medication use was hypertension (60.1% vs 45.9%), followed by Ischemic heart disease (33.7% vs 26.5%) and then malignant neoplasm (27.7% vs 24.5%). Patients with potentially inappropriate medication use were more likely to undergo elective surgery (70.0% vs 57.9%). The majority of the surgeries, 67.3%, were elective surgeries. Of the cohort, 32.7% had an emergency operation. The most frequent types of surgeries for those with and without potentially inappropriate medication use he most were orthopaedic 36.8% vs 40.1%, abdominal 14.9% vs 12.8%, and urology 10.6% vs 14.0%.

Figure 30 shows the development of potentially inappropriate prescribing use based on 2019 Beers criteria according to the medications filled in the year preceding a

surgical admission speciality over the study period 2006-2018. The prevalence was similar over the study period. This shows the prevalence of new potentially inappropriate medication use among the study cohort over the study period. The results indicate a decrease in new potentially inappropriate medication use since 2011, with an exception in 2017.

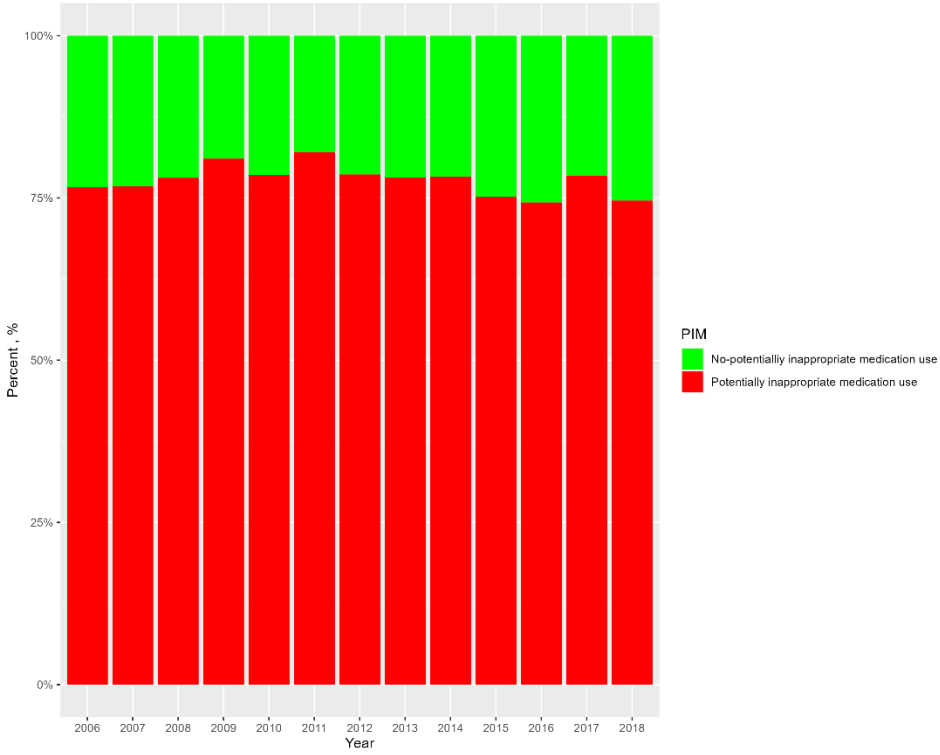

Figure 30 The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding surgical admission (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).

4.3.7 Potentially inappropriate medication use

In (Table 25) the most frequent Beers criteria and Beers criteria subgroups were met in the year prior to a surgical admission for the whole study cohort and additionally arranged by the medication use categories (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper polypharmacy). The median [IQR] number of criteria fulfilled for the entire cohort was 3 [1, 4]. The most frequently fulfilled Beers criteria medication were medications acting on the nervous system (50.0%), predominantly Z-drugs (36.2%), and benzodiazepines (22.7%), followed by medication acting on the gastrointestinal system (35.2%), most frequently proton pump inhibitors (34.0%) and pain medications (28.9%) most often, none-

selective NSAIDs (27.7%). Patients with hyperpolypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 4 [2, 5], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (72.3%), followed by medication acting on the gastrointestinal system (54.4%) and pain medication (37.6%). Patients with polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 1 [1, 2], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (42.9%), followed by pain medications (27.7%) and medication acting on the gastrointestinal system (27.3%). Patients with non-polypharmacy in the year prior to the admission fulfilled a median [IQR] number of criteria 0 [0,1], with the most commonly fulfilled Beers criteria were medications acting on the nervous system (15.3%), followed by pain medications (12.9%) and medication acting on the gastrointestinal system (8.5%).

A total of 1481 patients, 38.5% (95% CI 37.0-40.1), who were admitted for surgical admissions and did not fill a potentially inappropriate medication in the year preceding admission were prescribed a new potentially inappropriate medication use following discharge. Table 26 compares the patient characteristics, admitting speciality, comorbidity, and clinical outcomes between cohorts, between patients prescribed a new potentially inappropriate medication use following discharge and those who continued without filling a potentially inappropriate prescription. Patients prescribed a new, potentially inappropriate medication use following discharge compared to those who continued without filling a potentially inappropriate prescription were more likely to be female (60.0% vs 56.5%) and have increased comorbidity. Patients prescribed a new potentially inappropriate medication use following discharge were more likely to use multi-dose dispensing service prior to admission (28.4% vs 17.1%) and used a higher median [IQR] number of medications both prior to admission 5 [2,7] vs 3 [0,6] and post-discharge 9 [6,12] vs 3 [0,6]. Patients prescribed a new, potentially inappropriate medication were more likely to have malignant neoplasm (29.2% vs 19.4%), Ischemic heart disease (29.6% vs 20.3%) and hypertension (18.5% vs 15.4%) and less likely to have a diagnosis of mental illness (6.2% vs 11.4%) and dementia (1.8% vs 4.4%) and delirium (2.6% vs 3.9%). Patients prescribed a new, potentially inappropriate medication post-discharge were more likely to undergo cardiac surgery (14.9% vs 4.4%), vascular surgery (11.1% vs 8.2%) and gynaecology surgery (4.3% vs 1.7%) and less likely to undergo orthopedic surgery (28.6% vs 47.0%). They were also less likely to undergo emergency surgery (31.9% vs 48.3%).

Additionally, they were more likely to have higher median [IQR] risk scores for the likelihood of experiencing medication-related harm post-discharge, 12.57 [9.29,17.24] vs 11.33 [8.46,16.37] and have increased 30-days mortality (5.2% vs 0.3%).

Figure 31 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related risk factors. After adjustment for comorbidities

and admission information, receiving a new potentially inappropriate medication use following discharge was associated with higher odds of using multi-dose dispensing service (OR 2.52, 95% CI2.11-3.02), hyper-polypharmacy (OR 2.40,95% C 1.3.10), polypharmacy (OR 1.76,95% CI 1.51-2.05) and malignant neoplasm (OR 1.83, 95% CI 1.55-2.16), and having a diagnosis of dementia was associated with lower odds (OR 0.47, 95% CI 0.29-0.73) after adjustment for comorbidities and admission information.

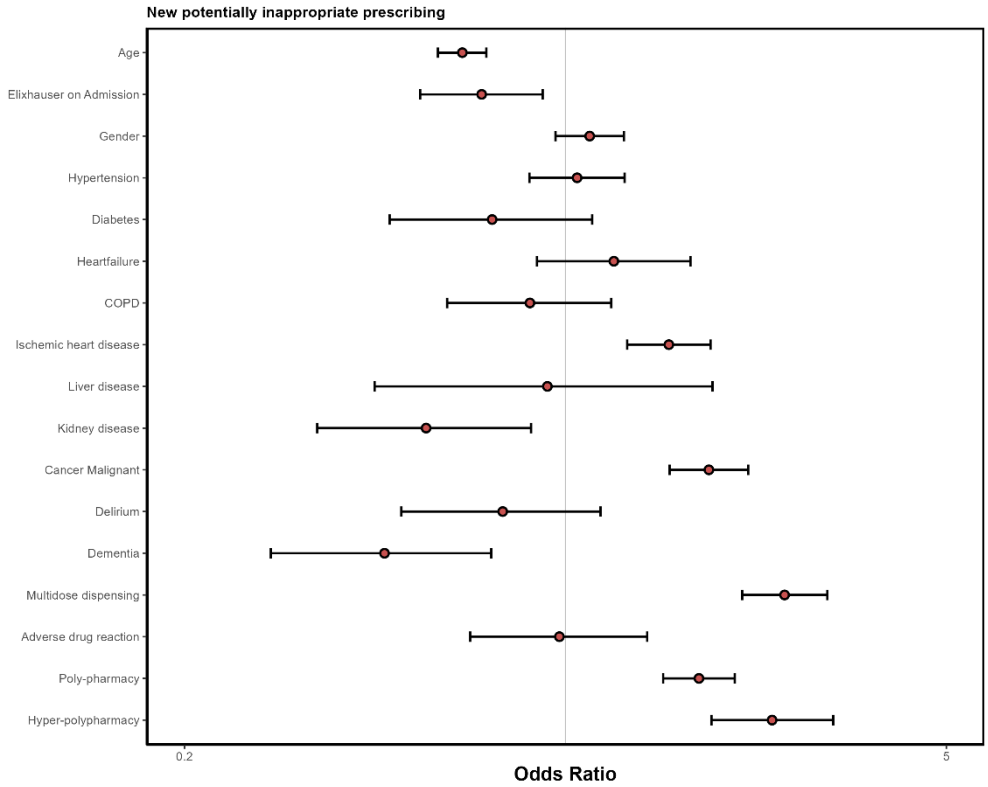

Figure 31 The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), Elixhauser comorbidity index class (compared with <1), individual comorbidities, multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of an adverse drug reaction diagnosis prior to a surgical admission, as covariates.

The association of potentially inappropriate medication use and a number of different medications filled (non-polypharmacy <5 medications, polypharmacy 5-9 medications and hyperpolypharmacy >10 medications) the year prior to admission were evaluated by using an unadjusted restricted cubic spline analysis. An unadjusted restricted cubic spline analysis revealed a strong non-linear relationship between the absolute number of different medications filled in the year preceding a surgical admission and the prevalence of potentially inappropriate medication usage based on the Beers criteria.

Error! Reference source not found. shows the relationship between an absolute umber of filled medications and the prevalence of potentially inappropriate medication by different organ systems based on the Beers criteria. The most frequent medication category to be prescribed as potentially inappropriate were medications acting on the central nervous and gastrointestinal systems. (**Error! Reference source not found.**) Further analyses were done for these subcategories and revealed a strong relationship between the increased burden of polypharmacy and the likelihood of having potentially inappropriate prescribing of benzodiazepines and Z-drugs among the medications acting on the central nervous system (Figure 33) and among medications acting on the gastrointestinal system for proton pump inhibitors (Figure 34). For the whole cohort, the most frequently added Beers criteria post-discharge were proton pump inhibitors (11.3%), Z-drugs (9.7%), benzodiazepines (6.4%), anti-psychotics (3.3%), anti-cholinergic (3.8 %) and cardiovascular (3.5%).

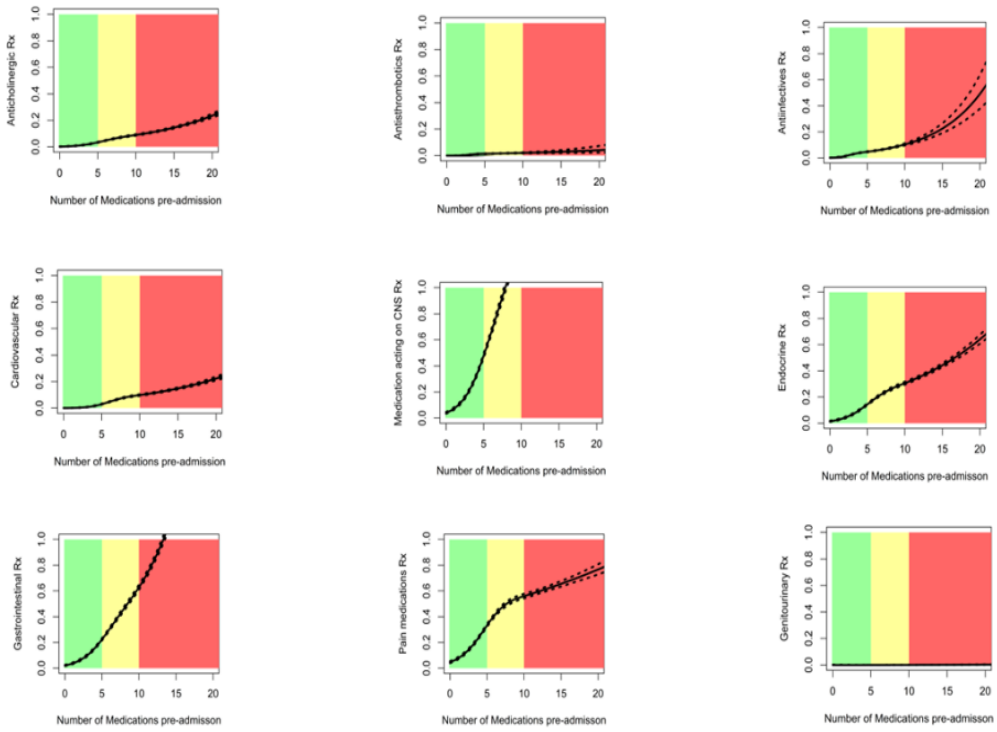

Figure 32 The association between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria.The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the polypharmacy category based on the different medications filled in the year preceding a surgical admission (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy).

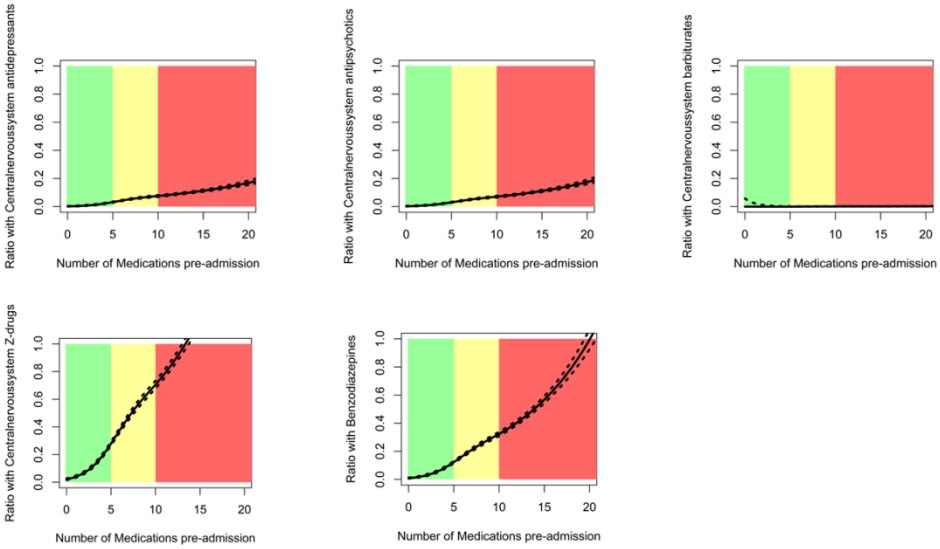

Figure 33 The association between the number of medications pre-admission and risk of potentially inappropriate medication use based on the 2019 Beers criteria for specific medications acting on the central nervous system Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission.

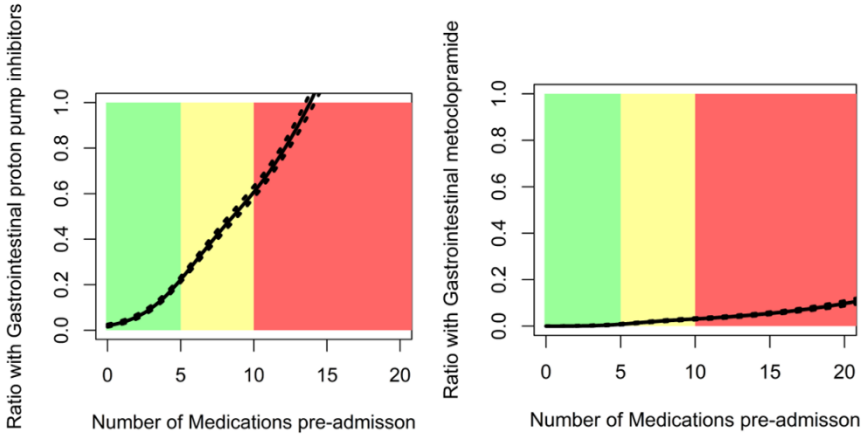

Figure 34 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission.

4.3.8 Clinical outcomes and survival post-discharge

The ratio of patients experiencing clinical outcomes of interest were compared based on whether the patients had potentially inappropriate medication use in the year prior to a surgical admission based on the 2019 Beers criteria. Patients with potentially inappropriate medication use were more likely to have a higher risk of readmission (< 30 days), 9.6% vs 8.3%. Patients with potentially inappropriate medication use were more likely to have a higher PRIME risk score for the likelihood of experiencing medication-related harm post-discharge, with a median [IQR] of 19.37 vs. 11.86. Finally, they were also more likely to have been diagnosed with an adverse drug reaction both prior to admission (8.0% vs. 3.4%) and post-discharge (6.3% vs. 2.8%). No statistical difference was observed for an extended hospital stay (≥ ten days) (Table 24)

The long-term survival of patients based on whether they had filled a potentially inappropriate medication in the year preceding hospital admission was visualised on a Kaplan-Meier plot. No difference in mortality was observed over time among patients who filled a potentially inappropriate medication compared to patients who did not fill a potentially inappropriate medication in the year preceding the admission to the hospital based on the 2019 Beers criteria.(Figure 35)

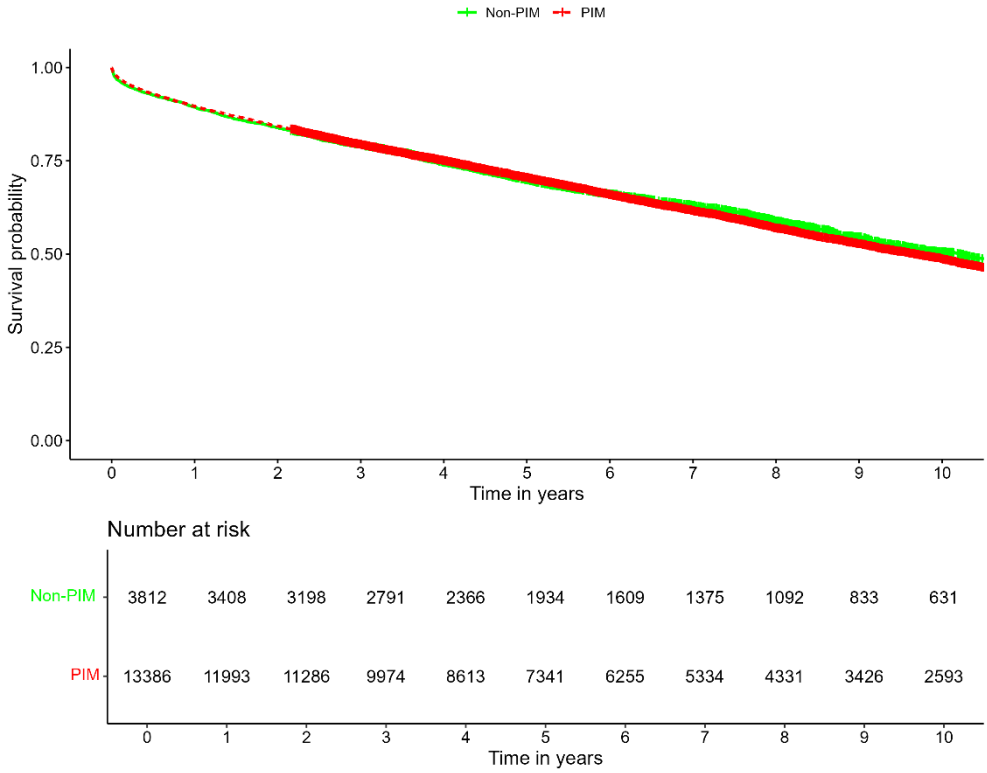

Figure 35 K Kaplan–Meier survival curve of long-term survival of patients compared based on whether they had filled a with potentially inappropriate medication before admission (green = No potentially inappropriate medication use (No PIM), and red = potentially inappropriate medication use.

Table 24 Patient characteristics for patients who filled a prescription for a potentially inappropriate medication use based on the 2019 Beers criteria prior to a surgical admission. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No potentially inappropriate medication use pre-admission	Potentially inappropriate medication use pre-admission	All patients	P-value
Total number of patients	3812 (22.2)	13386 (77.8)	17198	
Sex (female)	1620 (42.5)	7632 (57.0)	9252 (53.8)	<0.001
Age (median [IQR]), years	75 [70, 82]	75 [70, 81]	75 [70, 81]	<0.001
[65,75)	1807 (47.9)	6543 (49.1)	8350	
[75,85)	1398 (37.1)	5035 (37.8)	6433	
[85,95.)	565 (15.0)	1738 (13.1)	2303	
Multi-dose dispensing services	811 (21.3)	4822 (36.0)	5633 (32.8)	<0.001
Number of preoperative medications (median [IQR])	3 [1, 6]	10 [7,14]	9 [5, 13]	<0.001
Number of postoperative medications (median [IQR])	5 [2, 9]	11 [7, 15]	9 [6, 14]	<0.001
PRIME score (median [IQR])	11.86 [8.76, 16.69]	19.37 [13.57, 27.42]		
Elixhauser Comorbidity Index [IQR])	0.00 [0.00, 4.00]	2.00 [0.00, 5.00]	2.00 [0.00, 5.00]	<0.001
(<1]	2116 (55.5)	6387 (47.7)	8503 (49.4)	
(1-4]	765 (20.1)	2777 (20.7)	3542 (20.6)	
(4-5]	243 (6.4)	1047 (7.8)	1290 (7.5)	
(5-8]	228 (6.0)	877 (6.6)	1105 (6.4)	
(>8]	460 (12.1)	2298 (17.2)	2758 (16.0)	
Hospital Frailty Risk Score Class				
Low (< 5)	2927 (76.8)	9349 (69.8)	12276 (71.4)	
Med (5-15)	772 (20.3)	3462 (25.9)	4234 (24.6)	
High (> 15)	113 (3.0)	575 (4.3)	688 (4.0)	
Comorbidities				<0.001
Ischemic heart disease	1010 (26.5)	4510 (33.7)	5520 (32.1)	<0.001
Congestive heart failure	248 (6.5)	1295 (9.7)	1543 (9.0)	<0.001

Hypertension	1750 (45.9)	8045 (60.1)	9795 (57.0)	<0.001
Diabetes Mellitus	206 (5.4)	1877 (14.0)	2083 (12.1)	<0.001
Chronic obstructive pulmonary disease	611 (16.0)	3434 (25.7)	4045 (23.5)	<0.001
Liver disease	45 (1.2)	254 (1.9)	299 (1.7)	0.004
Chronic kidney disease	176 (4.6)	826 (6.2)	1002 (5.8)	<0.001
Malignant neoplasm	935 (24.5)	3711 (27.7)	4646 (27.0)	<0.001
Psychiatric	358 (9.4)	1837 (13.7)	2195 (12.8)	<0.001
Dementia	130 (3.4)	334 (2.5)	464 (2.7)	0.003
Delerium	267 (7.0)	1160 (8.7)	1427 (8.3)	0.001
Surgery Location and Classification				<0.001
Emergency operation	1604 (42.1)	4013 (30.0)	5617 (32.7)	<0.001
Abdominal	490 (12.8)	1984 (14.9)	2474 (14.4)	
Cardiac	325 (8.5)	720 (5.4)	1045 (6.1)	
Endocrine	35 (0.9)	ATH	209 (1.2)	
Gynaecology	102 (2.6)	860 (6.4)	962 (5.5)	
Neurosurgery	209 (5.5)	1252 (9.3)	1461 (8.4)	
Orthopaedic	1527 (40.1)	4927 (36.8)	6454 (37.5)	
Thoracic	61 (1.6)	328 (2.5)	389 (2.3)	
Urology	535 (14.0)	1421 (10.6)	1956 (11.4)	
Vascular	353 (9.2)	1184 (8.8)	1537 (8.9)	
Outcomes				
Fall diagnosis pre-admisson	8(0.2)	40(0.3)		0.457
Fall diagnosis post-discharge	5(0.1)	30(0.2)		0.358
Diagnosis of adverse drug reaction pre-admission (%)	131 (3.4)	1067 (8.0)	1198 (7.0)	<0.001
Diagnosis of adverse drug reaction post admission (%)	105 (2.8)	848 (6.3)	953 (5.5)	<0.001
Readmission within 30 days (%)	318 (8.3)	1282 (9.6)	1600 (9.3)	0.022
Mortality 30 days (%)	127 (3.3)	371 (2.8)		0.078
Length of stay (median [IQR])	3 [1, 6]	3 [1, 6]	3 [1, 6]	0.349
PRIME score (median [IQR])	11.86 [8.76, 16.69]	19.37 [13.57, 27.42]	17.37 [11.96, 25.15]	<0.001

[c] The Elixhauser comorbidity index is a severity index to quantify various patient comorbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient comorbidity burden. Unless specified otherwise, values are presented as count (%) or median (IQR).

Table 25 The table shows the subcategories of Beers Criteria filled, based on 2019 Beers criteria based on the patient's pre-admission polypharmacy burden estimated by the number of different medications filled in the year preceding admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Unless specified otherwise, values are presented as count (%) or median (IQR).

	Non-Polypharmacy pre-admission	Polypharmacy pre-admission	Hyper-Polypharmacy pre-admission	All patients pre-admission	P-value
Total number of patients	3629	6037	7532	17198	
Sex (female)				9252 (53.8)	<0.001
Potentially inappropriate medication use	1329 (36.6)	4841 (80.2)	7216 (95.8)	13386 (77.8)	<0.001
Age (median [IQR]), years	74.00 [69.00,80.00]	74.00 [69.00,80.00]	76.00 [71.00,82.00]	75.00 [70.00,81.00]	<0.001
[65,75)	1963 (54.7)	3099 (51.6)	3288 (43.9)	8350 (48.9)	
[75,85)	1158 (32.3)	2175 (36.2)	3100 (41.4)	6433 (37.7)	
[85,95.)	466 (13.0)	733 (12.2)	1104 (14.7)	2303 (13.5)	
PRIME score (median [IQR])	10.46 [8.10, 14.44]	15.00 [11.40, 19.89]	24.95 [18.63, 33.57]	17.37 [11.96, 25.15]	<0.001
Diagnosis of adverse drug reaction pre-admission (%)	95 (2.6)	337 (5.6)	766 (10.2)	1198 (7.0)	<0.001
Diagnosis of adverse drug reaction post admission (%)	92 (2.5)	285 (4.7)	576 (7.6)	953 (5.5)	<0.001
Beers criteria total score pre-admission (median [IQR])	0 [0, 1]	1 [1, 2]	4.[2, 5]	3 [1, 4]	<0.001
Beers criteria anticholinergics (%)	49 (1.4)	316 (5.2)	1016 (13.5)	1381 (8.0)	<0.001
Beers criteria Anticholinergics (antihistamines) (%)	48 (1.3)	285 (4.7)	964 (12.8)	1297 (7.5)	<0.001
Beers criteria Anticholinergics (antiparkinsonian) (%)	1 (0.0)	17 (0.3)	17 (0.2)	35 (0.2)	0.023
Beers criteria Anticholinergics (antispasmodics) (%)	0 (0.0)	15 (0.2)	40 (0.5)	55 (0.3)	<0.001
Beers criteria antithrombotic (%)	1 (0.0)	68 (1.1)	135 (1.8)	204 (1.2)	<0.001
Beers criteria anti-infective (%)	27 (0.7)	185 (3.1)	563 (7.5)	775 (4.5)	<0.001
Beers criteria cardiovascular (%)	24 (0.7)	314 (5.2)	1057 (14.0)	1395 (8.1)	<0.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.526
Beers criteria (cardiovascular disopyramide) (%)	2 (0.1)	7 (0.1)	30 (0.4)	39 (0.2)	<0.001
Beers criteria (cardiovascular dronedarone) (%)	0 (0.0)	3 (0.0)	19 (0.3)	22 (0.1)	<0.001

Beers criteria (cardiovascular digoxin) (%)	8 (0.2)	112 (1.9)	462 (6.1)	582 (3.4)	<0.001
Beers criteria (cardiovascular nifedipine) (%)	7 (0.2)	64 (1.1)	130 (1.7)	201 (1.2)	<0.001
Beers criteria (cardiovascular amiodarone) (%)	6 (0.2)	87 (1.4)	337 (4.5)	430 (2.5)	<0.001
Beers criteria central nervous system (%)	556 (15.3)	2591 (42.9)	5447 (72.3)	8594 (50.0)	<0.001
Beers criteria (central nervous system antidepressant) (%)	49 (1.4)	258 (4.3)	829 (11.0)	1136 (6.6)	<0.001
Beers criteria (central nervous system antipsychotics) (%)	46 (1.3)	279 (4.6)	789 (10.5)	1114 (6.5)	<0.001
Beers criteria (central nervous system barbiturates) (%)	0 (0.0)	6 (0.1)	15 (0.2)	21 (0.1)	0.015
Beers criteria (central nervous system benzodiazepines) (%)	165 (4.5)	979 (16.2)	2761 (36.7)	3905 (22.7)	<0.001
Beers criteria (central nervous system z-drugs) (%)	365 (10.1)	1779 (29.5)	4080 (54.2)	6224 (36.2)	<0.001
Beers criteria endocrine (%)	201 (5.5)	1048 (17.4)	2331 (30.9)	3580 (20.8)	<0.001
Beers criteria (endocrine androgens) (%)	7 (0.2)	45 (0.7)	110 (1.5)	162 (0.9)	<0.001
Beers criteria (endocrine estrogens) (%)	165 (4.5)	674 (11.2)	1348 (17.9)	2187 (12.7)	<0.001
Beers criteria (endocrine sulfonylurea) (%)	29 (0.8)	348 (5.8)	966 (12.8)	1343 (7.8)	<0.001
Beers criteria gastrointestinal (%)	307 (8.5)	1647 (27.3)	4101 (54.4)	6055 (35.2)	<0.001
Beers criteria (gastrointestinal metoclopramide) (%)	8 (0.2)	100 (1.7)	446 (5.9)	554 (3.2)	<0.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	301 (8.3)	1599 (26.5)	3955 (52.5)	5855 (34.0)	<0.001
Beers criteria Pain medications (%)	468 (12.9)	1671 (27.7)	2833 (37.6)	4972 (28.9)	<0.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.526
Beers criteria pain medications nonselective NSAID (%)	462 (12.7)	1614 (26.7)	2689 (35.7)	4765 (27.7)	<0.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	12 (0.3)	106 (1.8)	300 (4.0)	418 (2.4)	<0.001
Beers criteria (genitourinary) (%)	2 (0.1)	4 (0.1)	17 (0.2)	23 (0.1)	0.014

Table 26 Comparison of patients with no potentially inappropriate medication use pre-admission or post-discharge to patients with no potentially inappropriate medication use pre-admission but new potentially inappropriate medication use post-discharge. Unless specified otherwise, values are presented as count (%) or median (IQR).

	No potentially inappropriate medication use pre-admission nor new potentially inappropriate medication use post-discharge	New potentially inappropriate medication use post-discharge and but not pre-admission	p
Total number of patients	2366	1481	
Sex (male)	1029 (43.5)	593 (40.0)	0.038
Age median [IQR]), years	76.00 [70.00, 82.00]	74.00 [70.00, 80.00]	
Multi-dose dispensing services	405 (17.1)	421 (28.4)	<0.001
Number of pre-admission medications (median [IQR])	3.00 [0.00, 6.00]	5.00 [2.00, 7.00]	
Number of post-discharge medications (median [IQR])	3.00 [0.00, 6.00]	9.00 [6.00, 12.00]	
PRIME score (median [IQR])	11.33 [8.46, 16.37]	12.57 [9.29, 17.24]	
Elixhauser Comorbidity Index [IQR])			<0.001
(<1]	1389 (58.7)	741 (50.0)	
(1-4]	406 (17.2)	369 (24.9)	
(4-5]	154 (6.5)	96 (6.5)	
(5-8]	136 (5.7)	92 (6.2)	
(>8]	281 (11.9)	183 (12.4)	
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	1785 (75.4)	1163 (78.5)	
Med (5-15)	493 (20.8)	292 (19.7)	
High (> 15)	88 (3.7)	26 (1.8)	
Comorbidities			
Ischemic heart disease	481 (20.3)	438 (29.6)	<0.001
Congestive heart failure	146 (6.2)	104 (7.0)	0.329
Hypertension	364 (15.4)	274 (18.5)	0.013
Diabetes Mellitus	74 (3.1)	43 (2.9)	0.766
Chronic obstructive pulmonary disease	105 (4.4)	65 (4.4)	1.000
Liver disease	23 (1.0)	14 (0.9)	1.000
Chronic kidney	82 (3.5)	36 (2.4)	0.086

disease			
Malignant neoplasm	458 (19.4)	433 (29.2)	<0.001
Psychiatric	269 (11.4)	92 (6.2)	<0.001
Dementia	104 (4.4)	27 (1.8)	<0.001
Delerium	92 (3.9)	39 (2.6)	0.046
Surgery Location and Classification			
Emergency operation	1142 (48.3)	473 (31.9)	
Abdominal	290 (12.2)	205 (13.8)	
Cardiac	105 (4.4)	220 (14.9)	
Endocrine	20 (0.8)	15 (1.0)	
Gynaecology	40 (1.7)	63 (4.3)	
Neurosurgery	132 (5.6)	80 (7.0)	
Orthopaedic	1112(47.0)	424 (28.6)	
Thoracic	21(0.9)	40(2.7)	
Urology	347 (14.7)	198 (13.4)	
Vascular	195 (8.2)	165 (11.1)	
Outcomes			
Length of hospital stay (days)	2 [1, 5]	3[1, 8]	
Diagnosis of adverse drug reaction pre-admission (%)	79 (3.3)	55 (3.7)	0.599
Diagnosis of adverse drug reaction post-discharge (%)	52 (2.2)	55 (3.7)	0.007
Mortality 30 days (%)	5 (0.3)	123 (5.2)	<0.001

5 Discussion

This doctoral thesis is based on four observational cohort studies that examined the prevalence and incidence of polypharmacy and potentially inappropriate medication use among patients prior to admission and post-discharge from both surgical and internal medicine hospitalisation. The study identified that pre-admission polypharmacy/ hyperpolypharmacy and post-discharge new polypharmacy/hyperpolypharmacy were common among surgical and internal medicine patients, which aligns with the previously stated primary hypothesis. For the surgical population, the findings confirm that there is an association between preoperative polypharmacy and hyperpolypharmacy with higher short- and long-term mortality, more extended hospital stays and increased risk of readmission. In contrast, no association was found between pre-admission polypharmacy and hyperpolypharmacy, with the same clinical outcomes for patients admitted by internal medicine specialities. Finally, this doctoral thesis identified that potentially inappropriate medication use was common among internal medicine patients and strongly associated with polypharmacy and hyperpolypharmacy, which is in line with the previously stated hypothesis. There was no association between pre-admission polypharmacy /hyperpolypharmacy and potentially inappropriate medication use among patients admitted by internal medicine speciality on one hand and worse clinical outcomes on the other hand, which contradicts previously stated secondary hypothesis.

5.1 Comparison of surgical cohort and internal medicine cohort

The results of this thesis demonstrate the dissimilarity between surgical patients and internal medicine patients (Table 13 and Table 17). For both cohorts, patients were more likely to be females, with surgical patients at 57.0% vs internal medicine patients at 51.1%. However, patients admitted by internal medicine were older, with a median [IQR] 73 (60-82) vs [IQR] 55 (39-69) years. They also had a higher burden of comorbidity and frailty, including a higher Elixhauser comorbidity index, a median [IQR] 6 (0-12) vs [IQR] 0 (0-4). Similarly, most (45%) internal medicine patients had a medium-risk class. While most surgical patients (60%) had a low frailty risk class. The variation of comorbidity burden between different surgical subspecialties is known to affect clinical outcomes. [222] Based on the results of this thesis, there are extensive differences in comorbidity burdens between the two cohorts, which is likely reflected by the burden of polypharmacy. Patients admitted by internal medicine also used more medication, both prior to admission and post-discharge, with a median [IQR] 12 (7-18) vs [IQR] 6 (2-10) pre-admission and a median [IQR] 12 (7-17) vs [IQR] 6 (3-11) post-discharge. Mutli-dose dispensing service was used by 54.7% of patients admitted by

internal medicine compared to 13.7% among the surgical patients. The internal medicine patients were also more likely to have multiple admissions. Additionally, internal medicine patients were at more risk of medication-related harm post-discharge based on the PRIME risk assessment tool. However, the PRIME risk assessment tool has not been validated in older surgical population. This finding highlights that those two cohorts of hospitalised patients are vastly different and, therefore, need different approaches in clinical practice. These should also be investigated separately in research. In general, internal medicine patients are older, have higher comorbidity and increased frailty, use more medication, are more likely to use automated dispensing services and have multiple admissions compared to the surgical population. Most of the literature on hospitalised patients as one cohort might lead to bias for both cohorts.[141, 223] Our findings are in contrast with a recent study that concluded that surgical and internal medicine patients have similar burdens of comorbidity.[224] However, surgical patients in this study were older, with a median age of 63 [62,63], which is older than our surgical population cohort's median age of 55 [39, 69] and therefore are more likely to have higher comorbidity. Therefore, this thesis should encourage researchers to understand the importance of studying surgical and internal medicine patients separately. These findings also shed light on the importance of caring for surgical and internal medicine patients with different approaches. For surgical patients, there is a need for targeted intervention in optimising medication use and minimising the level of potentially inappropriate medication use prior to elective surgical admission, with a particular focus on medications and medical conditions known to affect surgical outcomes negatively, like the use of benzodiazepines or opioids [5] and addressing physical comorbidities like anemia [225] and increasingly psychological factors.[226] Additionally, increased follow-up of new medication use in relation to a surgical admission, like opioids, and increased focus on providing information and support regarding temporal medication treatments and guidance on how patients should taper medications if needed. As patients admitted to the internal medicine ward are more likely to use more medications and have a higher prevalence of potentially inappropriate medication use, they are more likely to have more complex needs and to benefit from a multidisciplinary approach for a comprehensive review of their medication treatment and increased follow-up after discharge in outpatient settings, general practitioner and community pharmacy. One solution could be establishing an outpatient clinic with multidisciplinary staff, such as internal medicine specialists, geriatricians, clinical pharmacists and nurses, where complex patients who need comprehensive review and increased follow-up could be referred. Unpacking the differences in the complexity of patient cohorts may give us guidance on how limited resources in healthcare should be utilised and how each patient cohort can receive optimal care support. Studies have evaluated the differences among different surgical specialities [227] and differences in comorbidities. [222] This result may also support us in prioritising resources in healthcare.

The use of multidose dispensing services is much higher among internal medicine patients (54.7%) compared to surgical patients (13.7%). Sjöberg et al. and Belfrage et al. both studied the association of multidose dispensing services and the appropriateness of treatment among older patients in Scandinavia and concluded that patients who used multidose dispensing services were using medications which were often of less appropriateness.[228, 229] This thesis identified an association between a higher number of medications and the use of multidose dispensing services, additionally increasing the likelihood of potentially inappropriate medication use.

Patients (≥65) admitted by internal specialists (14.6%) had a higher risk of medication-related harm post-discharge compared to surgical patients (9.0%) assessed by PRIME, the risk stratification tool, this finding could be applied to support directing increased follow-up post-discharge and the need for medication optimisation prior to discharge and enhanced focus of continuity of care after a hospitalisation. One opportunity would be to stratify patients to an appropriate level of intervention. For example, those with low risk can be referred to a community pharmacist for post-discharge follow-up, medium risk could go to a general practice-based pharmacist, and high risk go to a specialist pharmacist who has links with geriatricians and other speciality consultants in outpatient settings. The risk assessment could also be applied to different sub-specialities in order to prioritise the limited resources for those patient groups at the highest risk of medication-related harm post-discharge. The risk assessment could also be incorporated into the medical record to identify and prioritise patients in real time. This could also be applied to identify the patient who need increased follow-up post-discharge. One possibility would be to highlight this risk assessment in the discharge letter and make a referral to the general practitioner for an increased follow-up due to the high risk of medication-related harm post-discharge. Clinical pharmacists can support pharmacist-led follow-up post-discharge in order to support medication changes during hospitalisation. Additionally, this risk assessment of different patient groups could be used to prioritise the work of clinical pharmacists both within hospital care and general practice.

5.2 Prevalence and incidence of different medication use categories (non-polypharmacy, polypharmacy and hyperpolypharamacy)

The prevalence of polypharmacy and hyperpolypharmacy was high for both cohorts. However, it is higher among the internal medicine patients, which was anticipated as they have increased comorbidity and are older. The prevalence of non-polypharmacy, polypharmacy and hyperpolypharmacy among internal medicine patients was 15.1%, 22.9% and 62.5% compared with 42.2%, 32.3% and 25.5% for surgical patients, respectively. As discussed earlier, multiple studies have investigated the prevalence of polypharmacy and hyperpolypharmacy. However, the lack of uniform definitions used

for polypharmacy and hyperpolypharmacy in research makes them difficult to compare. The definition used in this thesis for polypharmacy refers to ≥5 medications, which is the most commonly applied criteria.[47] Applying a numerical value in defining polypharmacy and hyperpolypharmacy has its limitations, as the definition does not account for whether the medication use is appropriate [230], and there are also variations in the numerical threshold of medications in studies researching polypharmacy.[47] The majority of the studies are conducted in the general population [104, 105, 231-233], with some also in hospitalised patients. However, few studies distinguish between surgical patients.[106, 107] and internal medicine patients. These studies had a significantly lower prevalence of polypharmacy and hyperpolypharmacy compared to this thesis. The approach to studying the prevalence by joining all patients in a general hospital setting likely overestimates the prevalence in surgical patients and underestimates the prevalence among internal medicine patients. A recent systematic review exploring the prevalence in different settings (community, inpatient and outpatient) reported the pooled prevalence to be 37%.[101] However, the prevalence in hospital settings was highest at 52%.[48, 108] This study's limitation is that hospitalised patients are grouped together and do not distinguish between internal medicine and surgical patients. However, this doctoral project applied the same method for the surgical and internal medicine cohorts, making the comparison more reliable for the two cohorts.

Among the surgical population, older patients had increased co-morbidity and higher frailty burden and were at increased risk of polypharmacy and hyperpolypharmacy. They were also more likely to require an emergency surgery. This was not surprising as patients at more advanced ages and with multiple comorbidities are more likely to require more medication.[167]. Older surgical patients are likely to be more similar to the internal medicine patients. Other studies have identified similar patterns. For internal medicine, the pattern was quite different, which was surprising. The only patient characteristic differentiating those with higher medication use categories like polypharmacy (45.6%) or hyperpolypharmacy (65.9%) compared to non-polypharmacy (22.0%) among the internal medicine patients was the likelihood of using multidose dispensing services. These findings raise questions regarding the appropriateness of medication use among internal medicine patients, as there was no difference in comorbidity burden or frailty index. Therefore, increased medication use cannot be explained by increased comorbidities requiring a higher number of medications. One possible explanation for this could be that the coding in the databases does not capture more advanced stages of diseases that require additional treatment over time. One example could be patients diagnosed with diabetes mellitus type two are simply coded as diabetes mellitus type two whether the patient requires management with one or multiple antidiabetic agents. For both cohorts, surgical and internal medicine patients, there was an association between a higher number of medications and the likelihood of a diagnosis of adverse drug reactions, which is in line with previous studies.[234] However, studies have also highlighted that diagnoses of adverse drug reactions are under-

reported, and therefore, it may be assumed that the prevalence is higher in real life.[235] As there is the bulk of evidence reporting the association between polypharmacy and inappropriate medicine, the results of this study contain valuable information to identify subgroups of patients at increased risk of using multiple medications and, therefore, the heightened need to have their medication optimised during admission or post-discharge. Additionally, there was a strong association between the calculated risk of medication-related harm post-discharge with polypharmacy among both cohorts based on the PRIME risk assessment tool. That was anticipated since the variable included in the risk assessment is a number of measurements used.

The incidence of new postoperative or post-admission polypharmacy or hyperpolypharmacy was also evaluated among the two cohorts and was high compared to other studies.[104, 223] However, the comparison is difficult to make due to differences in the study population and follow-up time frame. These results raise concerns that hospital admission, either due to surgery or admission by an internal medicine speciality, may be a gateway into a new or accelerated rate of polypharmacy. This again highlights the importance of clear communication from the hospital site to the general practitioner during the transfer of care period, which has been identified as high-risk.[16]

In this thesis, the prevalence of polypharmacy and hyperpolypharmacy for both cohorts, surgical (2005-2018) and internal medicine patients (2010-2020), over the study period was similar. This is interesting as much research has reported the trend of increasing prevalence.[53] [108, 109] One interpretation of this is that there is an increased awareness among healthcare professionals and patients about polypharmacy and appropriate medication use in Iceland, for example, with the localised adaption of the WHO campaign Medication without Harm.[4]

One possible reason for increased medication usage is the proliferation of clinical guidelines focusing on specific conditions. This has led to a narrow focus rather than the broader scope needed to address multimorbid patients, which inevitably may lead to increased polypharmacy. Other reasons could be the demographic shift, with an increase in the aged population with associated multimorbidity and living longer with chronic conditions, and an increase in treatment options with continuously new medication being available and expanding the treatment options.

5.3 Medication use and multidose dispensing services

This thesis identified the most commonly used medication in the year before admission for both surgery and internal medicine admission. For the surgical population, the most common medications prior to admission were antibiotics (49.0%), cardiac medication (42.4%), and opioids (42.2%). It is also worth noting that 21.9% of filled prescriptions were for Z-drugs, 21.5% for antidepressants, and 14.8% for benzodiazepines. For internal medicine patients, the most commonly used medications prior to admission

were cardiac medications (74.5%), followed by antibiotics (60.7%) and opioids (51.0%) and Z-drugs (43.0%), antidepressants (37.9%), and benzodiazepines (29.0%).

For both cohorts, the most commonly used medications were the same; however, there was a difference in the prevalence of medications used. For most medications, the use of specific medications was about twofold for the internal medicine cohort compared to the surgical population, except for urinary medication, which was similar for both cohorts. The prevalence of antibiotics (60.7% vs 49.0%) and opioids (51.0% vs 42.2%) were less than twofold. The use of paracetamol/orphenadrine combinations and non-steroidal, anti-inflammatory medication were the only medications with higher prevalence among the surgical population compared to internal medicine patients, which might be logical since the majority of the surgical population is waiting for elective surgery and use of painkillers would be anticipated.

This high use of antibiotics and opioids among both study cohorts raises concern. A high prevalence of opioid usage would perhaps anticipated among the surgical population awaiting some surgeries where pain is the leading symptom, whereas a high prevalence among internal medicine patients is surprising. However, chronic pain is prevalent in the general population, with a reported prevalence of 43% in the general population in the United Kingdom, and would be anticipated to be higher among inpatients.[236] Additionally, chronic pain has been reported as a growing concern as it is associated with high use of opioid use.[237] The high prevalence of antibiotic use among both cohorts warrants further research, as there is growing antibiotic resistance worldwide.[238] These results, with the high consumption of antibiotics among both cohorts, raise concerns about appropriate antibiotic use and possible overprescribing and warrant further investigation. Additionally, the high prevalence of opioid use is worrisome among both cohorts, even though a higher prevalence of opioid use among patients waiting for elective surgery was anticipated. The high prevalence among internal medicine patients is alarming in light of the global trend towards increased use of opioids. The prevalence was higher than in other studies reporting on the prevalence of opioids in inpatient settings.[239] One possible explanation could be a different methodology. It is possible that this study overestimated the use of opioids as it relies on data on medication fillings. As there is limited evidence for long-term use of opioids for chronic pain and the use is associated with risk of, for example, overdose and misuse[240] , this high prevalence of opioid use among both cohorts sheds light on the need for strategies to address high opioid usage among Icelandic patients. A recent study has reported the trend of opioid use in Iceland is still rising[241] , which is in line with published data about opioid consumption in Nordic countries, where Iceland has had the highest consumption from 2013-2022.[211] Research has identified that preoperative opioid use is associated with worse clinical outcomes and increased readmission.[242] Therefore, the pre-operative period could be utilised to counsel patients and aim to reduce opioid consumption or stop prior to the surgery. Additionally, intervention in the pre-operative phase might decrease the risk of

persistent opioid use after discharge and medication-related harm associated with prolonged opioid usage.[243, 244] An admission to the hospital may be an opportunity to address long-term opioid use and counsel patients on the importance of appropriate medication usage and the possibility of deprescribing, and the availability of supportive tools and counseling. However, it is vital to collaborate closely with the general practitioner or community pharmacists to support the patient post-discharge. The high prevalence of medications such as benzodiazepines, antidepressants and Z-drugs highlights the lack of strategies and solutions for other medications to support anxiety and mood disorders by other measures than medications and additionally challenges with the process of deprescribing.[245, 246]

The most commonly added medications post-discharge after surgery were opioids, antibiotics, and anticoagulants. Among other frequently added medications were respiratory medications, proton pump inhibitors, corticosteroids, musculoskeletal, urinary medications, benzodiazepines and anti-diabetic medications. For the internal medicine cohort, the most commonly added medications were anticoagulants, antibiotics, opioids, proton pump inhibitors, antiplatelets, corticosteroids, respiratory medications and medication acting on the central nervous system like Z-drugs, antidepressants and antipsychotics.

These findings raise the concern that medications are frequently changed during hospitalisation. The reason for medication changes during hospitalisation may be due to several factors, such as new health conditions, inappropriate or ineffective mediation treatment prior to admission or symptoms requiring short-term treatment like insomnia, distress and pain. This observational study raised concerns that medications unrelated to the cause of hospitalisation often change. [114] However, the index admission may result in a sequence of events requiring treatment modification. The concern, therefore, could be more regarding the lack of support for these changes in the medication regime post-discharge. Several studies have highlighted the transfer of care from the hospital setting back to the general practitioner setting as a high-risk period due to numerous reasons, one of which is the lack of communication about changes in medication regime and what needs to be followed up by the general practitioner.[247] One interpretation of these findings of frequent changes in medication regime during hospitalisation and the risk during the transfer of care could be that healthcare professionals should aim to only make medication changes during a hospitalisation that are needed without delay. Additionally, the discharge letter should clearly explain all medication changes and the reasons for the changes during hospitalisation. If changes include high-risk medications, extra effort should be made to ensure safe transfer back to general practice. There is a need for a discussion within the healthcare settings on a certain division of labour, for example, which healthcare problems should be tackled within inpatient settings and who should follow them up.

The finding of this thesis, that antidepressants, benzodiazepines, and antipsychotics, especially among internal medicine patients, are among medications added post-discharge, raises concern about the pre-prescribing assessment and post-prescribing follow-up. In the case of new antidepressant therapy, which is seldom the first line of treatment for depression or anxiety, medications should only be added after a thorough assessment by applying assessment scales and with an appropriate plan for follow-up after initiation. While there are examples where antidepressants might be appropriate to initiate during hospitalisation, it can be very challenging to ensure proper follow-up to monitor effects and side effects is conducted following initiation of these medications during hospitalisation. The same applies to other medications, which, based on the results of this thesis, are frequently initiated for internal medicine and, to a lesser extent, for surgical patients, like antipsychotics, Z-medication, benzodiazepines and proton-pump inhibitors. These medications change after hospital admission, need revaluation and are most likely meant to be short-term. Antipsychotics have, in recent years, been increasingly used for insomnia or anxiety disorders, which are both indications where the treatment should be used short-term. The same applies to the use of benzodiazepines and, in some cases, also for proton pump inhibitors. If a medication initiated during hospitalisation should be used short-term, the aim should be to describe the treatment prior to discharge, and when that is not possible, a clear description of the medication changes and the need for reevaluation should be stated in the discharge letter. Additionally, patients should be counselled at the beginning of treatment and discharge regarding the treatment plan and shared decision-making method applied as appropriate.

This thesis identified a strong association between a higher number of medications and the use of multidose dispensing services, which is no surprise as one of the reasons to initiate this service is the use of multiple medicines simultaneously. However, as mentioned earlier, studies have identified the association between using multidose dispensing services and less medication appropriateness. Additionally, studies have raised concerns that patients using multidose dispensing services are less likely to have the medications optimised, and there is an association with uncritical renewals of prescriptions.[228, 248] Prescriptions for multidose dispensing services are usually renewed yearly. The findings of this thesis, supported by previous literature, highlight the need to regularly review medication use among patients with multi-dose dispensing services. While yearly renewal might provide a unique platform for medication optimisation in collaboration with the general practitioner, it is unclear how often this platform is used. Additionally, a yearly review may be inadequate in a multimorbid, frail population where the balance between medicines being helpful or harmful is delicate. This thesis highlighted that multidose dispensing service is often initiated following hospitalisation and may be a marker for an increased need for support with medication use post-discharge, which might be reasonable. However, a new multidose dispensing service after hospitalisation may also be problematic because medications initiated post-

discharge are often meant to be used short-term or new medications are being trialled or stopped soon after discharge. New medications are often initiated post-discharge and are intended to be short-term. Initiation of multi-dispensing services may reduce the likelihood that a reassessment of the medication is done. Another risk associated with initiating multidose dispensing service after hospital admission is the fact that newly qualified doctors are often responsible for prescribing medications at discharge, which then makes them accountable for long-term treatment. One possible solution would be to decrease the timeframe of the new prescribing period provided by the hospital prescriber and the need for the general practitioner to review the medications post-discharge prior to more extended prescriptions. If the timeframe is not limited, there is a heightened need for clear communication between the hospital and general practitioner settings. Initiating new multidose dispensing services post-discharge aligns poorly with the year-long prescription often preferred by the multidose dispensing services provider requests, at least in Iceland. One possible solution could be to exclude medications meant for short-term use from multidose dispensing services. However, that could lead to another more complex medication regime for patients. These results raise the importance of discussing how general practitioners should follow up on a newly initiated multidose dispensing service to ensure the medication changes during hospitalisation are promptly reviewed. As mentioned earlier, clinical pharmacists can support this process, and the community pharmacist's role in supporting this process should be investigated. As mentioned, these results should encourage an increased focus on regularly optimising patients' medication use with multidose dispensing services. Recently, clinical pharmacists within general practitioners' settings have started reviewing the medication regime before annual prescriptions renewals and providing feedback to the prescriber. This is a significant improvement; however, this links in with the need to change regulations so clinical pharmacists can be reimbursed for reviewing medication use the same way as general practitioners. Clinical pharmacists have the competencies to provide those services and can, therefore, support general practitioners struggling to provide the services due to their heavy workload. As mentioned in the introduction, collaborating between the two professions in providing comprehensive care has benefitted the patients. [184] The Royal Pharmaceutical Society (RPS) [249] and NICE[250] have advised healthcare professionals within the UK not to use multi-dose dispensing service as a first-choice intervention to support patients in managing their medications as there it does not always simplify the medication usage. Additionally, the RPS has provided guidance to support reviewing patients using multi-dose dispensing services and initiating such a service.[251] The guidance provides detailed support assessing each patient's risks and benefits of multidose dispensing service.[249] There is an urgent need for similar guidance within the Icelandic healthcare system.

Multidose dispensing services may contribute to an extra challenge when initiating deprescribing. These findings are concerning because multidose dispensing services

are commonly assumed to be supportive of addressing medication-related problems and are often initiated before patients are discharged from the hospital.

The semi-automation in the prescribing of medications within the general practitioners' settings may lead to medication being less likely to be reassessed and deprescribed when appropriate. One possible solution might be to have a clinical pharmacist pre-screen the renewal requests for the general practitioners and prioritise those renewals which the general practitioner should review and possibly prescribe. Clinical pharmacists could provide additional support if they were allowed supplementary prescribing. In many countries, pharmacists have been trained to prescribe. For example, in the United Kingdom, pharmacists will graduate in 2026 with prescribing allowances. The prescribing of pharmacists in the United Kingdom has been extensively studied and has shown that pharmacists are able to prescribe to the same standards as doctors; they have a higher rate of adhering to guidelines and make fewer errors when prescribing patients medications at hospital admission.[252, 253] However, even though adhering to guidelines is important to appropriately apply them at the individual level, especially for older and more frail people; otherwise, it may be a contributing factor to the development of polypharmacy.

5.4 Potentially inappropriate medications

This thesis identified that potentially inappropriate medication use pre-admission and post-discharge, based on the 2019 Beers criteria, is common among older internal medicine patients (≥65) admitted by internal medicine specialities and is strongly associated with polypharmacy and hyperpolypharmacy. This is in line with the previously stated hypothesis. However, no association was found between potentially inappropriate medication use and worse clinical outcomes, which contradicts our secondary hypothesis. Previous literature has investigated the prevalence and incidence of potentially inappropriate medication use among different study cohort participants and countries. Due to differences in methodological approach and heterogenic study, population comparison often proves difficult. This thesis applied the 2019 Beers criteria and identified the prevalence of potentially inappropriate medication use to be 82.7% for the whole cohort and, additionally, a strong association with higher levels of medication use (polypharmacy and hyperpolypharmacy), which is similar to previous studies.[254] The prevalence of potentially inappropriate medication use among the different medication use categories was 34.0% for non-polypharmacy, 77.7% for polypharmacy, and 96.4%. hyperpolypharmacy. This high prevalence of potentially inappropriate medication use is in line with a previous study reporting on a similar study population and applying the same criteria, where the prevalence of potentially inappropriate median use was reported to be 92%.[255] A reasonable explanation of this high prevalence of internal medicine patients admitted to hospitals represents a patient cohort at advanced age, increased comorbidity and frailty, and use of more medications compared to the outpatient- and general practitioner-based cohort. Therefore, a comparison with different study populations proves difficult. However, a

recent meta-analysis reported the prevalence of potentially inappropriate medication worldwide to range from 1.3%-95.2%, with a pooled prevalence of 36.7%.[256] This thesis has also identified an association between the female gender and the likelihood of potentially inappropriate medication use, which is in line with previous studies.[257] A possible explanation for that is that females are more frequently prescribed medication acting on the central nervous system (like benzodiazepine and Z-drugs), which are likely to be inappropriate. Additionally, women tend to have more interactions with healthcare providers over the life course [258] , which may provide additional opportunities for prescribing. The use of multidose dispensing services is also associated with the increased likelihood of potentially inappropriate medication use, which has also been identified in previous studies.[228, 229, 248] These results are worrisome since multidose dispensing services are often believed to aid patients with their medication usage and are often initiated when problems arise in relation to medication usage, for example, with medication adherence and complex medication regimens. Despite the fact that there is limited evidence behind the increased adherence as demonstrated in the REMIND trial.[259] The results of this thesis imply that multidose dispensing services have an association with both polypharmacy and an increased likelihood of potentially inappropriate medication use.

The strong association of potentially inappropriate medication use among older patients should encourage extra diligence when prescribing for this patient group and additional strategies to review their medication use in partnership with patients regularly. Additionally, the possibility of using alternative measures like diet, exercise, and counselling may often be overlooked. It could support more appropriate medication use and diminish inappropriate polypharmacy.

As mentioned previously, hospitalisation often leads to a change in medication regime and, therefore, the risk of new, potentially inappropriate medication use. This thesis has identified that new prescriptions of potentially inappropriate medication were common among those patients who did not have potentially inappropriate medication use before hospitalisation. Patients with increased comorbidity, male gender, or the following diseases: cancer, liver disease, kidney disease, diabetes, dementia, and delirium, were at increased risk of new potentially inappropriate medication use after discharge. Patients with new potentially inappropriate medication use were also at increased risk of being diagnosed with adverse drug reactions after discharge, which could be due to a prescribing cascade where a healthcare professional misdiagnoses an adverse drug reaction as a new medical condition requiring medical treatment. However, a hospital admission also provides the opportunity to identify potentially inappropriate medication use. Admission to the geriatric ward was associated with a reduced risk of a new potentially inappropriate medication use. One reason for this could be that the health care professional, especially a physician specialising in geriatric care, has the skills and knowledge to choose medications for this vulnerable patient group and, thus, is less likely to initiate a new, potentially inappropriate medication during hospitalisation Addtioanlly, they may be more aware of possible non-pharmacological intervention to

address health-related problems. [260] One possible explanation may be that These findings highlight the importance of judicious prescribing during hospitalisation and the need to upscale the skills and knowledge of all of those caring for older patients because as the population ages, all disciplines are required to care for patients at older ages, and they are admitted to a variety of internal medicine sub-specialities were there is less knowledge in geriatric care. These findings highlight the importance of exploring the appropriateness of medication use among older patients within the surgical wards. This interesting finding warrants further exploration into contributing factors leading to less inappropriate prescribing after discharge and how this factor may be replicated in other clinical areas.

5.5 Clinical outcomes

Clinical outcomes were studied for both a surgical cohort (≥18 and ≥65) and internal medicine (≥18 and ≥65). In the surgical cohort (≥18), polypharmacy and hyperpharmacy were linked to worse clinical outcomes such as short- and long-term mortality, length of hospitalisation, and 30-day readmission rate, which was in line with the previously stated hypothesis. However, that was not the case for the internal medicine patient cohort (≥18), which contradicts the previously stated hypothesis. The association of the same clinical outcomes were assessed for older patients (≥65), and the same pattern was observed. no association was found. This contradicts our secondary hypothesis that potentially inappropriate medication use was associated with adverse clinical outcomes.

For the surgical population, the association between polypharmacy and hyperpolypharmacy and clinical outcomes was largely in line with previous literature.[48, 104, 106, 232] . The reason for this is unclear, i.e. whether worse clinical outcomes are directly linked to polypharmacy or whether polypharmacy and hyperpolypharmacy serve as a proxy for multimorbidity. The potential mechanism could be related to polypharmacy being a marker of potentially inappropriate medication use, which might prompt the increased risk of worse clinical outcomes agitated by, for example, increased anticholinergic burden, increased risk of falls due to orthostatic and risk of respiratory complications. The results of this study cannot establish causality. However, further studies on polypharmacy among the surgical population could aim to identify the risk between different surgical cohorts. Additionally, studies should be aimed at assessing interventions that aim to optimise medication usage throughout the perioperative period. A recent systematic review studying the comanagement of internal medicine physicians and a multidisciplinary approach to caring for surgical patients was associated with better clinical outcomes, such as increased mortality and reduced length of hospital stay.[261] Additionally, a new guideline was published by the British Geriatrics Society on the perioperative care for patients with frailty, which highlights the importance of reviewing medication use, for example, for falls and delirium- risk.

On the contrary, no association was observed between the increased number of medications used by internal medicine patients and worse clinical outcomes, which contradicts previous literature. [262-264] This may be explained by the fact that patients among all medication use categories (non-polypharmacy, polypharmacy and hyperpolypharmacy) all had similar comorbidity and a frailty level. This is likely to be the driver behind observed differences among the surgical population, where there is an extensive difference in comorbidity and frailty among the patients with different medication use categories. It is also worth acknowledging that surgery is a major stressor event (the procedure, anaesthesia, immobility, and all the increased risks that having surgery has). This is an important difference between the two groups.

5.6 Large-scale Databases

An extensive part of this doctoral project was the generation of a large-scale database called the Internal Medicine Database, which will be maintained as a future research database for multiple research projects. In recent decades, there has been a proliferation of the use of large-scale databases, for example, in pharmacoepidemiological studies relying on prescription registry data and data from health registries. Before this doctoral project, another large-scale database covered all surgical admissions from 2005-2018. There have been multiple publications, ranging from studying medication use[5, 213], frailty [218], and clinical outcomes. Even though the Icelandic internal medicine database has recently been established, some publications have already been published, and more are in the process of being published.[8, 265] Several studies are ongoing or in the process of publication. The availability of quality data and the possibility to link it together using the personal identity number allows for the generation of databases, which subsequently makes it possible to study both patterns and trends in medication use and clinical outcomes additionally, it provides the possibility to study rarer medication use or smaller sub-groups of patients of interest, like certain sub-specialities of internal medicine and surgical care. The Icelandic perioperative and internal medicine databases contain a decade of patient-level data on medication use, comorbidities and outcomes related to hospital admission. A similar database, including patients in the general population, would benefit the Icelandic healthcare system by studying further medication use and sub-groups of patients requiring increased care. Future studies in pharmacoepidemiology in Iceland will rely on the two databases for patients in hospital settings. This can add considerably to new knowledge on medication use in clinical practice in hospital settings and can guide advancement in prescribing practices. However, in the coming years, hopefully, there will be an increased focus on providing real-time feedback on medication usage, prescribing practices, and health outcomes both nationally and on more localised platforms, such as specific settings or regional bases. This would allow for more prompt improvements in prescribing practices. Artificial intelligence will likely, in the coming years, be applied to support the analysis of large-scale databases and to guide prescription and medication use through medical records and prescribing tools.[266]

5.7 Solutions

Medication-related harm can decrease patients' quality of life in many ways and can include increased risk of hospital admissions, a more extended stay in the hospital, and increased morbidity and mortality. As mentioned in the introduction, medicine is the most commonly applied intervention in health care.[14] However, prescribing is also a delicate, complex intervention. It requires extensive knowledge of the prescriber, knowledge of pharmacology, communication skills, ability to assess the risk-benefit ratio for individual patients, consistently applying evidence-based practice and considering prescribers' clinical experience and perspective.[267] Even with the rapid proliferation of research studying the safety and effectiveness of medications, prescribers are often faced with decisions on medication for patient groups not included in clinical trials, like older patients.[268] Promoting and aiming to ensure appropriate prescribing rather than screening already prescribed medication should be a more effective intervention. However, there is most likely a need to do both to aim for safer medication use. With the increasing demand on health care systems, due to the lack of continuity of care and emphasis on single-disease guidelines and care of specific doctors for all subspecialties, there is a need to address potentially inappropriate medication use additionally after prescribing. When deciding on medication for older adults living with frailty, the prescriber needs to bear in mind outcome measures that are meaningful to the individual patient.[269]

The services provided in healthcare cover a range of linked processes, all of which have associated risks. The current paradigm of healthcare, being generally based on fragmented care and single-disease-oriented guidelines, seriously increases the chances of multidrug therapy as well. Therefore, we need to use multiple actions to promote safe healthcare. As discussed in the introduction, safe and effective medicine use requires multiple strategies and involvement from all stakeholders (patients, prescribers, health care professionals, and regulatory bodies). Strategies to increase the safe and effective use of medicine range from reviewing the education and training of healthcare students with a particular emphasis on those prescribing and all the way to empowering patients and their care to take increased responsibility for their medication use with increased knowledge and support through their lifelong journey of optimised health. Regulatory bodies need to facilitate better continuity of care and a multidisciplinary approach in order to make all healthcare professionals work at the top of their licenses by promoting strategies to support simultaneous care and ensure each service is provided at the right place, at the right time, and in a timely manner when needed. As previously mentioned, the safe and effective use of medicines needs to be addressed through multiple strategies in education, service provision, and research involving multiple stakeholders like patients, carers and health care providers. However, while focusing on tackling inappropriate medication use and inappropriate polypharmacy and associated harm, it is vital to additionally focus on how to prioritise strategies to prevent new potentially inappropriate prescribing and polypharmacy from

happening by, for example, increased training and education activities. A list of possible strategies/projects to address these three topics, education, services provision and research, are provided in Table 27. In the United Kingdom, an updated geriatric medicine curriculum was published, which may guide improvement in curriculum development in Iceland for healthcare professionals.[270]

There is an Icelandic phrase frequently mentioned, "þetta reddast," which can be translated to "it will all work out okay", and which Icelanders like to keep in mind when faced with challenges. However, this thesis and previously published studies and reports highlighting the high medication consumption among patients in Iceland and the lack of quality in medication use by older patients should urge us to use all measures to tackle this challenge, as there is so much at stake for Icelanders and the whole healthcare system.

5.8 Strengths and limitations

The current thesis has several strengths. A key strength of the present research is the ability to link the nationwide prescription database, which included 95% of prescriptions in Iceland, with clinical data from hospital and primary care settings. One of the strengths of this study is that it represents a comprehensive examination of all tertiary care and most of the secondary care of internal medicine patients in Iceland, as Landspitali is the country's main referral hospital. The extended study period also allows for many patients in the study cohort. Finally, another strength is that there is no loss of follow-up of patients. Additionally, it is worth mentioning that both databases will be maintained for future research projects.

Our study must also be considered with some limitations in mind. One is the retrospective design that relies on the data collected and documented in the healthcare system for clinical purposes. The study is limited by the absence of information on the patient's medication adherence, which may lead to an overestimation of the prevalence of polypharmacy and hyperpolypharmacy. However, it must be noted that over-the-counter medications were not included in the study, which may, on the other hand, lead to an underestimation of polypharmacy and hyperpolypharmacy. Additionally, a combination of medications often used in cardiology, such as angiotensin receptor blockers combined with a thiazide, were counted as one medication. This may lead to underestimation for some patients. The appropriateness of medication use was evaluated by applying the Beers criteria. Some medications on the Beers list are unavailable within the Icelandic health care system. Additionally, as previously stated, the use of databases as the source of data and the reliance on coding has limitations, such as more advanced stages of disease may not be captured in the coding. Artificial intelligence may help overcome this in the coming years.[271]

6 Conclusions

Polypharmacy and potentially inappropriate medication use are common among patients admitted to hospitals both for surgical and internal medicine care. New medication post-discharge for frequent, as well as new, potentially inappropriate medication among older (>65) patients admitted by internal medicine speciality. This thesis demonstrates that polypharmacy among surgical patients was associated with decreased short-term and long-term survival, more extended hospital stays and readmission rates. On the contrary, this thesis also demonstrates that polypharmacy and internal medicine patients were not associated with decreased short-term and long-term survival, more extended hospital stays and readmission rates. This thesis also demonstrated that potentially inappropriate medication use is prevalent among patients admitted by internal medicine speciality and associated risk factors among increased ages, male gender and increased comorbidity.

In the foreseeable future, tackling the challenges of the ageing of the population with multimorbidity and associated polypharmacy will become increasingly alarming in public health. There is no one-size-fits-all solution for addressing polypharmacy and inappropriate prescribing. Additionally, the aim is to initiate medication when there is a need and omit it when there is more harm associated with the treatment. This balance becomes more delicate as the patient becomes more frail. Therefore, multiple measures should be applied, ranging from upscaling educational activities, empowering patients and their carers, implementing multidisciplinary interventions that are both general and targeted at specific medication classes and patient groups, and using computerised prescribing aids when possible. There is a need to further support both healthcare providers and, escpeically, prescribers and patients with strategies to support safe and effective use of medications. The healthcare system is facing increased challenges with the increased ageing of the population, increased multimorbidity and associated risk of polypharmacy and inappropriate medication use. Therefore, it is necessary to add tools to the toolbox of Icelandic healthcare professionals and also the toolbox of patients. We need to increase the collaboration between healthcare professionals and skill shift. Finally, healthcare professionals and patients must apply cautious foresight when initiating new medication and planning an appropriate revision; otherwise, it will not all work out okay (Icelandic: "þetta reddast").

6.1 Strategies

As an additional result of the doctoral project, a workforce plan has been developed to support a wide range of strategies to promote the safe and effective use of medications in Iceland (Table 27).

Table 27 A list of possible strategies/projects to improve polypharmacy, medication appropriateness with improved education, services provision and research

Practice	Research	Education/training
Implementing a national medication review, for example, a version of polypharmacy guidance from Scotland for the target population as a collaborative multidisciplinary project. Training provided on polypharmacy guidance for pharmacists and doctors within the hospital and general practitioner settings.[14]	Establish a nationwide up-to-date database allowing to study polypharmarcy, medication appropriateness, medication use, medication-related harm, adverse drug reaction and prescribing practice. Variation in prescribing practices and data analytics to improve prescribing	Review the curriculum of all health care professionals in Icelandic Universities in relation to the syllabus covering safe and effective medicine use, such as polypharmacy, deprescribing, prescribing cascade, and inappropriate medication use.
Integrating the role of pharmacists in community pharmacies, hospitals, and general practitioners' care in national strategies to tackle polypharmacy and medication appropriateness	Study multidisciplinary interventions to promote appropriate and safe medication usage	Increased training of all health care professionals covering safe and effective use of medicine, like polypharmacy, deprescribing, prescribing cascade and inappropriate medication use
Update regulation for multidose dispensing service and develop guidelines on how to review and optimise the safe and effective use of multidose dispensing services	Neuroleptics (gabapentin, pregabalin) appropriate use	Increased multidisciplinary approach in education: Multidisciplinary training sessions for postgraduate foundation trainees' doctors and pharmacists in general practice settings on medication optimisation.
Establish outpatient service of a clinical pharmacist providing interventions to support patients with polypharmacy or at increased risk of medication-related harm. Multidisciplinary approach if possible.	Antidepressants appropriate use	
Implement virtual medication review and counselling nationwide to tackle inequalities of access to healthcare services.	Medication-induced delirium	
Clinical pharmacist-led follow-up post-discharge.	Medication-induced falls	
Increased instructions on medication use post-discharge among surgical patients, which medications are short-term, and deprescribing support if appropriate.	Antipsychotics Appropriate use	
Implement a medication use checklist for postoperative appointments in the hospital or with a general practitioner.	Explore possibilities to increase health literacy.	
Increased instructions on medication use post-	ADHD medication	

discharge among internal medicine patients, which medications are short-term, and deprescribing support if appropriate.	appropriate use and related admissions to hospital	
Increased emphasis on the environmental effect of medications and the vital role of pharmacists supporting sustainable medication use	The culture around prescribing in Iceland	
Implement a medication use checklist for post-admission appointments in hospitals or general practitioners. Explore the possibility of pharmacists' non-medical prescribing to support medication review and re-prescribing in general practice settings.		
Support a pilot group of clinical pharmacists through the independent prescribing course in collaboration with the medical profession and initiate supplementary prescribing as the first step.		
Regulatory adaptation is needed so pharmacists can create and update the centralised drug chart.		
Adapt regulation so Iceland Health Insurance can pay pharmacists to do medication reviews. This would increase the level of service in rural areas and access to pharmacists in private general practitioner settings.		
Create a national policy on deprescribing pathways		
Increased access to clinical pharmacy service outside of Reykjavík.		
Increased access to clinical pharmacy service in private general practitioner settings		
Increased access to clinical pharmacy service in nursing homes.		
Increase clinical pharmacy service in community pharmacies. Re-prescribing allowance. Clinical pathways like in the UK.		
Flag for general practitioners when a patient with polypharmacy/medication changes - post-admission, can the centralised drug chart be used?		
Empower patients to seek a medication review. Use the information board in general practice settings to inform patients. Replicate the campaign Me and my MedicineReplicate the campaign Me and my Medicine		
Academic detailing (high-risk medication or patient groups)		
Medication adherence – increased awareness-		
Analysis of up-to-date variations in clinical prescribing in different geological areas		

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Original Publications

Paper I

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Original Article

Epidemiology and association with outcomes of polypharmacy in patients undergoing surgery: retrospective, population-based cohort study

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Abstract

Background: The aim of this study was to determine the prevalence of preoperative polypharmacy and the incidence of postoperative polypharmacy/hyper-polypharmacy in surgical patients and their association with adverse outcomes.

Methods: This was a retrospective, population-based cohort study among patients older than or equal to 18 years undergoing surgery at a university hospital between 2005 and 2018. Patients were categorized based on the number of medications: non-polypharmacy (fewer than 5); polypharmacy (5–9); and hyper-polypharmacy (greater than or equal to 10). The 30-day mortality, prolonged hospitalization (greater than or equal to 10 days), and incidence of readmission were compared between medication-use categories.

Results: Among 55 997 patients, the prevalence of preoperative polypharmacy was 32.3 per cent (95 per cent c.i. 33.5 to 34.3) and the prevalence of hyper-polypharmacy was 25.5 per cent (95 per cent c.i. 25.2 to 25.9). Thirty-day mortality was higher for patients exposed to preoperative hyper-polypharmacy (2.3 per cent) and preoperative polypharmacy (0.8 per cent) compared with those exposed to non-polypharmacy (0.6 per cent) ($P < 0.001$). The hazards ratio (HR) of long-term mortality was higher for patients exposed to hyper-polypharmacy (HR 1.32 (95 per cent c.i. 1.25 to 1.40)) and polypharmacy (HR 1.07 (95 per cent c.i. 1.01 to 1.14)) after adjustment for patient and procedural variables. The incidence of longer hospitalization (greater than or equal to 10 days) was higher for hyper-polypharmacy (11.3 per cent) and polypharmacy (6.3 per cent) compared with non-polypharmacy (4.1 per cent) ($P < 0.001$). The 30-day incidence of readmission was higher for patients exposed to hyper-polypharmacy (10.2 per cent) compared with polypharmacy (6.1 per cent) and non-polypharmacy (4.8 per cent) ($P < 0.001$). Among patients not exposed to polypharmacy, the incidence of new postoperative polypharmacy/hyper-polypharmacy was 33.4 per cent (95 per cent c.i. 32.8 to 34.1), and, for patients exposed to preoperative polypharmacy, the incidence of postoperative hyper-polypharmacy was 16.3 per cent (95 per cent c.i. 16.0 to 16.7).

Conclusion: Preoperative polypharmacy and new postoperative polypharmacy/hyper-polypharmacy are common and associated with adverse outcomes. This highlights the need for increased emphasis on optimizing medication usage throughout the perioperative interval.

Registration number: NCT04805151 (http://clinicaltrials.gov).

Introduction

Annually, over 300 million surgical procedures are performed worldwide[1], and this number is expected to grow in the coming decades[2,3]. The surgical population is ageing at a higher rate than the general population, resulting in a significant growth in demand for surgical services. To optimize clinical outcomes for surgical patients, it is essential to identify subgroups at increased risk of poorer outcomes[2].

One such subgroup consists of surgical patients exposed to polypharmacy, the simultaneous use of multiple medications[4,5]. The most widely accepted definition for polypharmacy is the use of five or more medications[6–8], and, recently, hyper-polypharmacy, ten or more medications, has been introduced[9]. Polypharmacy and hyper-polypharmacy are associated with: increased risk of frailty[7]; reduced medication adherence[10]; increased likelihood of unplanned hospitalization[7,10]; loss of functional ability[10]; increased risk of drug interactions[10]; increased usage of healthcare resources[10]; and greater mortality[7]. One of the goals of the WHO is an increased focus on patients exposed to polypharmacy, in order to optimize their

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medications and reduce harm due to medication usage[11]. Another potential focus group is patients using multidose drug dispensing services, where medications are dispensed into one unit for each administration. The use of multidose drug dispensing services has increased, and there is growing evidence regarding its relation to polypharmacy[12] and suboptimal medication appropriateness[13–15].

While polypharmacy may be rational in individual patients with multiple diseases, its prevalence has been used as a quality indicator of prescribing practices[16]. Polypharmacy has been identified as the leading risk for inappropriate prescribing practices[16–18]. This stresses the importance of assessing medication appropriateness among patients exposed to polypharmacy to ensure that treatment is safe and effective.

Many studies on polypharmacy focus on the older population, specific medication classes[19], or general practice[20]. There is a lack of knowledge regarding the incidence of polypharmacy in the adult surgical population, although a recent study demonstrated that polypharmacy is associated with functional decline in older cardiac surgery patients[4].

The aim of this study was to determine the prevalence of preoperative polypharmacy and the incidence of postoperative polypharmacy/hyper-polypharmacy and their association with patient and procedural variables. Furthermore, the authors studied the association between preoperative polypharmacy and postoperative outcomes.

It was hypothesized that preoperative and postoperative polypharmacy is common, especially among older patients, patients with a high co-morbidity and frailty burden, and patients undergoing more complicated surgery. It was further hypothesized that preoperative polypharmacy and hyper-polypharmacy is associated with increased short- and long-term mortality, a longer primary hospitalization, and a higher risk of readmission.

Methods

Study population

This study was a retrospective, population-based cohort study that included all patients older than or equal to 18 years undergoing their first surgery at Landspitali - The National University Hospital of Iceland, during the study interval, between December 2005 and December 2018. The hospital performs all tertiary surgeries and serves as the primary hospital for all surgery for most of the nation.

Ethical approval was obtained from the National Bioethics Committee of Iceland (VSN-14-139-V1) and the Data Protection Authority of Iceland. All databases used for research were de-identified before statistical analysis, and all work was compliant with the General Data Protection Regulation of the European Union. The study protocol was published on clinicaltrials.gov before analysis (NCT04805151)[21], and the study reporting adheres to the STROBE guidelines for reporting of observational studies in epidemiology[20].

Clinical data

This study used the Icelandic perioperative database, a retrospective database that includes clinical data on all surgical procedures performed at Landspitali. Database assembly has been described previously[19]. The database contains information on surgery type and anatomical location using the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP; version 1.14) for surgical classifications[22]. Patient co-morbidities were registered based on ICD9/10 coding from primary care and hospital. The co-morbidity burden was described by calculating the Charlson co-morbidity index and the Elixhauser co-morbidity index, and the frailty risk was assessed by using the hospital frailty risk score[23]. Adverse reactions were defined as any documentation of ICD9/10 codes for adverse drug effect (Y40–59, X40–59, T36–59). Information on filled medications was from the Prescription Medicines Registry of the Directorate of Health database. This national electronic database includes real-time information about all outpatient drug prescriptions in Iceland. Its accuracy is determined regularly by comparing prescribed medications against dispensed medications and is estimated to be 95 per cent. The database includes all prescribed regular and as-required medications, but does not include over-the-counter, topical, and herbal medications. This study obtained data on filled prescriptions 1 year before surgery and up to 1 year after surgery and whether a multidose drug dispensing service was used[19].

Exposure variable definition

The primary exposure was the extent of medication use, defined as the number of different medications filled in the year preceding surgery (preoperative) and the year after surgery (postoperative). Patients were also grouped into categories of non-polypharmacy (fewer than 5), polypharmacy (5–9), and hyper-polypharmacy (greater than or equal to 10) based on their preoperative and postoperative polypharmacy. Furthermore, for each individual, the numbers of medications within different anatomical/pharmacological groups (Anatomical Therapeutic Chemical (ATC) first level) and pharmacological/therapeutical subgroups (ATC second level) were counted in the year preceding surgery and the year after surgery.

Outcome data

The following outcomes were considered: short- and long-term mortality; long primary hospital stay (greater than or equal to 10 days); and risk of readmission (fewer than 30 days).

Statistical analysis

Data analysis was conducted from May 2021 to October 2021. Statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria) version 4.0.3, via R studio (RStudio PBC, Boston, MA, USA), version 1.4.1106. Descriptive statistics were used to present the number of medications. The distribution of the group into preoperative and postoperative medication-use categories was described as a percentage with a 95 per cent c.i. calculated using Pearson–Klopper in the binom package in R. Logistic regression was used to compare univariate and multivariate patient and procedural variables between groups of varying preoperative and postoperative medication use.

Adverse outcomes were compared between categories of medication use using chi-squared tests. Similarly, adverse outcomes were compared between patients with and without an increase in polypharmacy from the year preceding surgery to the year after surgery (increase from no polypharmacy to polypharmacy/hyper-polypharmacy or polypharmacy to hyper-polypharmacy). The association between long-term survival and risk of readmission was plotted using Kaplan–Meier methods and modelled using a Cox proportional hazard risk model. The proportionality assumption was assessed using the cox.zph function in R, quantifying changes in Schoenfeld residuals against time.

To visualize the relationship between 30-day mortality, 30-day readmission, and long primary hospital stay (greater than or equal to 10 days), and the number of medications filled in the year preceding surgery, a restricted cubic spline analysis was performed, with predefined knots of 0, 5, and 10 to mimic the polypharmacy and hyper-polypharmacy classes. No missing data were identified in the variables used for this study.

Results

Clinical characteristics of the patient cohort by preoperative filling

The cohort included 55 997 surgical patients 18 years and older. Of the cohort, 32 136 were female (57.0 per cent), and the median age was 55 (interquartile range (i.q.r.) 39–69) years. Of those, 23 606 (42.2 per cent (95 per cent c.i. 41.7 to 42.6)), 18 988 (32.3 per cent (95 per cent c.i. 33.5 to 34.3)), and 14 303 (25.5 per cent (95 per cent c.i. 25.2 to 25.9)) experienced preoperative non-polypharmacy (fewer than 5), polypharmacy (5–9), and hyper-polypharmacy (greater than or equal to 10) respectively (*Fig. 1*). *Table 1* compares the patient characteristics, including co-morbidities and medication usage, of the patient cohort based on varying degrees of polypharmacy. Most surgeries were elective (65.8 per cent), and elective surgeries were more common among patients exposed to polypharmacy and hyper-polypharmacy than non-polypharmacy. For the cohort, orthopaedic surgical procedures were most common, followed by abdominal, gynaecological, and neurological procedures. Hypertension was the most common co-morbidity among patients exposed to hyper-polypharmacy (55.8 per cent) and polypharmacy (35.0 per cent). However, a benign neoplasm was most common among patients exposed to non-polypharmacy (*Table 1*). With increasing preoperative polypharmacy, there was a higher median age and a higher proportion of female patients. There was also a higher underlying burden of co-morbidity and frailty risk measured by composite indices and individual diagnoses.

The authors assessed reclassification of polypharmacy classification if a shorter window of time to fill before surgery was considered (*Fig. S1*). This revealed that, for example, if only the last 6 months before surgery were considered to classify polypharmacy, roughly 60 per cent of the patients would remain within their medication-use category compared with a 12-month filling window. Similarly, if antibiotics were removed from the list of medications, 80.2 per cent of patients exposed to polypharmacy and 79.9 per cent exposed to hyper-polypharmacy would have remained within their medication-use category.

Types of medications used and multidose dispensing

The most common classes of medications filled before surgery for the whole group were antibiotics (49.0 per cent), cardiac medications (42.4 per cent), and opioids (42.2 per cent) (*Table S1*). For the group with preoperative hyper-polypharmacy, the most commonly filled medication classes were cardiac medications (77.8 per cent), followed by antibiotics (75.0 per cent) and opioids (67.0 per cent). Similarly, patients exposed to polypharmacy most commonly filled antibiotics (56.4 per cent), followed by cardiac medications (50.9 per cent) and opioids (46.8 per cent), and patients exposed to non-polypharmacy most commonly filled antibiotics (27.7 per cent), followed by opioids (23.6 per cent) and paracetamol/orphenadrine combinations (20.7 per cent) in the year preceding surgery.

Of the 55 997 patients, 7680 (13.7 per cent) used a multidose drug dispensing service before surgery. Patients who used multidose drug dispensing services before surgery were older, more likely to undergo cardiac and orthopaedic surgery, and had a higher burden of major co-morbidities and frailty risk, including diagnoses affecting cognitive function (delirium, dementia, and psychiatric diagnoses). They were also more likely to have a previous diagnosis of an adverse drug reaction (*Table S2*). After surgery, 8.1, 22.7, and 69.1 per cent of patients exposed to non-polypharmacy, polypharmacy, and hyper-polypharmacy utilized multidose drug dispensing services respectively.

Incidence of new postoperative polypharmacy/hyper-polypharmacy

Of 23 606 patients who were not exposed to preoperative polypharmacy, the incidence of new postoperative polypharmacy/hyper-polypharmacy was 33.4 per cent (95 per cent c.i. 32.4 to 34.0), and the incidence of new postoperative hyper-polypharmacy was 16.3 per cent (95 per cent c.i. 16.0 to 16.7). For patients exposed to polypharmacy, the incidence of

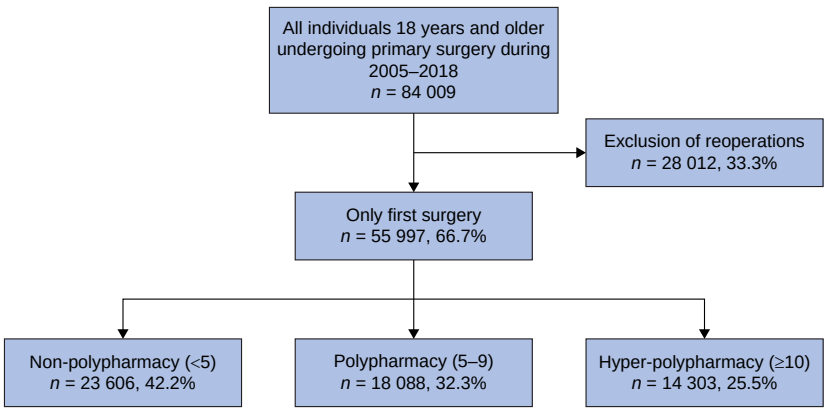


Fig. 1 CONSORT diagram of participant inclusion based on the number of medications filled in the year preceding surgery (fewer than 5 medications = non-polypharmacy, 5–9 medications = polypharmacy, and greater than or equal to 10 medications = hyper-polypharmacy)

Table 1 Patient characteristics of the patient cohort based on the number of different medications filled in the year preceding surgery (fewer than 5 medications = non-polypharmacy, 5–9 medications = polypharmacy, and greater than or equal to 10 medications = hyper-polypharmacy)

	Non-polypharmacy	Polypharmacy	Hyper-polypharmacy	All patients	P
Total patients	23 606 (42.2)	18 088 (32.3)	14 303 (25.5)	55 997	
Female	12 310 (52.1)	10 806 (59.7)	9020 (63.1)	32 136 (57.4)	<0.001
Age (years), median (i.q.r.)	45.00 (32.00–59.00)	58.00 (43.00–69.00)	67.00 (55.00–76.00)	55.00 (39.00–69.00)	<0.001
Multidose dispensing services before surgery	916 (3.9)	2148 (11.9)	4616 (32.3)	7680 (13.7)	<0.001
Number of preoperative medications, median (i.q.r.)	2.00 (1.00–3.00)	7.00 (6.00–8.00)	13.00 (11.00–16.00)	6.00 (2.00–10.00)	<0.001
Number of postoperative medications, median (i.q.r.)	3.00 (1.00–5.00)	7.00 (5.00–10.00)	13.00 (9.00–17.00)	6.00 (3.00–11.00)	<0.001
Elixhauser co-morbidity index*, median (i.q.r.)	0.00 (0.00–3.00)	0.00 (0.00–4.00)	3.00 (0.00–8.00)	0.00 (0.00–4.00)	<0.001
Hospital frailty risk score class					
Low (<5)	18 096 (76.7)	10 586 (58.5)	5034 (35.2)	33 716 (60.2)	
Medium (5–15)	5201 (22.0)	6894 (38.1)	7402 (51.8)	19 497 (34.8)	
High (>15)	309 (1.3)	608 (3.4)	1867 (13.1)	2784 (5.0)	
Co-morbidities					<0.001
Ischaemic heart disease	952 (4.0)	2416 (13.4)	4248 (29.7)	7616 (13.6)	
Congestive heart failure	220 (0.9)	425 (2.3)	1358 (9.5)	2003 (3.6)	
Hypertension	2787 (11.8)	6330 (35.0)	7976 (55.8)	17 093 (30.5)	
Diabetes mellitus	334 (1.4)	1026 (5.7)	2360 (16.5)	4381 (7.8)	
Chronic obstructive pulmonary disease	1814 (7.7)	2839 (15.7)	4323 (30.2)	8976 (16.0)	
Liver disease	147 (0.6)	223 (1.2)	361 (2.5)	731 (1.3)	
Chronic kidney disease	128 (0.5)	316 (1.7)	961 (6.7)	1405 (2.5)	
Malignant neoplasm	2632 (11.1)	3093 (17.1)	3343 (23.4)	9068 (16.2)	
Benign neoplasm	4444 (18.8)	5007 (27.7)	5657 (39.6)	15 108 (27.0)	
Psychiatric	1759 (7.5)	2139 (11.8)	3003 (21.0)	6901 (12.3)	
Delirium	449 (1.9)	674 (3.7)	1020 (7.1)	2143 (3.8)	
Surgery location and classification					<0.001
Emergency operation	10 247 (43.4)	5072 (28.0)	3841 (26.9)	19 160 (34.2)	
Abdominal	4781 (20.3)	3415 (18.9)	2439 (17.1)	10 635 (18.9)	
Cardiac	499 (2.1)	726 (4.0)	596 (4.2)	1821 (3.3)	
Endocrine	464 (2.0)	340 (1.9)	238 (1.7)	1042 (1.9)	
Gynaecology	4450 (18.8)	2978 (16.5)	1469 (10.3)	8897 (15.9)	
Neurosurgery	2309 (9.8)	2335 (12.9)	1770 (12.4)	6414 (11.4)	
Orthopaedic	6983 (29.6)	4490 (24.9)	4221 (29.5)	15 694 (28.1)	
Thoracic	417 (1.8)	306 (1.6)	386 (2.7)	1109 (2.0)	
Urology	1397 (5.9)	1468 (8.1)	1307 (9.1)	4172 (7.4)	
Vascular	1335 (5.6)	1243 (6.9)	1142 (8.0)	3720 (6.7)	

Values are *n* (%) unless otherwise indicated. *The Elixhauser co-morbidity index is a severity index to quantify various patient co-morbidities from multiple chronic diseases into a single number that can be used to assess and correct for patient co-morbidity burden. i.q.r., interquartile range.

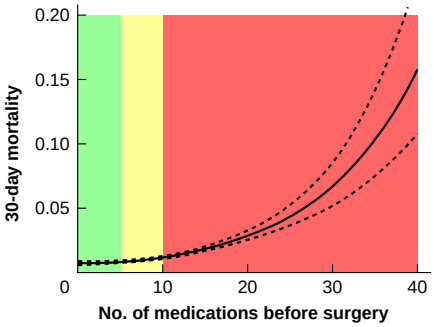


Fig. 2 Association between the number of medications before surgery and 30-day mortality

The figure shows the result of restricted cubic spline analysis of the proportion of patients with the three outcomes. Colours indicate the number of different medications filled in the year preceding surgery: green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy.

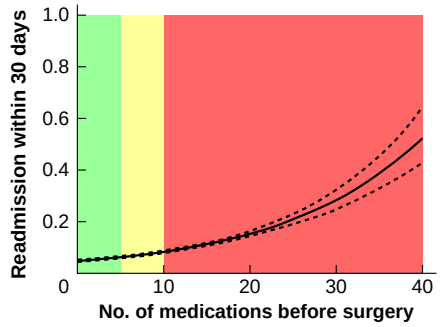


Fig. 3 Association between the number of medications before surgery and the risk of readmission within 30 days

The figure shows the result of restricted cubic spline analysis of the proportion of patients with the three outcomes. Colours indicate the number of different medications filled in the year preceding surgery: green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy.

new postoperative hyper-polypharmacy was 28.9 per cent (95 per cent c.i. 28.3 to 29.6). Patients who had an increase in their number of medications, moving from either non-polypharmacy to polypharmacy or polypharmacy to hyper-polypharmacy were older and had a longer hospital stay compared with those with no change. They had a lower Elixhauser co-morbidity index and

a lower hospital frailty risk index classification and were more likely to have a malignant neoplasm (23.3 *versus* 14.0 per cent) ($P < 0.001$). Additionally, these patients were more likely to have undergone cardiac surgery (6.4 *versus* 2.3 per cent) ($P < 0.001$) or vascular surgery (10.9 *versus* 5.5 per cent) ($P < 0.001$) (*Table S3*).

Clinical outcomes of patients with varying preoperative medication use

An unadjusted restricted cubic spline analysis revealed a strong relationship between the absolute number of different medications filled in the year preceding surgery and the incidence of 30-day mortality, the risk of readmission within 30 days, and a long primary hospital stay (*Fig. 2*, *Fig. 3*, and *Fig. 4*).

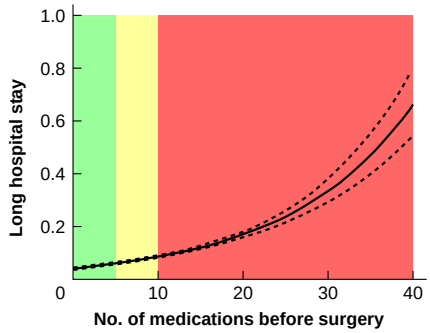


Fig. 4 Association between the number of medications before surgery and a long primary hospital stay (greater than or equal to 10 days)

The figure shows the result of restricted cubic spline analysis of the proportion of patients with the three outcomes. Colours indicate the number of different medications filled in the year preceding surgery: green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy.

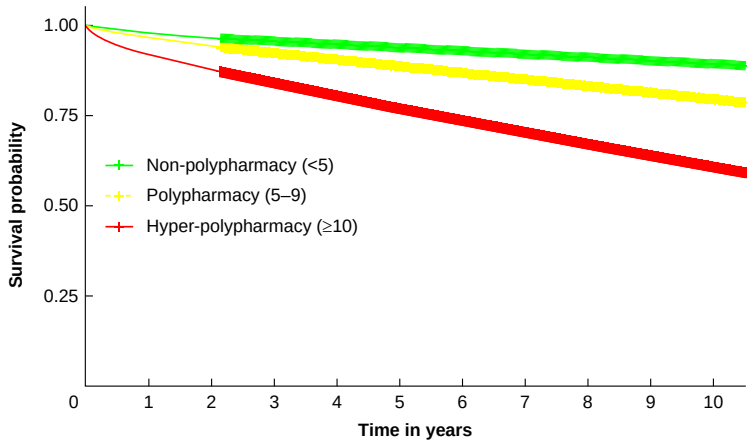
Thirty-day mortality for patients exposed to preoperative hyper-polypharmacy was 2.3 per cent, compared with 0.8 and 0.6 per cent for patients exposed to polypharmacy and non-polypharmacy respectively ($P < 0.001$). A long primary hospital stay (greater than or equal to 10 days) was more common for patients exposed to hyper-polypharmacy (11.3 per cent) and polypharmacy (6.3 per cent) compared with non-polypharmacy (4.1 per cent) ($P < 0.001$). Similarly, the incidence of 30-day readmission was higher for patients exposed to hyper-polypharmacy (10.2 per cent) compared with polypharmacy (6.1 per cent) and non-polypharmacy (4.8 per cent) ($P < 0.001$). Patients who were readmitted within 30 days had a higher incidence of a diagnosis of adverse drug reactions within 30 days compared with those who did not get readmitted (1 *versus* 0.1 per cent) ($P < 0.001$).

Long-term survival

Fig. 5 compares long-term survival between groups of variable polypharmacy classification with 1-year all-cause mortality. After adjustment for age, sex, length of stay, co-morbidities (hypertension, diabetes, chronic obstructive pulmonary disease, ischaemic heart disease, liver disease, chronic kidney disease, malignant neoplasm, and benign neoplasm), Elixhauser co-morbidity index, procedural classification and urgency, there was a higher hazards ratio (HR) of long-term mortality for patients exposed to hyper-polypharmacy (HR 1.32 (95 per cent c.i. 1.25 to 1.40)) and polypharmacy (HR 1.07 (95 per cent c.i. 1.01 to 1.14)) compared with non-polypharmacy (HR 1.00 (reference)).

Discussion

This study identified that preoperative polypharmacy/hyper-polypharmacy and new postoperative polypharmacy/hyper-polypharmacy were common among surgical patients,



No. at risk

Non-polypharmacy (<5)	23 606	23 076	22 807	21 069	18 916	16 734	14658	13 393	11 751	9944	8159
Polypharmacy (5–9)	18 088	17 449	17 079	15 618	13 943	12 347	10831	9807	8467	7039	5629
Hyper-polypharmacy (≥10)	14 303	13 142	12 556	11 242	9812	8481	7297	6450	5477	4479	3570

Fig. 5 Survival of cohort based on polypharmacy classification

A Kaplan–Meier survival curve of long-term survival of patients compared based on the number of medications before surgery (green, fewer than 5 medications = non-polypharmacy; yellow, 5–9 medications = polypharmacy; and red, greater than or equal to 10 medications = hyper-polypharmacy). Thicker lines represent 95% confidence intervals.

especially older patients, with a high co-morbidity and frailty risk burden. In addition, the findings confirm that preoperative polypharmacy is associated with a higher short- and long-term mortality, a longer primary hospital stay, and a higher risk of readmission.

Previous studies have investigated polypharmacy, and the prevalence and incidence vary among countries, although there appears to be an overall rise in the trend of polypharmacy[7,24–29]. These studies are often difficult to compare due to the lack of a coherent definition of polypharmacy and variation in the study population.

Most literature regarding polypharmacy uses similar definitions, but has a focus on the epidemiology in a general population and mostly in older patients[4,5,25–27,29]. In a Scottish study of patients from a general population (older than or equal to 20 years), the prevalence of polypharmacy was 16.3 per cent and that of hyper-polypharmacy was 5.8 per cent[30]. Similarly, a study of general practice patients (older than or equal to 18 years) in Switzerland found that the prevalence of either polypharmacy or hyper-polypharmacy was 24 per cent[28]. Likewise, a Danish study of general practice older adults (older than or equal to 65 years) found the prevalence of polypharmacy and hyper-polypharmacy to be 29.0 and 5 per cent respectively[26]. Finally, a Swedish study of general practice older adults (older than or equal to 65 years) found the prevalence of polypharmacy to be 44.0 per cent and that of hyper-polypharmacy to be 11.7 per cent[27]. All of these are substantially lower than our reported rates of polypharmacy (32.3 per cent) and hyper-polypharmacy (25.5 per cent). However, it should be kept in mind that the authors describe a surgical population that likely has a higher disease burden, in particular in the year preceding surgery. Indeed, the observed prevalence of preoperative polypharmacy and hyper-polypharmacy is close to the reported prevalence in two studies conducted in surgical populations, although the target populations were older. A Canadian study on elective non-cardiac surgery patients (older than 65 years) reported a 54.8 per cent prevalence of polypharmacy[5] and a study from the Netherlands on older patients (older than 70 years) undergoing cardiac surgery reported the prevalence of polypharmacy and hyper-polypharmacy to be 67 and 26 per cent[4].

The authors found that the incidence of new postoperative polypharmacy in the year after surgery was 33.4 per cent, and new hyper-polypharmacy was 6.7 per cent among patients not exposed to preoperative polypharmacy, and the incidence of new postoperative hyper-polypharmacy for patients exposed to preoperative polypharmacy was 28.9 per cent. A Danish study of older adults (older than or equal to 65 years) estimated the 5-year incidence of polypharmacy to be 46.9 per cent and that of hyper-polypharmacy to be 17.7 per cent, slightly lower than identified in the current study. It should be kept in mind that the population and follow-up time were different[26]. These findings raise questions about whether surgery or admission to hospital may be a gateway into new or an accelerated rate of polypharmacy or hyper-polypharmacy.

Patient factors associated with polypharmacy and hyper-polypharmacy were not unexpected, as older patients are more likely to have multiple co-morbidities potentially requiring medications[7,30]. Previous studies have shown similar results[31]. Interestingly, a high hospital frailty risk score class is associated with polypharmacy, but not hyper-polypharmacy, potentially due to the patients being more sensitive to adverse drug effects and a shift towards deprescribing in this patient cohort.

It was found in the current study that the rate of multidose drug dispensing service utilization increased with levels of polypharmacy, co-morbidity burden, and age. Multidose drug dispensing services may be convenient for patients taking multiple medicines, especially those with worse cognitive function. Annual renewal of prescriptions for a multidose drug dispensing service may also give a unique platform periodically for medication optimization if used appropriately. Unfortunately, the use of multidose drug dispensing services also makes it more challenging to deprescribe, and increased automation in renewal could potentially discourage deprescribing. Studies of older adults (older than 75 years) have identified multidose drug dispensing services as a risk factor for uncritical renewals and insufficient medication optimization[13,27]. This subgroup of patients therefore warrants special attention to ensure their medications are optimally managed, both before surgery and after surgery.

The most common classes of prescriptions filled in the year preceding surgery for the whole group were antibiotics (49.0 per cent), cardiac medications (42.4 per cent), and opioids (42.2 per cent). The high prescription rates for antibiotics and opioids are concerning. The high usage rate of antibiotics raises questions about overuse and should be researched further due to increasing concern regarding the development of antibiotic resistance. Even though a high prevalence of opioid users was expected in a surgical population that is predominantly awaiting elective surgery, it is likely that these patients might benefit from medication counselling during their wait for surgery to reduce the risk for persistent postoperative opioid use and the harmful effects from prolonged opioid usage[19,32].

The clinical outcomes associated with degree of polypharmacy were largely consistent with the previous literature documenting the association of polypharmacy with adverse clinical outcomes[5,7,25,26,29]. Despite a clear dose–response relationship and a biological plausibility, it is unclear whether these adverse clinical outcomes are directly mediated by polypharmacy, such as by adverse drug effects, or if they serve as a marker of co-morbidity burden only. While causality cannot be established, a potential mechanism explaining the connection between polypharmacy and the risk of readmission and mortality could be mediated through a risk of inappropriate prescribing that sets a patient at risk of increased anticholinergic burden, at risk of falls via orthostatism, and at risk of respiratory complications. This is a topic of further research.

One of the study's strengths is that it makes use of a centralized nationwide Prescription Medicines Registry that allows detailed information to be obtained; it includes over 95 per cent of all prescriptions in the country, and the ability to link different registries to collect information via the personal identification number. A key strength is the large number of participants included in an extensive surgical database and complete follow-up for survival analysis. Another strength is that all surgeries were performed at the same national hospital.

A notable limitation is the dependence of classifying polypharmacy burden based on the number of different ACT classes filled. Using this method may overestimate the number of medications the participants take regularly. It might include medications solely used in the perioperative interval like antibiotics and opioids, which might inflate the number of medications and increase the incidence. However, it also does not include over-the-counter medications, which can contribute to polypharmacy. Also, combination therapies (such as combinations of angiotensin-converting-enzyme inhibitors and

diuretics), count as a single medication in the data set. For particular subgroups of patients, such as patients with hypertension, the methodology underestimates the degree of polypharmacy[33]. It is not possible to state that the readmission, mortality, or longer hospital stay was directly related to medication-related problems.

While the presence of polypharmacy/hyper-polypharmacy certainly associates with a higher burden of co-morbidity and frailty, this is highly associated with the potential for inappropriate prescribing and could be used to identify patients who would benefit from medication review. A special emphasis should be put on medications listed as potentially inappropriate for older patients based on criteria such as the Beers criteria or screening tool for older persons prescriptions/screening tool to alert to right treatment criteria and the appropriate use of antibiotics, pain medications, and sedatives in the perioperative interval. Additionally, patients at risk of new postoperative polypharmacy could be identified and guided towards targeted follow-up focused on medication review and deprescribing, ideally within a multidisciplinary team involving clinical pharmacists, primary care physicians, or geriatricians when appropriate.

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Author contributions

Freyja Jónsdóttir (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Anna B. Blöndal (Conceptualization, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Aðalsteinn Guðmundsson (Conceptualization, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Ian Bates (Conceptualization, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Jennifer M. Stevenson (Conceptualization, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), and Martin I. Sigurðsson (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The study permissions do not allow individual patient data sharing.

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Paper II

BMJ Open

The association of degree of polypharmacy before and after among hospitalised internal medicine patients and clinical outcomes: a retrospective, population-based cohort study

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ABSTRACT

Objectives To determine the prevalence and incidence of polypharmacy/hyperpolypharmacy and which medications are most prescribed to patients with varying burden of polypharmacy.

Design Retrospective, population-based cohort study.

Setting Iceland.

Participants Including patients (≥18 years) admitted to internal medicine services at Landspitali – The National University Hospital of Iceland, between 1 January 2010 with a follow-up of clinical outcomes through 17 March 2022.

Main outcomes measures Participants were categorised into medication use categories of non-polypharmacy (<5), polypharmacy (5–10) and hyperpolypharmacy (>10) based on the number of medications filled in the year predischarge and postdischarge. The primary outcome was prevalence and incidence of new polypharmacy. Secondary outcomes were mortality, length of hospital stay and re-admission.

Results Among 85 942 admissions (51% male), the median (IQR) age was 73 (60–83) years. The prevalence of preadmission non-polypharmacy was 15.1% (95% CI 14.9 to 15.3), polypharmacy was 22.9% (95% CI 22.6 to 23.2) and hyperpolypharmacy was 62.5% (95% CI 62.2 to 62.9). The incidence of new postdischarge polypharmacy was 33.4% (95% CI 32.9 to 33.9), and for hyperpolypharmacy was 28.9% (95% CI 28.3 to 29.5) for patients with preadmission polypharmacy. Patients with a higher level of medication use were more likely to use multidose drug dispensing and have a diagnosis of adverse drug reaction. Other comorbidities, including responsible subspeciality and estimates of comorbidity and frailty burden, were identical between groups of varying polypharmacy. There was no difference in length of stay, re-admission rate and mortality.

Conclusions Preadmission polypharmacy/hyperpolypharmacy and postdischarge new polypharmacy/hyperpolypharmacy is common amongst patients admitted to internal medicine. A higher level of medication use category was not found to be associated with demographic, comorbidity and clinical outcomes. Medications that are frequently inappropriately prescribed were among the most prescribed medications in the group. An increased focus on optimising medication usage is needed after hospital admission.

Trial registration number NCT05756400.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Connection between the nationwide prescription database, which included 95% of prescriptions in Iceland, with clinical data from hospital and primary care settings.
⇒ Comprehensive examination of all tertiary care and most of secondary care of internal medicine patients in Iceland, as Landspitali is the main referral hospital for the country.
⇒ Extended study period allowing many patients in the study cohort.
⇒ Limitations include the absence of information on the patient's medication adherence, which may lead to an overestimation of the prevalence of polypharmacy and hyperpolypharmacy.
⇒ The study does not include over-the-counter medications, which may lead to an underestimation of polypharmacy and hyperpolypharmacy.

INTRODUCTION

Polypharmacy refers to the simultaneous use of multiple medicines.[1] The most widely accepted definition for polypharmacy refers to the use of 5 or more medications, but more recently, hyperpolypharmacy has been defined as the use of 10 or more medications.[2] Polypharmacy has predominantly been studied in older populations,[3–5] and only a minority of studies describe the epidemiology in populations including younger adults.[1 6] The prevalence varies among studies depending on study settings, applied definitions and study period. A recent meta-analysis reported pooled prevalence of polypharmacy was 37% (95% CI 31% to 43%).[7] The Global

Patient Safety Challenge, released by WHO in 2017, highlights high-risk situations, polypharmacy and transitions of care as three key areas to focus on to prevent avoidable medication-related harm.[8]

Improved survival of the population will likely result in increased burden of multimorbidity and, consequently, polypharmacy in the upcoming years.[9–11] Increasing multimorbidity and associated polypharmacy is associated with several adverse health consequences, including increased likelihood of potentially inappropriate prescribing,[12] hospitalisation,[13–15] re-admission[16] and death.[15 17 18] Prescription of multiple medications simultaneously may be appropriate and clinically needed in certain instances. Nevertheless, inappropriate prescribing of multiple medications simultaneously contributes to adverse health outcomes if medications are used when no longer clinically indicated.[19] Polypharmacy is associated with higher age (45% ≥65 years vs 25% <65 years), and management in certain healthcare settings have been identified as patient-related risk factors for developing polypharmacy (community 20% vs outpatients 37% vs inpatients 52%).[7]

Studies have shown that a medication review, where healthcare professionals identify inappropriate prescribing during hospitalisation, is associated with reduced risk of re-admission.[20 21] Deprescribing is 'the withdrawal process of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes, and should be a part of a medication review'.[22–24] Clinical trials on safety aspects of new medicine usually exclude older patients with multiple comorbidities, which may lead to limited knowledge of the potential risk of taking numerous medications.[25] Additionally, there has been a significant increase in clinical guidelines addressing specific conditions that risk shifting the focus on individual conditions rather than how multiple coexisting conditions and their treatments interact.[7 26 27] System-related risk factors for polypharmacy include poorly updated medical records and automated medication re-prescribing.[28]

Polypharmacy in patients admitted to internal medicine is likely prevalent as this population carries a significant burden of comorbidities and frailty. Furthermore, an acute admission to the internal medicine ward may increase the burden of polypharmacy.

The study aimed to determine the prevalence of preadmission polypharmacy and incidence of postdischarge polypharmacy/hyperpolypharmacy and their association with patient factors, admitting subspeciality, and clinical outcomes.

We hypothesised that predischarge and postdischarge polypharmacy is common, especially among: (1) Older patients and (2) Patients with a high comorbidity and frailty burden. We further hypothesised that preadmission polypharmacy and hyperpolypharmacy were associated with: (1) Increased short-term and long-term mortality; (2) A more extended primary hospitalisation; and (3) A higher risk of re-admission.

METHODS

Study population

The study was a retrospective, population-based cohort study that included all patients ≥18 years hospitalised in internal medicine wards at Landspitali – The National University Hospital of Iceland during the study period between 1 January 2010, with a follow-up of clinical outcomes through 17 March 2022. The hospital serves as the primary hospital for approximately 75% of the nation and the tertiary hospital for the whole country. While the hospital has subspeciality-specific wards (eg, haematology, oncology, cardiology, pulmonology), patients with generic admission diagnoses not requiring subspecialty care are often admitted to general internal medicine or any subspeciality wards with bed availability.

All data sources used for research were de-identified before statistical analysis, and all work was compliant with the General Data Protection Regulation of the European Union. The study protocol was published on clinicaltrials.gov before analysis (NCT05756400), and the study reporting adheres to the STROBE guideline reporting of observational studies in epidemiology.[29]

Patient and public involvement

None

Clinical data

The processing of variables for this study from various electronic data sources resulted in the generation of the Icelandic Internal Medicine Database. This retrospective database includes clinical data on all patients admitted to internal medicine services at Landspitali – the National University Hospital of Iceland, between 1 January 2010 and 31 December 2020. The database contains baseline patient characteristics such as gender, age and admitting internal medicine subspecialty. If the patient was transferred between services (1.8% of admissions), the service primarily available for the admission was documented as the admitting service. The database also included information on whether the patient was admitted to the intensive care unit and whether the admission was linked to rehabilitation, geriatric or palliative care services following discharge from the acute service. Information on the date of admission and discharge, as well as the length of acute admission and length of acute and rehabilitation admission, was also registered. An admission to the internal medicine ward was defined as any admission for patients to an inpatient status within internal medicine service regardless of its duration. This excluded patients who solely received care in the acute and emergency departments.

Patient comorbidities were gathered from hospital information and primary care coded with *the* International Statistical Classification of Diseases, and Related Health Problems, tenth revision, (ICD10) classification system, and these diagnoses were also used to estimate the comorbidity and frailty burden using the van Walraven Modified Score,[30] the Elixhauser Comorbidity Index[31]

and the Hospital Frailty Risk Score.[32] Information on the date of death was collected from the Iceland Causes of Death Register. While establishing this Internal Medicine Database, no patients were lost to follow-up for mortality outcomes. Adverse drug reactions were defined as any documentation of ICD10 codes for adverse drug effects (Y40–59, X40–59, T36–59).

Medication data

Information on filled/dispensed medications from the Prescription Medicines Registry of the Directorate of Health database spanning 1 year before admission and 1 year postdischarge was gathered. The Icelandic Prescription Registry provides real-time information about all outpatient drug prescriptions in Iceland. Its accuracy is estimated frequently by comparing prescribed medications against dispensed medications and is estimated to be 95%. The database includes all prescribed regular and as-required drugs but does not include over-the-counter, topical and herbal medications. Medication information was coded based on the Anatomical Therapeutical Chemical (ATC) classification. The database also includes information that can be used to identify whether a multidose drug dispensing service was used.[33]

Exposure variable definition

The primary exposure was the extent of medication use, defined as the number of different medications filled in the year preceding (preadmission) and the year following discharge (postdischarge). Patients were separated into three groups based on these medication use categories of non-polypharmacy (<5), polypharmacy[5–9] and hyperpolypharmacy (≥10) based on their predischarge and postdischarge medication filling. Furthermore, the number of medications within different anatomical/pharmacological groups (ATC first level) and pharmacological/therapeutical subgroups (ATC second level) filled in the year preceding and following admissions were counted. The medication use category was also estimated after eliminating antibiotics from the medication database to estimate the burden of polypharmacy without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification.

Outcome data

Primary outcomes included prevalence of preadmission and incidence of new postdischarge polypharmacy. Secondary outcomes were mortality (short-term, < 30 days and long-term mortality), length of hospital stay (number of days, ≥10 days) and re-admission (number of days until re-admission, re-admission <30 days).

Statistical analysis

Data analysis was undertaken from December 2022 through March 2023. All statistical analyses for this study were conducted using R V.4.2.2 (The R Foundation for Statistical Computing R, Vienna, Austria), via R studio V.2022.12.0 (RStudio PBC, USA). Descriptive statistics were used to exhibit the number of medications. The distribution of the medication use into categories of varying polypharmacy predischarge and postdischarge was described as a percentage with a 95% CI calculated using the Pearson-Klopper method to obtain binomial probability in the *binom* package in R. Logistic regression was used to compare patient and admission properties between the medication use categories predischarge and postdischarge, mortality within 30 days and re-admission within 30 days. The Kaplan Meier plot was used to plot long-term mortality between different medication use categories. No missing data were identified in the variables used for this study.

Adverse outcomes were compared between categories of medication use using χ^2 tests. Likewise, adverse outcomes were contrasted between patients with and without an increase in polypharmacy from the year preceding admission to the year following discharge (an increase from no polypharmacy to polypharmacy/hyperpolypharmacy or polypharmacy to hyperpolypharmacy).

RESULTS

Clinical characteristics of the patient cohort

The cohort included 85 942 individual admissions to internal medicine at the Landspitali University Hospital for 38 338 patients with a median (IQR) 1 (1–3) admission, ranging from 1 to 40 admissions. Of the cohort, 43 914 were male (51.1%), and the median (IQR) age was 73 (60–82) years. Most of the study population had a high burden of comorbidity (Elixhauser Comorbidity Score (39%>8) and a risk of frailty (medium or high Hospital Frailty Risk Index classification (62.5%)). The most common comorbidity was hypertension (54.1%), chronic obstructive pulmonary disease (32.3%), ischaemic heart disease (30.8), malignant neoplasm (25.0%) and congestive heart failure (20.2%).

Admissions were most common to cardiology (21.7%), general medicine (13.5%) and pulmonology (10.6%). Most patients used a multidose drug dispensing service (54.7%) before admission (online supplemental table S1). Table 1 also compares admitting specialty and medication usage for the patient cohort based on varying degrees of polypharmacy.

Clinical characteristics of the patient cohort by preadmission filling

The prevalence of preadmission non-polypharmacy was 15.1% (95% CI 14.9% to 15.3%), polypharmacy was 22.9% (95% CI 22.6% to 23.2%) and hyperpolypharmacy was 62.5% (95% CI 62.2 to 62.9) (figure 1). Patients with a higher level of medication use category were more likely to be male and have a previous diagnosis of adverse drug reaction. Patients with hyperpolypharmacy were more likely to use multidose drug dispensing services (65.9%) compared with polypharmacy (45.6%) and non-polypharmacy (22.0%). Patients who used multidose

Table 1 Patient characteristics of the patient cohorts are based on the number of medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy)

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Total number of patients	12 926 (15.1)	19 554 (22.9)	53 462 (62.5)	85 942	
Sex (male)	6664 (51.6)	10 052 (51.4)	27 198 (50.9)	43 914 (51.1)	0.250
Age, (median (IQR)), years	72.00 (60.00, 83.00)	73.00 (60.00, 82.00)	73.00 (60.00, 82.00)	73.00 (60.00, 82.00)	0.877
(15, 25)	227 (1.8)	351 (1.8)	960 (1.8)	1538	0.558
(25, 35)	475 (3.7)	708 (3.7)	1875 (3.5)	3058	
(35, 45)	598 (4.7)	936 (4.8)	2501 (4.7)	4035	
(45, 55)	1024 (8.0)	1590 (8.2)	4360 (8.2)	6974	
(55, 65)	1923 (15.0)	2968 (15.3)	7996 (15.1)	12 887	
(65, 75)	2838 (22.1)	4067 (21.0)	11 534 (21.7)	18 439	
(75, 85)	3360 (26.2)	5207 (26.9)	13 879 (26.2)	22 446	
(85, 95)	2384 (18.6)	3563 (18.4)	9954 (18.8)	15 901	
Multidose dispensing services	2838 (22.0)	8919 (45.6)	35 235 (65.9)	46 992 (54.7)	<0.001
Number of preadmission medications (median (IQR))	2.00 (1.00, 3.00)	7.00 (6.00, 8.00)	16.00 (13.00, 21.00)	12.00 (7.00, 18.00)	<0.001
Number of postdischarge medications (median (IQR))	5.00 (2.00, 8.00)	9.00 (6.00, 12.00)	15.00 (10.00, 20.00)	12.00 (7.00, 17.00)	<0.001
Number of preadmission medications without antibiotics (median (IQR))	2.00 (0.00, 3.00)	6.00 (5.00, 8.00)	14.00 (11.00, 19.00)	11.00 (6.00, 16.00)	<0.001
Elixhauser Comorbidity Index (IQR))	6.00 (0.00, 12.00)	6.00 (0.00, 13.00)	6.00 (0.00, 12.00)	6.00 (0.00, 12.00)	0.804
(<1)	3492 (27.0)	5245 (26.8)	14 523 (27.2)	23 260 (27.1)	0.791
(1–4)	1911 (14.8)	2963 (15.2)	8039 (15.0)	12 913 (15.0)	
(4–5)	860 (6.7)	1355 (6.9)	3608 (6.7)	5823 (6.8)	
(5–8)	1618 (12.5)	2351 (12.0)	6421 (12.0)	10 390 (12.1)	
(>8)	5045 (39.0)	7640 (39.1)	20 871 (39.0)	33 556 (39.0)	
Hospital Frailty Risk Score class					0.976
Low (< 5)	4823 (37.3)	7334 (37.5)	20 111 (37.6)	32 268 (37.5)	
Medium (5–15)	5844 (45.2)	8828 (45.1)	24 070 (45.0)	38 742 (45.1)	
High (> 15)	2259 (17.5)	3392 (17.3)	9281 (17.4)	14 932 (17.4)	
Comorbidities					
Ischaemic heart disease	4017 (31.1)	5967 (30.5)	16 477 (30.8)	26 461 (30.8)	0.545
Congestive heart failure	2644 (20.5)	3952 (20.2)	10 734 (20.1)	17 330 (20.2)	0.621

Continued

Table 1 Continued

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Hypertension	7081 (54.8)	10 554 (54.0)	28 855 (54.0)	46 490 (54.1)	0.236
Diabetes mellitus	2108 (16.3)	3143 (16.1)	8804 (16.5)	14 055 (16.4)	0.438
Chronic obstructive pulmonary disease	4118 (31.9)	6379 (32.6)	17 288 (32.3)	27 785 (32.3)	0.353
Liver disease	405 (3.1)	658 (3.4)	1635 (3.1)	2698 (3.1)	0.109
Chronic kidney disease	1311 (10.1)	2054 (10.5)	5268 (9.9)	8633 (10.0)	0.032
Malignant neoplasm	3265 (25.3)	4821 (24.7)	13 376 (25.0)	21 462 (25.0)	0.431
Psychiatric	2094 (16.2)	3284 (16.8)	8812 (16.5)	14 190 (16.5)	0.354
Dementia	253 (2.0)	402 (2.1)	1139 (2.1)	1794 (2.1)	0.438
Delerium	1183 (9.2)	1715 (8.8)	4800 (9.0)	7698 (9.0)	0.480
Internal medicine speciality					0.129
General internal medicine	1741 (13.5)	2671 (13.7)	7205 (13.5)	11 617 (13.5)	
Geriatrics	1072 (8.3)	1611 (8.2)	4602 (8.6)	7285 (8.5)	
Cardiology	2746 (21.2)	4269 (21.8)	11 646 (21.8)	18 661 (21.7)	
Endocrine	198 (1.5)	315 (1.6)	864 (1.6)	1377 (1.6)	
Gastroenterology	1112 (8.6)	1598 (8.2)	4293 (8.0)	7003 (8.1)	
Infectious diseases	733 (5.7)	1111 (5.7)	2901 (5.4)	4745 (5.5)	
Haematology	665 (5.1)	958 (4.9)	2783 (5.2)	4406 (5.1)	
Nephrology	302 (2.3)	479 (2.4)	1299 (2.4)	2080 (2.4)	
Neurology	1107 (8.6)	1699 (8.7)	4316 (8.1)	7122 (8.3)	
Oncology	853 (6.6)	1218 (6.2)	3391 (6.3)	5462 (6.4)	
Dermatology	79 (0.6)	106 (0.5)	257 (0.5)	442 (0.5)	
Pulmonology	1352 (10.5)	2054 (10.5)	5674 (10.6)	9080 (10.6)	
Rheumatology	588 (4.5)	923 (4.7)	2699 (5.0)	4210 (4.9)	
Rehabilitation	144 (1.1)	207 (1.1)	597 (1.1)	948 (1.1)	
Palliative care	234 (1.8)	335 (1.7)	935 (1.7)	1504 (1.8)	
Linked admissions					
Geriatrics	467 (3.6)	687 (3.5)	2007 (3.8)	3161 (3.7)	0.283
Palliative care	127 (1.0)	173 (0.9)	534 (1.0)	834 (1.0)	0.375
Rehabilitation	125 (1.0)	215 (1.1)	530 (1.0)	870 (1.0)	0.371
Intensive care unit admission	715 (5.5)	1127 (5.8)	2937 (5.5)	4779 (5.6)	0.366
Outcomes					

Continued

Table 1 Continued

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Number of preadmission medications (median (IQR))	2.00 (1.00, 3.00)	7.00 (6.00, 8.00)	16.00 (13.00, 21.00)	12.00 (7.00, 18.00)	<0.001
Number of postdischarge medications (median (IQR))	5.00 (2.00, 8.00)	9.00 (6.00, 12.00)	15.00 (10.00, 20.00)	12.00 (7.00, 17.00)	<0.001
Number of preadmission medications without antibiotics (median (IQR))	2.00 (0.00, 3.00)	6.00 (5.00, 8.00)	14.00 (11.00, 19.00)	11.00 (6.00, 16.00)	<0.001
Diagnosis of adverse drug reaction preadmission (%)	506 (3.9)	1436 (7.3)	7393 (13.8)	9335 (10.9)	<0.001
Diagnosis of adverse drug reaction postdischarge (%)	388 (3.0)	946 (4.8)	3793 (7.1)	5127 (6.0)	<0.001
Next admission (median (IQR))	118.00 (26.00, 438.00)	124.00 (26.00, 463.25)	128.00 (27.00, 468.00)	125.00 (27.00, 462.00)	0.031
Mortality <30 days (%)	853 (6.6)	1266 (6.5)	3519 (6.6)	5638 (6.6)	0.857
Re-admission within 30 days (%)	1961 (15.2)	2946 (15.1)	7973 (14.9)	12 880 (15.0)	0.717
Length of stay (median (IQR))	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	0.630

Values are presented as count (%) or median (IQR) unless specified otherwise. Linked admissions refers to whether the admission was linked to rehabilitation, geriatric or palliative care services following discharge from the acute service.

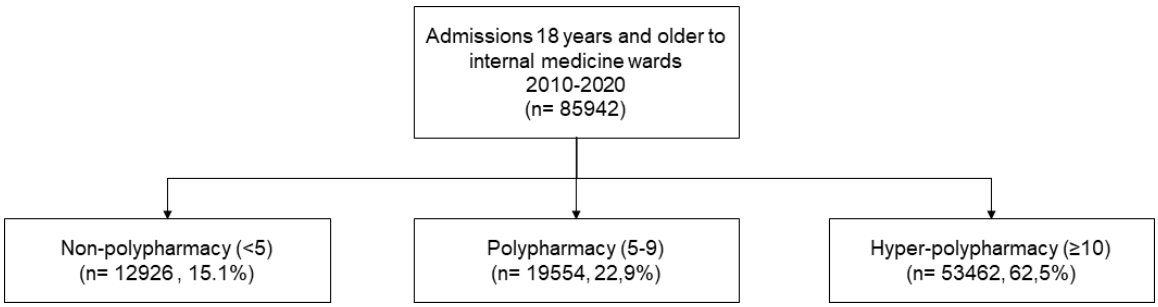

Figure 1 A consort diagram of participant inclusion based on the number of different medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy).

drug dispensing services before admission were more likely to have a previous diagnosis of an adverse drug reaction. Figure 2 shows a comparison of the medication use categories separated into three groups based on the medication use categories of non-polypharmacy (<5), polypharmacy[5–9] and hyperpolypharmacy (≥10) and over the observation period 2010–2020. If antibiotics were excluded from the medication list the patients, 87.9% of patients with polypharmacy and 90.8% with hyperpolypharmacy would have remained within their medication use category. There was no change in the prevalence of polypharmacy/hyperpolypharmacy over the study period.

Types of medications used and multidose dispensing

The most common classes of medications filled in the year preceding preadmission are medications acting on the central nervous system. A total of 80.6% of the group filled prescriptions within this category, including opioids (51.0%), Z-drugs (43%), antidepressants (37.9%) and benzodiazepines (29.0%). The second most filled medication class was cardiac medications (74.5%) (table 2).

For the group with preadmission hyperpolypharmacy, the most filled medication class was medications acting on the nervous system (94.4%), including opioids (65.7.0%), antidepressants (50.2%) and benzodiazepines (40.2%). The second most filled medication class was cardiac medications (87.4%). Similarly, in patients with polypharmacy, the most filled medications class was medications acting on the nervous system (74.1%), including opioids (34.6%), antidepressants (24.6%) and benzodiazepines (14.9%). The second most filled medication class was cardiac medications (69.9%). In patients with non-polypharmacy, the most filled medication class was medications acting on the nervous system (33.5%), including opioids (14.8%), antidepressants (7.2%) and benzodiazepines (4.0%); the second most filled medication class was cardiac medications (27.7%).

Incidence of new postdischarge polypharmacy/hyperpolypharmacy

Of 85942 admissions, 18.4% (95% CI 18.2% to 18.7%) had an increase in the medication use category, moving

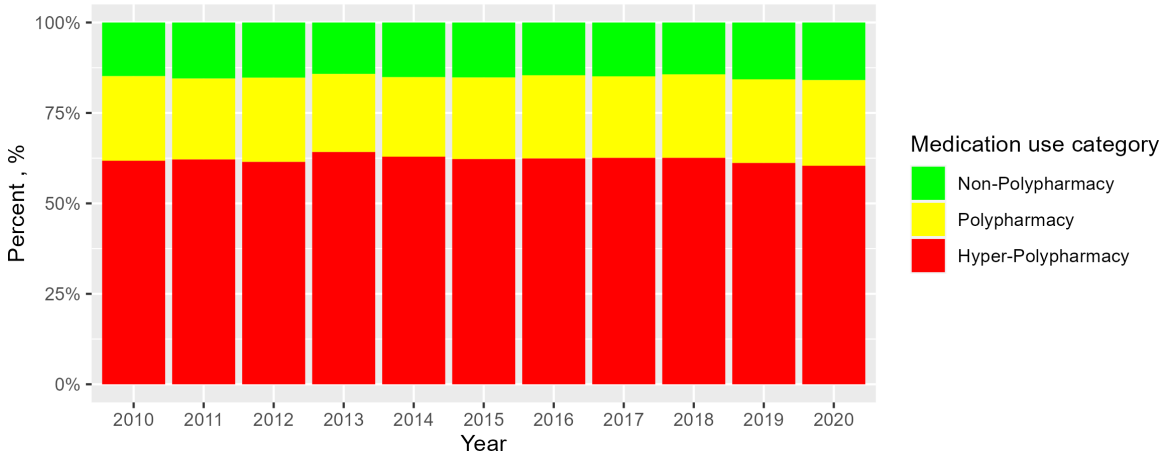

Figure 2 The annual prevalence of the medication use categories over the study period 2010–2020. Colours indicate the medication use categories (green <5 medications = non-polypharmacy, yellow 5–9 medications = polypharmacy and red ≥10 medications = hyperpolypharmacy) filled in the year preceding admission by internal medicine.

Table 2 The table shows the patients' patterns of preadmission prescribed medications

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Total number of patients	12 926 (15.1)	19 554 (22.9)	53 462 (62.5)	85 942	
Preadmission medication					<0.001
Proton pump inhibitors	1163 (9.0)	5352 (27.4)	33 063 (61.8)	39 578 (46.1)	
Antidiabetics	281 (2.2)	1632 (8.3)	10 481 (19.6)	12 394 (14.4)	
Anticoagulants	729 (5.6)	5303 (27.1)	27 087 (50.7)	33 119 (38.5)	
Antiplatelets	365 (2.8)	3023 (15.5)	16 125 (30.2)	19 513 (22.7)	
Cardiovascular	3578 (27.7)	13 660 (69.9)	46 748 (87.4)	63 986 (74.5)	
Beta-blockers	1434 (11.1)	7386 (37.8)	29 415 (55.0)	38 235 (44.5)	
Calcium channel blockers	550 (4.3)	3198 (16.4)	15 536 (29.1)	19 284 (22.4)	
ACE inhibitors and angiotensin II receptor blockers	1582 (12.2)	7057 (36.1)	27 140 (50.7)	35 779 (41.6)	
Statins	997 (7.7)	5660 (28.9)	24 057 (45.0)	30 714 (35.7)	
Urinary	1241 (9.6)	4399 (22.5)	20 449 (38.2)	26 089 (30.4)	
Hormones	874 (6.8)	4464 (22.8)	29 318 (54.8)	34 656 (40.3)	
Corticosteroids	461 (3.6)	2896 (14.8)	23 863 (44.6)	27 220 (31.7)	
Medication acting on the nervous system	4330 (33.5)	14 485 (74.1)	50 477 (94.4)	69 292 (80.6)	
Antibiotics	2906 (22.5)	9120 (46.6)	40 158 (75.1)	52 184 (60.7)	
Opioids	1911 (14.8)	6766 (34.6)	35 120 (65.7)	43 797 (51.0)	
Paracetamol/orphenadrine combinations	1524 (11.8)	4188 (21.4)	16 400 (30.7)	22 112 (25.7)	
Non-steroidal anti-inflammatory drugs	1352 (10.5)	3389 (17.3)	11 921 (22.3)	16 662 (19.4)	
Selective COX-2 inhibitors	200 (1.5)	940 (4.8)	6236 (11.7)	7376 (8.6)	
Antipsychotics	362 (2.8)	1815 (9.3)	10 011 (18.7)	12 188 (14.2)	
Z-drugs	9281 (19.0)	11 613 (23.7)	28 060 (57.3)	48 954 (57.0)	
Benzodiazepines	522 (4.0)	2914 (14.9)	21 473 (40.2)	24 909 (29.0)	
Antidepressants	935 (7.2)	4804 (24.6)	26 832 (50.2)	32 571 (37.9)	
Antidementia	147 (1.1)	902 (4.6)	2269 (4.2)	3318 (3.9)	
Respiratory	1229 (9.5)	5147 (26.3)	27 612 (51.6)	33 988 (39.5)	
Antihistamin	281 (2.2)	1180 (6.0)	7725 (14.4)	9186 (10.7)	

The number of medications preadmission (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy). Values are presented as count (%) or median (IQR) unless specified otherwise.

either from non-polypharmacy to polypharmacy/hyperpolypharmacy or polypharmacy to hyperpolypharmacy (online supplemental table S2). The incidence of new postdischarge polypharmacy/hyperpolypharmacy was 55.5% (95% CI 54.7% to 56.4%). For patients with polypharmacy, the incidence of new postdischarge hyperpolypharmacy was 44.3% (95% CI 43.6% to 45.0%). The patient characteristics were comparable between the group of patients who had an increase in the polypharmacy burden and those who did not, apart from the fact that patients with increased polypharmacy burden after discharge were less likely to use multidose dispensing services at the time of admission (40.6% vs 57.9%). They were also less likely to have been diagnosed with adverse drug reactions before admission (12.0% vs 5.8%) or after discharge (6.2% vs 15.0%) than those with no change (online supplemental table S2). The most frequently added medications were anticoagulants (15.6%), antibiotics (14.9%), opioids (14.2%), proton pump inhibitors (13.2%), antiplatelets (12.0%), corticosteroids (10.3%), respiratory medications (9.6%) and medication acting on the central nervous system (8.9%), with Z-drugs (8.4%).

Clinical outcomes of patients with varying preadmission medication use

An unadjusted restricted cubic spline analysis revealed no relationship between the absolute number of different medications filled in the year preceding admission and the incidence of 30-day mortality (online supplemental figure S1), the risk of re-admission within 30 days (online supplemental figure S2), and with a prolonged length of primary hospital stay (>10 days) (online supplemental figure S3). Online supplemental figure S4 compares the long-term survival between the medication use categories, and there was no survival difference. Among the total cohort, 30-day mortality was 6.6%. The incidence of prolonged admission was 10.2%, and the 30-day re-admission rate was 15.0%.

DISCUSSION

This current study identified that preadmission polypharmacy/hyperpolypharmacy and postdischarge new polypharmacy/hyperpolypharmacy were common among internal medicine patients, which aligns with the previously stated primary hypothesis. However, no association was found between the category of medication use (non-polypharmacy <5, polypharmacy 5–9 and hyperpolypharmacy ≥10) and the patient characteristics, admitting internal subspecialities and clinical outcomes. This contradicts the secondary hypothesis that a higher category of medication use is associated with adverse clinical outcomes and increased comorbidity burden in this patient cohort. However, there is obviously an immense difference in the amount and different types of medication patients use depending on their medication use category (non-polypharmacy <5, polypharmacy 5–9 and hyperpolypharmacy ≥10).

Prevalence and incidence

Although this study aligns with previous studies claiming that preadmission polypharmacy/hyperpolypharmacy (22.9% and 62.5%) and postdischarge new polypharmacy/hyperpolypharmacy is common (55.5%), the prevalence is significantly higher in this cohort deriving from an inpatient hospital setting. A recent systematic review determined that the pooled estimated prevalence was 37%; however, the prevalence was higher among inpatients at 52%, like our study.[7] The prevalence of polypharmacy in the community setting was 20% and 37% in a cohort derived from an outpatient setting.[7] Similarly, a study focusing on surgical inpatients reported a prevalence of polypharmacy at 32.2% and hyperpolypharmacy at 23.5%.[34] This was anticipated as the internal medicine patients have higher comorbidity and frailty indices compared with the surgical population, which contains a substantial number of patients undergoing elective surgery.[34] The internal medicine patients were also older (73 vs 55 years).[34] Additionally, the results reveal that in the cohort, patients with a higher level of polypharmacy burden were more likely to be male. Previous evidence has been conflicting. A recent meta-analysis reported that there were no differences in polypharmacy prevalence in subgroup analyses based on sex.[7] In our entire cohort, the proportion of men, 43 914 (51.1%) vs 42 028 (48.9%) women, reflects the general population in Iceland (51.3% were male).[35] It is unclear why the level of polypharmacy is higher for this group but it is possible that a burden of frailty or disease is higher for men in this subgroup of society exposed to internal medicine admission.

The only patient characteristics differentiating patients with different levels of polypharmacy burden were the likelihood of using multidose dispensing services, which was higher with more polypharmacy burden, similar to a study on older adults.[36] Secondarily, patients with polypharmacy/hyperpolypharmacy were more likely to have been diagnosed with adverse drug reactions, which aligns with previous studies.[37] However, studies have reported that adverse drug reactions are under-reported and therefore it is likely that the prevalence is higher in real life. Therefore, the findings of our study raise various intriguing questions regarding the appropriateness of medication use among internal medicine patients with polypharmacy and hyperpolypharmacy, as they are unlikely to be explained solely by a higher comorbidity burden.

Potentially inappropriate prescribing

One interpretation of these findings is that a higher medication use category is due to potentially inappropriate prescribing. Polypharmacy has been identified as the leading risk for potentially inappropriate prescribing.[12] Potentially inappropriate medication is associated with adverse health and economic outcomes.[38 39] Among the medicines that are common in our patient cohort, in particular within the groups of patients with polypharmacy, are sedatives (43%) or benzodiazepines (29%). Polypharmacy, therefore, can be a helpful indicator of prescribing practice and medicine safety. However, healthcare professionals must identify when polypharmacy is inappropriate, as it can lead to adverse effects and poorer patient health outcomes.[38 40] Several criteria-based methods to identify inappropriate prescribing have been published; examples are the Beers criteria, the most widely used and recently updated.[41] Another widely used tool is a Screening Tool for Older Persons' potentially inappropriate Prescriptions (START (Screening Tool to Alert to Right Treatment) and STOPP (Screening Tool of Older Persons' Prescriptions)) criteria.[42] These tools are all only for older adults. There is a lack of tools to identify potentially inappropriate prescribing among all adults and studies focusing on polypharmacy among all adults and not solely older patients. Studies have shown that frailty is increasing among younger adults,[43] which emphasises the need for tools to address medication appropriateness regularly across the life course to hinder and prevent problematic polypharmacy through the life course.

Medications

Medications that are often predicted to be inappropriate[41 42] were more frequently used by patients with higher polypharmacy burden preceding the admission, including opioids (14.8% non-polypharmacy vs 34.6% polypharmacy vs 65.7% hyperpolypharmacy), benzodiazepines (4.0% vs 14.9% vs 40.2%) and proton pump inhibitors (7.3% vs 24.3% vs 51.5%). Our findings of high prevalence prescribing of those medication classes among internal medicines reveal the lack of solutions to tackle health problems like anxiety and mood disorder by other means than medication use and also challenges in the process of deprescribing.[44 45] It could also be linked to a lack of follow-up after hospital admission or new prescription that should be a short-term relief rather than long-term management, like benzodiazepines,[46] sedatives,[46] opioids[47] and proton pump inhibitors.[48]

Clinical outcomes

Contrary to the findings of numerous studies,[34 49–51] we did not find a link between the polypharmacy burden and clinical outcomes like mortality, longer hospital stay and re-admission rate. This may be because patients in all three medication use categories have similar burden of comorbidity (Elixhauser Comorbidity Score (39%>8) and risk of frailty (medium or high hospital frailty risk index classification)), which likely drives the observed difference in these outcomes in studies where there is a good correlation between comorbidity burden and polypharmacy. This study implies that the increased polypharmacy burden, like polypharmacy and hyperpolypharmacy, might be driven by potentially inappropriate medication use.

Strength and limitations

A key strength of the present research is the ability to link the nationwide prescription database, which included 95% of prescriptions in Iceland, with clinical data from hospital and primary care settings. One of the strengths of this study is that it represents a comprehensive examination of all tertiary care and most of secondary care of internal medicine patients in Iceland, as Landspitali is the main referral hospital for the country. The extended study period also allows for many patients in the study cohort. Finally, another strength is that there is no loss of follow-up of patients.

Among the limitations is a retrospective design that relies on the data collected and documented in the healthcare system for clinical purposes. The study is limited by the absence of information on the patient's medication adherence, which may, on the one hand, lead to an overestimation of the prevalence of polypharmacy and hyperpolypharmacy. We are also unable to determine if a medication was prescribed for short-term use only, which could overestimate the burden of polypharmacy. However, it must be noted that over-the-counter medications were not included in the study, which may, on the other hand, lead to an underestimation of polypharmacy and hyperpolypharmacy. Additionally, combination therapies frequently used in cardiology like thiazide and angiotensin receptor blockers are counted as one medication in this study, which may lead to underestimation in some patients using this methodology.

CONCLUSION

Preadmission polypharmacy and hyperpolypharmacy, new polypharmacy, and hyperpolypharmacy postdischarge are common among internal medicine patients. There appears to be no association between the level of medication use category and comorbidities and admitting specialty clinical outcomes in this selected population. It is, therefore, likely that the underlying disease does not explain polypharmacy in this population and serves as an indicator of potentially inappropriate prescribing. Recognition of polypharmacy and hyperpolypharmacy is significant, and increased emphasis is needed to review patients' medications regularly and after a hospitalisation.

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Paper III

CLINICAL RESEARCH STUDY

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Potentially Inappropriate Medication Use and Polypharmacy Before and After Admission to Internal Medicine for Older Patients

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ABSTRACT

BACKGROUND: With the aging of the population and the increase in chronic diseases, there is an inherent risk of polypharmacy and inappropriate medication use. This study aimed to determine the prevalence and incidence of potentially inappropriate medication use and its correlation with polypharmacy.

METHODS: This was a retrospective, population-based cohort study among patients ≥ 65 years hospitalized at The National University Hospital of Iceland from 2010-2020. Data on medication usage were retrieved from the National Prescription Medicine Registry. Based on the number of medications filled in the year prior to admission and post-discharge, participants were categorized as non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). The prevalence and incidence of potentially inappropriate medication use was assessed based on the 2019 Beers criteria. Regression models were used to correlate sociodemographic, clinical, and pharmacoepidemiologic variables and the odds of new potentially inappropriate medication use.

RESULTS: The cohort comprised 55,859 patients (48.5% male) with a median [interquartile range] age of 80 [73-86] years. The prevalence of inappropriate medication use in the year preceding admission was 34.0%, 77.7%, and 96.4% for patients with non-polypharmacy, polypharmacy, and hyper-polypharmacy, respectively. The incidence of new potentially inappropriate medication use was 46.7% (95% confidence interval 45.6%-47.6%) among those with no potentially inappropriate medication use pre-admission. Factors associated with higher odds of new potentially inappropriate medication use after discharge were the use of multi-dose dispensing services, dementia, polypharmacy, and hyper-polypharmacy.

CONCLUSIONS: An increased emphasis is needed to review and reevaluate the appropriateness of medication use among the older population in internal medicine.

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KEYWORDS: Aged; Hyper-polypharmacy; Medication-related problems; Polypharmacy; Potentially inappropriate medication

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INTRODUCTION

Polypharmacy refers to the use of multiple medicines, most commonly 5 or more, whereas hyper-polypharmacy has been defined as the use of 10 or more medications [1,2] It is estimated that multimorbidity, and consequently polypharmacy, will increase significantly in the coming years.[1,3-5]

The ratio of older individuals who fill potentially inappropriate prescriptions has been reported within the wide range of 11.5% to 62.5%.[6] Potentially inappropriate medication use is associated with adverse health and economic outcomes. An assessment of inappropriate medication practices may help to identify which sub-groups of patients may need additional interventions to tackle potentially inappropriate medication use.[7,8]

One of the most commonly used criteria to identify inappropriate medication use is the Beers criteria, which provides a list of potentially inappropriate medications in older adults (≥65 years), which has been linked to an increased risk of developing adverse drug reactions.[9,10]

Patients admitted to internal medicine services generally have a high burden of comorbidity and frailty. Recently, we identified that in this cohort, the prevalence of polypharmacy is high, and given that polypharmacy increases the likelihood of potentially inappropriate medication use, this is likely to be also true in this cohort.[11]

This study aimed to determine the prevalence and incidence of potentially inappropriate medication use in older patients admitted to internal medicine services and the correlation with polypharmacy. Furthermore, we studied the new potentially inappropriate medication use following admission and the correlation with internal medicine subspecialties and patient-specific variables. We hypothesized that pre- and post-discharge potentially inappropriate medication use was common among older patients with a high comorbidity and frailty burden. Our hypothesis was additionally that potentially inappropriate medication use pre-admission was correlated with a higher short- and long-term mortality, a longer primary hospitalization length of stay, and a higher risk of readmission.

CLINICAL SIGNIFICANCE

- The greater the number of medications prescribed to patients, the more likely there will be a potentially inappropriate medication.
- There is a link between multidose-dispensing services and potentially inappropriate medication use.
- Inpatients admitted to or transferred to a geriatric ward have less risk of a prescribed inappropriate medication upon discharge.
- Inpatients at increased risk of potentially inappropriate medication use should have their medications reviewed by healthcare providers soon after discharge.

METHODS

Study Population

This retrospective population-based cohort study included all patients ≥ 65 years admitted by internal medicine at Landspitali - The National University Hospital of Iceland between January 1, 2010, and December 31, 2020, and clinical outcomes through March 17, 2022. The National Bioethics Committee of Iceland (VSN-21-179) and the Data Protection Authority of Iceland approved the study, waiving individual consent. All databases used for research were de-identified before statistical analysis, and all work was compliant with the General Data Protection Regulation of the European Union. The study protocol was published on ClinicalTrials.gov before analysis (NCT04805151), and the study reporting adheres to the STROBE guideline reporting of observational studies in epidemiology.[12]

Clinical and Medication Data

We used the Icelandic Internal Medicine Database, which includes clinical and medication data for admissions by internal medicine. Generation of the database has been described previously.[11] The comorbidity burden was described using the Elixhauser Comorbidity Index, and the frailty risk estimated by calculating the Hospital Frailty Score.[13] For diagnosis of adverse drug reaction, we classified adverse drug reaction (the International Classification of Diseases codes, Y40-59, X40-59, T36-59) based on whether the diagnosis was made pre- or post-admission. Medication information was based on filled medications according to the Prescription Medicines Registry of the Directorate of Health database using the Anatomical Therapeutic Chemical classification. This national electronic database includes real-time information about all regular and as-required prescriptions but excludes those that were prescribed during hospitalization, over the counter, topical, and herbal medications. This study obtained data on filled prescriptions and whether an automated multidose drug dispensing service was used. These services, where tablets and capsules are removed from the original package and machine packed into plastic pouches, are frequently implemented to assist with medication adherence.

Exposure Variable Definition

The primary exposure was polypharmacy, classified by the number of medications filled in the year prior to admission to the hospital and the year following hospital discharge. The medication use categories used in this study were non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10).

Outcome Data

The primary outcome was the prevalence of potentially inappropriate medication use on admission, assessed by

applying the 2019 American Geriatrics Society Beers criteria.[10] All prescription medications filled were assessed for potentially inappropriate medication use by comparing them to the list of medications in the Beers criteria that are potentially inappropriate in most older adults, those that should typically be avoided.[10] The incidence of new potentially inappropriate medication use post-discharge was estimated for those patients without the exposure to potentially inappropriate medication use prior to admission only. Secondary outcomes evaluated were short (30-day) and long-term mortality, long primary hospitalization length of stay (≥ 10 days), and readmission within 30 days.

Statistical Analysis

Statistical analyses were performed using R (The R Foundation for Statistical Computing R, Vienna, Austria) version 4.0.3, via RStudio (Posit PBC [formerly RStudio PBC]), version 1.4.1106. Descriptive statistics were applied to describe the demographics, clinical characteristics, clinical outcomes, polypharmacy and potentially inappropriate medication use of the cohort based on the Beers criteria. The ratio of potentially inappropriate medication use was described using 95% confidence intervals (CIs) by applying the Pearson-Klopper in binom package in R.

A Restricted cubic spline was used to determine the likelihood of potentially inappropriate medication use by a number of prescribed medications, with prespecified knots at 0, 5, and 10 medications.

A multivariable logistic regression model was generated to estimate the patient- and admission-related risk factors of receiving a new prescription for a potentially inappropriate medication using age, sex (female compared with male), admitting specialty (compared with general medicine), Elixhauser Comorbidity Index (compared with <1), comorbidities, multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of fall or adverse drug reaction diagnosis prior to admission as covariates. The change in the incidence of potentially inappropriate medication use with time was assessed with Poisson regression. There were no missing variables identified although it is noted that the absence of a registration of a condition (diagnosis or medication) is coded as the condition not being present, which is an assumption.

RESULTS

Clinical Characteristics of the Patient Cohort and Potentially Inappropriate Medication Use

The study cohort included 55,859 admissions to internal medicine services for patients 65 years and older at Landspitali University Hospital. Of the admissions, 82.7% (95% CI 82.4-83.0) had potentially inappropriate medication use in the year prior to admission, without a change in the prevalence of potentially inappropriate medication use pre-admission over the study period (Supplementary Figure 1, available online). Table 1 compares the patient characteristics, admitting specialty, comorbidity, and clinical outcomes between the patient cohorts based on whether the patients had potentially inappropriate medication use prior to admission or not. Patients with potentially inappropriate medication use burden were more likely to be female (51.7% vs 48.3%), use more medications (4 [1-7] vs 13 [9-19]), and use multi-dose dispensing services (59.1% vs 40.9%). Their burden of comorbidity and frailty and the distribution among internal medicine specialties were similar.

Patients with potentially inappropriate medication use were more likely to have been diagnosed with adverse drug reaction prior to admission (12.3% vs 4.5%) and receiving such diagnoses post-discharge (6.7% vs 3.2%). There was no statistical difference in the length of stay, 30-day readmission rate, and 30-day mortality rate between the groups.

Incidence of New Potentially Inappropriate Medication Use

Table 2 compares the patient characteristics, admitting specialty, comorbidity, and clinical outcomes between cohorts, between patients who were prescribed a new potentially inappropriate medication following discharge (n = 4452, 53.4%, 95% CI 52.4-54.4) and those who continued without filling a potentially inappropriate prescription (n = 5094, 46.7%, 95% CI 45.6-47.6). Patients with prescriptions for new potentially inappropriate medications were less likely to use multi-dose dispensing services (36.9% vs 41.3%) and used a slightly higher number of medications both prior to admission and post-discharge (median [IQR] of 4 [2-7] vs 3 [0-6]). Post-discharge, the median number of medications was substantially higher among those patients with new potentially inappropriate prescriptions ([IQR] 9 [6-13] vs 4 [1-7]). They were also more likely to have a higher risk score for the likelihood of experiencing medication-related harm post-discharge, median [IQR] 10.70[7.17-14.54] vs 10.20 [7.44-15.30]).

Additionally, patients with new potentially inappropriate prescription were more likely to receive a diagnosis of an adverse drug reaction post-discharge (4.3% vs 2.2%). The comorbidity and frailty burden was comparable, as well as the distribution between admitting internal medicine subspecialties except for geriatrics, where patients were less likely to be prescribed new potentially inappropriate medication (6.3% vs 5.1%).

After adjustment for comorbidities and admission information, multi-dose dispensing service (odds ratio [OR] 1.26,95% CI 1.15-1.39), dementia (OR 1.29, 95% CI 1.01-1.65), pre-admission polypharmacy (OR 1.45,95% CI 1.32-1.60), and hyper-polypharmacy (OR 1.38,95% CI 1.22-1.59) were associated with higher odds of new potentially inappropriate medication use after discharge, but admission to internal medicine followed by transfer to geriatrics was associated with lower odds (OR 0.80, 95% CI 0.67-1.39), (Figure 1).

Table 1 Patient Characteristics of Patients Who Filled a Prescription for a Potentially Inappropriate Medication Pre-admission Based on the 2019 Beers Criteria*

	No Potentially Inappropriate Medication Use Pre-admission	Potentially Inappropriate Medication Use Pre-admission	All Patients	*P* Value
Total number of patients	9546 (17.1%)	46,313 (82.9%)	55,859	
Sex (male)	4748 (49.7)	22,371 (48.3)	27,119 (48.5)	.044
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	.055
Multi-dose dispensing services	3129 (32.8)	27,376 (59.1)	30505 (54.6)	<.001
Number of pre-admission medications (median [IQR])	4.00 [1.00, 7.00]	13.00 [9.00, 19.00]	12.00 [7.00, 17.00]	<.001
Number of post-discharge medications (median [IQR])	6.00 [3.00, 10.00]	13.00 [8.00, 18.00]	12.00 [7.00, 17.00]	<.001
Elixhauser Comorbidity Index [IQR])	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	.305
(<1]	1882 (19.7)	9079 (19.6)	10,961 (19.6)	.495
(1-4]	1351 (14.2)	6298 (13.6)	7649 (13.7)	
(4-5]	700 (7.3)	3467 (7.5)	4167 (7.5)	
(5-8]	1229 (12.9)	5785 (12.5)	7014 (12.6)	
(>8]	4384 (45.9)	21,684 (46.8)	26,068 (46.7)	
Hospital Frailty Risk Score class				.749
Low (< 5)	2707 (28.4)	12,910 (27.9)	15,617 (28.0)	
Med (5-15)	4654 (48.8)	22,690 (49.0)	27,344 (49.0)	
High (> 15)	2185 (22.9)	10,713 (23.1)	12,898 (23.1)	
Individual comorbidities				
Ischemic heart disease	3927 (41.1)	18,879 (40.8)	22,806 (40.8)	.506
Congestive heart failure	2687 (28.1)	12,793 (27.6)	15,480 (27.7)	.075
Hypertension	6307 (66.1)	30,467 (65.8)	36,774 (65.8)	.602
Diabetes mellitus	1754 (18.4)	8766 (18.9)	10,520 (18.8)	.213
Chronic obstructive pulmonary disease	3439 (36.0)	17,135 (37.0)	20,574 (36.8)	.075
Liver disease	198 (2.1)	1171 (2.5)	1369 (2.5)	.010
Chronic kidney disease	1261 (13.2)	6240 (13.5)	7501 (13.4)	.502
Malignant neoplasm	2675 (28.0)	12,605 (27.2)	15,280 (27.4)	.111
Psychiatric	1606 (16.8)	7604 (16.4)	9210 (16.5)	.339
Dementia	280 (2.9)	1431 (3.1)	1711 (3.1)	.438
Delerium	1213 (12.7)	5742 (12.4)	6955 (12.5)	.415
Internal medicine specialty				.025
Cardiology	2216 (23.2)	10,413 (22.5)	12629 (22.6)	
Dermatology	30 (0.3)	152 (0.3)	182 (0.3)	
Endocrinology	147 (1.5)	701 (1.5)	848 (1.5)	
Gastroenterology	634 (6.6)	3164 (6.8)	3798 (6.8)	
General internal medicine	1247 (13.1)	6275 (13.5)	7522 (13.5)	
Geriatrics	1157 (12.1)	6062 (13.1)	7219 (12.9)	
Hematology	411 (4.3)	1938 (4.2)	2349 (4.2)	
Infectious diseases	454 (4.8)	2155 (4.7)	2609 (4.7)	
Nephrology	235 (2.5)	1107 (2.4)	1342 (2.4)	
Neurology	707 (7.4)	3041 (6.6)	3748 (6.7)	
Oncology	496 (5.2)	2362 (5.1)	2858 (5.1)	
Palliative care	162 (1.7)	836 (1.8)	998 (1.8)	
Pulmonology	1111 (11.6)	5219 (11.3)	6330 (11.3)	
Rehabilitation	43 (0.5)	282 (0.6)	325 (0.6)	
Rheumatology	496 (5.2)	2606 (5.6)	3102 (5.6)	
Admissions linked with primary admission				
Geriatrics	551 (5.8)	2590 (5.6)	3141 (5.6)	.454
Palliative care	103 (1.1)	467 (1.0)	570 (1.0)	.660
Rehabilitation	73 (0.8)	301 (0.7)	374 (0.7)	.282
Intensive care unit admission	410 (4.3)	1928 (4.2)	2338 (4.2)	.566

Table 1 (*Continued*)

	No Potentially Inappropriate Medication Use Pre-admission	Potentially Inappropriate Medication Use Pre-admission	All Patients	*P* Value
Clinical outcomes				
Fall diagnosis post-discharge	16 (0.2)	128 (0.3)	144 (0.3)	.064
Length of hospital stay (days)	7.00 [3.00, 15.00]	7.00 [3.00, 15.00]	7.00 [3.00, 15.00]	.244
Diagnosis of adverse drug reaction pre-admission (%)	431 (4.5)	5684 (12.3)	6115 (10.9)	<.001
Diagnosis of adverse drug reaction post-discharge (%)	305 (3.2)	3100 (6.7)	3405 (6.1)	<.001
Next admission (median [IQR]	131.00 [29.00, 463.00]	132.00 [29.00, 455.00]	132.00 [29.00, 456.00]	.609
Mortality 30 days (%)	392 (4.1)	2033 (4.4)	4354 (7.8)	.227
Readmission within 30 days (%)	1486 (15.6)	7146 (15.4)	8632 (15.5)	.748

IQR = interquartile range.
*Values are presented as count (%) or median (IQR) unless specified otherwise.

Figure 2 shows the prevalence of potentially inappropriate medication across different burdens of pre-admission polypharmacy. Among patients with non-polypharmacy, the prevalence of potentially inappropriate medication use was 34.0% (95% CI 33.1-35.0). Among patients with polypharmacy, it was 77.7%, (95% Cl 76.9-78.4). Among patients with hyper-polypharmacy, it was 96.4% (95% Cl 96.2-96.6).

An unadjusted restricted cubic spline analysis revealed a non-linear relationship between the absolute number of different medications filled in the year preceding admission and the prevalence of potentially inappropriate medication use based on the Beers criteria. Figure 3 shows the relationship between the absolute number of filled medications and the prevalence of potentially inappropriate medication by organ system or therapeutic category. Among categories of potentially inappropriate medication use, patients most filled medications that act on the central nervous and gastrointestinal system. When medications within these two organ systems were further analyzed, a strong relationship was identified between increased pre-admission polypharmacy and the likelihood of having a prescription for benzodiazepines and Z-drugs (Supplementary Figure 2, available online), and medications that act on the gastrointestinal system, in particular proton pump inhibitors (Supplementary Figure 3, available online).

Supplementary Table 1 (available online) shows which Beers criteria subgroups were met for the whole cohort with varying degrees of polypharmacy prior to admission. The most commonly met Beers criteria in the whole cohort in the year prior to admission were medications that act on the central nervous system (59.2%), most commonly Z-drugs (43.1%), and benzodiazepines (31.2%). The second most common Beers criteria the cohort met was due to gastrointestinal medications (48.4%), most commonly proton pump inhibitors (45.8%).

Following discharge, the most frequently added medication that met the Beers criteria were proton pump inhibitors (15.3%), Z-drugs (9.2%), benzodiazepines (8.9%), antipsychotics (6.6%), anticholinergics (5.4%), cardiovascular (5.2%), and antihistamines (5.0%).

DISCUSSION

We identified that pre-admission and post-discharge potentially inappropriate medication use among internal medicine patients is widespread and correlated with increasing pre-admission polypharmacy. Interestingly, no correlation was found between potentially inappropriate medication use and clinical outcomes, such as short- and long-term mortality, length of hospitalization, and 30-day readmission rate. This contradicts our secondary hypothesis that potentially inappropriate medication use was correlated with adverse clinical outcomes. Residual confounding is also possible.

Few studies have focused on hospitalized internal medicine patients. Our study estimated that the prevalence of patients with any pre-admission potentially inappropriate medication use was 82.7%, which is in line with a recent inpatient cohort study where the prevalence in older individuals was reported to be 92% according to the same Beers criteria.[14] In the latest version of the Beers criteria published in 2023, there were notable updates, such as categorizing aspirin and rivaroxaban as medications to be avoided. Most other changes involved strengthening existing criteria with new evidence or clarifying language, which should not impact the findings of this study.[15]

Additionally, hospitalized patients represent a different cohort from a generalized outpatient cohort where a recent meta-analysis considered that the prevalence of potentially inappropriate medication use worldwide ranged from 1.3% to 95.2%, with a pooled prevalence estimate of 36.7%.[16] A likely reason for higher prevalence and incidence in our study population is that our hospital-based cohort is likely to be older, with greater multimorbidity and more medications compared with outpatient and community-based cohorts.

Table 2 Comparison of Patients with No Potentially Inappropriate Medication Use Pre-admission or Post-discharge to Patients with No Potentially Inappropriate Medication Use Pre-admission but New Potentially Inappropriate Medication Use Post-discharge*

	No Potentially Inappropriate Medication Use Pre-admission or New Potentially Inappropriate Medication Use Post-discharge	No Potentially Inappropriate Medication Use Pre-admission but New Potentially Inappropriate Medication Use Post-discharge	*P* Value
Total number of patients	5094	4452	
Sex (male)	2516 (49.4)	2232 (50.1)	.481
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 85.00]	.526
Multi-dose dispensing services	2690 (41.3)	1643 (36.9)	<.001
Number of pre-admission medications (median [IQR])	3.00 [0.00, 6.00]	4.00 [2.00, 7.00]	<.001
Number of post-discharge medications (median [IQR])	4.00 [1.00, 7.00]	9.00 [6.00, 13.00]	<.001
Number of pre-admission medications without antibiotics (median [IQR])	2.00 [0.00, 6.00]	4.00 [1.00, 6.00]	<.001
Elixhauser Comorbidity Index [IQR])			
<1	987 (19.4)	895 (20.1)	.328
1-4	722 (14.2)	629 (14.1)	
4-5	388 (7.6)	312 (7.0)	
5-8	682 (13.4)	547 (12.3)	
>8	2315 (45.4)	2069 (46.5)	
Hospital Frailty Risk Score class			.659
Low (<5)	1427 (28.0)	1280 (28.8)	
Med (5-15)	2504 (49.2)	2150 (48.3)	
High (>15)	1163 (22.8)	1022 (23.0)	
Individual comorbidities			
Ischemic heart disease	2140 (42.0)	1787 (40.1)	.067
Congestive heart failure	1432 (28.1)	1255 (28.2)	.951
Hypertension	3392 (66.6)	2915 (65.5)	.261
Diabetes mellitus	1841 (36.1	822 (18.5)	.854
Chronic obstructive pulmonary disease	18,976 (36.9)	1598 (35.9)	.819
Liver disease	101 (2.0)	97 (2.2)	.549
Chronic kidney disease	669 (13.1)	592 (13.3)	.837
Malignant neoplasm	1407 (27.6)	1268 (28.5)	.362
Psychiatric	836 (16.4)	770 (17.3)	.261
Dementia	133 (2.6)	147 (3.3)	.053
Delerium	643 (12.6)	570 (12.8)	.815
Internal medicine specialty			.747
Cardiology	1189 (23.3)	1027 (23.1)	
Dermatology	15 (0.3)	15 (0.3)	
Endocrinology	76 (1.5)	71 (1.6)	
Gastroenterology	327 (6.4)	307 (6.9)	
General internal medicine	666 (13.1)	581 (13.1)	
Geriatrics	633 (12.4)	524 (11.8)	
Hematology	226 (4.4)	185 (4.2)	
Infectious diseases	248 (4.9)	206 (4.6)	
Nephrology	120 (2.4)	115 (2.6)	
Neurology	365 (7.2)	342 (7.7)	
Oncology	254 (5.0)	242 (5.4)	
Palliative care	80 (1.6)	82 (1.8)	
Pulmonology	592 (11.6)	519 (11.7)	
Rehabilitation	29 (0.6)	14 (0.3)	
Rheumatology	274 (5.4)	222 (5.0)	
Admissions linked with primary admission			
Geriatrics	323 (6.3)	228 (5.1)	.012
Palliative care	49 (1.0)	54 (1.2)	.278

Table 2 (*Continued*)

	No Potentially Inappropriate Medication Use Pre-admission or New Potentially Inappropriate Medication Use Post-discharge	No Potentially Inappropriate Medication Use Pre-admission but New Potentially Inappropriate Medication Use Post-discharge	*P* Value
Rehabilitation	40 (0.8)	33 (0.7)	.898
Intensive care unit admission	113 (2.2)	192 (4.3)	.977
Clinical outcomes			
Length of hospital stay (days)	7.00 [3.00, 15.00]	7.00 [3.00, 14.00]	.024
Diagnosis of adverse drug reaction pre-admission (%)	223 (4.4)	208 (4.7)	.521
Diagnosis of adverse drug reaction post-discharge (%)	114 (2.2)	191 (4.3)	<.001
Next admission (median [IQR]	133.00 [29.00, 461.50	125.00 [28.00, 461.00]	.994
Mortality 30 days (%)	388 (7.6)	360 (8.1)	.416
Readmission within 30 days (%)	796 (15.6)	690 (15.5)	.947

IQR = interquartile range.
*Values are presented as count (%) or median (IQR) unless specified otherwise.

This study identified a correlation between the female sex and potentially inappropriate medication use (51.7% vs 48.3%), which is in accordance with previous studies.[8,17] Additionally, our study reports a link between the use of multidose-dispensing services and potentially inappropriate medication use, which is also in line with previous studies.[18] These findings raise concerns as the use of multidose dispensing services is often assumed to aid when concerns arise regarding compliance and complex medication use. However, our study implies that it could contribute toward both polypharmacy and potentially inappropriate medication use. However, a new multidose dispensing service initiated during hospital admission can be problematic as new medications are often being trailed and need to be altered or stopped shortly after discharge. This aligns poorly with long-term prescriptions that multidose dispensing services providers prefer, at least in our hospital system. It is prudent that there should be a mandate for a review by their primary

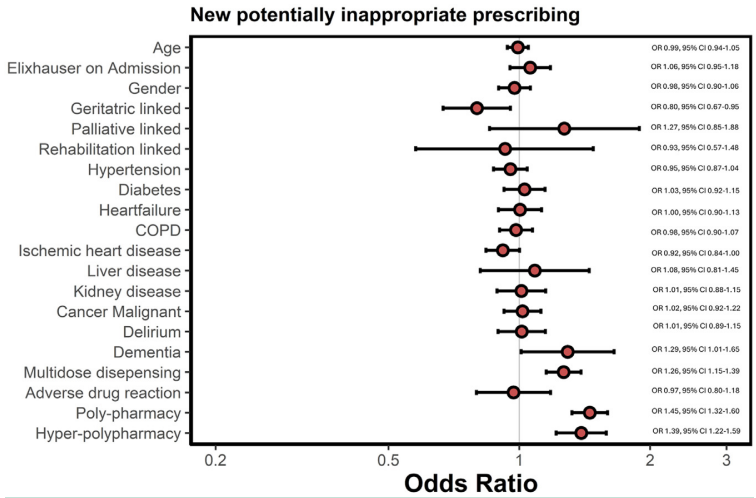

Figure 1 The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), admitting specialty (compared with general medicine), Elixhauser Comorbidity Index class (compared with <1), individual comorbidities, multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission, and a diagnosis of fall or adverse drug reaction diagnosis prior to admission as covariates.

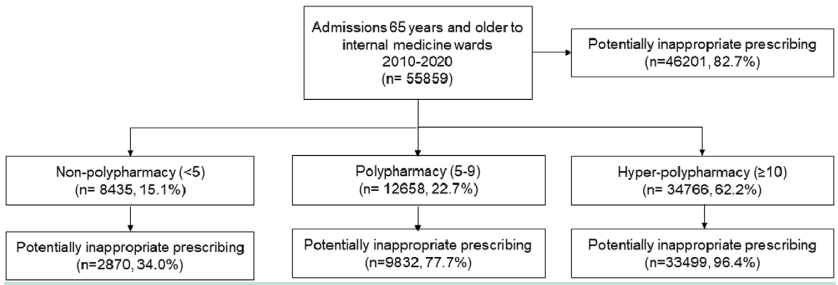

Figure 2 A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least 1 potentially inappropriate medication based on the 2019 Beers criteria.

care physicians prior to prescriptions of a longer duration with a frequent review to assess medication appropriateness.

Admission to the geriatric ward was associated with reduced odds of developing new, potentially inappropriate medication use post-discharge. This is potentially because healthcare professionals working in geriatric care are likely to have the knowledge and skills to identify inappropriate medication use and its potential harm for older patients and, therefore, be less likely to initiate new inappropriate medications. This highlights the importance of judicious prescribing during hospitalization and the need to upskill non-specialized areas in managing older adults. The most common potentially inappropriate medications used in this study were medications acting on the central nervous system, with Z-drugs the most commonly prescribed medications, followed by benzodiazepines. This is in line with a recent cohort study applying the Beers criteria in a cohort of evaluating internal medicine patients where the most frequently potentially inappropriate prescriptions were benzodiazepines. The difference between studies may be due to different prescription practices between the countries. Iceland, for example, has reported higher usage of medications acting on the nervous system compared to other countries.[19]

Several studies have identified interventions to address polypharmacy, potentially inappropriate medication use, and deprescribing opportunities.[20,21] A recent meta-analysis concluded that pharmaceutical interventions can improve

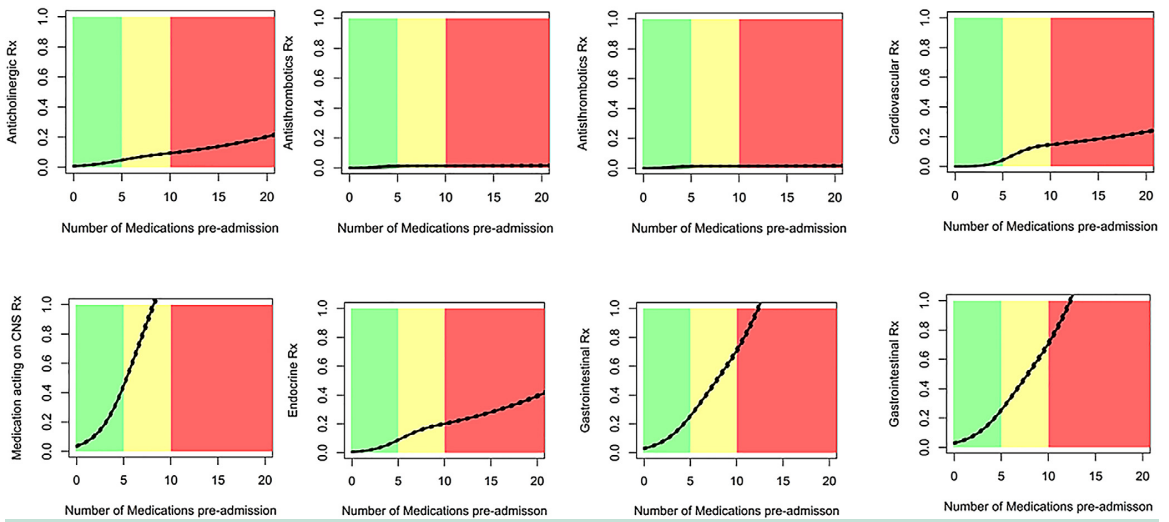

Figure 3 The correlation between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria. The figure shows the result of restricted cubic spline analysis of the proportion of patients with the 3 outcomes. Colors indicate the polypharmacy category based on the different medications filled in the year preceding admission by internal medicine. (green < 5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy).

prognosis in older adults by reducing polypharmacy, readmission rate, and the incidence of potentially inappropriate medication use.[20] However, there has to be a benchmark to address the potentially inappropriate use of medications, and likely, there will be no single solution. Ideally, patients at increased risk of potentially inappropriate medication use should be followed up after a hospital admission by their healthcare provider. However, the risk of potentially inappropriate medication use must be evaluated individually, and the use of potentially inappropriate medication may be appropriate when other possibilities like non-pharmacological approaches or medications with less risks are not available or the benefit in the alleviation of symptoms is great enough.

Contrary to the findings of numerous studies,[22,23] this study did not find a correlation between potentially inappropriate medication use and clinical outcomes, such as length of stay, readmission within 30 days, and mortality within 30 days. One reason for this may be the fact that both patient groups had similar burdens of comorbidity. However, it is also worth mentioning that clinical outcomes are multifactorial, and they are often dependent upon what support the patient has in the community. Additionally, we observed a correlation with the likelihood of being diagnosed with an adverse drug event post-discharge. This is in line with previous research.[24]

The current study has several strengths. A centralized nationwide prescription medicine registry was used that allows detailed information, which includes over 95% of all prescriptions in the country, and the ability to link different registries to collect information. The large number of participants included in an extensive database had a complete follow-up for clinical outcomes and with no loss of follow-up of patients.

A limitation is the dependence on using filled medications based on the prescription registry database. This method may overestimate the number of medications the participants take, as adherence still needs to be determined. Additionally, assessing comorbidity burden using diagnoses from hospital and primary care settings risks underreporting true comorbidities or their severity.

CONCLUSION

In conclusion, pre-admission and post-discharge potentially inappropriate medication use is common among internal medicine patients, and there is a correlation between polypharmacy and the increased likelihood of potentially inappropriate medication use. Specific sub-groups were at a more risk of developing increased potentially inappropriate medication use after discharge, whereas patients admitted to geriatrics had decreased risk. This demonstrates the need for an increased follow-up, medication review, and deprescribing following hospital discharge. Emphasis should be put on supporting the transition of care and providing information to patients, caregivers, and primary care physicians regarding the changes in medication during the hospital stay. A potential focus could be on those medications that should be used short-term or new medicines that should be re-evaluated shortly after discharge.

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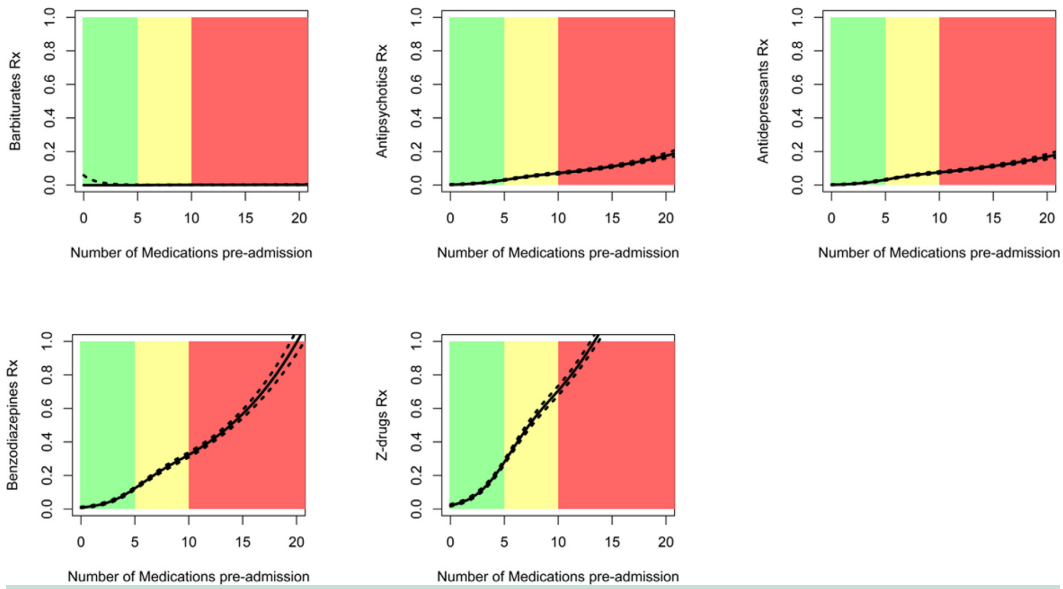
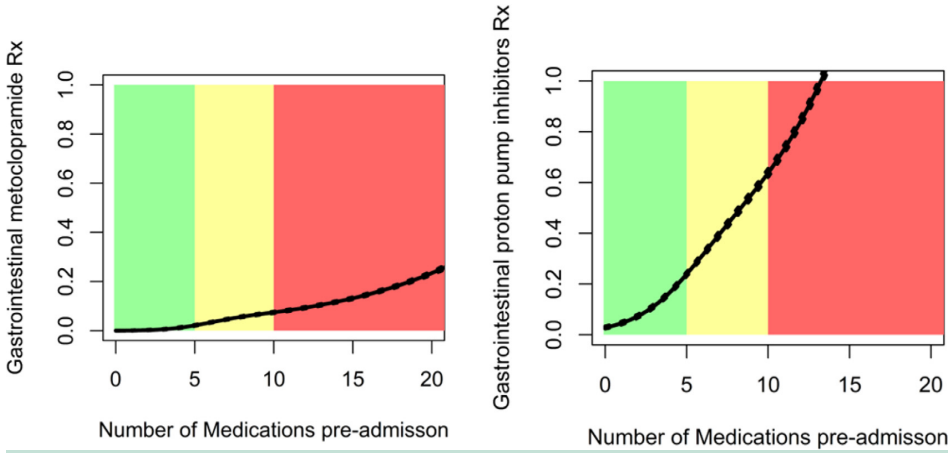
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2024.07.026.

Supplementary Figure 1 The prevalence of potentially inappropriate medication use based on the 2019 Beers criteria and medications filled in the year preceding admission by internal medicine (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).



Supplementary Figure 2 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for specific medications acting on the central nervous system. Colors indicate the number of different medications (green < 5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.



Supplementary Figure 3 The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on the gastrointestinal system. Colors indicate the number of different medications (green $<$ 5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red $\geq$ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.

Supplementary Table 1 Subcategories of the Beers Criteria Filled Based on the 2019 Beers Criteria and the Patients Pre-admission Polypharmacy Burden*

	Non-Polypharmacy Pre-admission	Polypharmacy Pre-admission	Hyper-Polypharmacy Pre-admission	All Patients Pre-admission	*P* Value
Total number of patients	8435 (15.1)	12,658 (22.7)	34,766 (62.2)	55,859	
Age (median [IQR]), years	74.00 [69.00, 80.00]	74.00 [69.00, 80.00]	76.00 [71.00, 82.00]	80.00 [73.00, 86.00]	<.001
[65, 75)	2594 (31.1)	3724 (29.8)	10,530 (30.6)	16,848 (30.5)	
[75, 85)	3360 (40.3)	5207 (41.7)	13,879 (40.4)	22,446 (40.7)	
[85, 95.)	2384 (28.6)	3563 (28.5)	9954 (29.0)	15,901 (28.8)	
Beers criteria total score pre-admission (median [IQR])	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	4.00 [2.00, 5.00]	3.00 [1.00, 4.00]	<.001
Beers criteria anticholinergics (%)	199 (2.4)	794 (6.3)	5302 (15.3)	6295 (11.3)	<.001
Beers criteria anticholinergics (antihistamines) (%)	179 (2.1)	730 (5.8)	4981 (14.3)	5890 (10.5)	<.001
Beers criteria anticholinergics (antiparkinsonian) (%)	15 (0.2)	45 (0.4)	198 (0.6)	258 (0.5)	.017
Beers criteria anticholinergics (antispasmodics) (%)	5 (0.1)	24 (0.2)	232 (0.7)	261 (0.5)	<.001
Beers criteria antithrombotic (%)	14 (0.2)	123 (1.0)	485 (1.4)	622 (1.1)	<.001
Beers criteria anti-infective (%)	46 (0.5)	342 (2.7)	2880 (8.3)	3268 (5.9)	<.001
Beers criteria cardiovascular (%)	75 (0.9)	859 (6.8)	6336 (18.2)	7270 (13.0)	<.001
Beers criteria (cardiovascular peripheral alpha) (%)	9 (0.1)	103 (0.8)	802 (2.3)	914 (1.6)	<.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	1 (0.0)	9 (0.0)	10 (0.0)	.178
Beers criteria (cardiovascular disopyramide) (%)	6 (0.1)	32 (0.3)	110 (0.3)	148 (0.3)	<.001
Beers criteria (cardiovascular dronedarone) (%)	2 (0.0)	38 (0.3)	148 (0.4)	188 (0.3)	<.001
Beers criteria (cardiovascular digoxin) (%)	29 (0.3)	369 (2.9)	3152 (9.1)	3550 (6.4)	<.001
Beers criteria (cardiovascular nifedipine) (%)	10 (0.1)	95 (0.8)	486 (1.4)	591 (1.1)	<.001
Beers criteria (cardiovascular amiodarone) (%)	21 (0.2)	261 (2.1)	2411 (6.9)	2693 (4.8)	<.001
Beers criteria central nervous system (%)	1102 (13.1)	5406 (42.7)	26550 (76.4)	33,058 (59.2)	<.001
Beers criteria (central nervous system antidepressant) (%)	105 (1.2)	575 (4.5)	3668 (10.6)	4348 (7.8)	<.001
Beers criteria (central nervous system antipsychotics) (%)	243 (2.9)	1131 (8.9)	6503 (18.7)	7877 (14.1)	<.001
Beers criteria (central nervous system barbiturates) (%)	1 (0.0)	36 (0.3)	136 (0.4)	173 (0.3)	<.001
Beers criteria (central nervous system benzodiazepines) (%)	369 (4.4)	2088 (16.5)	14,965 (43.0)	17,422 (31.2)	<.001
Beers criteria (central nervous system Z-drugs) (%)	539 (6.4)	3338 (26.4)	20,183 (58.1)	24,060 (43.1)	<.001
Beers criteria endocrine (%)	250 (3.0)	1450 (11.5)	8974 (25.8)	10,674 (19.1)	<.001
Beers criteria (endocrine androgens) (%)	24 (0.3)	114 (0.9)	713 (2.1)	851 (1.5)	<.001
Beers criteria (endocrine desiccated thyroid) (%)	1 (0.0)	0 (0.0)	11 (0.0)	12 (0.0)	.093
Beers criteria (endocrine estrogens) (%)	112 (1.3)	591 (4.7)	4082 (11.7)	4785 (8.6)	<.001
Beers (endocrine growth hormone) (%)	1 (0.0)	9 (0.1)	21 (0.1)	31 (0.1)	.165

Supplementary Table 1 (*Continued*)

	Non-Polypharmacy Pre-admission	Polypharmacy Pre-admission	Hyper-Polypharmacy Pre-admission	All Patients Pre-admission	*P* Value
Beers criteria (endocrine megestrol) (%)	1 (0.0)	2 (0.0)	12 (0.0)	15 (0.0)	.360
Beers criteria (endocrine sulfonylurea) (%)	113 (1.3)	769 (6.1)	4665 (13.4)	5547 (9.9)	<.001
Beers criteria gastrointestinal (%)	770 (9.1)	3669 (29.0)	22,579 (64.9)	27,018 (48.4)	<.001
Beers criteria (gastrointestinal metoclopramide) (%)	46 (0.5)	455 (3.6)	5936 (17.1)	6437 (11.5)	<.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	735 (8.7)	3418 (27.0)	21,448 (61.7)	25,601 (45.8)	<.001
Beers criteria pain medications (%)	929 (11.0)	2384 (18.8)	8694 (25.0)	12,007 (21.5)	<.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	3 (0.0)	3 (0.0)	.402
Beers criteria pain medications nonselective NSAID (%)	875 (10.4)	2230 (17.6)	7713 (22.2)	10,818 (19.4)	<.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	81 (1.0)	266 (2.1)	1577 (4.5)	1924 (3.4)	<.001
Beers criteria (genitourinary) (%)	2 (0.0)	21 (0.2)	129 (0.4)	152 (0.3)	<.001

IQR = interquartile range; NSAIDS = nonsteroidal anti-inflammatory drugs.

*Estimated by the number of different medications filled in the year preceding admission (< 5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%) or median (IQR) unless specified otherwise.

Paper IV

Epidemiology of potentially inappropriate medication use and association with polypharmacy among surgical inpatients: retrospective, population-based cohort study

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Background: The incidence of elderly patients with an increased burden of comorbidity and associated polypharmacy is rising. The study aimed to determine the prevalence of preadmission and post-discharge use of potentially inappropriate medication use among older surgical patients according to Beers criteria among patients admitted for a surgical procedures, and its association with polypharmacy.

Methods: A retrospective, population-based cohort study among patients ≥65 years undergoing surgery at Landspitali – The National University Hospital of Iceland between 2006-2018. Participants were categorized based on the number of medications filled in the year preceding admission and following discharge into classes of medication use: non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). The prevalence and incidence of potentially inappropriate medication use were compared between polypharmacy categories based on the 2019 American Geriatrics Society Beers criteria. The odds of new potentially inappropriate medication use was assessed with regression modeling correcting for sociodemographic, clinical, and pharmacoepidemiologic variables.

Results: The cohort comprised of 17 198 admissions (53.8% female) with a median [IQR] age of 75 [70,81]. The prevalence of any preoperative potentially inappropriate medication use in the whole cohort was 77.8% (95% CI 77.2-78.5). The prevalence among patients with non-polypharmacy (<5) was 36.6% (95% CI 35.1-38.2), with polypharmacy (5-9) 80.2% (95% CI 79.2-81.2) and with hyper-polypharmacy 95.8% (95% CI 95.3-96.2). Following surgery, the incidence of new potentially inappropriate medication use was 38.5% (95% CI 37.0-40.1). Factors associated with new potentially inappropriate medication use after discharge were female gender, increased comorbidity, and use of multidose dispensing service prior to admission. Patients with potentially inappropriate prescribing were more likely to undergo cardiac (14.9% vs. 4.4%), vascular (11.1% vs. 8.2%), and gynecological (4.3% vs. 1.7%) procedures. Additionally, patients with potentially inappropriate prescribing were are at increased risk of poorer clinical outcomes, medication-related harm (12.6 vs. 11.3), increased 30-

day mortality (5.2% vs. 0.3%), longer hospital stay (3 [1,8] vs. 2 [1,5] and increased 30-day readmission risk (11.3% vs. 6.5%).

Conclusions: There was a strong association between increased medication use and potentially inappropriate medication use. Hospitalization for surgery provides a potential opportunity to optimize medication use; however, appropriate follow-up is essential if medications are changed during a hospitalization, prior to admission.

Word count: 345 (max 250)

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT04805151

Introduction

With the aging of the global population, patients of higher ages and with increased comorbidities will more frequently undergo surgery in the foreseeable future. Over the years, vast advances in surgical and perioperative care have allowed more complicated patients to undergo surgical care. Around 300 million surgeries are made globally every year.[1] They are expected to increase in the coming years.[2, 3] Additionally, studies have predicted that increased multimorbidity and associated polypharmacy will increase in the coming years. [4-6] Identifying subgroups at higher risk of poorer clinical outcomes for surgical patients is essential to optimize their likelihood of optimal surgical outcomes.[2] In addition, identifying subgroups of surgical patients at increased risk of poorer clinical outcomes and the heightened risk of polypharmacy and potentially inappropriate medication use can support prioritizing limited resources within the healthcare settings to provide perioperative care to maximize patients' benefits and minimize the risk associated with a surgical admission.

Surgical patients with increased comorbidity and associated polypharmacy have been shown to have worse outcomes.[7, 8] Polypharmacy is the simultaneous use of multiple medications; the most commonly used definition is the use of five or more medications [9, 10] and recently hyper-polypharmacy, ten or more medications has been introduced.[11] Polypharmacy and hyper-polypharmacy have been identified as the leading risk factors for potentially inappropriate medication use, which has also been linked to worse health outcomes. World Health Organisation initiated a global health campaign with the aim to highlight the importance of optimizing medication use among those on polypharmacy with the aim of reducing medication-related harm.[12] A recent systematic review reported that half of all preventable medication-related harm was due to medications or therapeutic options and that the prevalence of preventable medication-related harm was among patients admitted to geriatric wards (17%) and followed by surgical wards (9%). [13] The use of multidose drug dispensing services where medications are packed into individual packages has increased, and

there is evidence that these services are associated with polypharmacy [8, 14, 15] and lack of medication appropriateness.[16-19]

Polypharmacy can be rational in individual patients' multimorbidity. However, it has also been identified as a possible quality indicator of prescribing practices.[20] Additionally, polypharmacy has been recognized as the proxy for inappropriate prescribing practices.[15, 19-22] This highlights the importance of evaluating medication appropriateness among patients with polypharmacy to ensure the treatment is optimized. Additionally, hospitalization has been linked to incidence of new polypharmacy and potentially inappropriate medication use. [8, 19, 23]

There are several studies on polypharmacy and potentially inappropriate medication use among older patients that have focused on the general practice[21] and among internal medicine patients admitted to hospital.[19] There is a need for increased knowledge of the prevalence and incidence of potentially inappropriate medication use among the older surgical population. Surgical patients and internal medicine patients have very different characteristics and it is likely that medication practices adjacent to hospitalization might benefit from different approaches to care. [24]

The study aimed to estimate the prevalence and incidence of potentially inappropriate prescribing and the association with the burden of polypharmacy among older ≥65 years surgical patients. Furthermore, we studied the potentially inappropriate prescribing and the association with patients- and procedural variables as well as medication classes. We hypothesized that pre- and post-discharge potentially inappropriate prescribing is common among older patients, patients with a high comorbidity and frailty burden. Our hypothesis was additionally that preoperative potentially inappropriate prescribing is associated with a higher short- and long-term mortality, a longer primary hospitalization length of stay, and a higher risk of readmission.

Methods

Study population

The retrospective population-based cohort study included all patients ≥65 years who underwent a procedure at Landspitali - The National University Hospital of Iceland, during the study period between December 2005 and December 2018, with an additional year of follow-up for filled medication and survival follow-up until 11th March 2021. The hospital provides secondary care surgery for most of Iceland, 75%, and the tertiary care surgical services for all subspecialities for the whole nation. The Ministry of Health provides funding for the hospital, which has a capacity of approximately 700 beds. The databases used for this study were de-identified before statistical analysis and compliant with the General Data Protection Regulation of the European Union. The research protocol was published on clinicaltrials.gov before analysis (NCT04805151)[25] The study reporting adheres to the STROBE guideline reporting of epidemiological observational studies.[26] Approval for the study protocol was received from National Bioethics Committee of Iceland (VSN-14-139-V1), and the Data Protection Authority of Iceland with individual consent waived.

Clinical and medication data

For this study The Icelandic perioperative database was used. This is a retrospective database containing clinical information on all surgeries performed at Landspitali. Its generation hashas been previously described.[27] The type and anatomical location of surgery is desribed using the NOMESCO (Nordic Medico-Statistical Committee) (NCSP-IS, version 1.14) surgical classifications.[28] Comorbidities were registered using the International Classification of Diseases 9th/10th revision (ICD9/10) from both the hospital and primary care databases.[29] The overall comorbidity burden was quantified by calculating the van Raven modified Elixhauser comorbidity index and categorized as (<1), (1-4), (5-8), and (>8).[30] The frailty risk was described by applying the Hospital Frailty Risk Score, categorized into low risk (<5), intermediate risk (5–15), and high risk (>15).[31] The diagnosis of adverse drug reaction either prior to admission or post-discharge was based on the ICE9/10 codes (Y40-59, X40-59, T36-59).

Information on filled medication information, coded with the anatomical Therapeutic Chemical (ATC) system, were retrieved from the National Prescription Medicines Registry of the Directorate of Health database. This study assessed medication fillings in the year prior to an admission to hospital and the year post-discharge and whether patients used multidose dispensing services. A service where all tablets and capsules are provided to patients removed from their original packages and put packages and often offered to support medication adherence. The national prescription registry includes information on all prescription medications prescribed regularly and as needed in Iceland in real-time. It is regularly assessed for accuracy and is deemed to be above 95%. The database does not include over-the-counter, topical, or herbal medications.

Exposure Variable Definition

The primary exposure was degree of polypharmacy using the number of different medications filled in the year prior to a surgical admission to hospital and the year following hospital discharge. In this study this was classified as non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). Additionally, the prevalence of the use of different medication classes was calculated based on the number of medications within the different anatomical/pharmacological groups (ATC 1st level) and pharmacological/therapeutical subgroups (ATC 2nd level) that were counted in the year preceding and the year following discharge to hospital.

Outcome Data

The primary outcome was the prevalence and incidence of potentially inappropriate medication use assessed by the 2019 AGS Beers criteria.[32] The evaluation was done by assessing all prescription medications filled and comparing them against the Beers criteria, that consitutes a list of medications deemed potentially inappropriate for most older adults that should typically be avoided. Additionally, the incidence of new potentially inappropriate medication use post-discharge was calculated for those patients not filling a potentially inappropriate medication prior to the admission. Other clinical outcomes evaluated were short-term (< 30 days) and long-term mortality, long primary hospitalization

length of stay (≥ 10 days), and risk of readmission (< 30 days), as well as the odds of receiving a diagnosis of an adverse drug reaction post-discharge.

Statistical analysis

Data analysis was performed from January 2023 to September 2024 using R (The R Foundation for Statistical Computing R, Austria) version 4.0.3, via R studio (RStudio PBC, USA), version 1.4.1106.

Descriptive statistics were applied to describe the demographics, clinical characteristics, surgical type, and clinical outcomes of the cohort, as well as the number of medications filled and categorized into non-polypharmacy, polypharmacy, and hyper-polypharmacy. Additionally, the prevalence and incidence of potentially inappropriate medication use were evaluated based on the 2019 Beers criteria. The ratio of potentially inappropriate medication use was described using 95% confidence interval by applying the Pearson-Klopper in binom package in R.

A Restricted cubic spline model was used to visualize the relationship between the medication use categories (non-polypharmacy, polypharmacy, and hyper-polypharmacy) and the ratio patients fillling a potentially inappropriate medication given their overall polypharmacy, with prespecified knots at 0, 5, and 10 medications.

A multivariable logistic regression model was generated to estimate the patient- and procedure-related risk factors of receiving a new prescription for a potentially inappropriate medication using age, sex (female compared with male), Elixhauser comorbidity index (compared with <1), comorbidities, multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of fall or adverse drug reaction diagnosis prior to admission, as covariates. The change in the incidence of potentially inappropriate medication use with time was assessed with Poisson regression. No missing variables were identified, although it is noted that the absence of a registration of a condition (diagnosis or medication) is coded as the condition not being present, which is an assumption.

Results

The study cohort included 30 082 patients (≥65 years) admitted undergoing surgery at Landspitali University Hospital during the study period from 2005-2018. Of these, 12 884 (42.8%) were non-first surgeries during the study period, either reoperations or subsequent unrelated surgeries. These seconeary surgeries excluded, resulting in a final study population of 17 198 patients (57.2%) undergoing their first surgery within the study period. (Figure 1) Of the whole cohort, 9252 (53.8%) were females, and the median age of all patients [IQR] was 75 [70,81]. Most of the study cohort had a low (<5) hospital frailty risk score class. They used a median [IQR] of 9 [5,13] medications in the year preceding the admission and 9 [6,14] post-discharge. Multidose dispensing service was used by 32.8% of the patients of the whole cohort; the most frequent comorbidity was hypertension (57.0%), ischemic heart disease (32.1%), malignant neoplasm (27.7%), chronic obstructive pulmonary disease (23.5%). The most frequent surgical procedures were orthopaedic (37.5), abdominal (14.4%), and urological (11.4%) procedures, and the majority of the surgical procedures were elective (67.3%).

Out of all patients included in the study cohort 13 386 (77.8%), 95% (CI 77.2-78.5) filled a prescription for at leas one potentially inappropriate medication use in the year preceding the surgical admission (Table 1). Figure 1 shows the prevalence of potentially inappropriate medication across different levels of pre-admission polypharmacy. Amongst patients with non-polypharmacy, the prevalence of potentially inappropriate medication use was 36.6% (95% CI 35.1-38.2) compared with 80.2%, (95% CI 79.2-81.2) and 95.8% (95% CI 95.3-96.2) for patients with polypharmacy and hyper-polypharmacy, respectively.

Table 1 shows the patients' characteristics, comorbidities, surgical procedures performed, and clinical outcomes compared between those patients filling or not filling a potentially inappropriate medication prior to surgery. Patients with potentially inappropriate medication use were more likely to be female (57.0% vs. 42.5%) and filling more medications both prior to and following admission; median [IQR] was 10 [7,14] vs. 3 [1,6] and post-discharge 11 [7,15] vs. 5 [2,9]. Multidose dispensing service was

more frequently used among those who had filled a potentially inappropriate medication, 36.0% vs. 21.3%. They also had higher burden of comorbidities quantified with Elixhauser comorbidity Index 2 [0,5] vs. 0 [0,4] and a higher Hospital Frailty Risk score class with 28.9% of patients with potentially inappropriate medication having high or medium Hospital Frailty Risk score vs those without 23.3%. All comorbidities registered, except dementia, were more common within patients with potentially inappropriate medication use prior to a surgical admission. The most common comorbidities among both groups were hypertension (60.1% vs 45.9%), followed by ischemic heart disease (33.7% vs 26.5%), and then malignant neoplasm (27.7% vs 24.5%).

Table 1 additionally compares the urgency and the surgical classification for the patients. Patients with potentially inappropriate medication use were less likely to undergo an emergency surgery (30.0% vs 42.1%). The most common type of surgery both patient groups underwent were orthopedics surgeries (36.8% vs. 40.1%), followed by abdominal surgeries (14.9 vs. 12.8%), and then urological surgeries (10.6% vs. 14.0%). Patients undergoing the following surgeries were more likely to use potentially inappropriate abdominal medications: neurosurgery (9.3% vs. 5.5%), (14.9% vs. 12.8%), gynecology (6.4% vs. 2.6%), and thoracic (2.5% vs. 1.6). Additionally, they were more likely to have a higher risk score for the likelihood of experiencing medication-related harm post-discharge, median [IQR] 10.7 [7.2-14.5] vs. 10.2 [7.4-15.3]). Figure 2 shows the prevalence of potentially inappropriate medication use based on 2019 Beers criteria based on medications filled in the year preceding surgical admission over the study period 2005-2018.

Incidence of new potentially inappropriate medication use

Table 2 compares the patient characteristics, type of surgery, comorbidity, and clinical outcomes between cohorts, between patients who were prescribed a new potentially inappropriate medication use following discharge 1481 (38.5%), 95% (CI 37.0-40.1) and those who continued without filling a potentially inappropriate prescription 2366 (61.5%), 95% CI 59.9-63.0). Patients with prescriptions for new potentially inappropriate medication were more likely to be of female gender (60.0% vs. 56.5%),

use multi-dose dispensing services preoperatively (28.4% vs. 17.1%), and used a higher number of medications both prior to admission 5[2,7] vs. 3[0,6] and post-discharge 9 [6,12] vs 3 [0,6]. Additionally, they had a higher Elixhauser risk score (4 [0,7] vs. 2 [0,6]) and a slightly higher Hospital frailty risk score of 4.45 [2.1,7.8] vs. 4.1 [1.8,7.9]. Patients prescribed a new potentially inappropriate medication were more likely to have malignant neoplasm (29.2% vs. 19.4%), ischemic heart disease (29.6% vs. 20.3%), and hypertension (18.5% vs. 15.4%) and less likely to have a diagnosis of mental illness (6.2% vs 11.4%), dementia (1.8% vs 4.4%) and delirium (2.6% vs 3.9%). Patients prescribed a new potentially inappropriate medication post-discharge were more likely to undergo cardiac surgery (14.9% vs. 4.4%), vascular surgery (11.1% vs. 8.2%), and gynecology surgery (4.3% vs. 1.7%), and less likely to undergo orthopedic surgery (28.6% vs. 47.0%). They were also less likely to undergo emergency surgery (31.9% vs 48.3%).

Patients prescribed a new, potentially inappropriate medication post-discharge were more likely to have a more extended hospital stay (3 [1,8] vs. 2 [1,5] days), a higher 30-day readmission risk (11.3% vs. 6.5%) and increased 30-day mortality (5.2% vs. 0.3%). Additionally, patients with new, potentially inappropriate prescription were more likely to receive a diagnosis of an adverse drug reaction both prior to hospital admission (3,7% vs. 3.3%) and post-discharge (3.7% vs. 2.2%). They were more likely to have higher median [IQR] PRIME risk scores for the likelihood of experiencing medication-related harm post-discharge, 12.6 [9.3,17.2] vs 11.3 [8.5,16.4].

Figure 3 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related risk factors. After adjustment for comorbidities and admission information, receiving a new potentially inappropriate medication use following discharge was associated with higher odds of using multi-dose dispensing service (OR 2.52, 95% CI2.11-3.02), hyper-polypharmacy (OR 2.40,95% C 1.3.10), polypharmacy (OR 1.76,95% CI 1.51-2.05) and malignant neoplasm (OR 1.83, 95% CI 1.55-2.16). However, having a diagnosis of dementia was associated with lower odds (OR 0.47,

95% CI 0.29-0.73) of filling a prescription for … after adjustment for comorbidities and admission information.

An unadjusted restricted cubic spline analysis revealed a non-linear relationship between the absolute number of different medications filled in the year preceding admission and the prevalence of potentially inappropriate medication use based on the Beers criteria. Figure 4 shows the relationship between the absolute number of filled medications and the prevalence of filling a potentially inappropriate medication by organ system or therapeutic category. Amongst categories of potentially inappropriate medication use, the highest proportion of patients filled medications that act on the central nervous and gastrointestinal system. When medications within these two organ systems were further analyzed, a strong relationship was identified between increased pre-admission polypharmacy and the likelihood of having filled a prescription for benzodiazepines and Z-drugs (Figure 5), and medications that act on the gastrointestinal system, in particular proton pump inhibitors (Figure 6).

Table 3 compares which Beers criteria subgroups were met for the whole cohort and separated based on varying degrees of polypharmacy prior to admission. The median [IQR] number of Beers criteria fulfilled for the entire cohort before admission was 3 [1, 4]; for those with hyper-polypharmacy, it was 4 [2, 5], polypharmacy 1 [1, 2] and non-polypharmacy 0 [0, 1]. The most commonly met Beers criteria in the entire cohort in the year prior to admission were for medications that act on the central nervous system (50.0%), most commonly z-drugs (36.2%), and benzodiazepines (22.7%). The second most commonly met Beers criteria were due to gastrointestinal medications (35.2%), most commonly proton pump inhibitors (34.0%). The most frequently added medication post-discharge that met Beers criteria were proton pump inhibitors (11.3%), Z-drugs (9.7%), benzodiazepines (6.4%), anti-psychotics (3.3%), anti-cholinergic (3.8%) and cardiovascular (3.5%) medications.

The long-term survival of patients based on whether they had filled a potentially inappropriate medication in the year preceding hospital admission was visualized on a Kaplan-Meier plot (figure 7). No difference in mortality was observed over time among patients who filled a potentially

inappropriate medication compared to patients who did not fill a potentially inappropriate medication in the year preceding the admission to the hospital based on the 2019 Beers criteria.

Discussion

This current study identified that pre-admission potentially inappropriate medication use among older surgical patients is common and rises with the increasing burden of polypharmacy. New post-admission potentially inappropriate medication use was also widespread among the surgical cohort. In addition, the findings confirm that pre-admission potentially inappropriate medication use is associated with higher short-term mortality, a more extended primary hospital stay, and a higher 30-day readmission rate.

Previous studies have investigated potentially inappropriate medication use, and the prevalence and incidence varies among countries., although there is an overall increasing prevalence of potentially inappropriate medication use.[33-39] These studies are however often difficult to compare due to methodological differences and heterogenic study populations.

Potentially inappropriate medication use can be assessed by various criteria.[40] Beers' criteria have been widely studied in general practice [41, 42] and hospital settings[24], but few have focused solely on surgical patients like this study. This study found that the prevalence of filling pre-admission potentially inappropriate medication use was 77.8%, which is slightly lower than 82.7% reported ina recently published study applying the same methodology in patients admitted by internal medicine.[19] The reported prevalence of potentially inappropriate medication use varies across settings, as this meta-analysis, which investigated the prevalence in outpatient settings, reported to range from 1.3-95.2% with a pooled prevalence of 36.7%. However, a recently published study on older internal medicine patients reveals the vast difference between patients admitted to internal medicine compared to surgical wards.[24] In general, internal medicine patients are older, have higher comorbidity and increased frailty, and use more medications compared to surgical patients and, therefore, are also more likely to use potentially inappropriate medications.[19] This current study and

303 the previously mentioned study among older internal medicine patients should encourage researchers
304 to study surgical patients and internal medicine patients, . These results also highlight the importance
305 of caring for them differently. The surgical patients may benefit from targeted interventions to
306 optimize medication therapy prior to elective surgery with the focus on minimizing the burden of
307 potentially inappropriate medication with a particular emphasis on medications and comorbidities
308 known to affect clinical outcomes in relation to surgery, for example, benzodiazepines or opioids [27] ,
309 and addressing physical comorbidities like anemia[43] and increasingly psychological factors. [44] For
310 patients with a high burden of comorbidities and associated polypharmacy or hyperpolypharmacy,
311 geriatricians and clinical pharmacists should provide specialized perioperative care. Likewise, there
312 needs to be a heightened focus on increased follow-up of new medicationsadded duringto surgical
313 admissions (such as opioids) empowering patients and their caregivers by providing sufficient
314 information and guidance on temporal treatments and support if tapering is needed. Even though the
315 surgical population is generally younger and with less comorbidities, there are also complex surgical
316 patients who might benefit from a perioperative multidisciplinary approach from internal medicine
317 specialists, geriatricians, clinical pharmacists, providing a comprehensive review, and increased
318 follow-up during transitions of care. With the limited resources within the healthcare setting,
319 unpacking the difference between internal medicine patients and surgical patients can guide how each
320 patient cohort can receive optimal care support. In this current study, patients admitted for surgical
321 admission had a lower risk of medication-related harm after discharge compared to internal medicine
322 patients (9.0% vs. 14.6%). Another possibility is to apply risk stratification tools such as the PRIME
323 tool,[45] a prediction model to identify patients at risk of experiencing medication-related harm post-
324 discharge. One possible application of the PRIME tool would be to apply risk stratification post-
325 discharge to guide support by stratifying patients to appropriate levels of follow-up; for example, low
326 risk could receive support from a community pharmacy, moderate-risk from general practitioners, and
327 high-risk medication-related harm from a geriatrician in outpatient settings. Likewise, risk stratification
328 could be incorporated into the medication notes to flag individual patients for increased supportive

329 care in real-time within the hospital to hinder medication-related harm post-discharge. Additionally,
330 the PRIME tool has the potential to prioritize the limited care among different sub-specialists for
331 patient groups at increased risk of medication-related harm post-discharge.

332 The results of this study show a correlation between female gender and potentially
333 inappropriate medication use (57.0% vs 43.0%), which is in line with previous studies.[42, 46, 47] Studies
334 have identified that females are more likely to have polypharmacy and hyperpharmacy, which is
335 associated with an increased risk of potentially inappropriate medication use.[8, 15, 24] This finding may
336 possibly be explained by the fact that females are more frequently prescribed medications acting on
337 the central nervous system, like benzodiazepine and Z-medications. They are also more likely to have
338 more frequent visits to healthcare providers, which may provide more opportunities for new
339 prescriptions. [48] The findings from this study should emphasize the need for healthcare practitioners
340 to be aware of gender differences in relation to the use of potentially inappropriate medication. There
341 are vast differences between the genders in relation to biological factors affecting the
342 pharmacokinetics and pharmacodynamics of medications.[49, 50] Potentially, these differences could be
343 addressed in criteria to assess potentially inappropriate medication use to provide a personalized and
344 patient-centered approach to medication management, making sure that healthcare services are
345 optimized for all.

346 This study identified an association between the use of multidose dispensing services and
347 potentially inappropriate medication use, which aligns with previous studies.[16] Multi-dose dispensing
348 is believed to support patients in their medication usage and is most frequently introduced when
349 problems arise in relation to medication usage. The services are often introduced to support patient
350 medication adherence despite the limited evidence supporting improvement in medication
351 adherence, as revealed in the REMIND study.[51] This study highlights the need to review medications
352 dispensed with multidose dispensing services regularly. Previous studies have identified multidose
353 dispensing services as a risk factor for uncritical renewals and insufficient medication optimization. [37,

[52] Annual renewal of prescriptions for patiens using multidose dispensing services could provide a unique opportunity to review medication prior to renewal, and this study and previous evidnce supports increasing the emphasis on such review. Due to the high workload in primary care, primary care physicians often struggle to provide these services, and therefore, support from clinical pharmacists that are ideally equipped with the competencies to support the review in collaboration with the primary care physician. Studies have shown that the collaboration between the two professions in providing comprehensive care has benefited patients. [53]

In line with the previously stated hypothesis, this study identified that potentially inappropriate medication use is associated with worse clinical outcomes, like extended hospital stay, increased readmission risk, mortality, and the likelihood of adverse drug reaction, which is largely in line with previous research (ref). It is not clear whether potentially inappropriate medication use directly causes poorer clinical outcomes or whether it serves as a marker of increased comorbidity. However, a range of studies has reported potentially inappropriate use might prompt poorer clinical outcomes through adverse drug events like increased anticholinergic burden, fall risk, delirium, extended hospital stay, readmission, and increased mortality. (ref) A recent systematic review identified the management of internal medicine physicians and a multidisciplinary team in perioperative care was associated with better clinical outcomes. [54]

The use of multidose dispensing services was associated with increased odds of developing new, potentially inappropriate medication use post-discharge. This is potentially due to patients who use multidose dispensing services being older and behaving with increased comorbidity and more complicated health services needs. This is worrisome due to the lack of regular reviewing and the risk of less critical renewals of medications supplied with multidose dispensing services, as discussed previously. There is an essential need to review new medication use after a surgical admission as they are often meant to be used short-term. Hyperpolypharmacy and polypharmacy were also associated with an increased risk of having new, potentially inappropriate medication use after a surgical

admission. Additionally, patients with malignant neoplasms were at increased risk of new, potentially inappropriate medication use. Even though patients with malignant neoplasm often require the use of multiple medications, which leads to an increased risk of the use of potentially inappropriate medications, there is a heightened need to review their medications regularly as malignant neoplasm is frequently managed as a chronic disease. (ref) Studies have reported that older patients with malignant neoplasm have increased frailty and geriatric syndrome compared to older adults without malignant neoplasm [55] and are more vulnerable to potentially inappropriate medication use, which may also affect cancer therapy negatively. [56] Diagnosis of dementia was associated with reduced odds of developing new, potentially inappropriate medication use post-discharge, perhaps due to awareness healthcare providers about increased risk of adverse drug events due to potentially inappropriate medication use like anticholinergic burden, fall risk, and delirium. (ref)

The most frequently potentially inappropriate medications filled in in the year prior to a surgical admission were medications acting on the central nervous system, like Z-drugs and benzodiazepines. Proton pump inhibitors were also frequently filled. The most frequently used new potentially inappropriate medications after a surgical admission were proton pump inhibitors, Z-drugs, and benzodiazepines. These medication categories are usually meant for short-term treatments, which should be reviewed shortly after admission. This highlights the need for clear counselling for patients and caregivers during the transition of care and handover to primary care following discharge.

The study's strengths include a nationwide centralized Prescription Medicine Registry, which allows detailed information, including over 95% of all prescriptions in the country, and the possibility of linking different registries together and collecting information via the personal identification number. Another strength is the high number of participants included in the extensive surgical database and complete follow-up for survival analysis. Another strength is that all the surgeries were performed at the same national hospital.

A limitation worth mentioning is the method of using filled medications based on the prescription registry database. This method can inflate the number of medications the participants take regularly due to a lack of information on medication adherence. Additionally, we cannot confirm that the increased risk of readmission, mortality, and extended hospitalization is due to medication-related problems.

Conclusion

This study revealed a strong association between the increased burden of potentially inappropriate medication use and polypharmacy and hyper-polypharmacy. Certain sub-groups were at more significant risk of developing increased potentially inappropriate medication use after admission and should emphasise the need for an increased follow-up and medication review. A surgical hospitalization is an opportunity to review and optimize patients' medication, and there is a an immense need to ensure appropriate follow-up and transition of care if medication is changed or temporarily added. A particular emphasis should be put on supporting the transition of care by providing information to patients, their careers, and their primary care physicians regarding the changes in medication during the hospital stay. A particular focus should be on those medications that should be used short-term or new medications that should be re-evaluated.

Additionally, our study highlights the need for increased follow-up for patients at risk of new post-admission potentially inappropriate medication, ideally a focused medication review and deprescribing by a multidisciplinary team involving clinical pharmacists, primary care physicians, or geriatricians when appropriate.

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Figure Legends

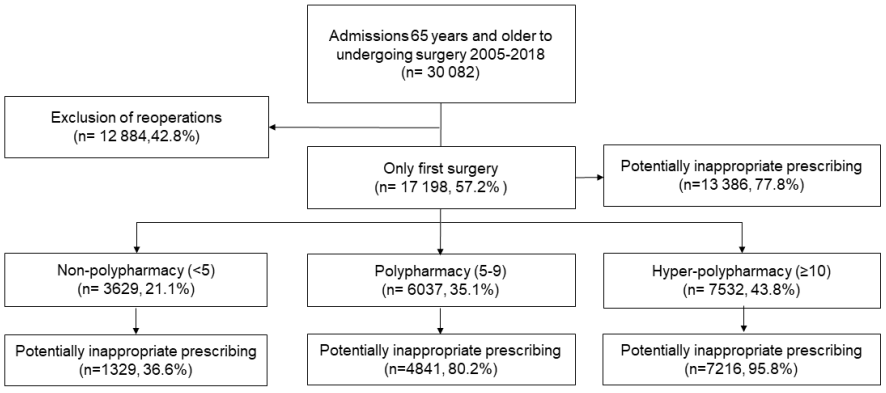

Figure 1.

A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding surgical admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medications based on 2019 Beers criteria.

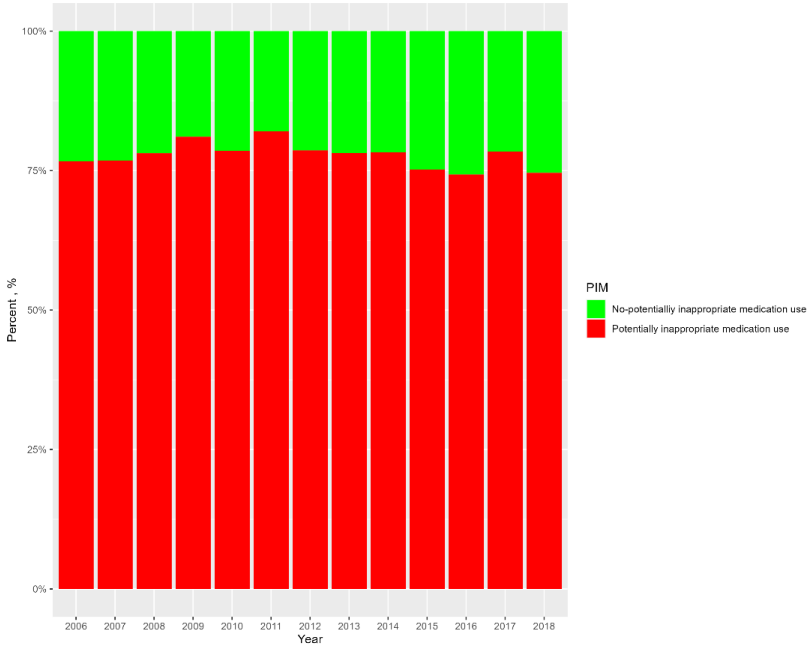

Figure 2.

The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding surgical admission (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).

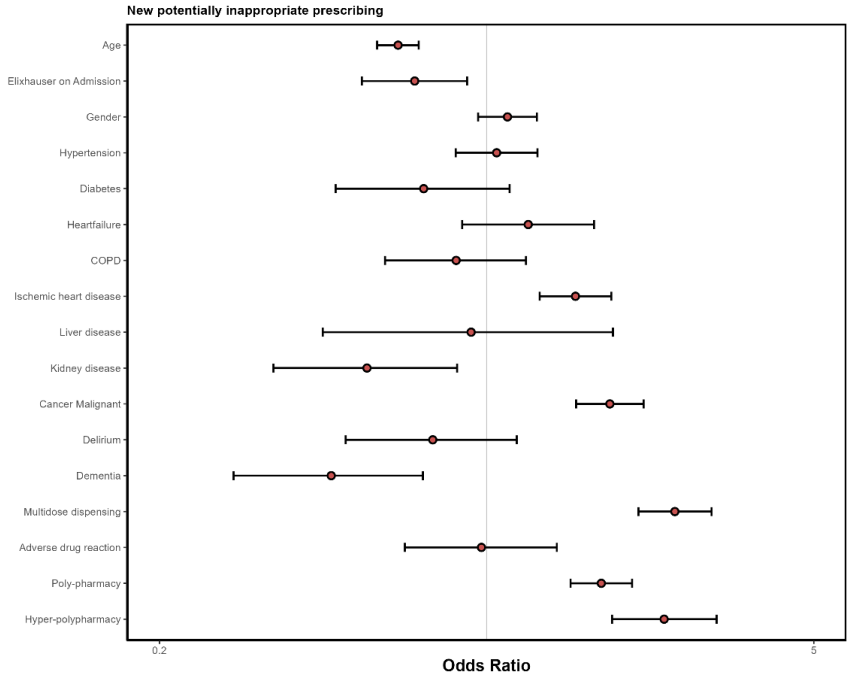

Figure 3.

The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), Elixhauser comorbidity index class (compared with <1), individual comorbidities, use of multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of an adverse drug reaction diagnosis prior to a surgical admission, as covariates.

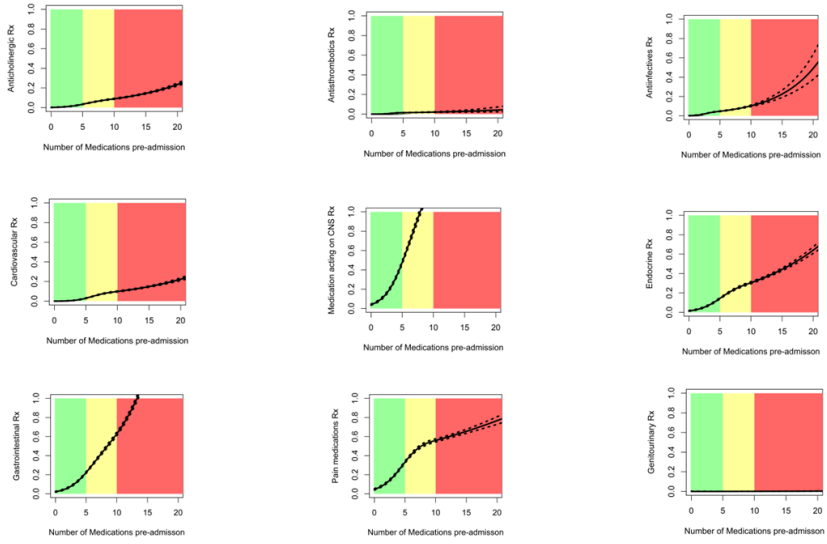

Figure 4.

The correlation between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria. The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colors indicate the polypharmacy category based on the different medications filled in the year preceding surgical admission (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy).

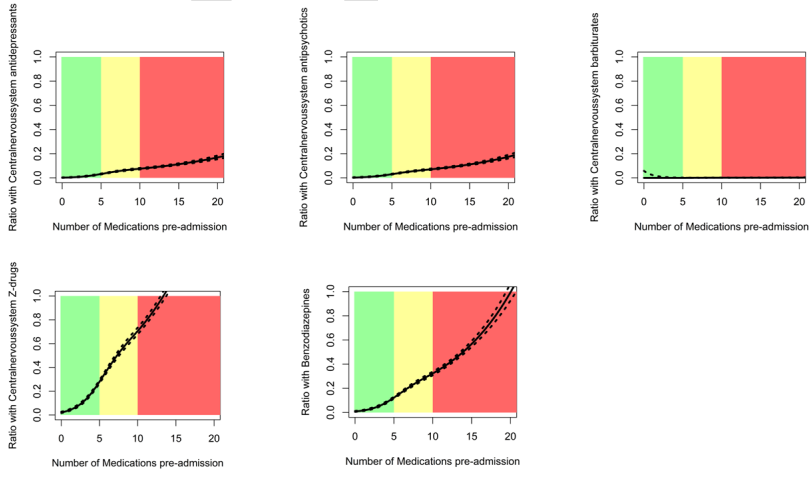

Figure 5.

The association between the number of medications pre-admission and risk of potentially inappropriate medication use based on the 2019 Beers criteria for specific medications acting on the central nervous system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission.

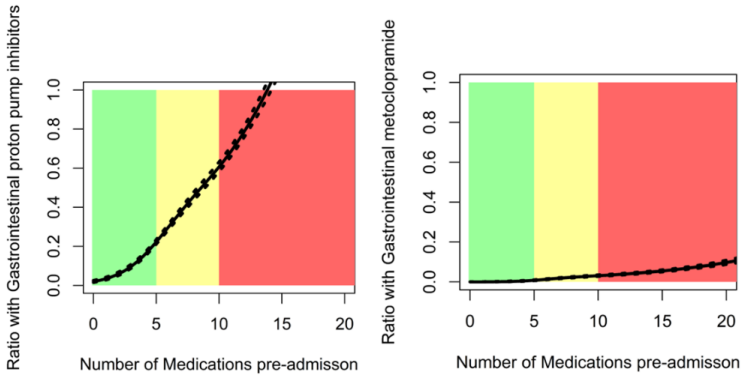

Figure 6.

The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission by internal medicine.

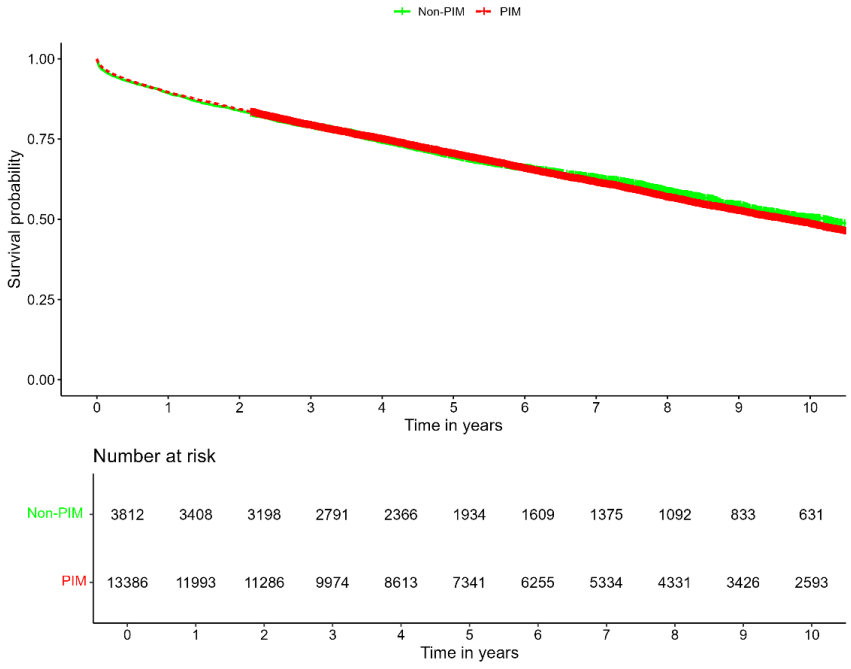

Figure 7.

Kaplan–Meier survival curve of long-term survival of patients compared based on whether they had filled a with potentially inappropriate medication before surgical admission (green = No potentially inappropriate medication use (No PIM), and red = potentially inappropriate medication use.

Tables

Table 1.

Patient characteristics for patients who filled a prescription for a potentially inappropriate medication use based on the 2019 Beers criteria prior to a surgical admission. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No potentially inappropriate medication use pre-admission	Potentially inappropriate medication use pre-admission	All patients	P-value
Total number of patients	3812 (22.2)	13386 (77.8)	17198	
Sex (female)	1620 (42.5)	7632 (57.0)	9252 (53.8)	<0.001
Age (median [IQR]), years	75 [70, 82]	75 [70, 81]	75 [70, 81]	<0.001
[65,75)	1807 (47.9)	6543 (49.1)	8350	
[75,85)	1398 (37.1)	5035 (37.8)	6433	
[85,95.)	565 (15.0)	1738 (13.1)	2303	
Multi-dose dispensing services	811 (21.3)	4822 (36.0)	5633 (32.8)	<0.001
Number of preoperative medications (median [IQR])	3 [1, 6]	10 [7,14]	9 [5, 13]	<0.001
Number of postoperative medications (median [IQR])	5 [2, 9]	11 [7, 15]	9 [6, 14]	<0.001
Elixhauser Comorbidity Index [IQR])	0.00 [0.00, 4.00]	2.00 [0.00, 5.00]	2.00 [0.00, 5.00]	<0.001
(<1]	2116 (55.5)	6387 (47.7)	8503 (49.4)	
(1-4]	765 (20.1)	2777 (20.7)	3542 (20.6)	
(4-5]	243 (6.4)	1047 (7.8)	1290 (7.5)	
(5-8]	228 (6.0)	877 (6.6)	1105 (6.4)	
(>8]	460 (12.1)	2298 (17.2)	2758 (16.0)	
Hospital Frailty Risk Score Class				
Low (< 5)	2927 (76.8)	9349 (69.8)	12276 (71.4)	
Med (5-15)	772 (20.3)	3462 (25.9)	4234 (24.6)	
High (> 15)	113 (3.0)	575 (4.3)	688 (4.0)	
Comorbidities				<0.001
Ischemic heart disease	1010 (26.5)	4510 (33.7)	5520 (32.1)	<0.001
Congestive heart failure	248 (6.5)	1295 (9.7)	1543 (9.0)	<0.001
Hypertension	1750 (45.9)	8045 (60.1)	9795 (57.0)	<0.001
Diabetes Mellitus	206 (5.4)	1877 (14.0)	2083 (12.1)	<0.001
Chronic obstructive pulmonary disease	611 (16.0)	3434 (25.7)	4045 (23.5)	<0.001
Liver disease	45 (1.2)	254 (1.9)	299 (1.7)	0.004
Chronic kidney disease	176 (4.6)	826 (6.2)	1002 (5.8)	<0.001
Malignant neoplasm	935 (24.5)	3711 (27.7)	4646 (27.0)	<0.001
Psychiatric	358 (9.4)	1837 (13.7)	2195 (12.8)	<0.001

Dementia	130 (3.4)	334 (2.5)	464 (2.7)	0.003
Delerium	267 (7.0)	1160 (8.7)	1427 (8.3)	0.001
Surgery Location and Classification				<0.001
Emergency operation	1604 (42.1)	4013 (30.0)	5617 (32.7)	<0.001
Abdominal	490 (12.8)	1984 (14.9)	2474 (14.4)	
Cardiac	325 (8.5)	720 (5.4)	1045 (6.1)	
Endocrine	35 (0.9)		209 (1.2)	
Gynaecology	102 (2.6)	860 (6.4)	962 (5.5)	
Neurosurgery	209 (5.5)	1252 (9.3)	1461 (8.4)	
Orthopaedic	1527 (40.1)	4927 (36.8)	6454 (37.5)	
Thoracic	61 (1.6)	328 (2.5)	389 (2.3)	
Urology	535 (14.0)	1421 (10.6)	1956 (11.4)	
Vascular	353 (9.2)	1184 (8.8)	1537 (8.9)	
Outcomes				
Diagnosis of adverse drug reaction pre-admission (%)	131 (3.4)	1067 (8.0)	1198 (7.0)	<0.001
Diagnosis of adverse drug reaction post admission (%)	105 (2.8)	848 (6.3)	953 (5.5)	<0.001
Readmission within 30 days (%)	318 (8.3)	1282 (9.6)	1600 (9.3)	0.022
Length of stay (median [IQR])	3 [1, 6]	3 [1, 6]	3 [1, 6]	0.349

Table 2.

Comparison of patients with no potentially inappropriate medication use pre-admission or post-discharge to patients with no potentially inappropriate medication use pre-admission but new potentially inappropriate medication use post-discharge. Values are presented as count (%) or median (IQR) unless specified otherwise

	No potentially inappropriate medication use pre-admission nor new potentially inappropriate medication use post-discharge	New potentially inappropriate medication use post-discharge and but not pre-admission	p
Total number of patients	2366	1481	
Sex (male)	1029 (43.5)	593 (40.0)	0.038
Age median [IQR]), years	76.00 [70.00, 82.00]	74.00 [70.00, 80.00]	
Multi-dose dispensing services	405 (17.1)	421 (28.4)	<0.001
Number of pre-admission medications (median [IQR])	3.00 [0.00, 6.00]	5.00 [2.00, 7.00]	
Number of post-discharge medications (median [IQR])	3.00 [0.00, 6.00]	9.00 [6.00, 12.00]	
PRIME score (median [IQR])	11.33 [8.46, 16.37]	12.57 [9.29, 17.24]	
Elixhauser Comorbidity Index [IQR])			<0.001
(<1]	1389 (58.7)	741 (50.0)	
(1-4]	406 (17.2)	369 (24.9)	
(4-5]	154 (6.5)	96 (6.5)	
(5-8]	136 (5.7)	92 (6.2)	
(>8]	281 (11.9)	183 (12.4)	
Hospital Frailty Risk Score Class			<0.001
Low (< 5)	1785 (75.4)	1163 (78.5)	
Med (5-15)	493 (20.8)	292 (19.7)	
High (> 15)	88 (3.7)	26 (1.8)	
Comorbidities			
Ischemic heart disease	481 (20.3)	438 (29.6)	<0.001
Congestive heart failure	146 (6.2)	104 (7.0)	0.329
Hypertension	364 (15.4)	274 (18.5)	0.013
Diabetes Mellitus	74 (3.1)	43 (2.9)	0.766
Chronic obstructive pulmonary disease	105 (4.4)	65 (4.4)	1.000

Liver disease	23 (1.0)	14 (0.9)	1.000
Chronic kidney disease	82 (3.5)	36 (2.4)	0.086
Malignant neoplasm	458 (19.4)	433 (29.2)	<0.001
Psychiatric	269 (11.4)	92 (6.2)	<0.001
Dementia	104 (4.4)	27 (1.8)	<0.001
Delerium	92 (3.9)	39 (2.6)	0.046
Surgery Location and Classification			
Emergency operation	1142 (48.3)	473 (31.9)	
Abdominal	290 (12.2)	205 (13.8)	
Cardiac	105 (4.4)	220 (14.9)	
Endocrine	20 (0.8)	15 (1.0)	
Gynaecology	40 (1.7)	63 (4.3)	
Neurosurgery	132 (5.6)	80 (7.0)	
Orthopaedic	1112(47.0)	424 (28.6)	
Thoracic	21(0.9)	40(2.7)	
Urology	347 (14.7)	198 (13.4)	
Vascular	195 (8.2)	165 (11.1)	
Outcomes			
Length of hospital stay (days)	2 [1, 5]	3[1, 8]	
Diagnosis of adverse drug reaction pre-admission (%)	79 (3.3)	55 (3.7)	0.599
Diagnosis of adverse drug reaction post-discharge (%)	52 (2.2)	55 (3.7)	0.007
Mortality 30 days (%)	5 (0.3)	123 (5.2)	<0.001

Table 3.

The table shows the patients' patterns of pre-admission prescribed medications and anticholinergic burden. The number of medications pre-admission stratified Values are presented as count (%) or median (IQR) unless specified otherwise.

	Non-Polypharmacy pre-admission	Polypharmacy pre-admission	Hyper-Polypharmacy pre-admission	All patients pre-admission	P-value
Total number of patients	3629	6037	7532	17198	
Sex (female)				9252 (53.8)	<0.001
Potentially inappropriate medication use	1329 (36.6)	4841 (80.2)	7216 (95.8)	13386 (77.8)	<0.001
Age (median [IQR]), years	74.00 [69.00,80.00]	74.00 [69.00, 80.00]	76.00 [71.00,82.00]	75.00 [70.00,81.00]	<0.001
[65,75)	1963 (54.7)	3099 (51.6)	3288 (43.9)	8350 (48.9)	
[75,85)	1158 (32.3)	2175 (36.2)	3100 (41.4)	6433 (37.7)	
[85,95.)	466 (13.0)	733 (12.2)	1104 (14.7)	2303 (13.5)	
PRIME score (median [IQR])	10.46 [8.10, 14.44]	15.00 [11.40, 19.89]	24.95 [18.63, 33.57]	17.37 [11.96, 25.15]	<0.001
Diagnosis of adverse drug reaction pre-admission (%)	95 (2.6)	337 (5.6)	766 (10.2)	1198 (7.0)	<0.001
Diagnosis of adverse drug reaction post admission (%)	92 (2.5)	285 (4.7)	576 (7.6)	953 (5.5)	<0.001
Beers criteria total score pre-admission (median [IQR])	0 [0, 1]	1 [1, 2]	4.[2, 5]	3 [1, 4]	<0.001
Beers criteria anticholinergics (%)	49 (1.4)	316 (5.2)	1016 (13.5)	1381 (8.0)	<0.001
Beers criteria Anticholinergics (antihistamines) (%)	48 (1.3)	285 (4.7)	964 (12.8)	1297 (7.5)	<0.001
Beers criteria Anticholinergics (antiparkinsonian) (%)	1 (0.0)	17 (0.3)	17 (0.2)	35 (0.2)	0.023
Beers criteria Anticholinergics (antispasmodics) (%)	0 (0.0)	15 (0.2)	40 (0.5)	55 (0.3)	<0.001
Beers criteria antithrombotic (%)	1 (0.0)	68 (1.1)	135 (1.8)	204 (1.2)	<0.001
Beers criteria anti-infective (%)	27 (0.7)	185 (3.1)	563 (7.5)	775 (4.5)	<0.001
Beers criteria cardiovascular (%)	24 (0.7)	314 (5.2)	1057 (14.0)	1395 (8.1)	<0.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.526
Beers criteria (cardiovascular disopyramide) (%)	2 (0.1)	7 (0.1)	30 (0.4)	39 (0.2)	<0.001
Beers criteria (cardiovascular dronedarone) (%)	0 (0.0)	3 (0.0)	19 (0.3)	22 (0.1)	<0.001
Beers criteria (cardiovascular digoxin) (%)	8 (0.2)	112 (1.9)	462 (6.1)	582 (3.4)	<0.001

Beers criteria (cardiovascular nifedipine) (%)	7 (0.2)	64 (1.1)	130 (1.7)	201 (1.2)	<0.001
Beers criteria (cardiovascular amiodarone) (%)	6 (0.2)	87 (1.4)	337 (4.5)	430 (2.5)	<0.001
Beers criteria central nervous system (%)	556 (15.3)	2591 (42.9)	5447 (72.3)	8594 (50.0)	<0.001
Beers criteria (central nervous system antidepressant) (%)	49 (1.4)	258 (4.3)	829 (11.0)	1136 (6.6)	<0.001
Beers criteria (central nervous system antipsychotics) (%)	46 (1.3)	279 (4.6)	789 (10.5)	1114 (6.5)	<0.001
Beers criteria (central nervous system barbiturates) (%)	0 (0.0)	6 (0.1)	15 (0.2)	21 (0.1)	0.015
Beers criteria (central nervous system benzodiazepines) (%)	165 (4.5)	979 (16.2)	2761 (36.7)	3905 (22.7)	<0.001
Beers criteria (central nervous system z-drugs) (%)	365 (10.1)	1779 (29.5)	4080 (54.2)	6224 (36.2)	<0.001
Beers criteria endocrine (%)	201 (5.5)	1048 (17.4)	2331 (30.9)	3580 (20.8)	<0.001
Beers criteria (endocrine androgens) (%)	7 (0.2)	45 (0.7)	110 (1.5)	162 (0.9)	<0.001
Beers criteria (endocrine estrogens) (%)	165 (4.5)	674 (11.2)	1348 (17.9)	2187 (12.7)	<0.001
Beers criteria (endocrine sulfonylurea) (%)	29 (0.8)	348 (5.8)	966 (12.8)	1343 (7.8)	<0.001
Beers criteria gastrointestinal (%)	307 (8.5)	1647 (27.3)	4101 (54.4)	6055 (35.2)	<0.001
Beers criteria (gastrointestinal metoclopramide) (%)	8 (0.2)	100 (1.7)	446 (5.9)	554 (3.2)	<0.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	301 (8.3)	1599 (26.5)	3955 (52.5)	5855 (34.0)	<0.001
Beers criteria Pain medications (%)	468 (12.9)	1671 (27.7)	2833 (37.6)	4972 (28.9)	<0.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.526
Beers criteria pain medications nonselective NSAID (%)	462 (12.7)	1614 (26.7)	2689 (35.7)	4765 (27.7)	<0.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	12 (0.3)	106 (1.8)	300 (4.0)	418 (2.4)	<0.001
Beers criteria (genitourinary) (%)	2 (0.1)	4 (0.1)	17 (0.2)	23 (0.1)	0.014

Appendix

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Reykjavík 21. september 2021
Tilv.: VSNb2021080012/03.01

Efni: 21-179 Faraldsfræði lyfjanotkunar sjúklinga sem leggjast inn á lyflækningadeildir Landspítalans

Umsókn þinni til vísindasiðanefndar hefur verið gefið númerið VSN-21-179. Við förum vinsamlegast fram á að það númer verði notað í samskiptum vegna þessarar umsóknar.

Á fundi sínum 21.09.2021 fjallaði vísindasiðanefnd um umsókn þína vegna ofangreindrar rannsóknaráætlunar. Meðrannsakendur þínir eru: Freyja Jónsdóttir, klínískur lyfjafræðing og lektor við lyfjafræðideild Háskóla Íslands og Landspítala. Er einnig doktorsnemi við Háskóla Íslands, Anna Bryndís Blöndal, lyfjafræðingur og lektor, Þróunarmiðstöð íslenskra heilsugæslu, Heilsugæslu höfuðborgarsvæðisins og Lyfjafræðideild Háskóla Íslands og Aðalsteinn Guðmundsson, öldrunarlæknir og klínískur lektor við læknadeild.

Um rannsóknarúrtakið í þessari gagnarannsókn segir í kafla B-1 í umsókn til nefndarinnar:
„Rannsóknarþýðið inniheldur alla sjúklinga (#18 ára) sem dvöldu í meira en 24 klst. á Landspítala á ábyrgð
lyflækningasviðs frá 1. janúar 2010 til 31. desember 2020. Áætlað er út frá tölum frá Landspítala að það séu um það bil 8000 einstaklingar sem leggjast inn á lyflæknisdeildir á ári og því mun tíu ára tímabil vera um það bil 80.000 innlagnir."

Um gagnaöflun í þágu rannsóknarinnar segir í kafla B-2:

„Landspítali
A) Sjúkraskrárkerfi, leguskráningarkerfi
B) Sjúkdómsgreiningar
C) Blóðprufugagnagrunnur
D) Grunnur sýkla-og veirurannsóknar
E) Hjartalínuritagrunnur
F) Blóðbankagrunnur
Landlæknisembætti
A) Lyfjagagnagrunnur
B) Samskiptaskrá heilsugæslunnar
C) Samskiptaskrá sjálfstætt starfandi sérfræðilækna

a) Óskað verður eftir eftirtöldum gögnum frá Landspítala, Embætti landlæknis, Hagstofu fyrir alla þátttakendur sem tilgreindir eru í B-1
Landspítali

1) Lista af innlögnum með innlagnarkóða (ábyrg sérgrein), dagsetningu innlagnar og útskriftar og sömuleiðis lista yfir ICD9/10 greiningar sem gefnar voru í legunni, og hvort sjúklingur lagðist inn á gjörgæsludeild (og legutími á gjörgæsludeild)
2) Blóðprufusvörum (blóðhag, bólgumerkjum, lifrarprófum, nýrnaprófum, hjartarprófum, blóðstorkumælingum, blóðgösum) merktum dagsetningum
3) Lista af sýklaræktunum og veirurannsóknum sem framkvæmdar eru hjá sjúklingunum
3) Lista af ICD9 og ICD10 greiningarkóðum sem gefnir hafa verið á legu-, göngu- og bráðamóttöku Landspítala
4) Lista af dánardegi hjá þeim sjúklingum sem eru látnir
5) Lista yfir búsetu og hjúskaparstöðu skv. skráningu í þjóðskrá
6) Hæð og þyngd úr sjúkraskrárkerfi Landspítala
7) Lista yfir blóðhlutagjafir sjúklinga úr rannsóknarkerfi Landspítala
8) Lista yfir tölulegar mælingar úr hjartalínuritakerfi Landspítala
Embætti landlæknis:
1) Lyfjagagnagrunnur Embættis landlæknis:
Yfirlit yfir lyfjanotkun 2 ár fyrir innlögn og 2 ár eftir innlögn, skráð sem ATC-kóði, Yfirlit yfir hvort einstaklingar hafa fengið útgefinn lyfseðil til lyfjaskömmtunar
2) Samskiptaskrá heilsugæslu
ICD9/10 greiningar og dagsetning greiningar fyrir einstaklinga í rannsókn
3) Samskiptaskrá sjálfstætt starfandi sérfræðilækna
ICD9/10 greiningar og dagsetning greiningar fyrir einstaklinga í rannsókn."

Dulkóðunarlykill sem tengir saman kennitölur og rannsóknanúmer er í vörslu aðalrannsakanda. Þessum dulkóðunarlykli verður eytt 12 mánuðum eftir birtingu á niðurstöðum rannsóknarinnar. Rannsóknargögnum verður eytt innan 5 ára frá rannsóknarlokum, eða í síðasta lagi 31. desember 2028 nema framhaldsleyfis verði óskað.

Vísindasiðanefnd sér því ekkert til fyrirstöðu að umsækjandi fái aðgang að þeim upplýsingum sem upp eru taldar í kafla B-2 í umsókn úr þar tilgreindum sjúkraskrám. Með vísan til 1. mgr. 12. gr. laga nr. 44/2014, um vísindarannsóknir á heilbrigðissviði, er rannsóknaráætlunin endanlega samþykkt með þeim almenna fyrirvara að lögbundið samþykki skráarhaldara skv. 2. mgr. 27. gr. laga nr. 44/2014 verður að liggja fyrir áður en vinna með heilbrigðisgögn viðkomandi stofnunar/skráarhaldara hefst.

Vakin er athygli á að innan gildistíma leyfis nefndarinnar er gert ráð fyrir gagnaöflun, úrvinnslu gagna og birtingu niðurstaðna. Einnig er vakin er athygli á að leyfi nefndarinnar miðast við rannsóknarlok sem tilgreind eru í umsókn, nema sótt verði um framlengingu á gildistíma leyfis innan þess tíma. Rannsóknarlok skv. umsókn eru 31.12.2028.

Vísindasiðanefnd áréttar að ábyrgðarmaður rannsóknarinnar ber ábyrgð á að sótt sé um viðeigandi leyfi fyrir rannsókninni hjá þeim stofnunum sem við á. Óheimilt er að hefja framkvæmd rannsóknarinnar fyrr en þau liggja fyrir. Afrit leyfa/samstarfsyfirlýsinga þurfa að berast nefndinni. Áréttað er að allar fyrirhugaðar breytingar á þegar samþykktri rannsóknaráætlun þurfa að koma inn til nefndarinnar til umfjöllunar. Jafnframt ber ábyrgðarmanni að sækja um breytingar til þeirra stofnanna, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna, um framangreint, ef við á.
Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina.
Minnt er á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju, f.h. vísindasiðanefndar,
Sunna Snædal, læknir, formaður

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Reykjavík 19. janúar 2021
Tilv.: VSNb2014100009/03.11

Efni: 14-139-V6 - Faraldsfræði og árangur bráðra líffærabilana eftir skurðaðgerðir á Íslandi.

Á fundi sínum 19.01.2021 fjallaði Vísindasiðanefnd um umsókn þína vegna viðbótar nr. 6 við ofangreinda rannsóknaráætlun. Í erindi þínu segir:

„Vísað er til ofangreindrar umsóknar um vísindarannsókn sem samþykkt var 28. október 2014 sl. og með síðari viðbótum, síðast 4. Desember 2018. Í umsókninni er óskað eftir samþykki til að kanna faraldsfræði, áhættuþætti og útkomur sjúklinga sem fá bráðar líffærabilanir í kjölfar aðgerða. Með bréfi þessu er óskað eftir því að fá heimild Vísindasiðanefndar til þess að safna eftirfarandi gögnum vegna sjúklinga í rannókninni:

a) Þjóðskrá: Búseta og hvort sjúklingur búi einn.
b) Lyfjagagnagrunni Landlæknis: Bakgrunnsupplýsingar um ávísandi lækni, kyn og aldur. Einnig hvort lyfi hafi verið ávísað á skömmtunarlyfseðil.
c) Samskiptaskrá heilsugæslu: Upplýsingar um hvort sjúklingur hafi fengið „Yfirferð lyfjalista" í heilsugæslu.
d) Sjúkraskrá Landspítala: Hvort að sjúklingur hafi fengið aðstoð frá útskriftarteymi fyrir útskrift.

Einnig er óskað eftir því að gagnasöfnunartímabilið verði framlengt út 31. Desember 2020, og gefin verði allt að 5 ár til úrvinnslu og greinaskrifa tengdum rannsóknarverkefninu svo að rannsóknartímabilinu ljúki að fullu 31. Desember 2025.

Að lokum er óskað eftir því að eftirtöldum samstarfsmönnum verði bætt við verkefnið, en þau munu öll vinna að úrvinnslu og greinarskrifum úr verkefninu

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Landlæknisembættið og vísindarannsóknarnefnd Landspítala munu fá tilkynningu þessa efnis senda"

Vakin er athygli á að innan gildistíma leyfis nefndarinnar er gert ráð fyrir gagnaöflun, úrvinnslu gagna og birtingu niðurstaðna. Einnig er vakin er athygli á að leyfi nefndarinnar miðast við rannsóknarlok sem tilgreind eru í umsókn, nema sótt verði um framlengingu á gildistíma leyfis innan þess tíma. Rannsóknarlok eru *31. desember 2025.*

Vísindasiðanefnd hefur farið yfir bréf þitt og gerir ekki athugasemdir við tilgreindar breytingar. Viðbót nr. 6 við ofangreinda rannsókn, er endanlega samþykkt af Vísindasiðanefnd.

Vísindasiðanefnd bendir á að ábyrgðarmaður rannsóknarinnar ber ábyrgð á að sótt sé um viðeigandi leyfi vegna viðbóta/breytinga hjá þeim stofnunum sem við á. Óheimilt er að hefja framkvæmd rannsóknarinnar fyrr en slík leyfi liggja fyrir. Afrit leyfa/samstarfsyfirlýsinga þurfa að berast nefndinni. Jafnframt ber ábyrgðarmanni að tilkynna þeim stofnunum, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna, um framangreint, ef við á. Óheimilt er að breyta framkvæmd rannsóknarinnar fyrr en slík leyfi liggja fyrir.

Með kveðju, f.h. Vísindasiðanefndar,

Sunna Snædal, læknir, formaður