Acute Kidney Injury

Incidence, risk factors, renal recovery and outcome

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Bráður nýrnaskaði

Nýgengi, áhættuþættir, endurheimt nýrnastarfsemi og lifun

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Ágrip

Bráður nýrnaskaði (BNS) er algengt vandamál bæði innan og utan sjúkrahúsa og tengist hærri tíðni fylgikvilla og dánartíðni. Langvinnur nýrnasjúkdómur (LNS) er áhættuþáttur fyrir BNS sem jafnframt er áhættuþáttur fyrir þróun á LNS og versnun á sjúkdómnum. Endurheimt fyrri nýrnastarfsemi eftir BNS er talinn sjálfstæður áhrifaþáttur fyrir horfur sjúklingsins, hinsvegar hefur skort rannsóknir þar sem ekki hefur náðst samstaða um skilgreiningu á endurheimt fyrri nýrnastarfsemi eftir BNS. Í dag er væg hækkun á kreatíníni í sermi (SKr) um 26,5 µmól/L innan 48 klukkustunda er hluti af greiningarskilmerkjum BNS en hinsvegar er lítið vitað um einkenni og afdrif þess hóps sem greinist með BNS einungis vegna þessa hluta skilmerkjanna.

Markmið þessarar ritgerðar var að kanna nýgengi BNS á sjúkrahúsi, meta endurheimt fyrri nýrnastarfsemi í kjölfar BNS og tengsl hans við langtímalifun. Enn fremur að kanna nýgengi og áhættuþætti fyrir BNS í kjölfar kviðarholsskurðaðgerða og meta tengsl við skammtímalifun. Um leið eru bornar saman mismunandi skilgreiningar á endurheimt fyrri nýrnastarfsemi í kjölfar BNS eftir skurðaðgerð með tilliti til tengsla þeirra við langtímalifun, þróunar á LNS og framgangs á undirliggjandi LNS. Að lokum að skoða einkenni þess hóps sem fær vægan BNS á stigi 1 og kanna hvort tengsl séu við langtímalifun, þróun á LNS eða framgang undirliggjandi LNS.

Allar rannsóknirnar fjórar voru afturskyggnar. Í Grein I voru allir einstaklingar skoðaðir sem fengu BNS á Landspítala á 20 ára tímabili frá 1993-2013. Í Grein II voru skoðaðir allir einstaklingar sem gengust undir kviðarholsskurðaðgerð á árunum 2007-2014. Í Grein III og Grein IV voru kannaðir allir einstaklingar sem gengust undir kviðarhols-, brjósthols-, æða- eða bæklunarskurðaðgerð á árunum 1998-2015. Sjúklinga-, sjúkdóma- og aðgerðarupplýsingum auk niðurstöðum blóðrannsókna var safnað úr rafrænum kerfum Landspítala og sértækum gagnasöfnum. SKr-hluti KDIGO-greiningarskilmerkja fyrir BNS var notaður í öllum greinum nema væg hækkun um 26,5 µmól/L innan 48 klukkustunda var útilokuð í Grein I. Fjölþátta línulegri aðhvarfsgreiningu var beitt við mat áhættuþátta og eins árs lifun. Cox-líkön og áhættuskora-pörun (propensity score matching) var notað við mat á langtímalifun, þróun á LNS og framgangi á LNS.

Nýgengi BNS á sjúkrahúsi var að meðaltali 25,8 per 1000 innlagnir/ári og jókst marktækt á rannsóknartímabilinu. BNS á sjúkrahúsi tengdist verri eins

árs lifun og lifunin var í öfugu sambandi við alvarleikastig BNS. Hinsvegar batnaði lifun sjúklinga með BNS á sjúkrahúsi á tímabilinu. Tíðni BNS var 6,8% í kjölfar kviðarholsskurðagerða og var algengust eftir aðgerðir á vélinda, milta, maga og opna könnunaraðgerð á kvið. Sjálfstæðir áhættuþættir fyrir BNS í kjölfar kviðarholsaðgerðar voru hækkandi aldur, karlkyn, undirliggjandi LNS, há ASA-flokkun og ef aðgerðin var enduraðgerð. BNS í kjölfar kviðarholsaðgerðar tengdist lengri legutíma, hærri tíðni skammtímafylgikvilla og verri 30 daga lifun. Þegar endurheimt á fyrri nýrnastarfsemi <1,5 x grunngildi SKr innan 30 daga náðist ekki var eins árs lifun síðri og að ná ekki endurheimt fyrri nýrnastarfsemi <1,25 x grunngildi SKr var tengt þróun á LNS og versnun á undirliggjandi LNS. Þriðjungur allra sjúklinga sem fengu BNS í kjölfar skurðaðgerðar fengu vægan BNS af stigi 1, en hann tengdist bæði þróun á LNS og versnun á undirliggjandi LNS en engin tengsl voru við eins árs lifun.

Greinarnar fjórar undirstrika að BNS er algengt vandamál, bæði í almennu sjúkrahúsþýði og í kjölfar skurðaðgerða. Það eru sjálfstæðir áhættuþættir fyrir BNS í kjölfar kviðaraholsaðgerða sem auðveldlega er hægt að meta fyrir aðgerð og nýta við áhættumat sjúklinga. BNS tengist verri skammtíma- og langtímalifun og þróun á LNS og versnun á undirliggjandi LNS. Að ná ekki endurheimt á fyrri nýrnastarfsemi undir 1,5 x grunngildi SKr innan 30 daga er tengt verri eins árs lifun og að ná ekki undir 1,25 x grunngildi SKr innan 30 daga er tengt þróun og versnun á LNS. Þessa niðurstöðu ætti að leggja til grundvallar þegar samstaða næst um skilgreiningu á endurheimt fyrri nýrnastarfsemi í kjölfar BNS í framtíðinni. Vægur BNS á stigi 1 er tengdur skammtímalifun og þróun og versnun á LNS. Þetta styður að væg hækkun SKr á að vera hluti skilgreiningar á BNS og sýnir mikilvægi nákvæmrar eftirfylgdar sjúklinga með BNS, sér í lagi ef ekki næst endurheimt á fyrri nýrnastarfsemi.

Lykilorð: Bráður nýrnaskaði, endurheimt fyrri nýrnastarfsemi, langvinnur nýrnasjúkdómur, lifun, nýgengi, vægur bráður nýrnaskaði.

Abstract

Acute kidney injury (AKI) is a common clinical problem both in the hospital and outpatient setting and is associated with increased morbidity and mortality. Chronic kidney disease (CKD) is a risk factor for developing AKI and AKI is a risk factor for development and progression of CKD. Renal recovery after AKI has been shown to be an independent determinant of patient morbidity and mortality, but studies have been impeded by lack of consensus on how to define renal recovery following AKI. A small absolute change in serum creatinine (SCr) of 26.5 µmol/L within 48 hours is included in the current diagnostic criteria of AKI. However, characteristics and long-term outcomes of the subgroup diagnosed with AKI solely by this part of the criteria, referred to as mild stage 1 AKI in this thesis, has not been studied.

The aim of this thesis was to evaluate the incidence, long-term survival and renal recovery of hospital-acquired AKI (H-AKI) and examine time-trends in its incidence and survival. Also to assess the incidence, risk factors and short-term survival of AKI following abdominal surgery. Furthermore, to compare different definitions of renal recovery following postoperative AKI with respect to association with long-term survival, development of incident CKD and progression of preexisting CKD. Finally, to examine the characteristics of mild stage 1 AKI and whether it is associated with long-term survival, development of incident CKD or progression of preexisting CKD.

All the studies reported in the papers were retrospective. Paper I included all patients with H-AKI over a 20-year period, from 1993 to 2013. All patients undergoing abdominal surgery in 2007-2014 were included in Paper II, and Paper III and IV included all patients undergoing abdominal, cardiothoracic, vascular or orthopedic surgery in 1998-2015. Data on patient characteristics, comorbidities, perioperative information and SCr measurements were collected from electronic hospital records, national registries and hospital databases. The SCr component of the KDIGO criteria was used to detect AKI in all Papers, except that the absolute increase in SCr of 26.5 µmol/L within 48 hours was excluded in Paper I. Multivariable logistic regression analyses were performed to evaluate risk factors and associations with one-year mortality. Cox proportional hazards regression analysis and propensity score matching were used to evaluate long-term survival, development of incident CKD and progression of preexisting CKD.

The mean incidence of H-AKI was 25.8 per 1000 admissions/year and increased significantly over the 20-year study period. H-AKI associated with worse one-year survival that followed an inverse relationship with the severity of H-AKI. However, survival of H-AKI patients improved over the study period. AKI occurred following 6.8% of all abdominal surgeries and was most common following surgery on the esophagus, spleen, stomach and after explorative laparotomy. Independent risk factors for AKI following abdominal surgery were older age, male sex, preoperative CKD, higher ASA class and if the surgery was a reoperation. AKI following abdominal surgery was associated with longer length of stay, more short-term complications and worse 30-day survival. Lack of renal recovery after AKI to a SCr < 1.5 x baseline within 30 days was associated with worse one-year survival and lack of recovery to a SCr < 1.25 x baseline within 30 days was associated with increased risk of developing incident CKD and progression of preexisting CKD. One-third of all postoperative AKI patients had mild stage 1 AKI, which was associated with both development of incident CKD and progression of preexisting CKD, but no association was found with one-year survival.

The four papers highlight that AKI is a common problem in both the general hospital population and following surgery. There are independent risk factors for development of AKI following abdominal surgery that can all be assessed preoperatively for patient risk stratification. AKI is associated with both short-term and long-term survival and development of incident CKD and progression of preexisting CKD. Moreover, lack of renal recovery to SCr below 1.5 x baseline value within 30 days associated with worse one-year survival and lack of recovery to SCr below 1.25 x baseline value was associated with development of CKD and progression of preexisting CKD. These results should be considered when a consensus on the definition of renal recovery is reached. Furthermore, mild stage 1 AKI was associated with short-term mortality and both development of CKD and progression of preexisting CKD. This supports the inclusion of small absolute increase in SCr in the AKI definition and the results emphasize the importance of meticulous follow-up of patients with AKI, particularly patients without renal recovery.

Keywords: Acute kidney injury, chronic kidney disease, incidence, mild acute kidney injury, renal recovery, survival.

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Contents

List of abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
AMI	acute myocardial infarction
ASA	American Society of Anesthesiology
CABG	coronary artery bypass grafting
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	chronic obstructive pulmonary disease
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
FDA	Food and Drug Administration
GFR	glomerular filtration rate
H-AKI	hospital-acquired acute kidney injury
HR	hazard ratio
HTN	hypertension
ICD-9	International Classification of Diseases, 9th revision
ICD-10	International Classification of Diseases, 10th revision

ICU	intensive care unit
IHD	ischemic heart disease
KDIGO	Kidney Disease: Improving Global Outcome
KIM-1	kidney injury molecule 1
LOS	length of stay
LUH	Landspitali – The National University Hospital of Iceland
MDRD	Modification in Diet and Renal Disease
MI	myocardial infarction
NGAL	neutrophil gelatinase-associated lipocalin
NOMESCO	Nordic Medico-Statistical Committee Classification of Surgical Procedures
OR	odds ratio
PSM	propensity score matching
RCRI	Revised Cardiac Risk Index
RIFLE	Risk, Injury, Failure, Loss of kidney function and End-stage renal disease
RRT	renal replacement therapy
SCr	serum creatinine
TIMP-2	tissue inhibitor of metalloproteinase-2
UK	United Kingdom
USA	United States of America
IGFBP-7	insulin growth factor binding protein-7

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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-IV):

I. Long TE*, Sigurdsson MI*, Sigurdsson GH, Indridason OS. (2016). Improved long-term survival and renal recovery after acute kidney injury in hospitalized patients, a 20 years experience. *Nephrology,* 21: 1027-1033. *Equal contribution to manuscript.

II. Long TE, Helgason D, Helgadottir S, Palsson R, Gudbjartsson T, Sigurdsson GH, Indridason OS, Sigurdsson MI. (2016). Acute kidney injury after abdominal surgery: Incidence, risk factors, and outcome. *Anesthesia & Analgesia*, 122: 1912–1920.

III. Long TE, Helgadottir S, Helgason D, Sigurdsson GH, Gudbjartsson T, Palsson R, Indridason OS, Sigurdsson MI. (2019). Postoperative acute kidney injury: Focus on renal recovery definitions, kidney disease progression and survival. *American Journal of Nephrology*, 49 (3): 175-185.

IV. Long TE, Helgason D, Helgadottir S, Sigurdsson GH, Palsson R, Sigurdsson MI, Indridason OS. (2019). Mild stage 1 postoperative acute kidney injury: Association with chronic kidney disease and long-term mortality. *Submitted for publication.*

In addition, some unpublished data are presented.

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Declaration of contribution

For Papers I-IV, the doctoral candidate, Þórir Einarsson Long, under guidance from his supervisors and co-authors helped design the study, conduct the study, analyze the data, and write the manuscript. He performed the statistical analysis for Papers II, III and IV. For Paper I, Martin Ingi Sigurdsson primarily performed the statistical analysis and co-wrote the manuscript.

1 Introduction

The focus of this doctoral thesis was to utilize epidemiological methods to examine acute kidney injury (AKI) in hospitalized patients and evaluate the incidence and risk factors for AKI and recovery of kidney function. Furthermore, the long-term outcomes of patients with AKI were studied, including the development of incident chronic kidney disease (CKD), progression of preexisting CKD and survival. Association with these outcomes can guide the search for a definition of renal recovery following AKI. Finally, the subgroup with the mildest form of AKI was examined and assessed whether mild AKI associated with incident CKD, progression of preexisting CKD and survival.

AKI is a clinical state where an individual loses part of his/her previous kidney function over a short period of time. This introductory chapter starts by describing the basic anatomy and function of the kidneys and how to assess kidney function. Subsequently, the definition of AKI, and the present knowledge on the pathogenesis, incidence, risk factors, renal recovery and survival after AKI. Finally, there is a short overview of CKD, its definition, progression and relation to AKI.

1.1 The kidney

The human body normally contains two kidneys. The kidneys are vital organs, each about the size of a fist, and are positioned in the retroperitoneal space. They constitute over 30 different cell types that form a large number of nephrons, the functional units of the kidney which are composed of the glomerulus, Bowman capsule and renal tubule (Figure 1) (Hall & Guyton, 2016). The main functions of the kidneys are:

- To regulate the balance of fluid and electrolytes to sustain homeostasis.
- To regulate acid-base balance.
- To excrete metabolic waste products such as urea, uric acid as well as foreign chemicals.
- To control arterial blood pressure, primarily through activation of the renin-angiotensin-aldosterone system.
- To metabolize, secrete and excrete peptides and hormones.

- To increase the production of red blood cells in the bone marrow by producing and releasing erythropoietin, which stimulates the rate of erythropoiesis.

The process of urine formation begins with filtration of blood in the glomerulus, the glomerular filtrate flows into the Bowman capsule and enters into the proximal tubule where around two-thirds of the filtrate is reabsorbed (Schrier, Coffman, Thomas M. Falk, Molitoris, & Neilson, 2012). The rest flows down the descending limb and then back up the thin and thick ascending limb of the loop of Henle. The filtrate passes past the juxtaglomerular apparatus and then into the distal convoluted tubule. Finally, the filtrate passes through the connecting tubule into the collecting ducts where water is either conserved or excreted. As the filtrate flows through these different structures of the nephron, a complex and tightly coordinated process of solute reabsorption and secretion occurs with the net result of precise control of water, electrolytes and acid-base balance needed for the maintenance of homeostasis (Hall & Guyton, 2016).

Glomerular filtration rate (GFR) is the flow of plasma from the glomerulus into the Bowman space over a specified time period and is the principal measure of kidney function (Schrier et al., 2012). The determinants of GFR are the net glomerular transcapillary filtration pressure and surface area. The net transcapillary filtration pressure is affected by a hydrostatic and oncotic pressure gradient between the glomerular capillary and the Bowman space (Gilbert & Weiner, 2017). Thus, the glomerular filtration rate is highly dependent on adequate renal hemodynamics as it is the driving force for the hydraulic pressure gradient.

The renal arteries branch into afferent arterioles and form the glomerulus. The efferent arterioles follow two different paths based on their location within the kidney (Schrier et al., 2012). Arterioles coming from glomeruli in the outer and mid cortex form a network surrounding the proximal and distal tubules. However, efferent arterioles arising from juxtamedullary glomeruli form the vasa recta that run parallel to the loop of Henle. This complex intrarenal microvasculature forms a gradient of decreasing oxygen tension from the renal cortex to the renal medulla that is relatively hypoxic (Evans et al., 2013).

The major determinant (approximately 80%) of kidney oxygen requirement is the active reabsorption of sodium and other solutes by the Na/K ATPase in the proximal tubules (Gilbert & Weiner, 2017). Because most of the reabsorption is dependent on the GFR, it drives the majority of the oxygen consumption. Intrarenal blood flow and intracapillary pressure is maintained by

autoregulation which is controlled through a complex interaction between the sympathetic nervous system and several neurohormonal mediators that affect different sections of the renal vasulature (Just, 2007; Schrier et al., 2012). For instance, when systemic blood pressure falls, GFR and renal oxygenation can be maintained to some extent by concurrent afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction.

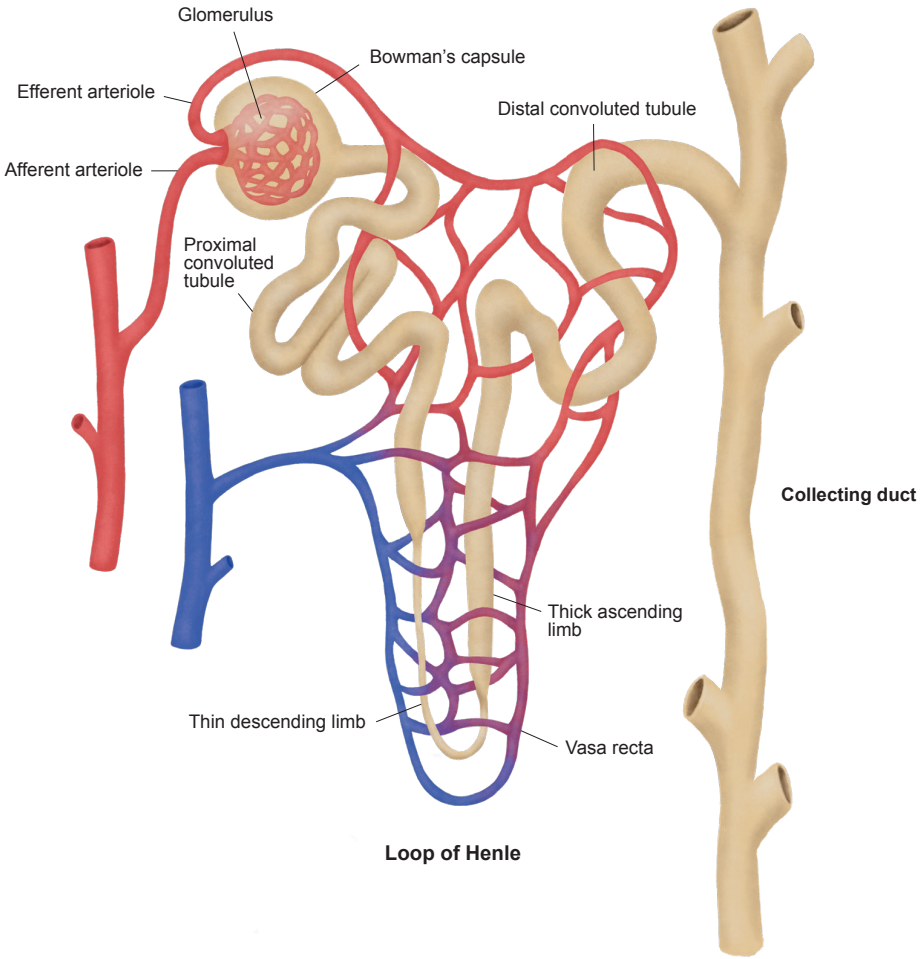


Figure 1. Nephron, the functional unit of the kidney. (Lilja Björk Runólfsdóttir, 2019)

1.2 Estimating kidney function

GFR equals the total amount of fluid filtered through all of the functioning nephrons per unit of time and is generally considered the best index to evaluate overall kidney function (A. Levey, Becker, & Inker, 2015). Decline in other functions of the kidney seems to correlate well with decline in GFR (Schrier et al., 2012). It can be assessed in a number of different ways. Direct measurements of GFR are possible by administering a substrate that is considered an ideal filtration marker (inulin, iohexol, iothalamate) because it is is freely filtered in the glomerulus and not reabsorbed, secreted or metabolized by the kidney tubules (Soveri et al., 2014). These measurements are time consuming and impractical and therefore seldomly used in routine clinical practice. Serum creatinine (SCr) is the most commonly used established endogenous filtration marker and is currently the mainstay in evaluation of kidney function in clinical practice.

Creatinine is a breakdown product of creatine phosphate which is primarily generated in muscle tissue. It is distributed in total body water and chiefly excreted by glomerular filtration (Schrier et al., 2012). The level of SCr is mostly determined by GFR but other factors can limit the use of SCr to estimate GFR. The absolute amount of creatinine in the body is affected by volume status, muscle mass and protein intake and its tubular secretion can be affected by medications and variability in the extrarenal excretion of creatinine. For this reason, the normal range of SCr is wide. However, SCr has a smaller intra-individual variation than measured GFR (Toffaletti & McDonnell, 2008). A considerable limitation of SCr as a biomarker for kidney function is its low sensitivity. SCr remains normal until around 50% of the total nephron function is lost (K. D. Liu & Brakeman, 2008). When functional nephrons are lost, other nephrons start to compensate by increasing their glomerular filtration (Sharma, Mucino, & Ronco, 2014). This compensatory mechanism of the kidneys is termed renal functional reserve.

1.2.1 Estimated glomerular filtration rate

Many equations have been developed to calculate an estimated GFR (eGFR) from serum creatinine. The Modification of Diet in Renal Disease (MDRD) Study equation (A. S. Levey et al., 2006) was developed in patients with CKD, it has been widely used and is a good estimator in patients with reduced kidney function but is considered inaccurate in patients with higher GFRs. In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based equation was published (A. S. Levey et al., 2009). It is derived from data from a large cohort of 8,254 individuals with diverse characteristics. In addition

to SCr, the equation includes age, sex and race. Unlike the MDRD Study equation, it is considered to be an accurate estimator of GFR for both patients with reserved kidney function as well as patients with reduced kidney function (Earley, Miskulin, Lamb, Levey, & Uhlig, 2012). The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on CKD from 2013 (KDIGO & CKD, 2013) recommend the use of the SCr-based CKD-EPI equation for estimation of GFR in clinical practice.

For many years, there has been a search for other endogenous biomarkers with more accuracy and sensitivity for estimating kidney function than SCr. Cystatin C is an endogenous filtration biomarker that is secreted by all cells, is freely filtered by the glomerulus and almost completely reabsorbed in the proximal tubule where it is almost entirely catabolized (Teo & Endre, 2017). As opposed to creatinine, cystatin C is not secreted by the renal tubules and, therefore, has many appealing qualities of a good filtration marker. Furthermore, cystatin C is less affected by diet, muscle mass and sex than creatinine. Cystatin C is mainly extracellular and, thus, has one-third of the volume distribution of creatinine. As this makes its half-life only one-third of the half-life of creatinine, cystatin C reaches steady state equilibrium three times faster. Early studies on cystatin C indicated superiority compared with creatinine (Dharnidharka, Kwon, & Stevens, 2002), while later studies have shown that a combination of cystatin C and creatinine-based eGFR outperforms both creatinine alone and cystatin C alone in evaluating and monitoring CKD (Inker et al., 2012).

1.2.2 Rapid changes in kidney function

In the clinical evaluation of long-term kidney function the parameter of choice is eGFR which is the mainstay in the evaluation and staging of chronic kidney disease as will be discussed further in chapter 1.5. However, eGFR is not a good marker to assess rapidly changing kidney function as the relationship between eGFR and SCr is far from linear (Damman, Voors, Navis, Van Veldhuisen, & Hillege, 2012). With sudden change in GFR, SCr takes around 12-77 hours to reach a steady state and the time to steady state increases with worsening kidney function (Chiou & Hsu, 1975).

Decreased urine output can be viewed as a physiological biomarker that reflects decreasing GFR and can be observed more closely than change in SCr (Md Ralib, Pickering, Shaw, & Endre, 2013). Changes in urine output must be considered according to context as rapid changes in urine output occur frequently in normal daily life. This was neatly demonstrated in a study on junior doctors at a UK hospital who were more often oliguric than their patients

(Solomon et al., 2010). However, oliguria for more than 4 hours in intensive care unit (ICU) patients is a good predictor of subsequent SCr elevation, but that only occurs in a small portion of patients with oliguria (Md Ralib et al., 2013). AKI episodes detected by decrease in urine output but no change in SCr are often milder in nature (Kellum et al., 2015).

Cystatin C has shown promise in evaluating rapid changes in kidney function as it reaches steady state three-times faster than SCr. However, it is much more expensive and not considered practical to measure repeatedly. Even though cystatin C changes faster than SCr there still is a considerable lag time from injury to the kidney to the subsequent decrease in GFR and the following rise in cystatin C. This is a problem of all filtration markers (Alge & Arthur, 2015). When evaluating rapidly changing kidney function it is considered more appropriate to measure change in SCr from individual baseline SCr instead of eGFR (Khwaja, 2012).

There has been a search for kidney injury-specific biomarkers that are not based on changes in GFR, or so called damage markers. The hope is to find a biomarker that is helpful in diagnosing AKI as soon as it occurs, creating a potential window of opportunity to perform supportive and therapeutic interventions. Markers of injury that have shown promise are for instance neutrophilic gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) (Alge & Arthur, 2015). Interestingly, a combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin growth factor binding protein-7 (IGFBP-7) assay has been approved by the Food and Drug Administration (FDA) in the United States to detect acute kidney injury, but it has not reached daily clinical practice (Pickering & Endre, 2016).

1.3 Acute kidney injury

Acute kidney injury (AKI) is a complex syndrome characterized by an abrupt deterioration of kidney function over hours and days (Khwaja, 2012). It can arise due to a primary problem within the kidney and/or secondary to systemic disorder. Its clinical manifestations can range from a mild elevation in SCr to an anuric kidney failure requiring renal replacement therapy (RRT).

AKI is a common problem both in the community and in the hospital setting (Wonnacott, Meran, Amphlett, Talabani, & Phillips, 2014), and there are recent studies indicating that the incidence of AKI is increasing (C. Y. Hsu et al., 2007; Lenihan, Colin R, Montez-Rath, Maria E., Mora Mangano, Christina T., Chertow, Glenn M., Winkelmayer, 2013; Xue, 2006). The acute phase of AKI can lead to complications such as fluid overload, electrolyte and acid-base disturbances and accumulation of nitrogenous waste products. The occurrence of AKI in hospitalized patients has been associated with excess hospitalization costs and prolonged length of stay (LOS) (Chertow, 2005; Silver, Long, Zheng, & Chertow, 2017). AKI is associated with increased both short-term and long-term mortality (H. E. Wang, Muntner, Chertow, & Warnock, 2012; Xue, 2006). Furthermore, it has been associated with both development of CKD and to promote progression of preexisting CKD (Ishani et al., 2011; Newsome et al., 2008).

1.3.1 Definition of AKI

There have been many different definitions of acute renal failure in the last decades and lack of consensus in the scientific and clinical community (Kellum, Levin, Bouman, & Lameire, 2002). This has made the evaluation and comparison of all epidemiological studies extremely difficult. The concept of acute kidney injury was first introduced in 2004 when the Acute Dialysis Quality Initiative (ADQI) put forward the RIFLE criteria (Table 1) (Bellomo, Ronco, Kellum, Mehta, & Palevsky, 2004). The RIFLE criteria defined AKI as a relative increase in SCr to 1.5 x baseline within 7 days. AKI was classified into three severity stages: Risk, Injury and Failure and two outcomes: Loss and End-Stage Renal Disease (ESRD). The criteria also defined AKI based on changes in urine output over time. Following several studies showing associations between minor changes in SCr and worse short-term survival (Chertow, 2005; Lassnigg, 2004; Levy et al., 2005) a modified version of the RIFLE criteria was published by the Acute Kidney Injury Network (AKIN), which added a small absolute SCr increase of 26.5 µmol/L (0.3mg/dL) to the definition of AKI and shortened the timeframe of SCr change to 48 hours (Mehta et al., 2007).

The currently used criteria were published in 2012 by KDIGO (Khwaja, 2012), combining the RIFLE and AKIN criterias. AKI was defined as either a relative increase of SCr to 1.5 x baseline within 7 days, or a small absolute change in SCr of 26.5 µmol/L within 48 hours. The criteria based on change in urine output were the same for all three definitions. Change in urine output is an early marker of AKI and is useful clinically, especially in the ICU. AKI detected solely by change in urine output are often mild episodes. The use of urine output in observational studies is generally difficult due to poor and often incorrect documentation of urine output during hospitalization. The three definitions are compared in Table 1.

Table 1. Comparing definitions of acute kidney injury.

Classification	Definition of AKI	Stage	SCr criteria for staging	Change in urine output
RIFLE	Increase in SCr to ≥ 1.5 x baseline in 7 days	Risk	1.5 - 1.99 x baseline	< 0.5 mL/kg/h for ≥ 6h
		Injury	2 - 2.99 x baseline	< 0.5 mL/kg/h for ≥ 12h
		Failure	≥ 3 x baseline or ≥ 44 µmol/L increase to > 354 µmol/L or need for RRT	< 0.3 mL/kg/h for ≥ 24h or anuria for ≥ 12h
AKIN	Increase in SCr of 26.5 µmol/L or ≥ 1.5x baseline within 48h	1	Increase of ≥ 26.5 µmol/L or ≥ 1.5-1.99 x baseline	< 0.5 mL/kg/h for ≥ 6h
		2	2 - 2.99 x baseline	< 0.5 mL/kg/h for ≥ 12h
		3	≥ 3x baseline or ≥ 26.5 µmol/L increase to > 354 µmol/L or need for RRT	< 0.3 mL/kg/h for ≥ 24h or anuria for ≥ 12h
KDIGO	Increase in SCr of 26.5 µmol/L in 48h or ≥ 1.5x baseline within 7 days	1	Increase of ≥ 26.5 µmol/L or ≥ 1.5-1.99 x baseline	<0.5 mL/kg/h for ≥ 6h
		2	2 - 2.99 x baseline	< 0.5 mL/kg/h for ≥ 12h
		3	≥ 3 x baseline or increase to > 354 µmol/L or need for RRT	< 0.3 mL/kg/h for ≥ 24h or anuria for ≥ 12h

Abbreviations: AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcome; RIFLE, risk, injury, failure, loss and end-stage renal disease; RRT, renal replacement therapy; SCr, serum creatinine.

1.3.2 Pathophysiology of AKI

There are many different causes of AKI that in clinical practice have conventionally been classified based on pseudo-anatomic locations in reference to the kidney into prerenal, intrarenal and postrenal (Schrier et al., 2012). The most common causes of prerenal AKI are associated with decreased kidney perfusion as a consequence of conditions such as hemorrhage, gastrointestinal fluid losses, burns, impaired cardiac output, decreased systemic vascular resistance or renal vasoconstriction. If kidney hypoperfusion is prolonged it can lead to ischemic intrarenal AKI characterized by acute tubular necrosis (ATN; Figure 2). ATN can also be caused by drugs and both endo- and exotoxins. Other common intrarenal causes are acute interstitial nephritis, glomerulonephritis and vasculitis. Common postrenal causes for AKI are mechanical obstruction (tumor, kidney stones, benign prostate hyperplasia) or a neurogenic bladder (Gilbert & Weiner, 2017; Schrier et al., 2012). This classification of AKI is by many considered an oversimplification and it has been suggested that the causes of AKI should rather be classified according to so called AKI paradigms, including renal hypoperfusion, sepsis-associated, hepatorenal, cardiorenal and nephrotoxic injury and urinary tract obstruction (Kellum & Prowle, 2018). Hemodynamic disturbances leading to prerenal state and ATN are the most common causes of AKI and will be the main focus below. Other renal and postrenal causes feature different pathophysiologic mechanisms that will not be elaborated further.

Systemic hypotension has been associated with AKI in many different studies (Raimundo et al., 2015; Salmasi et al., 2017; Sun, Wijeysundera, Tait, & Beattie, 2015). It has been demonstrated that even a short duration of decreased mean arterial pressure below 65 mmHg associates with postoperative AKI in surgical patients (Salmasi et al., 2017). Intrarenal microcirculatory dysfunction is also important in the pathophysiology of AKI. Since the peritubular capillaries arise from the efferent glomerular arterioles, any interruption of glomerular blood flow will impair peritubular perfusion (Matejovic et al., 2016).

Systemic inflammatory processes, such as sepsis, affect microcirculatory functions and cause ineffective intrarenal blood flow (Z. Wang et al., 2012). This can lead to hypoperfusion and ischemia in the kidney even when global perfusion of the kidney is adequate. This focal ischemia seems to occur predominantly in the vulnerable, relatively hypoxic outer medulla. Endothelial dysfunction triggered by several inflammatory mediators appears to play a

central role in the microcirculatory dysfunction during sepsis. This dysfunction leads to structural alterations of the endothelium with disruption of the glycocalyx, loss of cell-cell contact and consequently increased permeability (Bonventre & Yang, 2011). Disruptions of the glycocalyx and endothelial monolayer and upregulation of adhesion molecules results in enhanced leukocyte-endothelium interactions and inflammation (Rabb et al., 2016). Both endothelial injury and tubular injury trigger inflammatory activation of resident immune cells and invasion of white blood cells (Ostermann & Liu, 2017). Almost all immune cells have been implicated in the pathophysiological process of AKI (Singbartl, Formeck, & Kellum, 2019).

Tubular injury often occurs following microcirculatory dysfunction but it can also occur due to direct toxic effect of filtered substances (drugs, endo- or exotoxins) (Bonventre & Yang, 2011). The tubular cells undergo structural changes, tight junctions loosen up, and the cells detach from the basement membrane, loose polarity and swell (Figure 2). Further tubular injury may result in apoptosis and necrosis (Ostermann & Liu, 2017). Obstruction to the filtrate/urine flow anywhere from the tubules to the urethra can cause AKI. Causes can range from precipitation of insoluble drugs and substances, kidney stones, retroperitoneal fibrosis or bladder obstruction.

Venous congestion in the kidney can affect kidney function and has been associated with the development of AKI (Chen, Wang, Honore, Spapen, & Liu, 2018). Venous congestion increases pressure in the encapsulated kidney leading to compression of the tubules and decrease in the net transcapillary pressure gradient and subsequently decreased GFR. Venous congestion occurs mostly in congestive heart failure but can also be a result of intraabdominal hypertension or abdominal compartment syndrome (Mohmand & Goldfarb, 2011).

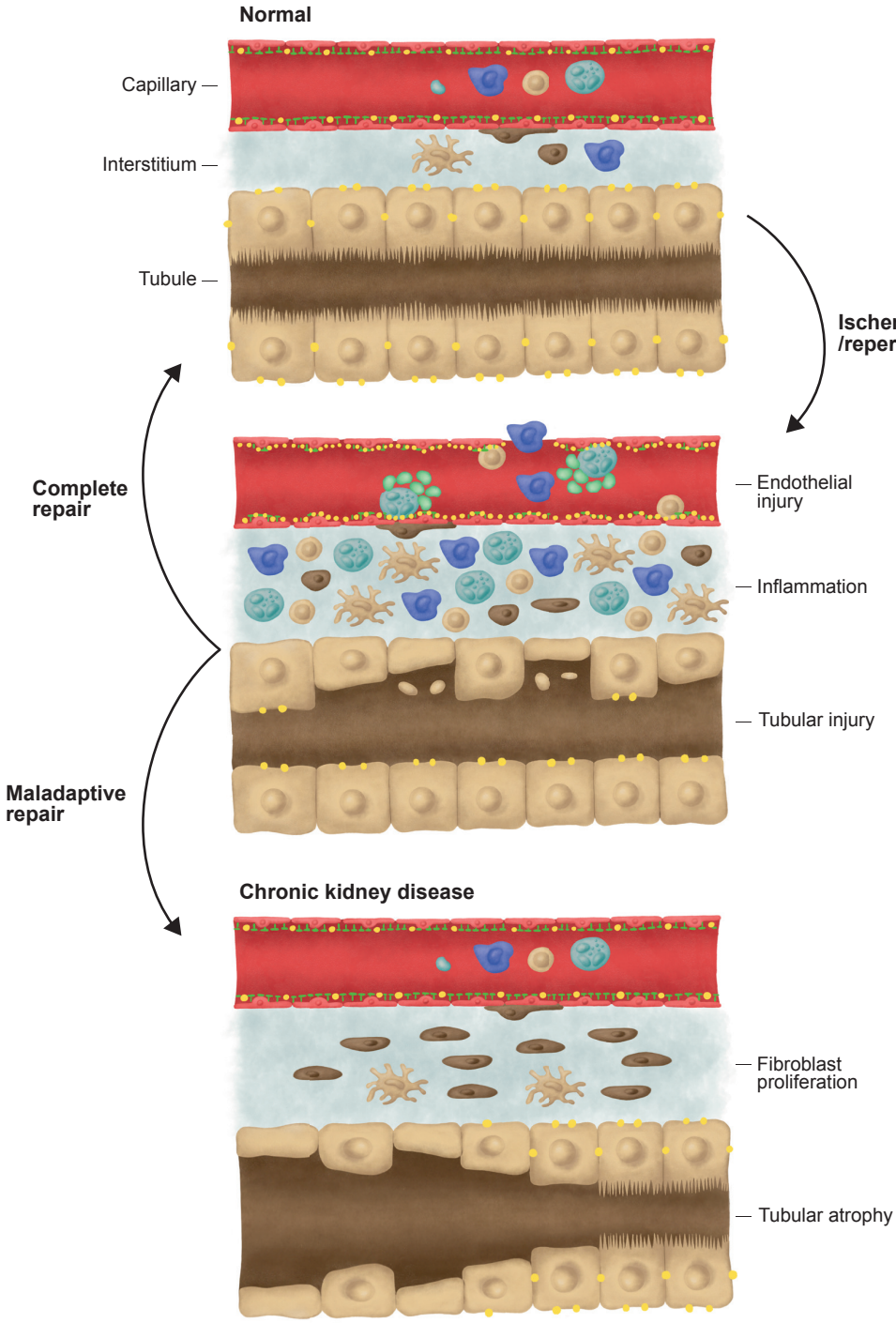


Figure 2. Acute tubular necrosis, maladaptive repair and renal fibrosis. (Lilja Björk Runólfsdóttir, 2019)

1.3.3 Incidence of AKI

Epidemiologic studies of AKI have over the years been hampered by different definitions of AKI and different patient cohorts being studied (Kellum et al., 2002). This problem has been reduced after a consensus on the definition of AKI was reached in 2004 and has made studies on the incidence of AKI more comparable. In the past many studies on the incidence of AKI have been based on diagnostic codes or have been limited to patients requiring renal replacement therapy. However, in recent years the use of a rise in creatinine from a baseline value has been increasing (Table 2).

Table 2 compares several studies and demonstrates the variability of the incidence rates of AKI. Studies on hospital acquired AKI (H-AKI) using creatinine-based definition (AKIN criteria) have reported incidence rates from 2-23% (Fang et al., 2010; H. E. Wang et al., 2012; Wonnacott et al., 2014), and a recent large study based on the KDIGO criteria reported an incidence of 6.7% in hospitalized patients (Kashani et al., 2017).

There is a great variability in the AKI incidence rates between cohorts which can probably largely be explained by difference in study populations. A meta-analysis from 2013 tried to evaluate the worldwide incidence of AKI and estimated the pooled incidence rate of AKI in hospitalized patients to be 21.6% (Susantitaphong et al., 2013). A multinational study reported a rate of AKI in the ICU of 58% (Hoste et al., 2015), compared to 6.4% (2.1% hospital-acquired and 4.3% community-acquired) in a general hospital ward (Wonnacott et al., 2014). This cohort variability is important as many studies focus on subgroups of patients, such as critical care patients, or take place in tertiary care facilities, the results of which can poorly be extrapolated to community hospitals or the general population.

There are indicators that the incidence of both community-acquired and hospital-acquired AKI is increasing (C. Y. Hsu et al., 2007; R. K. Hsu, Mcculloch, Dudley, Lo, & Hsu, 2013; Xue, 2006). This has partly been attributed to older age and higher comorbidity burden of hospitalized patients. However, many of those studies are large retrospective database studies that are based on diagnostic codes and can therefore be affected by changes in coding practices, clinical awareness and changes in the definition of AKI throughout the study period (Sawhney & Fraser, 2017). Furthermore, a recent population-based study on temporal trends of AKI demonstrated no significant increase in the incidence of AKI (Kashani et al., 2017).

Table 2. Overview of previous studies on the incidence of AKI in hospitalized patients.

Author	Period	Definition	Country	Clinical setting	Incidence
Xue *et al.*	1992-2001	ICD9	USA	All hospitalizations	2.4%
Liangos *et al.*	2001	ICD9	USA	All hospitalizations	1.9%
Zeng *et al.*	2010	KDIGO	USA	All hospitalizations	18.3%
Amin *et al.*	2000-2008	AKIN	USA	Myocardial infarction	22.5%
Cheng *et al.*	2013-2014	KDIGO	China	All hospitalizations	1.6%
Fang *et al.*	2004-2008	AKIN	China	All hospitalizations	3.2%
Wang *et al.*	2009-2010	AKIN	USA	All hospitalizations	22.7%
Wonnacott *et al.*	6-months (2011)	AKIN	USA	All hospitalizations	6.4%
Kashani *et al.*	2006-2014	KDIGO	USA	All hospitalizations	6.7%
Ali *et al.*	6-months (2003)	RIFLE	UK	Population	1,811 per million population

Abbreviations: AKIN, Acute Kidney Injury Network; ICD9, International Classification of Diseases, 9th revision; KDIGO, Kidney Disease: Improving Global Outcome; RIFLE, risk, injury, failure, loss of kidney function and end-stage renal disease; USA, United States of America; UK, United Kingdom.

1.3.4 Perioperative AKI

Perioperative AKI is a well known complication of surgery. In fact, it is estimated that approximately one-third of all in-hospital AKI cases are associated with surgical procedures (Uchino et al., 2005). When AKI complicates surgery it is associated with detrimental outcomes, including higher short-term and long-term mortality (Brown & Jeremiah R., 2010; Pearse et al., 2012).

There are many possible etiological factors in the perioperative setting predisposing to AKI development, including hemodynamic instability, exposure to both exo- and endogenous toxins, ischemia-reperfusion injury, renal artery embolization, tissue injury, inflammation and oxidative stress (Kellum & Prowle, 2018). Additionally, there are surgery-specific contributors to the development of AKI such as the use of cardiopulmonary bypass in cardiac surgery (Sirvinskas et al., 2008) and increased intraabdominal pressure complicating major abdominal surgeries (Mohmand & Goldfarb, 2011).

Perioperative AKI has mostly been studied following cardiovascular surgery. A recent meta-analysis of AKI yielded a median rate of 22% (Vandenberghe et al., 2016), but varied greatly according to the type of surgery from 11-20% following coronary artery bypass grafting (CABG) (Helgadottir et

al., 2016; S. Y. Li, Chen, Yang, & Chuang, 2011) to 41-55% following aortic dissection repair (J. Wang et al., 2018). Perioperative AKI following abdominal surgery is not as well studied. In 2014, Kim *et al.* studied the incidence of AKI following intraabdominal procedures (Kim, Brady, & Li, 2014), reporting an incidence of 1.1%. The risk of AKI was different between types of abdominal surgical procedures, for instance the risk of AKI following ileostomy was nearly six-fold compared with appendectomy. In a systematic review by O`Connor *et al.*, the incidence of perioperative AKI following major abdominal surgery ranged from 3% to 40% based on type of surgery and surgical cohort (O`Connor, Kirwan, Pearse, & Prowle, 2016). However, the investigators were not able to demonstrate a significant difference in the incidence of AKI between subgroups of abdominal surgical procedures in the pooled AKI cohort. This suggests that the type of surgery is not the only explanatory factor for incidence variability between studies, but also the substantial heterogeneity between study cohorts.

1.3.5 Risk factors for AKI

In current clinical practice, the effective treatment options for AKI are limited, making information on risk factors that predict AKI valuable. The risk factors for AKI can be classified as patient-specific factors that increase the susceptibility for AKI, and factors that can be considered as patient exposures. Well known patient-specific risk factors for AKI are increasing age (Grams et al., 2015) and underlying CKD (Chawla, Eggers, Star, & Kimmel, 2014). Furthermore, underlying comorbid diseases, including diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, chronic liver disease and chronic obstructive pulmonary disease (COPD) have been reported as predictors of AKI development (Khwaja, 2012). Importantly, there is increasing evidence suggesting that obesity is a predictor for AKI (Glance et al., 2010), which is in agreement with the rapidly increasing obesity epidemic in the recent decades (NCD Risk Factor Collaboration, 2017).

Many exposures can increase the risk of AKI, the best known are sepsis, major cardiac and non-cardiac surgery and nephrotoxins (Mehta et al., 2015). Furthermore, recent studies indicate that other factors that are potentially modifiable are associated with increased risk of AKI (Nie, Tang, Zhang, Feng, & Chen, 2017). These include hyperglycemia, hyperuricemia and hypoalbuminemia. However, whether correcting these factors ameliorates the increased risk of AKI currently lacks convincing evidence.

Risk scores can be informative for treating physicians when attempting to risk stratify patients, and are also helpful in the communication of risk to the

patient and his family. Several risk scores have been developed to help predict AKI in different clinical settings such as following cardiac surgery, general surgery, contrast exposure and for ICU patients (Inohara et al., 2015; Kheterpal et al., 2009; Kristovic et al., 2015; Malhotra et al., 2017). However, most of these risk scores have been developed at single-centers and have not been externally validated which has limited their use in clinical care.

1.3.6 Survival following AKI

Patients who are at high risk for developing AKI often have higher risk of increased mortality. Multiple studies have demonstrated that developing AKI further increases their risk of short-term mortality (Lenihan, Colin R, Montez-Rath, Maria E., Mora Mangano, Christina T., Chertow, Glenn M., Winkelmayer, 2013; Waikar, 2006). AKI in the general hospitalized population is associated with in-hospital mortality of around 11-21% (Liangos et al., 2006; H. E. Wang et al., 2012). In higher-risk patients admitted to the ICU, the 30-day mortality rate is around 40% (Gammelager et al., 2012). Furthermore, perioperative AKI is associated with increased short-term mortality (Pearse et al., 2012).

Since a consensus on the diagnostic criteria for AKI was reached in 2004, there has been increasing interest in studying long-term survival after a AKI episode. In a systematic review and meta-analysis of 48 studies with follow-up from 0.5-17 years (Coca, Yusuf, Shlipak, Garg, & Parikh, 2009), 15 studies were considered eligible for long-term survival analysis. Patients with AKI who survived hospital admission had a significantly higher mortality rate (8.9 per 100 person-years) than patients without AKI (4.3 per 100 person-years). Many large studies have subsequently been published on long-term survival after AKI; some of those are demonstrated in Table 3. Interestingly, many of these studies have shown that increase in long-term mortality has a dose-response relationship to the severity of AKI (Lafrance & Miller, 2010).

Previous studies have indicated that the survival of H-AKI is improving (Kolhe, Muirhead, Wilkes, Fluck, & Taal, 2016; Waikar, 2006; Xue, 2006). However, these studies are mostly based on diagnostic codes and changes in coding practices and clinical practice are likely to have changed over the last decades (Sawhney, Mitchell, Marks, & Fluck, 2015). However, one study on AKI following myocardial infarction that used changes in SCr to define AKI reported decreasing in-hospital mortality from 20% to 14% from 2000 to 2008, but this needs to be studied further (Amin, 2012).

Table 3. Summary of the largest studies on long-term mortality following AKI. (Fortrie, Geus, & Betjes, 2019)

Study	Setting	Definition	Number	Follow-up	Stage	Adjusted risk
Bihorac *et al.*	ICU	RIFLE	10,518	Max 14 yrs	R	1.18 (1.08 - 1.29)
					I	1.43 (1.29 - 1.59)
					F	1.57 (1.40 - 1.75)
Coca *et al.*	Noncardiac surgery	AKIN	35,302	Mean 3.7 yrs	I	1.24 (1.17 - 1.31)
					II	1.64 (1.43 - 1.88)
					III	1.96 (1.63 - 2.37)
Fuchs *et al.*	ICU	AKIN	12,399	Max 2 yrs	I	1.26 (1.14 - 1.40)
					II	1.28 (1.11 - 1.47)
					III	1.61 (1.30 - 1.99)
Ishani *et al.*	Hospital	ICD9	233,803	Max 2.3 yrs	AKI	2.38 (2.31 - 2.46)
James *et al.*	Coronary angiography	AKIN	14,782	Median 1.6 yrs	I	2.00 (1.69 - 2.36)
					II/III	3.72 (2.92 - 4.76)
Lafrance *et al.*	Hospital	AKIN	864,933	Mean 2.3 yrs	I	1.36 (1.34 - 1.38)
					II	1.46 (1.42 - 1.50)
					III	1.59 (1.54 - 1.65)
Liotta *et al.*	CABG	Mild (ΔSCr 0 - 26.5 µmol/L)	25,665	Mean 6 yrs	Mild	1.07 (1.00 - 1.15)
		Moderate (ΔSCr 26.5 - 44 µmol/L)			Moderate	1.33 (1.19 - 1.48)
		Severe (ΔSCr > 44 µmol/L)			Severe	2.11 (1.92 - 2.32)
Parikh *et al.*	AMI	Mild (ΔSCr 26.5 - 35 µmol/L)	147,007	Max 10 yrs	Mild	1.15 (1.12 - 1.18)
		Moderate (ΔSCr 35 - 88 µmol/L)			Moderate	1.23 (1.20 - 1.26)
		Severe (ΔSCr > 88 µmol/L)			Severe	1.33 (1.28 - 1.38)
Ryden *et al.*	CABG	Mild (ΔSCr 26.5 - 43 µmol/L)	27,929	Mean 5 yrs	Mild	1.30 (1.17 - 1.44)
		Moderate (ΔSCr 44 - 88 µmol/L)			Moderate	1.65 (1.48 - 1.83)
		Severe (ΔSCr > 88 µmol/L)			Severe	2.68 (2.37 - 3.03)

Abbreviations: AKIN, Acute Kidney Injury Network; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting.

1.3.7 Renal recovery after AKI

Following an AKI episode, it is far from certain that patients recover their kidney function. Studies have reported that renal recovery ranges from 54% to 97% based on different definitions used and different study cohorts (Macedo, Bouchard, & Mehta, 2008; Palevsky et al., 2008). Reaching renal recovery is an independent determinant of both morbidity and mortality (Lafrance & Miller, 2010; Pannu, James, Hemmelgarn, & Klarenbach, 2013). However, previous studies have demonstrated that even if a patient reaches clinical renal recovery, he is still at increased risk of developing incident CKD and progression of preexisting CKD following AKI (Coca, Singanamala, & Parikh, 2012; Gammelager et al., 2013).

Following an AKI episode, the tubular endothelium starts to repopulate by regenerating surviving endogenous tubular cells (Ferenbach & Bonventre, 2015). Under certain circumstances, the repair of the tubular endothelium becomes maladaptive with inflammation, fibrosis and decreased vascular density leading to CKD. The severity, type and duration of injury, as well as premorbid renal functional reserve (age, preexisting CKD) are risk factors for maladaptive repair (J. Liu et al., 2017). Many different definitions of renal recovery following AKI have been used in prior studies but no consensus has been reached on a comprehensive definition. Most definitions of renal recovery used in previous studies fall into one of three categories:

1. Freedom from renal replacement therapy (Bagshaw et al., 2005)
2. Absolute thresholds of SCr or eGFR (Palevsky et al., 2008)
3. Relative changes in SCr or eGFR (Lafrance & Miller, 2010; Pannu et al., 2013)

Most studies evaluating renal recovery have focused on patients requiring renal replacement therapy and have defined renal recovery as freedom from dialysis (Duran & Concepcion, 2014; Palevsky et al., 2008). Though freedom from dialysis is an important measure, it is not sensitive for important endpoints such as development of de novo CKD or progression of preexisting CKD not requiring RRT.

Absolute changes in SCr have been used in studies such as the ATN Study from 2008 (Palevsky et al., 2008) that defined complete renal recovery as reaching SCr within 44 μmol/L of baseline SCr and partial renal recovery as freedom from dialysis, but SCr > 44 μmol/L above baseline SCr. In 2012,

KDIGO defined complete renal recovery as reaching a GFR > 60 mL/min/1.73 m^2 and partial recovery as freedom from RRT but GFR < 60 mL/min/1.73m^2 for less than 90 days (Khwaja, 2012). The problem with using absolute SCr changes and absolute GFR thresholds to define renal recovery are that both are skewed and dysfunctional in patients with underlying CKD.

In 2004, ADQI put forward a definition of renal recovery based on relative changes in SCr in parallel to their concurrent definition of AKI (Bellomo et al., 2004). Complete renal recovery was defined as a return of SCr to within 1.5 x baseline SCr and partial recovery as freedom from RRT, but failure to return to within 1.5 x baseline SCr. This definition has the advantage that it is relatively comparable in patients with and without underlying CKD. Its foundation is however not very strong as the definition of renal recovery is merely based on being disease-free, that is no longer fulfilling the RIFLE criteria for AKI. The ideal definition is one that can quantify lost kidney function as well as residual kidney function and reserve, and have prognostic value (Chawla et al., 2017).

Few studies have examined definitive thresholds of renal recovery based on relative SCr (Jones et al., 2012; Korenkevych et al., 2016). Pannu *et al.* found that not reaching a SCr level < 1.55 x baseline associated with mortality (Pannu et al., 2013). However, for the development of ESRD or doubling of baseline SCr the threshold for renal recovery was SCr < 1.25 x baseline. Currently, there is lack of evidence to guide timing, frequency and methods to evaluate kidney function following an AKI episode. The current KDIGO guidelines recommend to evaluate patients three months following AKI for resolution, or new onset CKD or progression of preexisting CKD (Khwaja, 2012).

There has been ambiguity regarding the terminology of AKI that has not reached renal recovery, but does not fulfill the definition of CKD as the reduction in kidney function has not been sustained for 90 days. In 2012, the KDIGO AKI workgroup proposed the concept of acute kidney disease (AKD), defined as a GFR < 60 mL/min/1.73 m^2 or other evidence for kidney disease for < 90 days to address individuals with a condition in between definitions of AKI and CKD. However, the clinical significance of this definition is uncertain. In 2017, the ADQI workgroup proposed a stage 0 of AKD with A, B and C subgroups. Where stage 0C includes patients with SCr above baseline but within 1.5 x baseline (Chawla et al., 2017).

1.3.8 Duration of AKI

Current definition of AKI (KDIGO) classifies AKI severity based on the magnitude of SCr elevation from baseline. As mentioned earlier, a dose-response relationship has been reported between the relative increase of SCr (AKI stage) and mortality (Lafrance & Miller, 2010). Furthermore, the rise in SCr is required to occur rapidly, or within 2 – 7 days to fulfill the definition of AKI. In the past few years, there has been a growing body of evidence suggesting that a third parameter of AKI is important, i.e. the duration of AKI (Coca, King JR, Rosenthal, Perkal, & Parikh, 2011; Perinel et al., 2015). A study from 2010 on almost 5,000 patients undergoing cardiac surgery demonstrated a stepwise relationship between duration of AKI, defined as fulfilment of the AKIN criteria for AKI in < 2 days, 3 – 6 days or > 7 days, with long-term mortality (Brown & Jeremiah R., 2010). More studies have followed and shown similar results (Coca et al., 2011; Wu, Chen, Wang, Ting, & Chen, 2014).

1.3.9 Mild AKI

Shortly after the RIFLE criteria were published in 2004, defining AKI as an increase in SCr of at least 1.5 x baseline, several studies demonstrated that even smaller changes in SCr were associated with increased mortality (Chertow, 2005; Lassnigg, 2004; Loef, 2004). Thus, the following AKIN and KDIGO criteria for AKI included an absolute elevation in SCr of 26.5 µmol/L within 48 hours (Khwaja, 2012; Mehta et al., 2007). Since then there have been studies showing an association between small changes in SCr and the development and progression of CKD (Ishani et al., 2011), but existing data are limited.

As described in chapter 1.2, the sensitivity of SCr for detecting rapid changes in kidney function is low. Therefore, it is aspiring to include small changes in SCr in the definition of AKI in an attempt to maximize the possible sensitivity of the definition. However, the use of small absolute changes in SCr to define AKI creates a partly skewed definition as it represents variable scenarios in different patients based on their previous kidney function (Testani, McCauley, Chen, Shumski, & Shannon, 2010). This notion could lead to misclassification of patients and hamper risk stratification, particularly in those with CKD. This could also lead to overdiagnosis of AKI in patients with CKD and mild non-pathological fluctuations in SCr.

1.4 Chronic kidney disease

Chronic kidney disease is the 14th leading cause of death worldwide and is estimated to become an even more common cause of death in forthcoming years according to the World Health Organization (Mathers & Loncar, 2006). The prevalence of CKD in high-income countries is estimated around 10-16% (Hallan, 2006), but data is limited in low-income countries. An Icelandic study, based on eGFR and proteinuria, from 2005 reported a relatively low prevalence of CKD in Iceland, or 7% in males and 12% in females (Viktorsdottir et al., 2005). CKD is a common disease pathway that arises secondarily to many heterogenous primary kidney diseases and/or systemic diseases. They all have in common that they alter the function and/or structure of the kidney irreversibly, and this occurs over months or years. The most common causes of CKD and ESRD in high- and middle-income countries are diabetic nephropathy and hypertensive nephrosclerosis, whereas other diseases like glomerular, tubulointerstitial and hereditary diseases are less common (Table 4).

The evaluation of CKD is based on eGFR, assessing presence and quantity of proteinuria and structural damage visible on imaging studies. Current international guidelines by KDIGO (KDIGO & CKD, 2013) define CKD as a decreased eGFR < 60mL/min/1.73 m^2 and/or markers of kidney damage on urinalysis such as proteinuria or hematuria for at least 3 months, or structural abnormalities on imaging studies. CKD is staged into six eGFR-based and three proteinuria-based stages that are demonstrated in Table 5.

Table 4. Major causes of severe chronic kidney disease. Data from the U.S. Renal Data System (USRDS, 2012).

Cause	Percent of cases
Diabetes mellitus	44.9
Hypertension	27.2
Glomerulonephritis	8.2
Chronic interstitial nephritis or obstruction	3.6
Hereditary or cystic disease	3.1
Secondary glomerulonephritis or vasculitis	2.1
Neoplasms or plasma cell dyscracias	2.1
Miscellaneous conditions	4.6
Uncertain or unrecorded cause	5.2

Table 5. KDIGO classification of CKD based on GFR and proteinuria.

GFR Stage	eGFR (mL/min/m^2)
G1	> 90
G2	60 - 89
G3a	45 - 59
G3b	30 - 44
G4	15 - 29
G5	< 15
Albuminuria Stage	**AER or ACR (mg/24h or mg/g)**
A1	< 30
A2	30 - 299
A3	≥ 300

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

1.4.1 Progression of CKD

Many epidemiological studies have shown that the prevalence of CKD increases with age, which is not surprising as the normal physiological decline in GFR is estimated to be approximately 1 mL/min/1.73m^2 per year (Epstein, 1996). CKD development and progression is thought to occur in three phases, beginning with a cause-specific injury and an acute response to the tissue damage (Zhong, Yang, & Fogo, 2017). Subsequently, a misdirected repair process occurs with inflammation and fibrosis of the injured nephrons. The final stage is progressive loss of remaining nephrons that compensate by hyperfiltration, leading to increased intra-glomerular pressure, mesangial and endothelial hyperplasia and increased glomerular permeability (Schrier et al., 2012). Thus, the primary causes of incident CKD appear to be somewhat different from those driving the subsequent progression of CKD. Of course there can be a mixture of both occurring simultaneously. This partly explains why progression rates of CKD differ dramatically between individuals with same primary kidney disease (Ruggenenti, Cravedi, & Remuzzi, 2012; Zhong et al., 2017).

Although there is a small proportion of CKD patients that maintain a stable kidney function for years, the natural course of CKD is marked by progression. The GFR decline in CKD has over the years been assumed to follow a linear or even loglinear trajectory (Zhong et al., 2017). However, recent studies have indicated that the natural pattern of CKD progression follows a more stepwise and irregular course (L. Li et al., 2012). Thus, it is important to monitor patients

with CKD in order to identify those patients whose CKD is likely to progress. Over any five-year period, less than 2% of CKD patients progress to ESRD. That is, 1% of CKD stage 2, 3% of CKD stage 3 and 20% of CKD stage 4 patients end up requiring dialysis therapy or kidney transplantation (Keith, Nichols, Gullion, Brown, & Smith, 2004).

The prediction of CKD progression is difficult, especially when the follow-up time is short. Part of the problem is the lack of consensus definition for CKD progression and sensitive or specific biomarkers for early prediction of progressive CKD. Internationally validated risk prediction models have been developed to help clinicians distinguish between patients at high and low risk of rapid progression (Tangri et al., 2017; Wojciechowski, Tangri, Rigatto, & Komenda, 2016). The single most dominant risk factor for accelerated progression of CKD is proteinuria; others include hypertension, recurrent AKI episodes, diabetic nephropathy, older age, male sex, smoking and obesity. There has been controversy regarding whether proteinuria is really a pathogenic risk factor or only a marker of disease severity (Gilbert & Weiner, 2017). However, the fact that reducing proteinuria with pharmacologic agents, such as angiotensin-converting enzyme inhibitors (ACEi), decreases the rate of progression in both diabetic and non-diabetic CKD patients, supports a role for proteinuria in the pathogenesis of the disease (Inker et al., 2014).

The management of CKD is based on treating the underlying primary kidney disease and decreasing the rate of progression by controlling important risk factors (Webster, Nagler, Morton, & Masson, 2017). This involves limiting proteinuria, tight control of blood pressure, smoking cessation, weight control, exercise and dietary advice and avoiding nephrotoxic agents. Additionally, the treatment focuses on limiting and treating complications of CKD such as anemia, mineral bone disease, acid-base disturbances and cardiovascular complications. Importantly, patients with CKD are 5-10 times more likely to die from comorbid diseases, primarily cardiovascular diseases, than to progress to ESRD (USRDS, 2012).

1.4.2 Bidirectional relationship between AKI and CKD

In recent years there has been increasing emphasis on the connection between AKI and CKD. The relationship seems to be somewhat complicated as CKD is a risk factor for AKI, and AKI is a risk factor for development and progression of CKD. Many of patient-specific risk factors for AKI (i.e. age, diabetes mellitus and hypertension) are also risk factors for developing CKD. Interestingly, the most important risk factor for developing AKI is preexisting CKD (Xue, 2006).

Over a decade ago, the common belief was that patients who recovered kidney function following AKI had benign long-term outcomes. However, for the past 10 years studies have shown a strong reproducible association between even mild AKI episodes and development of incident CKD, progression of preexisting CKD and survival (Coca et al., 2012; Wald et al., 2009). Furthermore, the severity, duration and frequency of AKI seem to associate with CKD development and progression. These factors suggest that clinicians should consider AKI and CKD as an integrated model of decreased GFR and diminished renal functional reserve (Chawla et al., 2014; Chawla & Kimmel, 2012).

2 Aims

The focus of this thesis was to examine hospital-acquired and postoperative AKI with emphasis on its incidence, risk factors, renal recovery and its effect on long-term kidney function and survival. The aims of the four papers that form the backbone of this thesis were:

Paper I – To determine the incidence of H-AKI and whether it associates with long-term survival, and to assess time-trends in incidence and survival over the 20 year study period. Furthermore, to evaluate renal recovery following H-AKI.

Paper II – To determine the incidence of postoperative AKI following abdominal surgery. Also, evaluate risk factors for developing AKI following abdominal surgery and examine association with short-term complications, length of hospital stay and short-term survival.

Paper III – To evaluate different definitions of renal recovery following postoperative AKI and how these different definitions associate with long-term survival, development of incident CKD and progression of preexisting CKD. Furthermore, assess the duration of AKI and whether it associates with these outcomes.

Paper IV – To examine the extent and characteristics of postoperative mild stage 1 AKI and whether it associates with survival, development of incident CKD or progression of preexisting CKD in the following 5 years after surgery.

3 Materials and methods

3.1 Study design and patient sample

This thesis is based on four cohort studies, using observational data collected in a retrospective manner. All studies were approved by the National Bioethics Committee, the Icelandic Data Protection Authority and the Chief Medical Officer of Landspitali–The National University Hospital of Iceland (LUH). All patients were admitted and treated at LUH. A short summary of methods of Papers I-IV is demonstrated in Table 6. The thesis is based on three seperate cohorts with a considerable overlap between them.

Cohort I (Paper I) – Consisted of all adult patients admitted to LUH from June 1, 1993, to May 31, 2013.

Cohort II (Paper II) – Consisted of all adult patients that underwent abdominal surgery at LUH between January 1, 2007, and December 31, 2014.

Cohort III (Papers III-IV) – Consisted of all adult patients that underwent abdominal, cardiothoracic, vascular or orthopedic surgery at LUH from January 1, 1998 to December 31, 2015, and developed postoperative AKI.

Table 6. Summary of study sample and methods of papers I-IV.

	Paper I	Paper II	Paper III	Paper IV
Study population	Patients admitted to LUH	Patients who underwent abdominal surgery at LUH	Patients with AKI following abdominal cardiothoracic vascular or orthopedic surgery	Patients with AKI following abdominal cardiothoracic vascular or orthopedic surgery
Study period	1993 - 2013	2007 - 2014	1998 - 2015	1998 - 2015
AKI cases (N)	10,419	264	3,928	3,928
Outcome measure	Incidence, long-term survival and renal recovery of H-AKI	Incidence, risk factors and 30-day mortality of postoperative AKI	Renal recovery, long-term mortality and development or progression of CKD after postoperative AKI	Association of mild stage 1 AKI with long-term mortality and development or progression of CKD

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; H-AKI, hospital-acquired acute kidney injury; LUH, Landspitali – The National University Hospital of Iceland.

3.2 Data collection and sources

The clinical data collected for this thesis were obtained from various databases which are described in the following subsections. The data were subsequently linked based on the government-issued national identification numbers given to all individuals that live in Iceland.

3.2.1 Landspitali – The National University Hospital of Iceland patient registry

Landspitali – The National University Hospital of Iceland is the only tertiary care referral hospital in Iceland and additionally it serves as a primary hospital for over 70% of the Icelandic population. Furthermore, it accomodates the only nephrology clinic in Iceland.

Data were extracted from the LUH data warehouse that contained information on all patient admissons from June 1, of 1993 to December 31, of 2015, including data on age, sex and length of stay. All International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) diagnostic codes were obtained to determine previously diagnosed comorbid conditions (Paper I-IV) and short-term in-hospital complications (discharge diagnoses) after surgery (Paper II and IV) (Table 7).

Table 7. The International Classification of Diseases Tenth (ICD-10) and Ninth revision (ICD-9) codes used for determining comorbid conditions and complications.

	ICD - 10 code	ICD - 9 code
Comorbidity		
Hypertension	I10 - I15	401 - 405
Congestive heart failure	I50	428
Ischemic heart disease	I20 - I25	410 - 414
Chronic obstructive pulmonary disease	J40 - J44	490 - 492
Diabetes mellitus	E10 - E14	249 - 250
Cerebrovascular stroke	I60 - 64	438 - 436
Liver disease	K70 - K76	570 - 573
Malignant neoplasm	C00 - C97	140 - 209
Benign neoplasm	D00 - D49	210 - 229
Chronic kidney disease	N18 - N19	585 - 587
Complication		
Myocardial infarction	I21 - 24	410
Pulmonary embolism	I26	415
Deep vein thrombosis	I80.2	453
Pneumonia	J12 - J18	480 - 486
Cellulitis	L03	681 - 682
Clostridioides difficile infection	A04.7	008.45
Sepsis	A41	038
Urinary tract infection	N30	599

3.2.2 Landspitali – The National University Hospital of Iceland surgical database

Data on all surgical procedures performed at LUH from January 1, 1998 to December 31, 2015 were collected from the LUH surgical database (Paper II-IV). Surgical codes based on the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP-IS, version 1.14, www.nowbase.org), were used to identify and group together surgical operations. This classification system is based on 3 characters which defines anatomical location and a 2-digit number that further specifies the surgical procedure. All surgical procedures were divided into major/minor, laparoscopic/non-laparoscopic, and emergency/non-emergency surgery groups for further analysis.

For the period from January 1, 2007 to December 31, 2015, data on operative time (skin-to-skin), and the American Society of Anesthesiology (ASA) physical status classification (Saklad, 1941) were available and obtained.

3.2.3 National serum creatinine database

The Icelandic national serum creatinine database contains results of all SCr measurements performed at LUH in 1993-2016. In addition, it contains the results of all SCr measurements performed in Iceland from 2008-2016. The measurement of SCr was standardized in 2008. The database was used to determine baseline SCr, diagnose CKD and AKI and for long-term monitoring of kidney function.

3.2.4 Icelandic End-Stage Renal Disease Registry

Landspitali – The National University Hospital of Iceland is the only center for dialysis treatment in Iceland. All patients that undergo treatment for ESRD (hemodialysis, peritoneal dialysis or kidney transplant) are included in the registry. The data were used to exclude patients receiving treatment for ESRD before admission (Paper I) or surgery (Paper II-IV), and also as an outcome measure, namely ESRD requiring dialysis (Paper I).

3.2.5 Statistics Iceland

Statistics Iceland is a large national database that collects and maintains demographic data in Iceland (www.statice.is). For all studies, data on mortality was collected from Statistics Iceland. Follow-up information on patient survival status was complete for all patients living in Iceland. The last follow-up dates of survival status were January 1, 2014 (Paper I), March 30, 2015 (Paper II) and May 20, 2016 (Paper III-IV).

3.3 Definitions

3.3.1 Estimation of baseline creatinine

In Paper I, patients‘ lowest SCr measurement in the six months preceding the peak SCr measurement during hospital admission was considered as baseline SCr. However, in Papers II-IV the most recent preoperative SCr measurement was used as baseline and no SCr older than 30 days was included. The longer timeframe for estimating baseline SCr in Paper I was chosen as this was a study on a general cohort of all hospitalized patients where the exact timing of the insult causing AKI frequently could not be determined, and also to have a larger cohort eligible for the assessment of the development of AKI. The shorter timeframe in Papers II-IV was selected to most accurately reflect the baseline prior to insult during surgery and to be able to detect very mild AKI, in order to to fully utilize the SCr component of the KDIGO definition of AKI but minimizing the risk of overdiagnosing AKI.

3.3.2 Definition and classification of acute kidney injury

Paper I – A modification of the SCr component of the KDIGO criteria was used, defining AKI as an increase in SCr to ≥ 1.5 x baseline, set as patients lowest SCr measurement in the preceding six months. The severity was classified into stage 1 (SCr 1.5 – 1.9 x baseline), stage 2 (SCr 2.0 – 2.9 x baseline), and stage 3 (SCr ≥ 3 x baseline, ≥ 354 µmol/L [4.0 mg/dL] or initiation of renal replacement therapy). To decrease the risk of overdiagnosing AKI, the KDIGO criteria was modified by omitting the absolute SCr elevation of ≥ 26.5 µmol/L (0.3 mg/dL) to define stage 1 AKI given the considerable time period allowed between baseline and the maximum SCr. Moreover, the analysis was limited to patients who had their maximum SCr value during hospital admission.

Paper II-IV – AKI was defined according to the SCr component of the KDIGO criteria using values available within 7 days following surgery. AKI episodes occurring more than 7 days after surgery were omitted, as these might not be directly associated with the surgical procedure. Patients were categorized as either non-AKI or AKI, and severity of AKI classified as stage 1 (SCr ≥ 26.5 µmol/L above baseline over 48 hours or 1.5 – 1.9 x baseline over 7 days), stage 2 (SCr 2.0 – 2.9 x baseline), and stage 3 (SCr ≥ 3 x baseline, ≥ 354 µmol/L with at least 26.5 µmol/L elevation from baseline, or initiation of RRT) (Khwaja, 2012).

In Paper III and Paper IV, mild stage 1 AKI was defined as an increase in SCr of ≥ 26.5 µmol/L above baseline within 48 hours, but limited to a relative increase in SCr < 1.5 x baseline within 7 days. Patients were considered to have a prior history of AKI if they had experienced an episode of AKI, fulfilling the same criteria as defined in the corresponding paper, in a previous admission or surgical procedure (Paper I-IV).

3.3.3 Definition of chronic kidney disease

In all four papers, the definition of CKD was based on eGFR calculated from measured SCr, as data on proteinuria and structural abnormalities of the kidneys were not available. In Paper I and Paper II, the MDRD equation (A. S. Levey et al., 2006) was used to calculate eGFR from baseline SCr measurement, and CKD was defined as eGFR < 60mL/min/1.73m^2. For SCr measurements before 2008, the MDRD equation for non-standardized SCr (A. S. Levey, Bosch, Lewis, & Greene, 1999) was used, but thereafter the MDRD equation for standardized SCr (A. S. Levey et al., 2006). However, in Paper III and Paper IV, eGFR was calulated using the CKD-EPI equation (A. S. Levey et al., 2009), and CKD was defined as eGFR persistently < 60 mL/min/1.73m^2

using two or more SCr measurements at least three months apart. If two preoperative SCr measurements were not available, the baseline SCr value was used to estimate preoperative GFR (13% of cases). CKD was staged according to the KDIGO GFR criteria (Stevens, Levin, & Members, 2013) into stages 3a, 3b, 4 and 5.

MDRD equation (non-standardized SCr):

$eGFR = 186.3 \times (SCr\ (in\ \mu mol/L)/88.4)^{-1.154} \times age^{-0.203} \times 0.742\ (if\ female) \times 1.212\ (if\ black)$

MDRD equation (standardized SCr):

$eGFR = 175 \times (SCr\ (in\ \mu mol/L)/88.4)^{-1.154} \times age^{-0.203} \times 0.742\ (if\ female) \times 1.212\ (if\ black)$

CKD-EPI equation:

$eGFR = 141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.1018\ (if\ female) \times 1.159\ (if\ black)$

If female: $\kappa = 0.7$, $\alpha = -0.329$

If male: $\kappa = 0.9$, $\alpha = -0.411$

In Paper III and Paper IV, incident CKD stage 3 and above following AKI was defined as a decline in eGFR to < 60 mL/min/1.73m^2 for at least 3 months postoperatively or the initiation of RRT in patients with preoperative eGFR > 60 mL/min/1.73m^2. Progression of preexisting CKD was defined as an increment of at least one CKD stage maintained for the minimum of 3 months among patients with preexisting CKD stages 3–4 (eGFR 15–60 mL/min/1.73 m^2).

3.3.4 Risk scores and comorbidity assessment

Comorbid diseases were evaluated based on ICD-9 and ICD-10 diagnostic codes recorded before the onset of AKI. The codes were used to calculate risk scores in order to further quantify the comorbid burden of patients.

The van Walraven modification of the Elixhauser Comorbidity Index was calculated from the patients' preoperative ICD-10 diagnostic codes (Paper IV) to estimate comorbidities. The Elixhauser Comorbidity Index is a method for categorizing comorbidities based on diagnostic codes (Elixhauser, Steiner, Harris, & Coffey, 1998). The van Walraven modification calculates a score that weighs in each comorbid condition based on its association with increased risk of death in previous studies (Walraven, Quan, & Forster, 2009). Its purpose is to decrease degrees of freedom (get a single number instead of 20 variables).

The Revised Cardiac Risk Index (RCRI) preoperative risk factor score was generated in Paper II. RCRI was calculated using information on prior diagnoses of cerebrovascular event, congestive heart failure, ischemic heart disease and type 1 diabetes, the presence of high-risk surgery (defined as open surgery entering at least the peritoneum), and a preoperative SCr level > 176.8 µmol/L (Lee, Marcantonio, & Mangione, 1999). For analysis in Paper II, a non-renal RCRI score was also calculated by excluding the SCr part of the index.

The American Society of Anesthesiology physical status classification (ASA score) was included in Paper II (Saklad, 1941). The patients' ASA score was evaluated preoperatively by the treating anesthesiologist, who classified the patients' physical state into six classes:

Class I, a normal healthy patient.

Class II, mild systemic disease.

Class III, severe systemic disease, not incapacitating.

Class IV, severe systemic disease that is a constant threat to life.

Class V, not expected to survive without the operation.

Class VI, already been declared brain-dead and organs are being removed for transplantation (excluded from analysis in Paper II).

3.4 Special methodological considerations

Though many methodological factors were comparable between papers, there were some important differences that are described in further detail in this chapter.

3.4.1 Incidence of acute kidney injury and survival (Paper I)

The objective of Paper I was to estimate the incidence of H-AKI in hospitalized patients, to estimate whether it associates with long-term outcomes and whether the incidence has changed over time. All patients admitted to LUH from June 1, 1993, to May 31, 2013, were included. Excluded from analysis were patients younger than 18 years of age, patients requiring treatment for ESRD before admission and patients without an Icelandic government-issued identification number.

Incidence of AKI was calculated per 1000 admissions/year, excluding admissions to the psychiatric and obstetric wards. Clinical variables and

outcomes were compared between patients with H-AKI and two separate control groups. One control group comprised all individuals with baseline SCr but without AKI. Another control group was created by assigning each AKI patient a control without AKI based on propensity score matching (PSM), described in further detail in section 3.8.3. Survival analysis was also performed separately for subsets of patients with eGFR below and above 60 mL/min/1.73m^2. Follow-up SCr measurements were used to examine renal recovery of patients after AKI. Renal recovery was defined as reaching a SCr value less than 1.5 x baseline value during follow-up.

A sensitivity analysis was performed by analyzing the data with and without two predefined groups of patients likely with preexisting kidney disease:

1. Patients with glomerular disease and vasculitis (N00 - N08 and M31 (ICD-10) or 580 - 583 (ICD-9)).

2. Patients with glomerular disease, urolithiasis, vasculitis and other autoimmune disease possibly affecting kidneys (N00 - N08, N20 - N23 and M30 - M39 (ICD-10) or 446, 580 - 583, 592, 594 and 710 (ICD-9)).

3.4.2 Acute kidney injury following abdominal surgery (Paper II)

The objective of Paper II was to estimate the incidence of AKI following abdominal surgery, identify patient- and procedure-related risk factors for postoperative AKI and assess outcomes of these patients. All patients who underwent abdominal surgical procedures at LUH between January 1, 2007, and December 31, 2014, were included. Excluded from the study were individuals younger than 18 years of age, those who underwent genitourinary or abdominal vascular procedures, patients requiring treatment for end-stage renal disease before surgery, and patients without an Icelandic government-issued identification number.

The abdominal surgeries were categorized into anatomical subgroups and divided into major and minor surgical procedures (Table 8). The incidence of postoperative AKI was calculated per 1000 surgeries. Univariate and multivariate logistic regression analysis was used to evaluate patient- and procedure-related risk factors for postoperative AKI, further described in section 3.8.1. Hospital LOS as a function of AKI was examined using a generalized linear model, adjusting for preoperative LOS and time until peak SCr level.

Table 8. NOMESCO classification codes used to categorize surgical procedures into subgroups.

	NOMESCO surgical procedure code
Major surgical procedures	
Esophageal surgery	JCA, JCB, JCC, JCD, JCE, JCW
Gastric surgery	JDC, JDD, JDA, JDH, JDW
Liver and other biliary surgery	JKB, JKC, JKD, JKF, JKW, JJA, JJB, JJW
Pancreatic surgery	JLA, JLB, JLC, JLD, JLW
Spleen surgery	JMA, JMB, JMW
Explorative laparotomy and peritoneal/adhesions surgery	JXA, JFL, JFW, JAH, JAK (00, 03, 10), JAL (10, 20, 23, 30, 50, 96), JAM, JAN, JAQ00, JAW96
Open intestinal surgery	JFA (00, 10, 16, 60, 63, 70, 73, 76, 80, 83, 86, 96), JFB (00, 10, 13, 20, 30, 33, 40, 43, 46, 50, 60, 63, 96), JFC (00, 10, 20, 30, 40, 50), JFD (00, 03, 10, 13, 20, 23, 96), JFF (00, 10, 13, 20, 23, 26, 30, 40, 50, 60, 96), JFG (except 40), JFH (except 01, 11), JGA (except 97), JAJ, JGB (except 01, 11, 31, 97), JGC (except 01, 97), JGW96
Minor surgical procedures	
Hernia surgery	JAA, JAB, JAC, JAD, JAE, JAF, JAG
Peritoneal/adhesions, laparoscopic	JAK (01, 04), JAL (01, 11, 21, 24, 31, 51, 97), JAW97
Diaphragm and gastro-esophageal reflux surgery	JBA, JBB, JBC, JBW
Gastric bypass and volume reduction	JDE, JDF
Appendectomy	JEA, JAA, JAK
Cholecystectomy	JKA
Intestinal surgery, laparoscopic	JFA (17, 71, 74, 81, 84, 97), JFB (01, 21, 31, 34, 41, 44, 47, 51, 61, 64, 97), JFC (01, 11, 21, 31, 41, 51), JFD04, JFF (01, 11, 21, 24, 27, 31, 41, 51, 97), JFG40, JFH (01, 11) JGA97, JGB (01, 11, 31, 97), JGC97, JGW97

The classification system is based on a three character groups of surgical procedures. Each group is divided into subgroups based on two-digit numbers. If the surgical group included all subgroups, the subgroups (numbers) are not presented in the table. Abbreviations: NOMESCO; Nordic Medico-Statistical Committee Classification of Surgical Procedures.

3.4.3 Renal recovery after postoperative acute kidney injury (Paper III)

The objective of Paper III was to compare different definitions of renal recovery after postoperative AKI, with a focus on the association with development of incident CKD or progression of prior CKD and long-term survival. Furthermore, to examine a possible relationship between the duration of AKI and these outcomes.

All patients who experienced postoperative AKI following abdominal, cardiothoracic, vascular, or orthopedic surgery at LUH from January 1, 1998, to December 31, 2015, were included. Excluded from the study were individuals younger than 18 years of age, patients with recurrent AKI episodes, those who underwent genitourinary or abdominal vascular procedures, patients with eGFR < 15 mL/min/1.73m^2, those who required treatment for ESRD before surgery and patients who were without an Icelandic government-issued identification number.

The following definitions of renal recovery were examined for their association with development of incident CKD or progression of preexisting CKD and one-year mortality:

1. Reduction in SCr to < 1.1 × the baseline SCr at days 10, 20 and 30 after surgery.

2. Reduction in SCr to < 1.25 × the baseline SCr at days 10, 20 and 30 after surgery.

3. Reduction in SCr to < 1.5 × the baseline SCr at days 10, 20 and 30 after surgery.

The definitions above were selected based on definitions previously used in studies on renal recovery (Kellum, Sileanu, Bihorac, Hoste, & Chawla, 2017; Pannu et al., 2013) and the ADQI Workgroup consensus statement (Chawla et al., 2017). Individuals with mild stage 1 AKI, defined as an increase in SCr of ≥ 26.5 µmol/L (0.3 mg/dL) within 48 hours but without a rise to 1.5 x baseline within 7 days, were considered to have recovered kidney function to SCr < 1.10 x baseline, had they reached SCr < 26.5 µmol/L above baseline within the given timeframes.

In the analysis of mortality, efforts were made to minimize the effect of early deaths in the examination of long-term outcomes, which was one of the primary objectives of the study. Hence, patients who died during hospital stay, within

the first 30 days following surgery, were excluded. In the analysis, a categorical variable was generated by dividing AKI patients into groups according to the return of SCr to < 1.1 x baseline, 1.1–1.25, 1.25–1.5, and > 1.5 x baseline at 10, 20, and 30 days following AKI. Furthermore, patients were divided into 4 groups based on duration of AKI, categorized as SCr > 1.5 x baseline for < 2 days, 3–6 days, > 6 days, or no recovery (SCr not reaching <1.5 x baseline). Patients who died within 90 days of surgery were excluded from the kidney-specific outcome analysis, as they needed to have eGFR measurements at least 90 days apart for the determination of incident CKD or progression of preexisting CKD.

In the analysis of kidney-specific outcomes, both the development of incident CKD in patients without preoperative CKD and progression of preexisting CKD were examined. These two outcomes were analyzed both separately and as a combined kidney outcome measure.

3.4.4 Mild stage 1 acute kidney injury and outcomes (Paper IV)

All patients who had postoperative AKI following abdominal, cardiothoracic, vascular, or orthopedic surgery at LUH from January 1, 1998, to December 31, 2015, were included. Excluded from the study were individuals younger than 18 years of age, patients with recurrent AKI episodes, those who underwent genitourinary or abdominal vascular procedures, patients with eGFR < 15 mL/min/1.73m^2, and patients who required treatment for end-stage renal disease before surgery or were without an Icelandic government-issued identification number. Patients who died in the hospital during the first 30 days following surgery were excluded from the survival analysis to minimize the effect of early deaths on long-term survival. Furthermore, patients who died within 90 days of surgery were excluded from kidney outcome analysis as they needed to have eGFR determinations at least 90 days apart for the evaluation of development of incident CKD or progression of preexisting CKD.

3.5 Data management and statistical analysis

For all papers, raw data processing was performed using custom JAVA scripts. Scripts were verified by comparing the program output with manual examination of data from a random subset of patients. Data visualization and statistics were performed using R, versions 3.0.3 (Paper I and II), and 3.3.2. (Paper III-IV), in R Studio, version 1.0.136 (R Development Core Team, 2015). In Paper I and II, the level of statistical significance was set at a p-value < 0.01, while in Paper III and IV it was set at a p-value < 0.05.

In all studies, continous variables were compared using either the 2-sample t-test and Wilcoxon rank sum test or the analysis of variance and Kruskal-Wallis test on the other hand, according to the normality of data. Normality of data was assessed graphically with a Q-Q plot. Categorical variables were compared using the x^2 test. Assessment of change in incidence over time was done with Poisson regression (Paper II-IV). Several different methods were used to compare multiple variables and adjust for confounding factors. These methods are described further in the following sections.

3.5.1 Multivariable logistic regression analysis

In Paper II, a multivariable logistic regression analysis was used to evaluate patient- and procedure-related risk factors for postoperative AKI following abdominal surgeries. The assessment of linearity of the continuous variables, age and duration of surgery that were included in the AKI model, was performed by plotting the logit of AKI $(log(p/[1-p])$, where p is the proportion of patients with AKI) in groups of individuals with increasing age or surgery duration. The duration of the surgical procedure was dichotomized at 100 minutes after observing a sharp increase in the logit of AKI around that duration. Interaction was tested between variables included in the model.

A multivariable logistic model was originally built by using all known preoperative variables demonstrating a univariate association with AKI (at $p < 0.01$). Using the step function in R, variables were discarded in a backward stepwise manner to further refine the model and optimize the Akaike information criterion (Leeuw, 1974). Several other models were also assessed that are not displayed in the thesis. No intraoperative or postoperative factors were included in the model as the intent was to assess preoperative risk factors to support preoperative decision-making. Included in the final model were: age, sex, previous diagnoses of CKD, hypertension, ischemic heart disease, COPD, ASA classification and whether the procedure was a reoperation.

In Paper III, multivariable logistic regression models were used to evaluate association of renal recovery definitions and one-year survival. The models were constructed with forward addition of variables, using the step function in R, to identify independent risk factors, and also with manual selection of variables of clinical importance. Surgical procedures were categorized as abdominal, cardiothoracic, vascular, or orthopedic surgeries and each category divided into major and minor surgeries for analysis. The final model in the survival analysis was adjusted for age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart

disease, congestive heart failure, COPD and neoplasm, type of surgery, and time period.

In Paper IV, a multivariable logististic regression model was constructed to estimate the association of mild stage 1 AKI with one-year survival. Variables were selected based on univariate comparison between groups, presumed association with mortality and clinical importance. Surgical procedures were categorized as abdominal, cardiothoracic, vascular, or orthopedic surgeries and each category divided into major and minor surgeries for analysis. Variables included in the final model were: age, sex, CKD stage, previous history of hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure, COPD and malignancy, year of surgery, type of surgery and diagnosis of myocardial infarction or sepsis during the hospitalization.

The goodness of fit of all models was assessed using the Hosmer and Lemeshow test from the Resource Selection package in R.

3.5.2 Cox proportional hazards regression analysis

Cox proportional hazards models were built in Paper I and Paper III. In Paper I, a model was constructed to compare long-term survival between AKI patients and controls, adjusting for covariates. In the Cox proportional hazards regression analysis of propensity score-matched groups, the analysis was stratified by pairs of cases and its controls. In Paper III, models were generated to assess the association of different renal recovery criteria with the development of incident CKD or progression of preexisting CKD stage 3 and above in the 5 years following surgery. The proportional hazards assumption was tested for all models utilizing the cox.zph function in R.

3.5.3 Propensity score matching

Control groups generated by the method of propensity score matching were used for outcome analyses in all four papers. The method attempts to mimic randomization by creating a case-control-matched control group which is comparable for all covariates included in the matching except the insult in question, with the aim of minimizing selection bias. The method searches for the control patient from the pool of potential controls that is the closest match to every case (ratio of 1:1). The matching is based on an estimated distance between the case and control. The distance is the probability of the control patient to be a case based on a logistic regression model of preselected matching variables (Austin, 2011).

Propensity score matching was carried out using the nearest neighbour method from the MatchIt package in R. Variables with known or presumed association with the outcome were selected for each matching. To evaluate the quality of matching, the standardized mean differences for each variable were compared between the matched groups. The caliper argument was used to set a standardized mean difference at a fixed upper limit of 0.1. Differences in survival curves between groups after propensity score matching were assessed with a case/control stratified log-rank test (Austin, 2011).

In Paper I, three propensity score-matched control groups were generated for comparison of long-term survival between H-AKI patients and patients without AKI. This was done for all H-AKI patients and also for subgroups of patients with eGFR > 60 mL/min/1.73m^2 and with eGFR < 60 mL/min/1.73m^2 before H-AKI. The following parameters were used for matching: age, sex, baseline eGFR, year of inclusion and previous history of hypertension, diabetes mellitus, ischemic heart disease, COPD, liver disease, malignant neoplasms and benign neoplasms.

In Paper II, a propensity score-matched control group was generated to compare both length of hospital stay and 30-day survival of postoperative AKI patients with a matched control group of patients without AKI. The following parameters were used for matching: age, sex, baseline eGFR, ASA score, year of surgery, type of surgery, emergency surgery, operative time, diagnosis of myocardial infarction or sepsis during hospitalization, and previous history of ischemic heart disease, congestive heart failure, hypertension, diabetes mellitus, COPD, liver disease, and both malignant and benign neoplasms.

In Paper III, the propensity score matching method was employed, in addition to multivariable logistic regression analysis and Cox proportional hazards regression analysis, to assess the relationship between renal recovery and incident or progressive CKD and also one-year survival. Groups with different levels of renal recovery were compared to propensity score- matched control group of patients who recovered kidney function to a SCr level of <1.1 x baseline. In the survival analysis, the following parameters were used for matching: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease, congestive heart failure, COPD and neoplasm, type of surgery, and time period. In the analysis of incident CKD and progression of CKD, the following parameters were used for matching: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease and congestive heart failure, and time period.

In Paper IV, incident or progressive CKD and survival of patients with mild stage 1 AKI was compared with a propensity score-matched control group without AKI. This comparison was performed separately for groups with and without preoperative CKD stage 3 and above. In the survival analysis, the following parameters were used for matching: age, sex, baseline eGFR, previous history of hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure, COPD, liver disease and malignancy, year of surgery, type of surgery and diagnosis of myocardial infarction or sepsis during the hospitalization. In the analysis of incident or progressive CKD, the following parameters were used for matching: age, sex, baseline eGFR, previous diagnosis of hypertension, diabetes, ischemic heart disease or congestive heart failure, year of surgery and type of surgery.

4 Results

This thesis is based on four papers examining different aspects of AKI in the hospital setting. Paper I begins by evaluating the extent of AKI in the general hospitalized population, whether its incidence has changed over time and how it associates with survival. In the following Papers II-IV, the focus is set on more specific features of AKI in a surgical cohort. Paper II examines postopertive AKI after abdominal surgery, its incidence, risk factors and short-term survival. Paper III examines different definitions of renal recovery following postoperative AKI and their association with long-term survival and development of incident CKD or progression of preexisting CKD. Finally, Paper IV focuses on the incidence of mild stage 1 AKI and whether it associates with long-term survival and development of incident CKD or progression of preexisting CKD.

4.1 Paper I – Incidence of acute kidney injury and survival

During the 20 year study period, there were 401,388 admissions to LUH (Figure 3). A total of 45,607 patients had a baseline SCr measurement available in the six month period before admission. Of those patients, 25,274 experienced their peak SCr during hospitalization. The median (range) time period from baseline SCr to peak SCr was 27 (1-183) days. H-AKI occurred in 10,419 (41%) patients with 19%, 11% and 12% having stage 1, 2 and 3 AKI, respectively. Characteristics of this cohort are demonstrated in Table 9. When the cohort was restricted to include only patients with a baseline SCr measurement available within 7 days prior to the peak SCr (n=19,607, 42%), 83% of the patients had the same AKI stage as when a baseline SCr up to six months before admission was used.

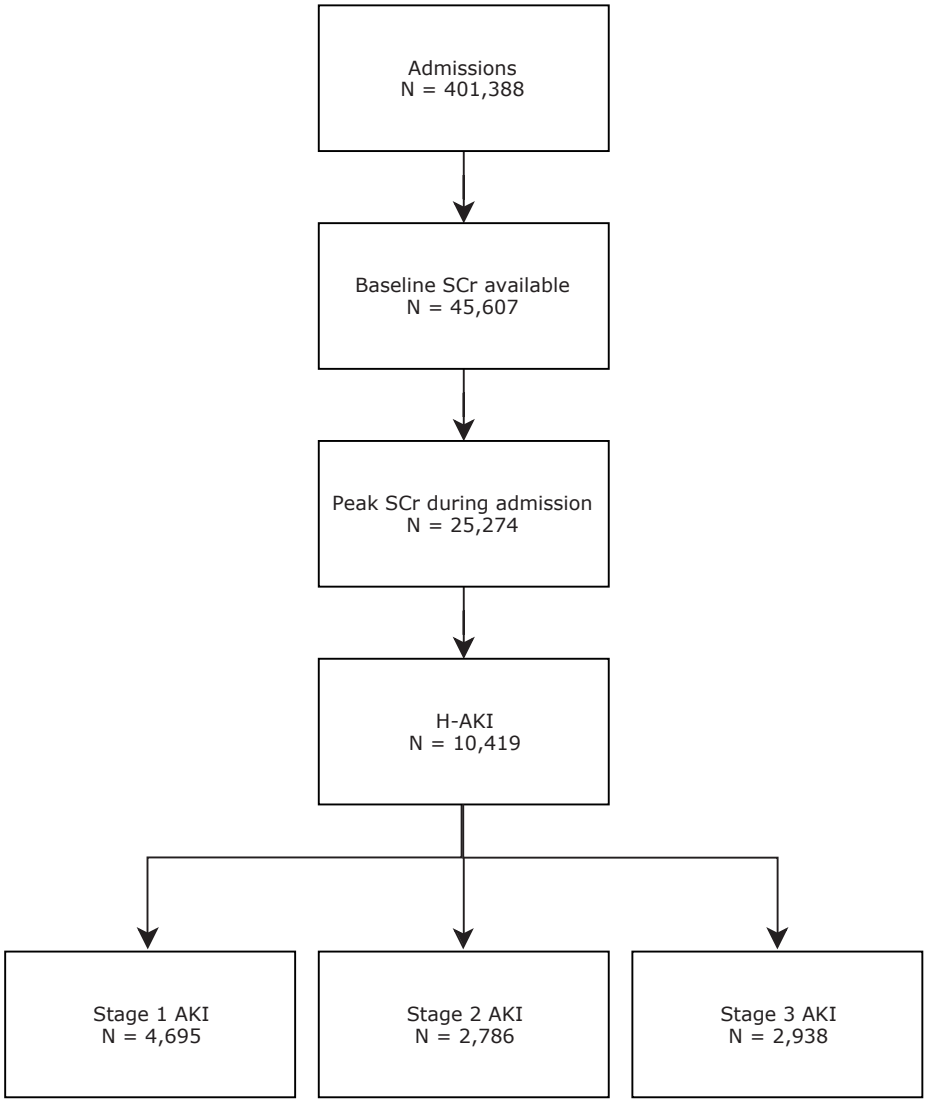


Figure 3. Flowchart demonstrating the number of patients admitted to the hospital, those with available SCr, patients with H-AKI and the number of patients with each stage of AKI. Abbreviations: SCr, serum creatinine; H-AKI, hospital-acquired acute kidney injury

Table 9. Characteristics of patients without AKI and patients with H-AKI stage 1, stage 2 and stage 3.

	No AKI	Stage 1	Stage 2	Stage 3	p-value
N (%)	14,855 (59)	4,695 (19)	2,786 (11)	2,938 (12)	
Age, years	57.8 [39.7 - 75.9]	74.1 [61.1 - 82.7]	75.2 [64.8 - 82.6]	72.9 [62.2 - 80.8]	< 0.001
Sex, female	7,118 (48)	2,317 (53)	1,448 (53)	1,265 (44)	< 0.001
Baseline SCr, µmol/L	80 [66 - 93]	83 [62 - 97]	79 [59 - 95]	147 [63 - 159]	< 0.001
Hypertension	1,293 (9)	852 (18)	668 (24)	819 (28)	< 0.001
Diabetes mellitus	489 (3)	336 (7)	299 (11)	396 (13)	< 0.001
COPD	690 (5)	503 (11)	380 (14)	358 (12)	< 0.001
Ischemic heart disease	2,670 (18)	1,435 (31)	987 (35)	1,001 (34)	< 0.001
Liver disease	103 (0.7)	50 (1.1)	65 (2.3)	86 (2.9)	< 0.001
Malignant neoplasm	1,593 (11)	1,229 (26)	873 (31)	946 (32)	< 0.001
Benign neoplasm	1,304 (9)	884 (19)	647 (23)	779 (27)	< 0.001
eGFR > 90	5,791 (39)	1,703 (36)	1,082 (39)	979 (33)	
eGFR 60 - 90	6,274 (42)	1,785 (38)	1,031 (37)	707 (24)	
eGFR 30 - 60	2,405 (16)	1,125 (24)	667 (24)	624 (21)	
eGFR 15 - 30	332 (2)	82 (2)	6 (0.2)	344 (12)	
eGFR < 15	53 (0.3)	0 (0)	0 (0)	284 (9)	< 0.001

Data presented as median (interquartile range) for continuous variables or number and percentage for categorical variables.
Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; SCr, serum creatinine.

4.1.1 Incidence of acute kidney injury

The incidence of H-AKI was 25.8 (95% CI, 20.9-30.7) per 1000 admissions/year. Throughout the 20 year study period, the incidence increased steadily ($p < 0.001$), averaging 18.6 (95% CI, 14.7-22.5) per 1000 admissions/year in 1993–1997, 25.2 (95% CI, 24.0–26.5) in 1998–2002, 28.9 (95% CI, 25.6–32.2) in 2003–2007 and 29.9 (95% CI, 26.7–33.1) in 2008–2013.

4.1.2 Survival after hospital acquired acute kidney injury

A total of 51% of H-AKI patients were alive one-year after the AKI episode. In a multivariable Cox hazards model there was a stepwise increase in the hazard for mortality with increasing severity of H-AKI ($p < 0.001$; Table 10). Survival of patients with H-AKI was significantly lower than in PSM controls without AKI ($p < 0.001$; Figure 4A), and an inverse relationship was observed between the

severity of AKI and survival ($p < 0.001$; Figure 4B). Association with lower survival was persistent in subgroups of patients both with and without eGFR < 60mL/min/1.73m^2 before admission ($p < 0.001$; Figure 4C and 4D). Furthermore, the results were similar after exclusion of the predefined groups of patients with kidney-specific diagnoses (data not shown).

A trend over time was observed with significant improvement in survival following H-AKI. One-year survival was 47% in 1993–1997, 47% in 1998–2002, 54% in 2003–2007 and 57% in 2008–2013 (Figure 5; $p < 0.001$). When compared to the first five-year period, the adjusted hazard ratio for death was 0.85 (0.81-0.89), 0.67 (0.64 - 0.71), and 0.57 (0.53 - 0.60) for each subsequent 5-year interval ($p < 0.001$; Table 5). The results remained similar when only the PSM controls were used in the analysis. Moreover, this association remained apparent when only patients with stage 2 and stage 3 where included (data not shown).

There was change over time in the median (IQR) number of SCr measurements per patient which increased from from 2 (1 - 4) in the first 5 year period to 8 (2 - 21) in the last period ($p < 0.001$). However, time trends for underlying comorbid conditions of these patients moved in opposite directions over the study period. There was an increase in the proportion of patients with hypertension, diabetes and benign neoplasms ($p < 0.001$), but no change over time was observed for ischemic heart disease, COPD or malignant neoplasms (Table 11).

Table 10. Risk factors for mortality among 25,274 hospitalized patients. Multivariable Cox proportional hazards regression analysis.

	HR (95% CI)	p-value
No AKI	1.00	
H-AKI Stage 1	1.54 (1.47 - 1.61)	< 0.001
H-AKI Stage 2	2.00 (1.90 - 2.11)	< 0.001
H-AKI Stage 3	2.76 (2.62 - 2.90)	< 0.001
Age (per 10 years)	1.75 (1.73 - 1.78)	< 0.001
Baseline eGFR (per 10)	1.02 (1.01 - 1.02)	< 0.001
Female gender (vs. male)	0.88 (0.85 - 0.91)	< 0.001
HTN	0.97 (0.92 - 1.01)	0.155
DM	1.24 (1.16 - 1.32)	< 0.001
COPD	1.49 (1.41 - 1.57)	< 0.001
IHD	0.99 (0.96 - 1.03)	0.785
Liver disease	1.54 (1.34 - 1.76)	< 0.001
Malignant neoplasms	2.08 (2.00 - 2.17)	< 0.001
Benign neoplasms	1.14 (1.09 - 1.20)	< 0.001
1993-1997	1.00	
1998-2002	0.85 (0.81 - 0.89)	< 0.001
2003-2007	0.67 (0.64 - 0.71)	< 0.001
2007-2013	0.57 (0.53 - 0.60)	< 0.001

Abbreviations: AKI, acute kidney injury; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTN, arterial hypertension; IHD, ischemic heart disease.

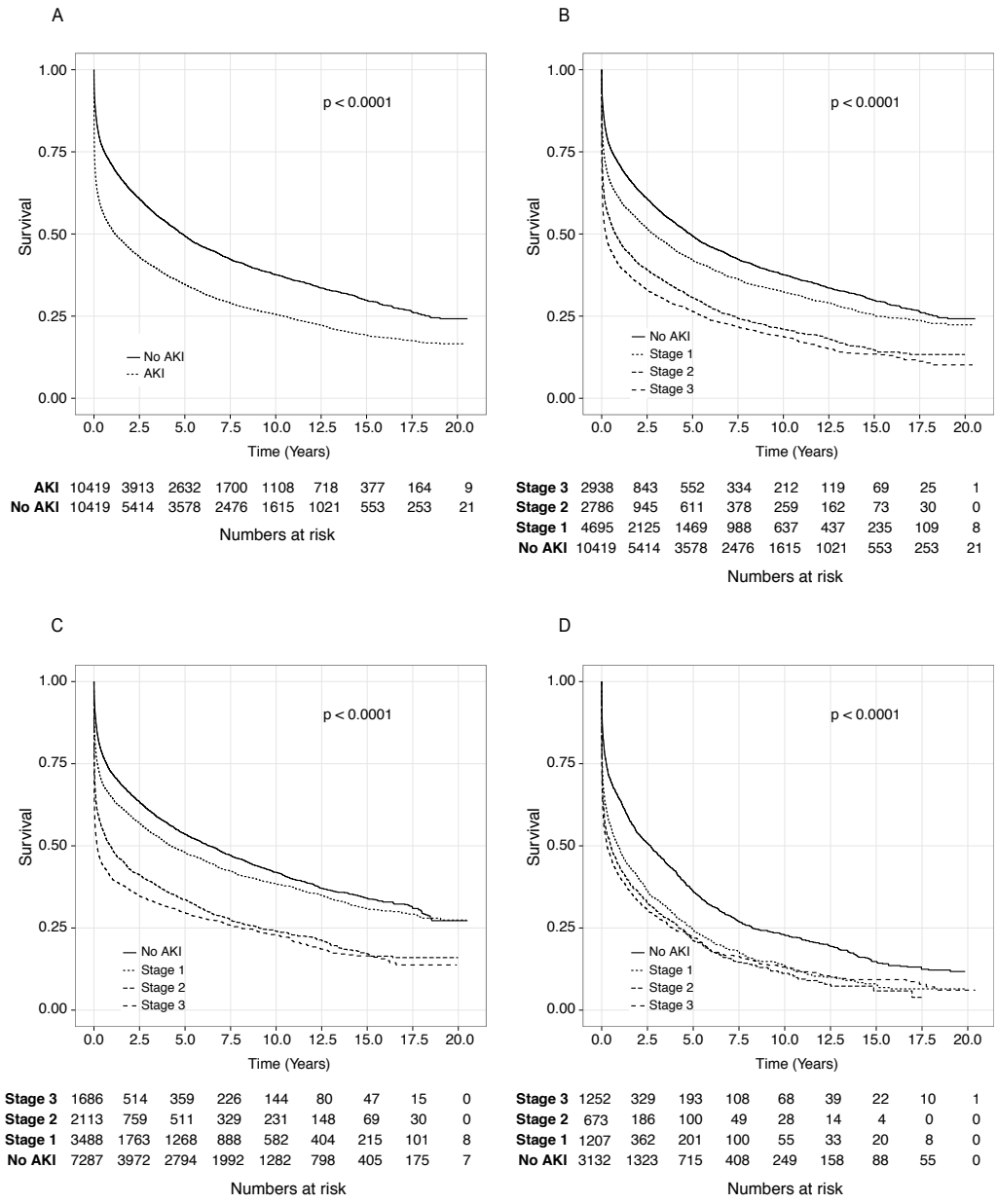
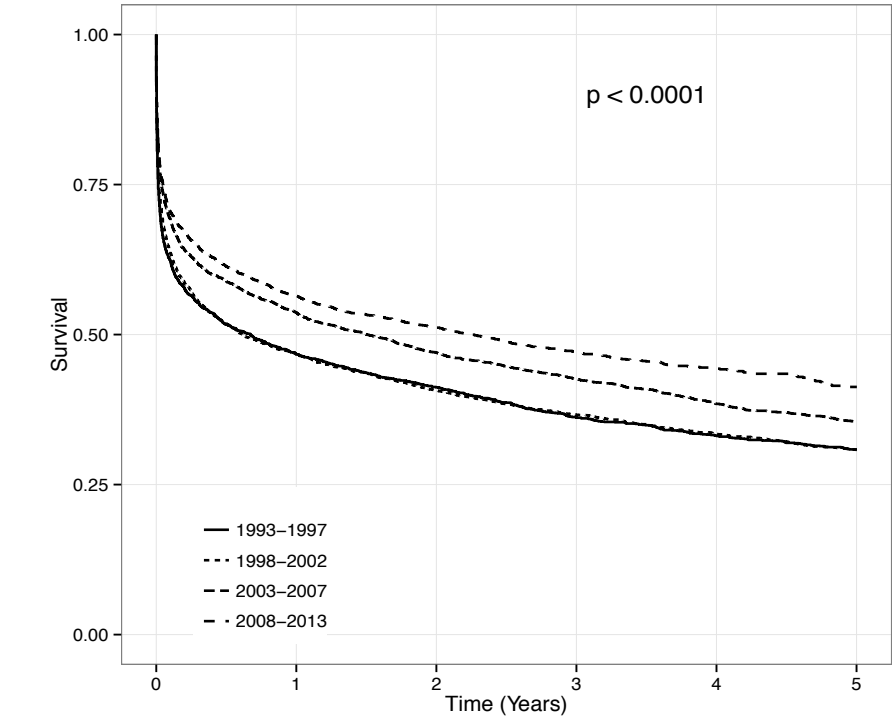


Figure 4. Survival plots for all patients with acute kidney injury during hospitalization (H-AKI) compared to propensity score-matched control group of non-AKI patients. **A:** Comparing H-AKI to no AKI. **B:** Survival of patients without AKI, stage 1, stage 2 and stage 3 H-AKI. **C:** Survival of patients with baseline eGFR > 60 mL/min per 1.73m^2 compared between those with H-AKI and no AKI. **D:** Survival of patients with baseline eGFR < 60 mL/min per 1.73m^2 compared between those with H-AKI and no AKI. Abbreviations: AKI, acute kidney injury.



2008–2013	2972	1516	1037	710	453	203
2003–2007	2866	1538	1346	1220	1102	1017
1998–2002	2744	1283	1118	1005	918	845
1993–1997	1837	858	757	665	609	567

Numbers at risk

Figure 5. Survival of patients with hospital acquired acute kidney injury based on year of diagnosis, divided into four 5-year intervals. Kaplan-Meier plot compared with log-rank test.

Table 11. Classification of comorbid disease groups using ICD-9 and ICD-10 diagnostic codes, and trends in comorbidity throughout the study period.

Comorbidity	1993-1997	1998-2002	2003-2007	2008-2013
Hypertension (%)	15	18	27	27
Diabetes mellitus (%)	7	10	10	12
COPD (%)	12	11	13	12
Ischemic heart disease (%)	34	33	33	32
Liver disease (%)	2	2	2	2
Malignant neoplasm (%)	31	29	28	30
Benign neoplasm (%)	11	19	25	29
eGFR < 60 (%)	31	29	30	31

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, arterial hypertension; ICD, international classification of diseases; IHD, ischemic heart disease.

4.1.3 Kidney outcomes following H-AKI

Of the 10,419 patients with H-AKI, 7,030 (67%) recovered their kidney function with a reduction in SCr to below 1.5 x baseline during follow-up. The rate of renal recovery was inversely associated with the stage of AKI, with 88%, 58% and 44% of stage 1, 2 and 3 AKI patients achieving renal recovery, respectively ($p < 0.001$; Figure 6). A total of 293 (3%) H-AKI patients received treatment for ESRD during follow-up, of whom 2, 1 and 290 patients had stage 1, 2 and 3 H-AKI, respectively.

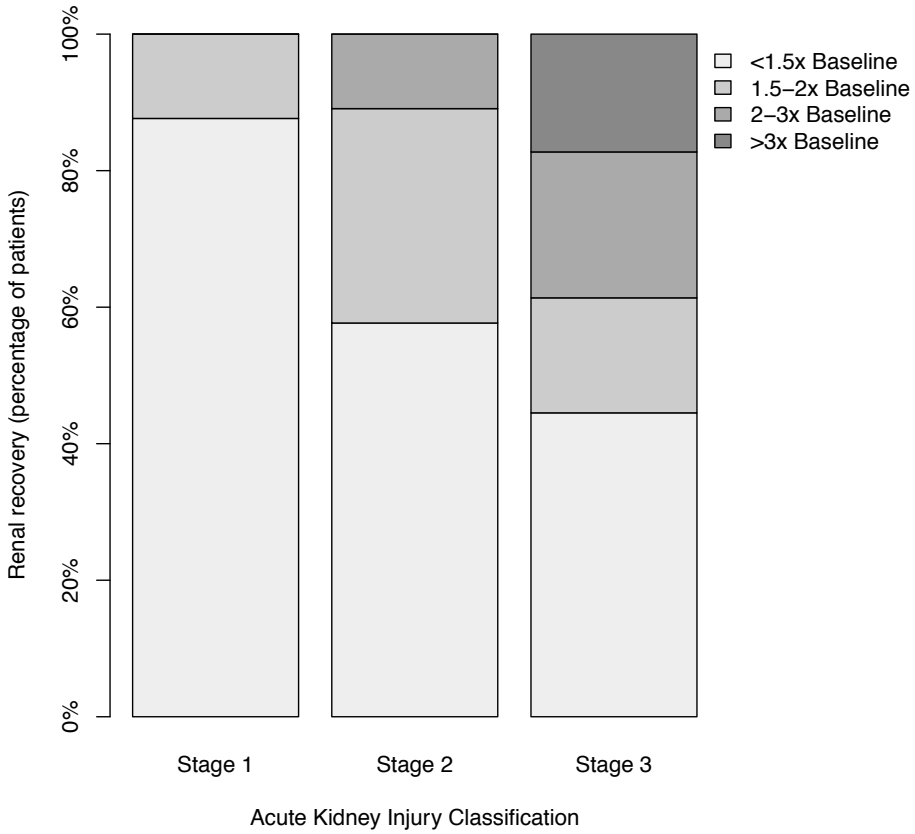


Figure 6. Renal recovery of patients with stage 1, 2 and 3 AKI. The different shades in the bars represent the proportion of patients different rate of renal recovery estimated with the average of the last three serum creatinine measurements during follow-up.

4.2 Paper II – Acute kidney injury following abdominal surgery

Paper II focused on postoperative AKI following abdominal surgery at LUH in 2007-2014. Evaluation of the incidence of AKI, risk factors for the development of AKI and short-term survival.

There were 11,552 surgical procedures performed during the study period, for which 3,902 (33.8%) pre- and postoperative SCr measurements were available (Figure 7). Patients who underwent pre- and postoperative SCr measurement had significantly higher ASA score, longer hospital stay and higher 30-day mortality than patients without SCr measurements.

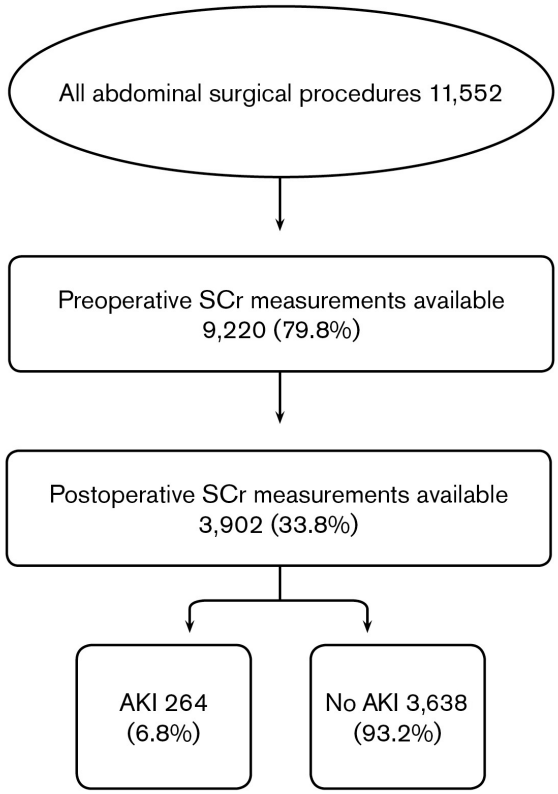


Figure 7. Flowchart describing the study cohort undergoing abdominal surgery. Abbreviations: AKI, acute kidney injury; SCr, serum creatinine.

4.2.1 Incidence of AKI

AKI occurred following 264 (6.8%) abdominal procedures among 236 patients during the study period. Of these, 172 (4.4%), 49 (1.3%), and 43 (1.1%) were classified as AKI stages 1, 2, and 3, respectively (Table 12). The highest incidence of AKI was observed after explorative laparotomy (12.8%), and esophageal (12.7%), splenic (9.6%), and gastric surgeries (9.4%, Table 12).

Among patients with available pre- and postoperative SCr, the incidence of AKI was 67.7 (99% CI, 57.7–78.6) per 1000 surgeries. Given the assumption that none of the individuals who were missing either pre- or postoperative SCr experienced AKI, the incidence of AKI would be 22.9 (99% CI, 19.4–26.7) per 1000 surgeries. There was no significant change in the incidence of AKI over time. The incidence was 75.1 (99% CI, 60.9–93.6) cases per 1000 surgeries in 2007–2010 and 60.3 (99% CI, 60.9–93.6) cases per 1000 surgeries in 2011 to 2014 ($p = 0.08$).

Table 12. Incidence of postoperative AKI following different types of abdominal surgery.

Surgery	Surgical procedures	Patients	Pre- and postop. SCr available	AKI[a]	Stage 1[a]	Stage 2[a]	Stage 3[a]
All abdominal procedures	11,552	10,022	3,902 (33.8)	264 (6.8)	172 (4.4)	49 (1.3)	43 (1.1)
Laparoscopic surgery	6,604	6,317	1,041 (15.8)	35 (3.4)	26 (2.5)	6 (0.6)	3 (0.3)
Emergency surgery	4,391	4,199	1,638 (37.3)	134 (8.2)	78 (4.8)	26 (1.6)	30 (1.8)
Non-emergency surgery	7,161	6,287	2,264 (31.6)	130 (5.7)	94 (4.2)	23 (1.0)	13 (0.5)
Major surgical procedures	3,023	2,562	2,077 (68.7)	189 (9.1)	119 (5.7)	37 (1.8)	33 (1.6)
- Esophageal surgery	130	126	79 (60.8)	10 (12.7)	6 (7.6)	2 (2.5)	2 (2.5)
- Gastric surgery	294	277	267 (90.8)	24 (9.0)	16 (6.0)	3 (1.1)	5 (1.9)
- Liver & other biliary surgery	443	426	206 (46.5)	17 (8.3)	9 (4.4)	5 (2.4)	3 (1.5)
- Pancreatic surgery	78	76	77 (98.7)	7 (9.1)	3 (3.9)	2 (2.6)	2 (2.6)
- Spleen surgery	102	98	83 (81.4)	8 (9.6)	6 (7.2)	2 (2.4)	0 (0.0)
- Explorative laparotomy	1,114	1,034	626 (56.2)	81 (12.9)	43 (6.9)	22 (3.5)	16 (2.6)
- Open intestinal surgery	1,342	1,100	1,179 (87.9)	107 (9.1)	70 (5.9)	23 (2.0)	14 (1.2)
Minor surgical procedures	8,529	7,902	1,825 (21.4)	75 (4.1)	53 (2.9)	12 (0.7)	10 (0.5)

[a] Patients with both pre- and postoperative SCr available. Abbreviations: AKI, acute kidney injury; SCr, serum creatinine.

4.2.2 Risk factors for postoperative AKI

Patients who developed postoperative AKI were older, had more comorbid conditions, underwent more complex surgical procedures and were more likely to have a prior history of AKI than patients without AKI (Table 13). The frequency of AKI increased with more advanced stage of CKD at baseline, being 13%, 18% and 22% for stages 3, 4 and 5, respectively ($p < 0.001$).

Table 14 demonstrates the results of univariable analyses of the association of clinical characteristics, preoperative diagnoses and perioperative factors with postoperative AKI. In a multivariable model that included only variables available to the clinician preoperatively, female sex (odds ratio [OR] = 0.68; 99% CI, 0.47–0.98), hypertension (OR = 1.75; 99% CI, 1.10–2.74), preoperative CKD (OR = 1.68; 99% CI, 1.12–2.50), ASA classification of IV (OR = 9.48; 99% CI, 3.66–29.2) or V (OR = 21.4; 99% CI, 5.28–93.6), and reoperation (OR = 4.30; 99% CI, 2.36–7.70) were independently associated with postoperative AKI (Table 14).

Table 13. Characteristics of patient- and surgery-related factors among surgical procedures with and without AKI.

	No AKI N= 11,288	AKI N= 264	p-value
Age, years	62 (50 - 73)	69 (60 - 78)	< 0.001
Sex, female	2,004 (55.1)	119 (45.1)	0.017
Previous history of AKI	187 (5.1)	46 (17.4)	< 0.001
Hypertension	435 (12.0)	72 (27.3)	< 0.001
Diabetes mellitus	155 (4.3)	28 (10.6)	< 0.001
Ischemic heart disease	534 (14.7)	71 (26.9)	< 0.001
Congestive heart failure	151 (4.2)	31 (11.7)	< 0.001
COPD	143 (3.9)	25 (9.5)	< 0.001
Liver disease	54 (1.5)	10 (3.8)	0.009
Malignant neoplasm	855 (23.5)	72 (27.3)	0.184
Benign neoplasm	734 (20.2)	59 (22.3)	0.443
Baseline creatinine	74 (63 - 89)	87.5 (71.8 - 120)	< 0.001
eGFR > 60	2,877 (80.3)	149 (56.9)	
eGFR 30 - 60	604 (16.9)	88 (33.6)	
eGFR < 30	102 (2.8)	25 (9.5)	< 0.001
ASA classification:			
- ASA I	550 (15.5)	9 (3.6)	
- ASA II	1,778 (50.2)	80 (31.9)	
- ASA III	1,034 (29.2)	89 (35.5)	
- ASA IV	168 (4.7)	61 (24.3)	
- ASA V	13 (0.4)	12 (4.8)	< 0.001
Emergency surgery	1,505 (41.4)	133 (50.4)	0.005
Explorative laparotomy	546 (15.0)	80 (30.3)	< 0.001
Open bowel resection	1,072 (29.5)	107 (40.5)	< 0.001
Esophageal surgery	69 (1.9)	10 (3.8)	< 0.001
Gastric surgery	242 (6.7%)	25 (9.5)	< 0.001
Liver and other biliary surgery	189 (5.2)	17 (6.4)	< 0.001
Pancreatic surgery	70 (1.9)	7 (2.7)	< 0.001
Spleen surgery	75 (2.1)	8 (3.0)	< 0.001
Laparoscopy	1,304 (35.8)	73 (27.7)	0.009
Minor surgery	1,842 (50.6)	89 (33.7)	< 0.001

Abbreviations: AKI, acute kidney injury; ASA, American Society of Anesthesiology; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Table 14. Risk factors for postoperative AKI after abdominal surgery. Univariable and multivariable logistic regression analysis.

	Unadjusted OR (99% CI)	p-value	Adjusted OR (99% CI)	p-value
Age, per year	1.03 (1.02 - 1.04)	< 0.001	1.01 (1.00 - 1.03)	0.01
Sex, female	0.66 (0.47 - 0.91)	0.001	0.68 (0.47 - 0.98)	0.007
Prior history of AKI	3.89 (2.42 - 6.09)	< 0.001		
Hypertension	2.70 (1.83 - 3.94)	< 0.001	1.75 (1.10 - 2.74)	0.002
Congestive heart failure	3.07 (1.74 - 5.14)	< 0.001		
Ischemic heart disease	2.05 (1.39 - 2.97)	< 0.001	0.58 (0.30 - 1.08)	0.03
Diabetes mellitus	2.54 (1.40 - 4.35)	< 0.001		
COPD	2.56 (1.37 - 4.45)	< 0.001	1.54 (0.78 - 2.87)	0.09
Liver disease	1.56 (0.66 - 3.17)	0.14		
Benign neoplasm	1.19 (0.80 - 1.74)	0.25		
Malignant neoplasm	1.27 (0.87 - 1.82)	0.09		
CKD (eGFR < 60 mL/min/1.73 m^2)	3.09 (2.20 - 4.33)	< 0.001	1.68 (1.12 - 2.50)	< 0.001
Procedure-related factors				
Emergency surgery	1.46 (1.05 - 2.03)	0.003		
Reoperation	5.19 (3.05 - 8.57)	< 0.001	4.30 (2.36 - 7.60)	< 0.001
Operative time > 100 min	1.58 (1.14 - 2.21)	< 0.001	Not used	
ASA (compared with ASA I)				
- ASA II	2.74 (1.21 - 7.80)	0.004	1.83 (0.77 - 5.32)	0.10
- ASA III	5.26 (2.31 - 14.88)	< 0.001	2.40 (0.96 - 7.18)	0.02
- ASA IV	22.7 (9.56 - 65.9)	< 0.001	9.48 (3.66 - 29.2)	< 0.001
- ASA V	56.4 (15.0 - 231)	< 0.001	21.4 (5.28 - 93.57)	< 0.001
RCRI risk factors >1	3.19 (2.21 - 4.54)	< 0.001	1.65 (0.90 - 3.01)	< 0.001
Nonrenal RCRI factors >1	2.57 (1.74 - 3.73)	< 0.001		
Type of surgery				
Explorative laparotomy	2.51 (1.71 - 3.59)	< 0.001	Not used	
Open intestinal surgery	1.63 (1.26 - 2.28)	< 0.001	Not used	
Esophageal surgery	2.04 (0.75 - 4.58)	0.04		
Gastric surgery	1.40 (0.75 - 2.41)	0.14		
Liver and other biliary surgery	1.26 (0.60 - 2.34)	0.38		
Pancreatic surgery	1.39 (0.41 - 3.48)	0.42		
Splenic surgery	1.48 (0.49 - 3.55)	0.30		

Abbreviations: AKI, acute kidney injury; ASA, American Society of Anesthesiology; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; RCRI, Revised Cardiac Risk Index.

4.2.3 Outcomes following postoperative AKI

Patients with postoperative AKI had a higher rate of complications than patients without AKI, including perioperative pneumonia, myocardial infarction, and sepsis (Table 15) and the rate increased with rising severity stage of AKI ($p < 0.001$). Furthermore, 111 (42%) AKI patients were admitted to ICU and 31 (11.7%) required transient renal replacement therapy. Length of stay in hospital was significantly longer in AKI patients, with a median (IQR) of 16 days (7-34) vs. 6 (4-11) days among patients without AKI. The 30-day mortality was higher in AKI patients than in patients without AKI, 17.8% vs. 2.1% ($p < 0.001$).

Table 15. Comparison of short-term complications after abdominal surgical procedures in patients with and without postoperative AKI.

	No AKI n = 3,638	AKI n = 264	p-value
Myocardial infarction	23 (0.6)	9 (3.4)	< 0.001
Pulmonary embolism	15 (0.4)	2 (0.8)	0.735
Pneumonia	71 (2.0)	15 (5.7)	< 0.001
Sepsis	27 (0.7)	19 (7.2)	< 0.001
Hospital stay, days	6 (4 - 11)	16 (7 - 34)	< 0.001
30-day mortality	76 (2.1)	47 (17.8)	< 0.001

Data are presented as median (interquartile range) for continuous variables or number (percentage) for categorical variables. Abbreviations: AKI, acute kidney injury.

4.2.3.1 Propensity score-matched analysis

When compared with a propensity score-matched control group, the AKI patients had a significantly longer length of stay in hospital (16 vs. 10 days, $p < 0.001$). However, after adjusting for the duration of preoperative hospital stay (0.3 days longer LOS per day of preoperative hospital stay; $p = 0.01$) and time until peak SCr was reached (4.3 days longer LOS for each postoperative day until peak SCr, $p < 0.001$), AKI was no longer associated with longer LOS (5.7 days longer for patients with AKI versus those without AKI; $p = 0.02$).

Postoperative AKI was associated with increased 30-day mortality of 18% when compared with the propensity score-matched control group without AKI with a 30-day mortality of 5% ($p < 0.001$). Furthermore, there was a dose-response relationship between the severity of AKI and mortality, with a 30- day mortality of 12.3%, 19.1%, and 43.2% in patients with AKI stages 1, 2, and 3, respectively, compared with 5.3% in the propensity score–matched control group ($p < 0.001$; Figure 8).

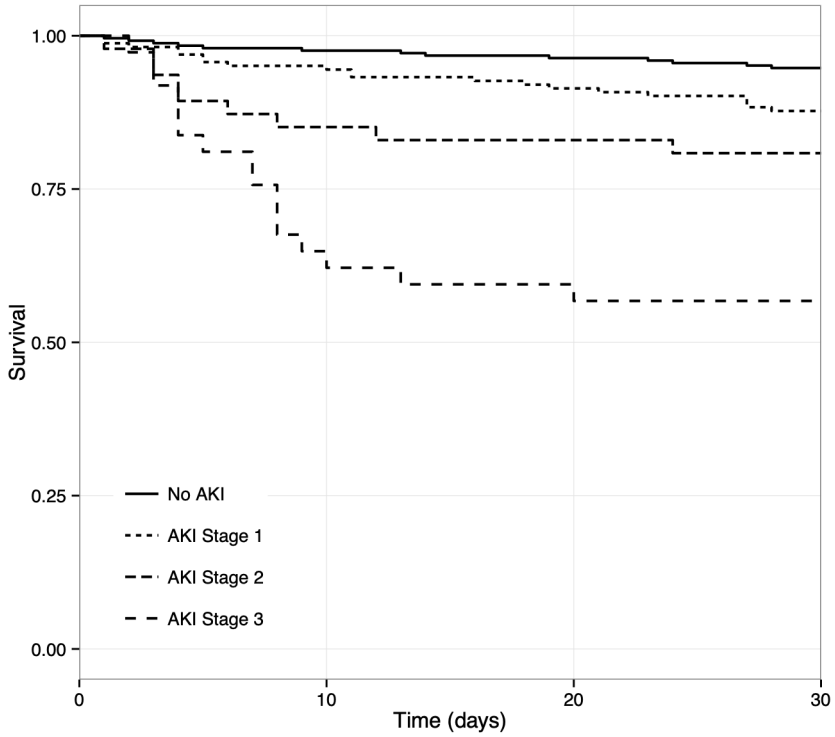


Figure 8. 30-day survival of patients with acute kidney injury stages 1, 2, and 3 compared with a propensity score–matched control group.
Matched for: age, sex, baseline eGFR, ASA score, year of surgery, type of surgery, emergency surgery, operative time, diagnosis of myocardial infarction or sepsis during hospitalization, and previous history of ischemic heart disease, congestive heart failure, hypertension, diabetes mellitus, COPD, liver disease, and both malignant and benign neoplasms.

4.3 Paper III – Defining renal recovery after postoperative acute kidney injury

The focus of Paper III was to examine different definitions of renal recovery after postoperative AKI based on association with development of incident CKD, progression of preexisting CKD and long-term survival.

During the 18-year study period, pre- and postoperative SCr measurements were available for 48,873 (42%) surgical procedures performed on 30,600 patients at LUH. These measurements were used for the assessment of postoperative AKI (Figure 9). Of these, 11,638 (24%) were abdominal, 19,694 (40%) cardiothoracic, 3,660 (8%) vascular, and 13,881 (28%) orthopedic procedures.

Excluded from analysis were patients who died within 30-days of surgery during the index hospital admission (N = 450), patients with preexisting CKD stage 5 (N = 207) and those with recurrent AKI episodes (N = 751). Thus, 2,520 cases of first AKI episodes remained for the analysis with 1,910 (76%), 370 (15%), and 240 (10%) cases of AKI stages 1, 2, and 3, respectively.

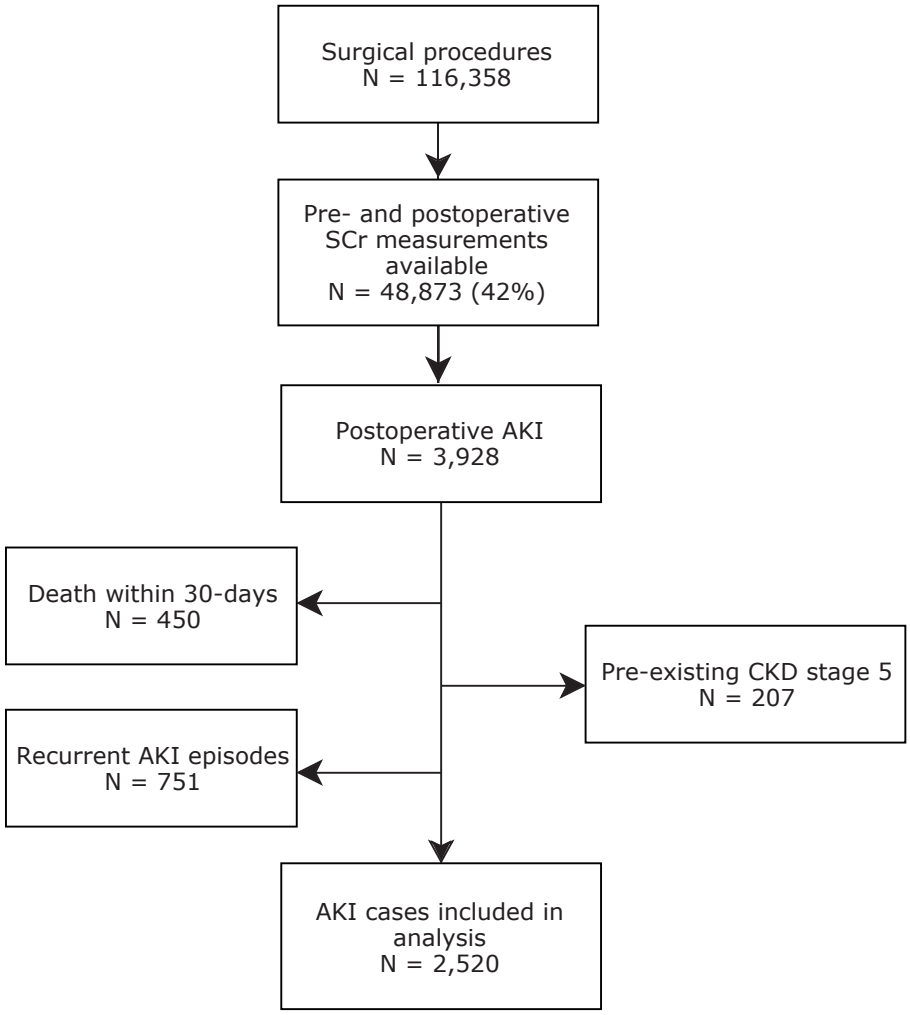


Figure 9. Flowchart outlining the study cohort and exclusion of patients for analysis. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; SCr, serum creatinine.

4.3.1 Renal recovery

Patients with postoperative AKI were divided into four groups according to different definitions of renal recovery. The groups were: Reduction in SCr to < 1.1 x baseline, 1.1 - 1.25 x baseline, 1.25 - 1.5 x baseline, and > 1.5 x baseline at 10, 20 or 30 days after surgery.

The rate of renal recovery was very different between the four groups, ranging from 57% in patients reaching SCr < 1.1 x baseline to 80% in those

reaching SCr < 1.5 x baseline within 30 days (Table 16). Individuals with mild stage 1 AKI, (increase in SCr of 26.5 µmol/L, but not reaching < 1.5 x baseline) and recovery below the 26.5 µmol/L increase are all included in the group with reduction in SCr to < 1.10 x baseline. The rate of renal recovery had an inverse association with the severity of AKI. The 499 (20%) patients who did not achieve renal recovery to < 1.5 x baseline SCr were more commonly male, older and sustained more severe AKI than the 2,021 (80%) who recovered (Table 17).

Table 16. Comparison of different renal recovery categories at 30 days following surgery, by AKI stage.

	Return of SCr to:			
	< 1.10	1.10 - 1.25	1.25 - 1.50	> 1.50
AKI stage				
1	1,169 (61%)	184 (10%)	220 (12%)	337 (18%)
2	164 (44%)	45 (12%)	74 (20%)	87 (24%)
3	112 (47%)	18 (7%)	35 (15%)	75 (31%)
All stages	1,445 (57%)	247 (10%)	329 (13%)	499 (20%)

Abbreviations: AKI, acute kidney injury; SCr, serum creatinine.

Table 17. Comparison of characteristics of AKI patients with and without renal recovery, defined as a return of SCr to <1.5 × baseline within 30 days.

	Recovery N = 2,021	No recovery N = 499	p-value
Age, years	74 (66–81)	74 (65–82)	0.95
Sex, female	824 (40.8)	256 (51.3)	< 0.001
AKI stage			
Stage 1	1,573 (77.8)	337 (67.6)	
Stage 2	283 (14.0)	87 (17.4)	
Stage 3	165 (8.2)	75 (15.0)	< 0.001
Baseline SCr, μmol/L	91 (74–116)	80 (63–105)	< 0.001
eGFR > 60ml/min/1.73m^2	1,167 (57.3)	311 (61.2)	
Preexisting CKD stages 3–4			
Stage 3A	424 (20.8)	90 (17.7)	
Stage 3B	315 (15.5)	70 (13.8)	
Stage 4	115 (5.7)	28 (5.5)	0.293
Hypertension	549 (27.2)	118 (23.6)	0.160
Diabetes mellitus	220 (10.9)	50 (10.0)	0.632
Ischemic heart disease	904 (44.7)	182 (36.5)	0.001
Congestive heart failure	357 (17.7)	66 (13.2)	0.021
COPD	163 (8.1)	31 (6.2)	0.195
Liver disease	35 (1.7)	9 (1.8)	1
Neoplasm	581 (28.7)	131 (26.3)	0.29
Type of surgery			
Abdominal			
Major	262 (13.0)	62 (12.4)	
Minor	135 (6.7)	42 (8.4)	
Cardiothoracic			
Major	716 (35.4)	141 (28.3)	
Minor	274 (13.6)	77 (15.4)	
Vascular			
Major	72 (3.6)	13 (2.6)	
Minor	71 (3.5)	14 (2.8)	
Orthopedic			
Major	420 (20.8)	120 (24.0)	
Minor	71 (3.5)	30 (6.0)	0.009
Time period			
1998-2003	656 (79.4)	170 (20.6)	
2004-2009	676 (79.1)	179 (20.9)	
2010-2015	689 (82.1)	150 (17.9)	0.227

Data are presented as median (interquartile range) for continuous variables or number (percentage) for categorical variables. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

4.3.1.1 Development of incident CKD and progression of CKD

There were 10,432 patients with preoperative CKD stage 3 or 4, of whom 1,042 (10%) developed postoperative AKI, comprising 41% of all AKI cases. The median (IQR) follow-up time for assessment of kidney function after AKI was 3.4 (1.2–7.1) years. Of the 2,180 AKI patients alive 90 days after surgery, and therefore eligible for assessment of CKD, all (100%) had adequate number of SCr measurements available for assessment of the development of incident CKD stages 3–5 or progression of preexisting CKD.

During five-year follow-up, 11,895 (30%) patients developed incident CKD or had a progression of preexisting CKD, of whom 10,643 (25%) patients had not developed AKI, and 941 (56%), 175 (58%), and 136 (68%) had experienced AKI stages 1, 2, and 3, respectively. Incident CKD within five-years of surgery occurred in 687 (53%) AKI patients with preserved preoperative kidney function, and progression of preexisting CKD within five-years developed in 565 (64%) AKI patients with preoperative CKD stage 3 and above.

When AKI patients were compared with a propensity score-matched control group without AKI, the risk of both incident CKD and progression of preexisting CKD stage 3 and above within 5 years increased with the severity stage of AKI (< 0.001; Figure 10). Compared with propensity score-matched patients with a recovery of SCr to < 1.10 x baseline within 30-days, those with a return of the SCr to > 1.5 x baseline within 30-days (p = 0.014; Figure 11) and to 1.25–1.5 x baseline within 30-days (p = 0.016) had significantly worse combined kidney outcome. However, this was not the case for patients with a reduction in SCr to 1.10– 1.25 x baseline within 30-days (p = 0.76).

Similarly, Cox analysis demonstrated an increased hazard for the combined kidney outcome in AKI patients who did not achieve a return of the SCr to < 1.5 x baseline, as well as in those who reached recovery of SCr to 1.25–1.5 x baseline, within 10, 20, and 30 days (Table 18).

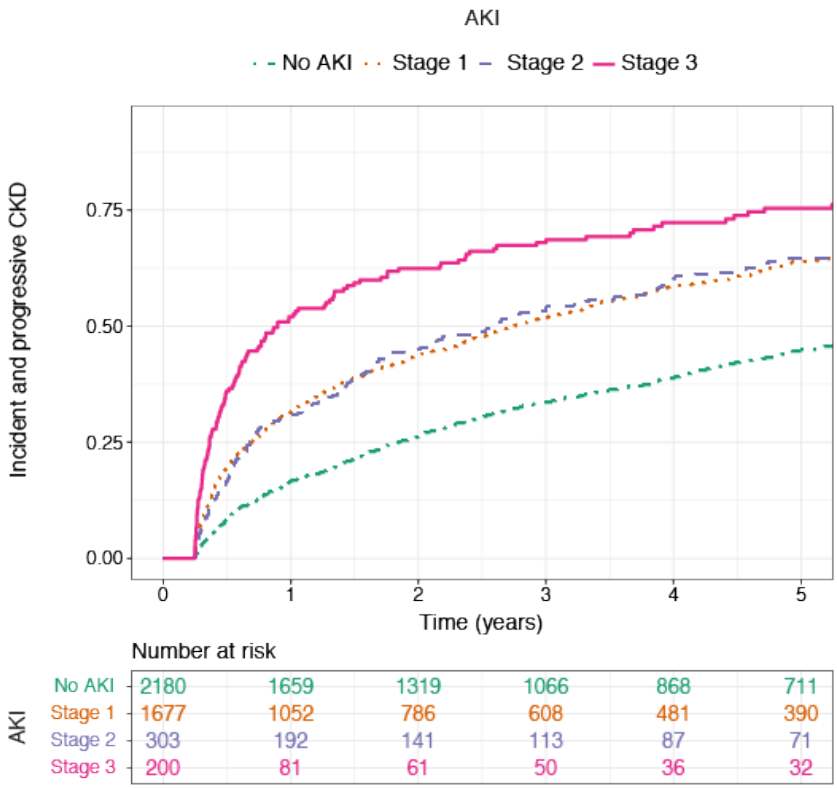


Figure 10. Rate of cumulative outcome of incident CKD stage 3 and above and progression of preexisting CKD among patients with stage 1, 2, and 3 AKI and a propensity score-matched control group without AKI.
Matched for age, sex, preexisting CKD stage 3 and above, previous diagnosis of hypertension, diabetes, ischemic heart disease and congestive heart failure, and time period. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.

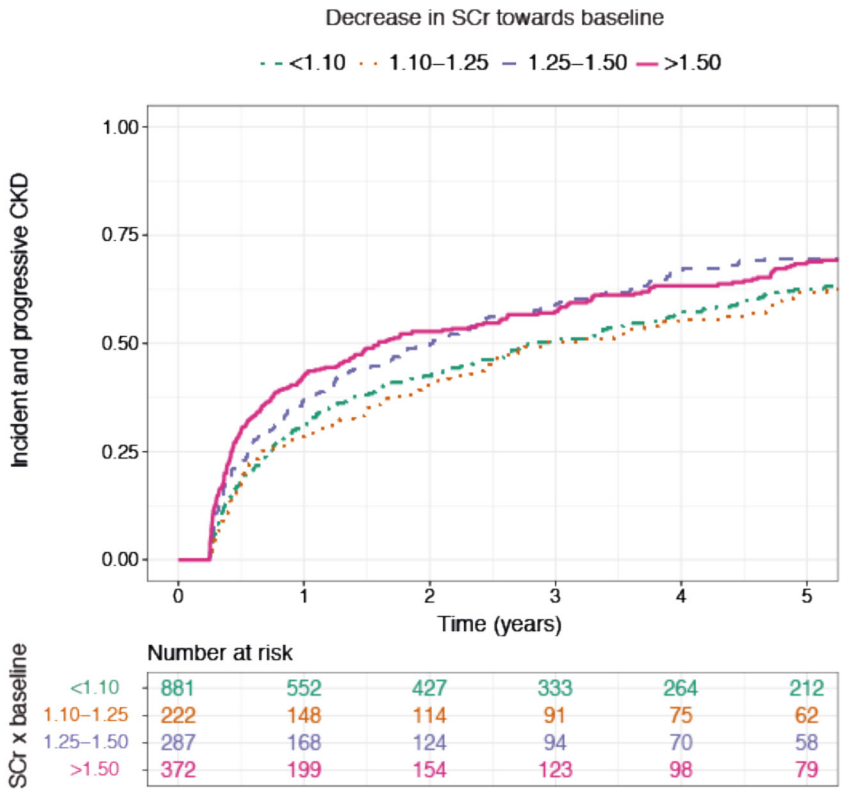


Figure 11. Rate of cumulative outcome of incident CKD stage 3 and above and progression of preexisting CKD among individuals within different renal recovery categories.
Matched for: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease and congestive heart failure, and time period. Abbreviations: CKD, chronic kidney disease; SCr, serum creatinine.

Table 18. The 5-year risk of incident CKD stage 3 and above or progression of pre-existing CKD, by different renal recovery criteria as categorical variables, at 10, 20 and 30 days. Cox regression analysis (N = 2,180).

Renal recovery categories	Unadjusted	p-value	Adjusted	p-value
	HR (95% CI)		HR (95% CI)	
10 days				
Return of SCr to:				
< 1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.83 (0.67 - 1.04)	0.098	0.96 (0.77 - 1.20)	0.717
1.25 - 1.50 x baseline	1.23 (1.05 - 1.43)	0.011	1.32 (1.13 - 1.56)	< 0.001
> 1.50 x baseline	1.21 (1.06 - 1.39)	0.006	1.38 (1.19 - 1.59)	< 0.001
20 days				
Return of SCr to:				
< 1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.91 (0.75 - 1.11)	0.358	1.00 (0.82 - 1.22)	0.989
1.25 - 1.50 x baseline	1.15 (0.98 - 1.36)	0.087	1.26 (1.07 - 1.49)	0.007
> 1.50 x baseline	1.25 (1.08 - 1.44)	0.002	1.42 (1.23 - 1.65)	< 0.001
30 days				
Return of SCr to:				
< 1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.94 (0.78 - 1.14)	0.514	1.03 (0.84 - 1.25)	0.800
1.25 - 1.50 x baseline	1.22 (1.03 - 1.43)	0.019	1.32 (1.12 - 1.57)	0.001
> 1.50 x baseline	1.27 (1.09 - 1.47)	0.002	1.50 (1.29 - 1.75)	< 0.001

The adjusted model included age, sex, preexisting chronic kidney disease stages 3-4 and acute kidney injury stage (stratified), surgery category (stratified), previous diagnosis of hypertension, diabetes, ischemic heart disease and congestive heart failure, and time period. Abbreviations: CI, confidence interval; HR, hazard ratio; SCr, serum creatinine

4.3.1.2 Survival

One-year survival of AKI patients was 84% compared with 91% in patients without AKI, but early deaths during admission within 30-days of surgery were excluded ($p < 0.001$). Patients with postoperative AKI who recovered kidney function based on return of SCr to < 1.5 x baseline within 30-days had significantly better one year mortality (87%) than patients not recovering to below 1.5 x baseline SCr within 30-days (75%; $p < 0.001$). A multivariable logistic regression analysis comparing the different definitions of renal recovery at 10, 20 and 30 days after AKI showed that not reaching SCr < 1.5 x baseline was associated with worse one-year survival ($p < 0.001$; Table 19). Similarly, when compared with a propensity score-matched control group, one-year survival of patients without recovery defined as return of SCr to < 1.5 x baseline within 10, 20 or 30 days was significantly worse ($p < 0.001$). However, one-year survival was similar in all patient groups with this level of recovery (Figure 12).

Table 19. Risk of mortality at one year following AKI by renal recovery criteria as categorical variables, at 10, 20, and 30 days. Logistic regression (n = 2,520).

Renal recovery categories	Unadjusted	p-value	Adjusted	p-value
	OR (95% CI)		OR (95% CI)	
10 days				
Return of SCr to:				
<1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.74 (0.44 - 1.17)	0.22	0.81 (0.47 - 1.33)	0.42
1.25 - 1.50 x baseline	1.11 (0.79 - 1.52)	0.54	1.25 (0.88 - 1.76)	0.20
>1.50 x baseline	2.18 (1.72 - 2.77)	< 0.001	2.37 (1.82 - 3.09)	< 0.001
20 days				
Return of SCr to:				
< 1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.82 (0.52 - 1.24)	0.37	0.91 (0.56 - 1.41)	0.68
1.25 - 1.50 x baseline	1.09 (0.77 - 1.52)	0.60	1.22 (0.85 - 1.74)	0.27
> 1.50 x baseline	2.32 (1.81 - 2.95)	< 0.001	2.50 (1.91 - 3.26)	< 0.001
30 days				
Return of SCr to:				
<1.10 x baseline	1.00		1.00	
1.10 - 1.25 x baseline	0.82 (0.53 - 1.23)	0.36	0.89 (0.57 - 1.36)	0.60
1.25 - 1.50 x baseline	0.96 (0.67 - 1.34)	0.80	1.09 (0.71 - 1.64)	0.69
> 1.50 x baseline	2.34 (1.83 - 3.00)	< 0.001	2.40 (1.85 - 3.12)	< 0.001

The adjusted model included age, sex, preexisting CKD stages 3–4, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease, congestive heart failure, chronic obstructive pulmonary disease and neoplasm, type of surgery, and time period. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CI, confidence interval; OR, odds ratio; SCr, serum creatinine.

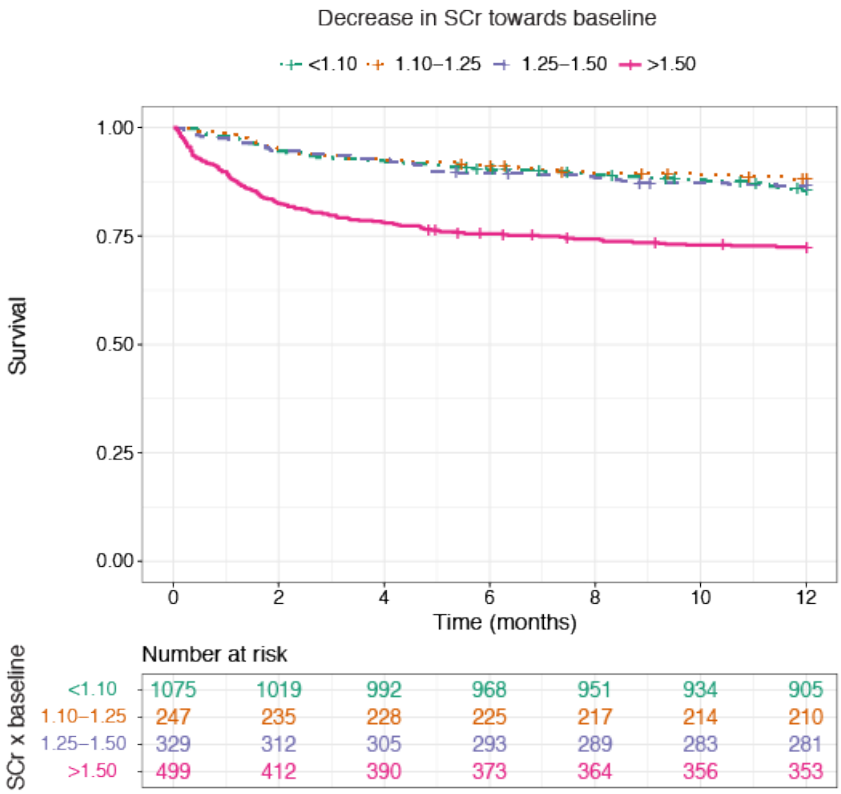


Figure 12. One-year survival of AKI patients with different levels of renal recovery at 30 days.
Matched for: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease, congestive heart failure, chronic obstructive pulmonary disease and neoplasm, type of surgery, and time period. Abbreviation: SCr, serum creatinine.

4.3.2 Duration of AKI

The duration of AKI was defined as the number of days from meeting the diagnosis criteria of AKI until the SCr had returned to < 1.5 x baseline. The duration of AKI was ≤ 2 days in 1,353 cases (54%), 3-6 days in 435 cases (17%) and > 6 days in 302 (12%) cases. A total of 430 (17%) cases did not achieve renal recovery during follow-up. In the 5 year period following AKI, 676 (56%), 222 (58%), and 157 (57%) with an AKI duration of ≤ 2 days, 3–6 days, and > 6 days, respectively, developed incident CKD or progression of preexisting CKD, compared with 64% of AKI patients without recovery (p = 0.039). Compared with a propensity score-matched control group with duration of AKI < 2 days, there was no significant association between the duration of

AKI and development of incident CKD or progression of preexisting CKD in the following 5 years, as long as the patients reached renal recovery based on reduction in SCr to < 1.5 x baseline (p = 0.59; Figure 13).

One-year survival was 85%, 82%, 86% and 67% in patients with duration of AKI of < 2 days, 3-6 days, > 6 days or no recovery, respectively. Patients with duration of AKI of 3–6 days and > 6 days had similar one-year survival as a propensity score-matched control group of patients with duration of AKI < 2 days (p = 0.16). However, patients without renal recovery (SCr < 1.5 x baseline) had significantly worse one-year survival (p < 0.001; Figure 14).

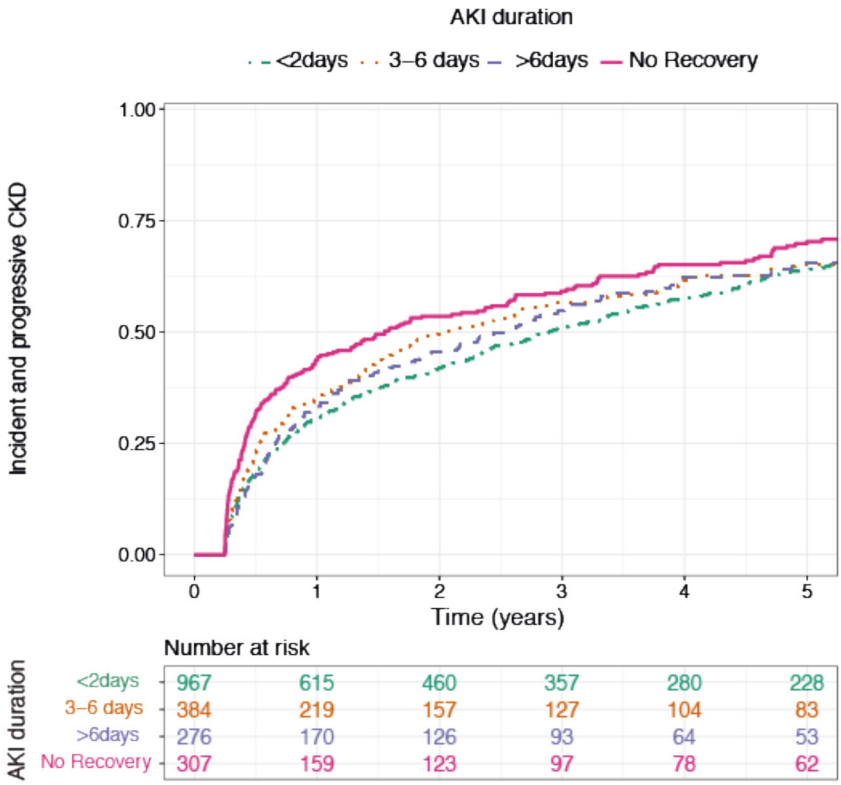


Figure 13. Cumulative incident stage 3 CKD or higher or progression of preexisting CKD based on duration of AKI, with cases propensity score-matched to individuals with AKI duration less than 2 days.
Matched for: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease and congestive heart failure, and time period. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; SCr, serum creatinine.

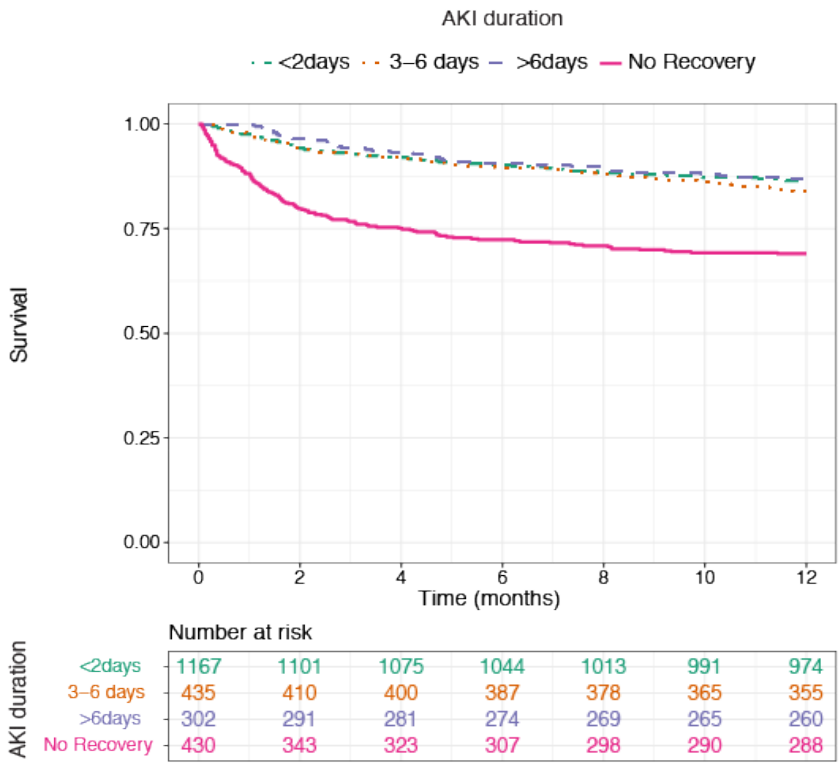


Figure 14. One-year survival of patients with variable duration of AKI compared with propensity score-matched controls with duration of AKI less than 2 days. Matched for: age, sex, preoperative kidney function, AKI stage, previous diagnosis of hypertension, diabetes, ischemic heart disease, congestive heart failure, chronic obstructive pulmonary disease and neoplasm, type of surgery, and time period. Abbreviations: AKI, acute kidney injury; SCr, serum creatinine.

4.4 Paper IV – Mild stage 1 postoperative AKI

In Paper IV, the focus was on mild stage 1 AKI in the postoperative setting, its incidence and, whether patients with this form of AKI differed from other AKI patients regarding comorbidity burden, and whether mild AKI associates with development of incident CKD, progression of preexisting CKD or long-term survival.

AKI was present following 3,516 (7.4%) surgical procedures, of which 1,161 (2.4%) were mild stage 1 AKI and 2,355 (5%) more severe form of AKI. The incidence of mild stage 1 AKI was 24.5 per 1000 surgeries/year and decreased gradually throughout the study period (-3% per year, 95% CI, -2% to -5%; $p < 0.001$). Figure 15 is a flowchart illustrating the total study cohort, exclusion of patients and stratification of AKI categories for the remaining analyses.

Patients with mild stage 1 AKI had a higher comorbidity burden than both patients without AKI and patients with more severe AKI ($p < 0.001$; Table 20). Underlying CKD before surgery was present in 56% of mild stage 1 AKI patients compared with 22% in patients without AKI and 38% in patients with more severe AKI.

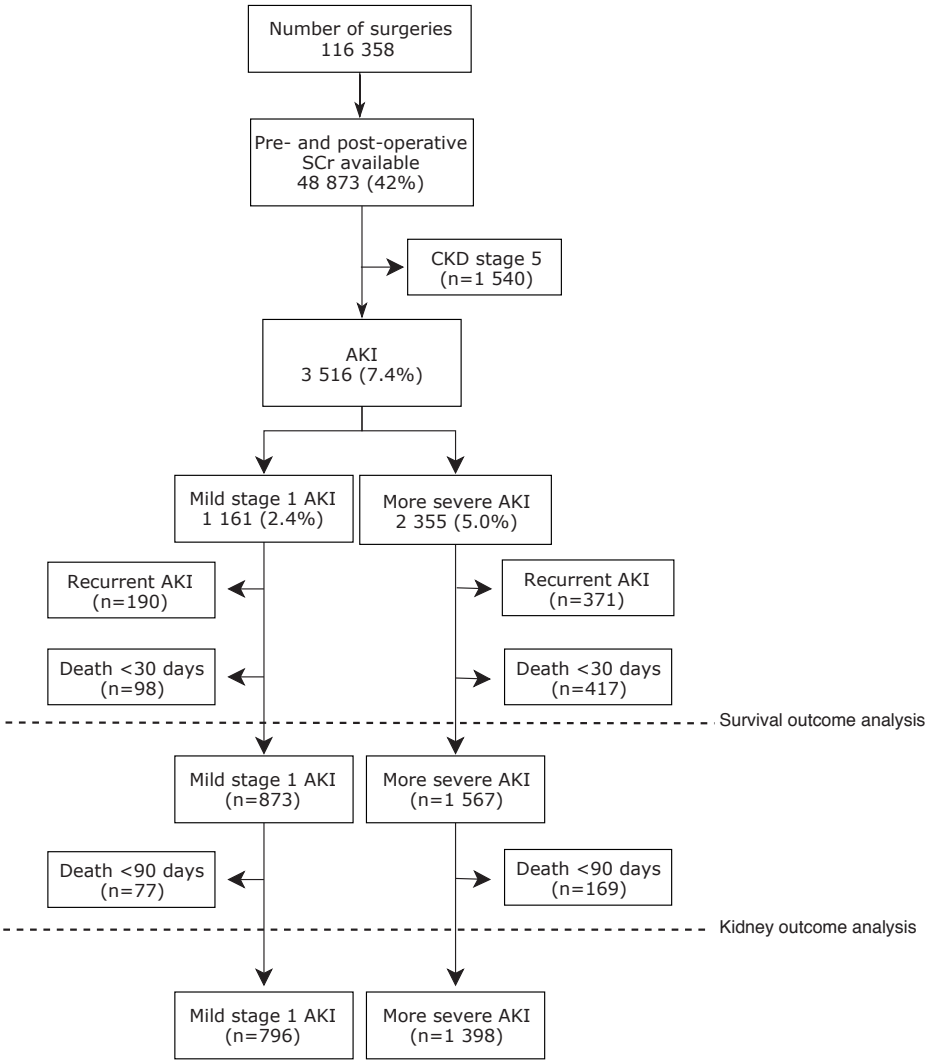


Figure 15. Flowchart showing the total study cohort, exclusion of patients and stratification of AKI categories for analysis.
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; SCr, serum creatinine.

Table 20. Baseline characteristics between groups of patients with no AKI, mild stage 1 AKI and more severe AKI.

	No AKI N = 43,817	Mild stage 1 AKI N = 1,161	More severe AKI N = 2,355	p-value
Patient-related factors				
Age, years	68 (57–77)	75 (68–81)	74 (65–81)	< 0.001
Sex, male	23,566 (54)	772 (66)	1,306 (55)	< 0.001
Baseline SCr, µmol/L	79 (66–96)	110 (88 –148)	87 (68–114)	< 0.001
Preexisting CKD category				
No CKD	34,131 (78)	508 (44)	1,458 (62)	
Stage 3a	5,739 (13)	264 (23)	447 (19)	
Stage 3b	3,043 (7)	267 (23)	314 (13)	
Stage 4	904 (2)	122 (10)	136 (6)	< 0.001
Hypertension	7,380 (17)	346 (30)	616 (26)	< 0.001
Diabetes mellitus	2,848 (6)	167 (14)	259 (11)	< 0.001
Ischemic heart disease	12,757 (29)	586 (50)	982 (42)	< 0.001
Congestive heart failure	3,956 (9)	276 (24)	409 (17)	< 0.001
COPD	2,717 (6)	92 (8)	202 (9)	< 0.001
Liver disease	560 (1)	13 (1)	48 (2)	0.005
Neoplasm	11,221 (26)	353 (30)	698 (30)	< 0.001
Preoperative morbidity assessment				
Elixhauser comorbidity index:				
>1	10,001 (23)	344 (30)	680 (29)	< 0.001
Type of surgery				
Abdominal				
- Major	5,928 (14)	133 (11)	375 (16)	
- Minor	4,681 (11)	81 (7)	143 (6)	
Cardiothoracic				
- Major	9,674 (22)	392 (34)	700 (30)	
- Minor	7,649 (17)	224 (19)	424 (18)	
Vascular				
- Major	782 (2)	42 (4)	72 (3)	
- Minor	2337 (5)	44 (4)	85 (4)	
Orthopedic				
- Major	9,706 (22)	204 (18)	454 (19)	
- Minor	3,060 (7)	41 (4)	102 (4)	< 0.001
Length of stay, days	6 (3–10)	10 (5–19)	12 (6–24)	< 0.001

Data are presented as median (interquartile range) for continuous variables or number (percentage) for categorical variables. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SCr, serum creatinine.

4.4.1 Incident CKD or progression of preexisting CKD following mild stage 1 AKI

Incident CKD stage 3-5 in the five years following surgery occurred in 6,888 (26%), 198 (57%) and 497 (60%) patients without AKI, with mild stage 1 AKI and with more severe AKI, respectively ($p < 0.001$). In patients with preoperative CKD, there was progression of CKD the following five years in 3,755 (57%), 260 (74%) and 310 (75%) patients without AKI, with mild stage 1 AKI and those with more severe AKI, respectively ($p < 0.001$). End-stage renal disease occured in 43 (0.1%) patients without AKI, 4 (1%) patients with mild stage 1 AKI and 4 (0.4%) patients with more severe AKI ($p < 0.001$).

Mild stage 1 AKI was associated with development of incident CKD within five years in patients without preoperative CKD when compared with a propensity score-matched control group without AKI (57% vs 41%, $p < 0.001$; Figure 16A). Furthermore, mild stage 1 AKI was also associated with progression of preexisting CKD within five years following surgery when compared with a propensity score-matched control group without AKI (74% vs 63%, $p < 0.001$; Figure 16B).

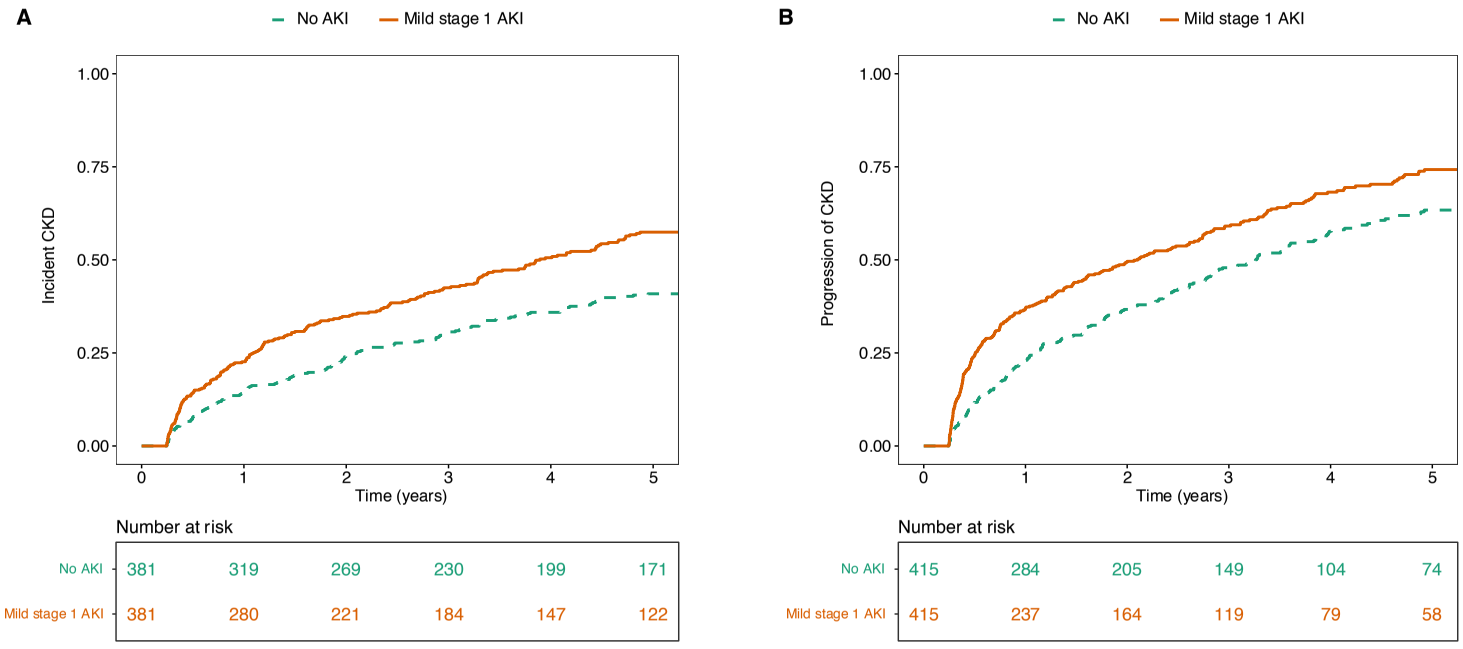


Figure 16. Development of incident CKD and progression of preexisting CKD following AKI compared with a propensity score-matched control group.A: Incident CKD within five years of surgery in patients without preoperative CKD who experienced mild stage 1 AKI compared with a propensity score-matched control group without AKI ($p < 0.001$). B: Progression of CKD within five years after surgery in patients with preoperative CKD who developed mild stage 1 AKI compared with a propensity score matched control group without AKI ($p < 0.001$). Matched for: age, sex, baseline eGFR, previous diagnosis of hypertension, diabetes, ischemic heart disease or congestive heart failure, year of surgery and type of surgery. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.

4.4.2 Survival following mild stage 1 AKI

One-year survival of patients without preoperative CKD was 92%, 87% and 71% in patients without AKI, mild stage 1 AKI and those with more severe AKI, respectively. One-year survival of patients with preoperative CKD stages 3 and 4 was 80%, 73% and 63% in patients without AKI, mild stage 1 AKI and more severe AKI, respectively. In-hospital deaths within 30-days were excluded from the remaining analysis of long-term survival.

Mild stage 1 AKI was not associated with worse one-year survival in individuals without preoperative CKD when compared with a propensity score-matched control group without AKI (94% vs 94%, p = 0.660; Figure 17A). Furthermore, mild stage 1 AKI was not associated with worse one-year survival in patients with preexisting CKD stages 3 and 4 compared with a propensity score matched control group without AKI (83% vs 82%, p = 0.870; Figure 17B).

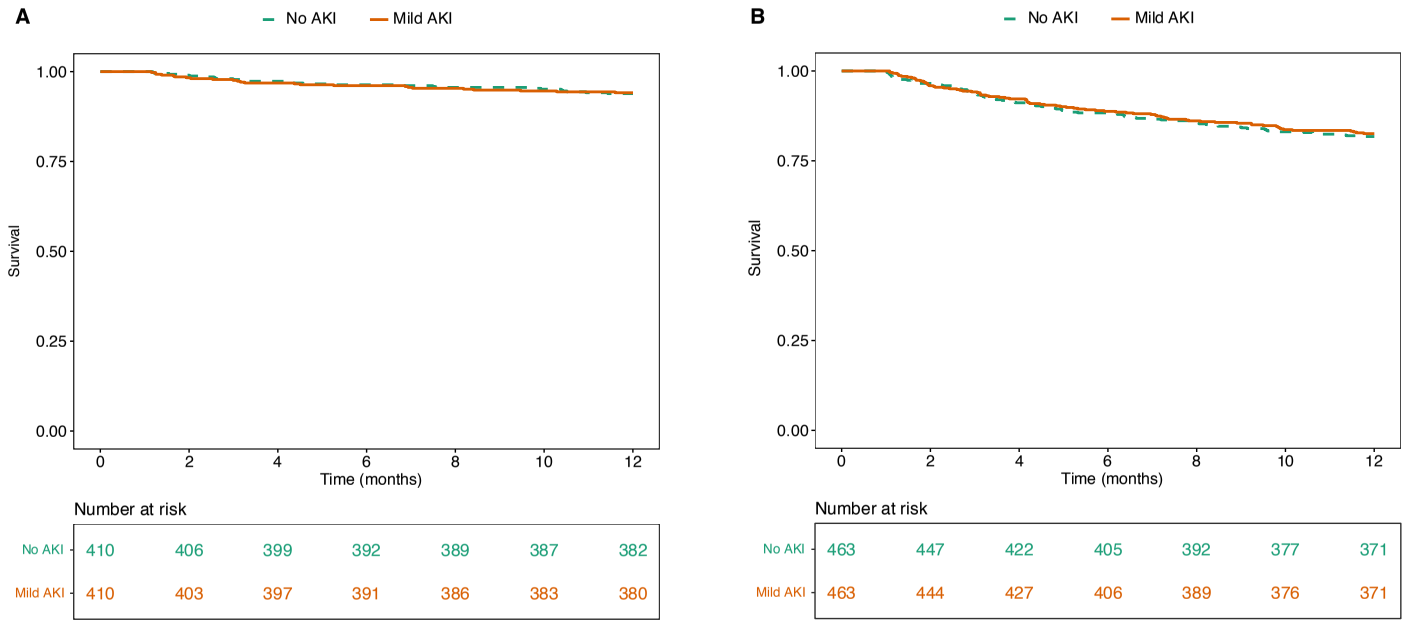


Figure 17. A: One-year survival of patients without preoperative CKD who developed mild stage 1 AKI compared with a propensity score-matched control group without AKI. **B**: One-year survival of patients with preoperative CKD who developed mild stage 1 AKI compared with a propensity score-matched control group without AKI. Individuals who died within 30-days were excluded. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.

5 Discussion

This thesis is based on four observational studies that examined the extent of AKI in hospitalized patients and its association with outcomes. The results demonstrate an overall incidence of AKI of 25.8 per 1000 hospital admissions/year, with a rise in the incidence over the past two decades. AKI was found to occur following 6.8% of all abdominal surgeries. Independent risk factors for developing postoperative AKI following abdominal surgery are older age, male sex, preoperative CKD, ASA score and reoperation. H-AKI and postoperative AKI associated with decreased short- and long-term survival in a dose-dependent manner. However, survival following AKI in hospitalized patients improved significantly through the study period. Postoperative AKI was associated with both development of incident CKD and progression of preexisting CKD. The duration of AKI did not associate with long-term outcomes, whereas lack of recovery of AKI defined as a return of SCr to < 1.5 x baseline within 30-days was associated with worse one-year survival and not reaching recovery defined as reduction in SCr to < 1.25 x baseline within 30-days associated with increased risk of incident CKD and progression of preexisting CKD. One-third of all postoperative AKI patients had mild stage 1 AKI which associated with both development and progression of preexisting CKD, but not with one-year survival. It should be stressed that given the retrospective nature of the studies, causal relationships cannot be demonstrated.

5.1 Incidence of AKI in hospitalized patients

The mean incidence of H-AKI was 25.8 per 1000 admissions/year during a 20-year study period in Paper I. This can be compared to the incidence of 1.6% reported for hospitalized patients in 2017 by Cheng *et al.*, utilizing the SCr component of the KDIGO criteria (Cheng, Wu, Liu, & Mao, 2017), and another study from 2010 that demonstrated an incidence of 3.2% in a hospital cohort where AKI was defined according to the SCr component of the AKIN criteria (Fang et al., 2010). A much higher incidence of AKI has been reported in a number of studies in hospitalized patients that detected AKI using a change in SCr (H. E. Wang et al., 2012; Zeng, Mcmahon, Brunelli, Bates, & Waikar, 2014). Wang *et al*., for instance, reported an incidence of H-AKI of 23%, potentially explained by the exclusion of patients with only one or no SCr measurement from the incidence denominator. Another factor that can partly

explain the variation between studies are differences between patient cohort characteristics. Furthermore, in Paper I, the small absolute increase in SCr of 26.5 µmol/L within 48 hours was not included in the definition of AKI in order to minimize the risk of overdiagnosing AKI due to a potentially long period from baseline SCr assessment, thereby likely reducing the overall incidence. As was demonstrated in Paper IV, patients with mild stage 1 AKI constitute around one-third of all postoperative AKI patients. In addition to the effect it has on estimation of the incidence of AKI, it likely affected the mean comorbidity burden and particularly may have led to underreporting of the rate of underlying CKD. Moreover, it may also have influenced the association of AKI with short-term survival.

Over the 20-year study period in Paper I, the incidence of AKI increased significantly from 18.6 to 29.9 per 1000 admissions/year. Many other studies have demonstrated increasing incidence of AKI. However, most of these studies have used diagnostic and billing codes to capture AKI cases (Waikar, 2006; Xue, 2006). Very limited data exist on time trends in the incidence of AKI based on change in SCr and the few studies that have been reported have shown conflicting results. One study on patients with acute myocardial infarction that used the AKIN criteria demonstrated a decrease in the incidence of AKI in the time period 2000-2008 (Amin, 2012). Another study from the UK, showed a 15% increase in AKI cases from 2001 to 2014, defined using the KDIGO criteria (Sawhney & Fraser, 2017). Interestingly, the investigators demonstrated that the increase in AKI incidence in the same cohort reached almost 300% when diagnostic ICD-10 codes were used to detect AKI.

A number of factors can affect the evaluation of the incidence of AKI, particularly in studies relying in diagnostic codes to detect cases. These factors can affect both the numerator and denominator of the incidence calculation. Factors that influence the detection of AKI affect the numerator, this is where the evolution in diagnostic criteria (RIFLE, AKIN, KDIGO) is an important factor. Recent changes in the diagnostic criteria, increased awareness of AKI and improved coding practices may have influenced the detection rate of AKI and affected coding. Furthermore, at institutions where coding is linked to billing there is likely a greater incentive to document a diagnosis of AKI and this can affect the coding as well.

The use of change in SCr to detect AKI eliminates all of these confounding factors, but is hampered by the availability and definition of baseline SCr (Siew et al., 2012). Additionally, studies have shown that the frequency of SCr measurements increases a patient's probability to fulfill the diagnostic criteria

for AKI, i.e. the intensity of sampling can establish ascertainment bias due to the fact that patients at risk are more likely to be more frequently monitored (Sawhney et al., 2016). Lin *et al.* demonstrated through simulation that fluctuations in SCr because of sample variation could be sufficient to cause a false-positive AKI diagnosis (Lin et al., 2015). This problem likely applies to Paper I given the definition of the baseline SCr as the lowest SCr within 6 months of admission. This could possibly increase the incidence of AKI to some extent although it is mitigated by avoiding the absolute increase in SCr of 26.5 µmol/L to define AKI. This phenomenon could also apply to Paper IV, where the focus was on a small change in SCr of 26.5 µmol/L that might have caused an overestimation of mild stage 1 AKI. The impact of fluctuations in SCr on the results of Paper II and Paper III was probably less.

There are a number of factors that influence the denominator of the AKI incidence estimation. The most important one is variability of the study cohorts. Many studies have focused on the incidence of AKI in a demarcated subgroup of patients, for instance patients admitted to ICU, those undergoing a specific type of surgery or patients with a specific cause of AKI, e.g. sepsis (Hoste et al., 2015; Schiffl & Fischer, 2008). Furthermore, tertiary care hospitals and referral centers have different patient mix and case load, therefore limiting the precision of extrapolation of data to a population cared for in a community hospital. When the assessment of AKI incidence is based on change in SCr, the handling of patients without baseline and follow-up SCr can affect the estimation, i.e. whether they are included in the denominator or not.

In Paper I, the incidence of H-AKI was studied in an acute care hospital serving the general population and should therefore be easily generalizable. In the study, AKI was defined using SCr measurements obtained over a long period of time. This likely gives a more accurate baseline determination but also increases the number of patients included in the study. However, a considerable limitation is the lack of available baseline SCr measurements in all papers and postoperative SCr measurements in Papers II-IV, that form the basis for the criteria used to detect AKI. In order to circumvent this problem the studies would have to be done in a prospective manner.

5.2 AKI following abdominal surgery

In Paper II, the incidence of AKI following abdominal surgery was 67.7 per 1000 procedures. This is likely an overestimation of the incidence of AKI, as the denominator included only patients with available pre- and postoperative SCr. Individuals without available SCr had shorter length of stay, shorter

operative time, lower ASA scores and lower 30-day mortality and were therefore unlikely to have developed AKI. However, some of these patients may have developed subclinical AKI. If all patients were included in the denominator, the incidence was 22.9 per 1000 surgeries, which is probably an underestimation of the true incidence.

It is important to study AKI following abdominal surgery, as it likely has a different pathophysiology from other forms of postoperative AKI and, therefore, may also have different risk factors. Furthermore, abdominal surgeries are very common procedures that yield many AKI episodes, making information on risk factors and factors of prognostic value very important. Limited number of studies have examined AKI following all types of abdominal surgery, and the few studies that have been published have focused on a small subgroup of surgeries. One large database study revealed a low incidence of AKI of 1.1% following 15 different types of commonly performed abdominal surgical procedures (Kim et al., 2014). This low incidence rate can largely be explained by the rather narrow definition of AKI as postoperative SCr above 177 µmol/L (2 mg/dL). In 2017, O´Connor *et al.* (O'Connor et al., 2017) studied AKI defined by the KDIGO criteria among all major non-cardiac surgeries. They reported an overall incidence rate of 6.8%, which is the same rate as was observed following abdominal surgeries in Paper II.

In Paper II, there was marked variability in the incidence of AKI between types of abdominal surgery. The highest incidence of AKI was noted following explorative laparotomy and esophageal, pancreatic and open intestinal surgery. This is somewhat comparable to the study of O´Connor *et al.* where AKI occurred most often following upper gastrointestinal, hepatobiliary and colorectal surgery (O'Connor et al., 2017). All these surgical procedures are open abdominal surgeries so that renal blood flow should not be compromised due to increased intra-abdominal pressure during surgery, but perhaps afterwards. However, a possible reason for the high AKI rate is that these are all major surgeries causing substantial inflammatory response. In addition, these surgeries are often performed in an emergency setting which can also increase the detection rate of AKI as patients undergoing high-risk surgeries have more frequent SCr measurements carried out.

Late complications of abdominal surgery, such as abscess formation and anastomotic leaks, often do not present until at least 5 - 7 days postoperatively. Patients with late complications who do not undergo reoperation therefore may develop AKI with SCr peaking later than 7 days following surgery, possibly causing an underestimation of the true incidence of AKI.

5.3 Risk factors for AKI

The independent preoperatively assessable risk factors for developing AKI following abdominal surgery were advanced age, male sex, preoperative CKD, ASA score and whether the surgery was a reoperation. Age, male sex and underlying CKD have all been reported previously and are known risk factors for developing AKI in general as well as postoperative AKI (Goren & Matot, 2015). The ASA score is widely used by perioperative physicians as part of a preoperative risk stratification in every day clinical practice (Hackett, Oliveira, Jain, & Kim, 2015). The association between the ASA score and risk of developing AKI underlines the usefulness of the ASA score for risk assessment prior to surgery. Importantly, information on age, sex, CKD status, ASA score and whether the surgery is a reoperation is an easily obtained information in the preoperative setting that can guide the perioperative physician in communicating with surgeons, the patient and his family the risk of AKI following surgery. The ASA score is a rough estimate of a patient's physiological reserve based on a subjective evaluation of the patient's comorbidity burden (Saklad, 1941). Paper II demonstrated that the ASA score is a good predictor of the risk of postoperative AKI, which indicates that the risk of AKI correlates with decreased physiological reserve. The independent predictors of AKI from Paper II could be used to develop a risk index that might be valuable in predicting the development of postoperative AKI following abdominal surgery. However, it would have to be internally and externally validated before deemed fit for clinical use.

Although risk factors that can be assessed preoperatively are important for preoperative risk stratification, there are also intraoperative and postoperative factors that are associated with postoperative AKI. Several factors have been shown to be important such as duration of surgery, intraoperative hypotension and bleeding (Srisawat et al., 2018; Walsh et al., 2013). Furthermore, perioperative fluid therapy has been demonstrated to affect the incidence of postoperative AKI after abdominal surgery (Myles et al., 2018).

5.4 Development and progression of CKD following AKI

Postoperative AKI associated with both incident CKD and progression of preexisting CKD in the 5 years following surgery. The association was present for all stages of AKI, but increased with the severity as the development or progression of CKD occurred in 56%, 58% and 68% of stage 1, 2 and 3 AKI, respectively. The rate of CKD development and progression in the 5 years following surgery observed in our study is quite high. The cohort that sustained

AKI had a high comorbidity burden and had a median age of 74 years at the time of AKI. These patients were therefore at risk for both developing CKD and to experience progression of preexisting CKD. A number of studies have demonstrated an association between AKI and development of CKD, but few have examined association with progression of CKD (Amdur, Chawla, Amodeo, Kimmel, & Palant, 2009; Coca et al., 2012; Ishani et al., 2011). Amdur *et al.* reported that 13% of patients with AKI and 20% of patients with acute tubular necrosis developed stage 4 CKD. A large systematic review by Coca *et al.* found the rate of incident CKD to be 25.8 per 100 person-years following AKI, but a lot of heterogeneity was present between studies.

Progression of preexisting CKD was defined as an increase of at least one CKD stage, maintained for a minimum of 90 days, in the 5 years following surgery. The definition could potentially skew the assessment of progression of CKD as the absolute change in eGFR needed for a patient to advance to the next CKD stage varied between patients according to their baseline eGFR. However, since this was a time to event analysis, the patients should be randomly distributed with respect to their baseline eGFR (within CKD stage). The progression to a higher stage is then based on chance of progressing from a baseline within a certain time. It is clear that there are some limitations to this arbitrary definition of progression, but the requirements of maintaining the same CKD stage for 90 days, as in Paper III and IV, do make the definition much more robust with respect to fluctuations. KDIGO suggest defining progression of CKD as a drop in eGFR category accompanied by a 25% or greater drop in eGFR (KDIGO & CKD, 2013). There is, however, at the present time no consensus on the definition of CKD progression and this limits comparison between studies (Decker & Kendrick, 2014). Future work on consensus agreement on the definition of CKD progression is very important for the comparison of studies on CKD.

The development of incident CKD in a given patient was defined as a new decrease in eGFR to < 60 mL/min/1.73m^2, sustained for a minimum of 90 days. Unfortunately, there was no information on proteinuria or structural abnormalities of the kidneys. A small case-control study from 2014 found that patients with AKI are more likely to have proteinuria following the AKI episode, and that proteinuria following AKI associated with progression of CKD (Horne et al., 2014). In Paper III-IV, patients with preoperative eGFR above 60 mL/min/1.73m^2 were considered to have normal kidney function. However, this is of course an imprecise estimate and, hence, it is possible that patients who developed incident CKD following AKI had less physiological and/or renal

functional reserve than patients who maintained their kidney function following an AKI episode (Göcze, Wiesner, Schlitt, & Bergler, 2017).

Mild stage 1 AKI was also associated with incident CKD and progression of preexisting CKD. Interestingly, the majority of patients who developed postoperative mild stage 1 AKI had underlying CKD, or 56%. They also had higher comorbidity burden in general than patients with more severe AKI. Previous reports on the association of mild stage 1 AKI and incident CKD or progression of preexisting CKD are very limited. A large study of Medicaid beneficiaries in the United States with myocardial infarction showed an association of a small absolute SCr increase of as low as 9 μmol/L during hospitalization with the development of ESRD (Newsome et al., 2008). However, the timeline for SCr changes was not well characterized and the more subtle kidney-specific outcomes, such as the development of incident CKD or progression of preexisting CKD, were not studied. Another study demonstrated that small changes in SCr of 1.01-1.24 x baseline within seven days of cardiac surgery associated with the development of incident and progressive CKD (Ishani et al., 2011). Before Paper IV, no study had examined the association between mild stage 1 AKI, as defined by the established KDIGO criteria, and long-term development of incident CKD and progression of preexisting CKD.

It is unknown what the small absolute increments in SCr consistent with mild stage 1 AKI truly reflect. It is possible that, despite being very small, the elevation of SCr reflects true injury to the kidney that triggers a cascade of inflammation, maladaptive repair and fibrosis and subsequent development of incident CKD or progression of preexisting CKD. Interestingly, the group of patients who suffered mild stage 1 AKI had much greater comorbidity burden and, in particular higher prevalence of CKD than patients with more severe AKI. It is therefore possible that the surgical insult merely stresses the kidney and uncovers reduced renal functional reserve. In other words, the surgery leads to detection of underlying kidney disease that would otherwise have been clinically silent until years later if it were to progress. If this notion holds true, a surgical operation could be viewed as a functional “stress test” for the kidneys. Moreover, mild stage 1 AKI seems to have long-term clinical value as demonstrated in Paper IV.

The results therefore emphasize the importance of long-term care for patients with mild stage 1 AKI. Patients who develop mild stage 1 AKI should be seen by a general practitioner, internist or a nephrologist shortly after discharge for risk assessment, overview of medications and management of

risk factors such as blood pressure, proteinuria and comorbid diseases, aiming to prevent or delay the development of CKD or progression of preexisting CKD.

5.5 Survival following AKI

H-AKI and postoperative AKI were associated with decreased short-term and long-term survival, with an inverse relationship between the severity of AKI and survival (Papers I-III). Furthermore, there was a significant improvement in survival of H-AKI throughout the 20-year study period in Paper I. Many studies have demonstrated an association between AKI and decreased short-term survival (Ali et al., 2007; Waikar, 2006). Since a consensus on the definition of AKI was reached, there has been an increased focus on the association of the disorder with long-term survival. However, large studies on long-term survival following H-AKI defined by the KDIGO criteria are limited (Coca et al., 2009). A very large study on US veterans reported in 2010, that defined AKI using the AKIN criteria, showed an increased risk of death in patients who survived the first 90-days after AKI and that the risk increased with rising severity of AKI (Lafrance & Miller, 2010). Several previous reports have demonstrated the association between the severity of AKI and decreased survival (Sawhney et al., 2017; Wonnacott et al., 2014). This underscores the appropriateness of the of the current criteria for definition and classification of AKI.

In addition to Paper I, several studies have suggested that the survival of AKI patients has been improving over the last two decades (Kolhe et al., 2016; Waikar, 2006). However, most of these studies have been based on administrative diagnostic codes that can be affected by factors such as increase in the awareness of AKI, leading to increased detection of milder AKI episodes that likely have more favorable prognosis and, therefore, may improve the survival estimates (Sawhney & Fraser, 2017). A paper by Amin *et al.*, that reported a study of AKI following myocardial infarction in the time period 2000-2008, using the AKIN criteria, demonstrated improved short-term patient survival (Amin, 2012). Interestingly, unlike in many other studies, a decrease in the incidence of AKI was also reported. The authors suggested that this might be related to increased awareness of AKI as a potential complication of myocardial infarction and coronary angiography.

There are several factors that can explain improving survival of AKI in cohort of general hospital patients. Over the 20-year period that was examined in Paper I, there were changes in many aspects of patient care. Surgery generally became less invasive and the more common use of laparoscopic and endoscopic interventions resulted in fewer major open surgeries (Fecso,

Szasz, Kerezov, & Grantcharov, 2017). In addition, the Surviving Sepsis Campaign was launched in 2004 with recommendations for more rapid and intensive antimicrobial therapy and fluid resuscitation for sepsis-induced hypoperfusion and septic shock, leading to better outcomes of these patients (Levy et al., 2010; Rhodes et al., 2017). During these two decades, there has been increased awareness of AKI that likely has led to better general care of these patients.

In our study, even postoperative mild stage 1 AKI was associated with decreased short-term survival. However, there was no association between mild stage 1 AKI and long-term survival after exclusion of in-hospital deaths within 30 days of surgery. Few studies have examined long-term survival following mild elevations in SCr. A study on patients undergoing cardiothoracic surgery showed that compared to a decrease in SCr of 9-27 μmol/L within 48 hours postoperatively, a stable SCr or increase of 0-88 μmol/L associated with a nearly threefold increase in 30 day mortality (Lassnigg, 2004). Similar to the findings in Paper IV, the investigators found no association with long-term survival. This study is not quite comparable to Paper IV, as the change in SCr within 48 hours was estimated after admission to an ICU after surgery and may therefore have classified some patients that reached a SCr of 1.5 x baseline within 7 days as a small increase. Furthermore, the baseline SCr in that study was probably overestimated as a large group of patients recovered with a return of the SCr to well below the estimated baseline after surgery. Two other publications have reported that mild elevations in SCr in patients with myocardial infarction associate with decreased long-term survival after excluding in-hospital mortality (Mody et al., 2018; Newsome et al., 2008). One of the studies defined mild AKI as an increase in SCr of only 9 μmol/L during admission. In that study, the baseline SCr was determined on the day of admission for myocardial infarction and, thus, was likely overestimated. The other study showed an association between an increase in SCr of 26.5-44 μmol/L, calculated as the difference between admission SCr and peak SCr, with decreased long-term survival. The authors used criteria to diagnose and stage AKI based on absolute changes in SCr from baseline that have not been validated. Furthermore, it is likely that the baseline SCr in that study was also overestimated as it was measured when the patients presented with acute coronary syndrome. This would lead to an underestimation of the rise in SCr and subsequent misclassification of the AKI episode. This is a possible explanation for the observed association with long-term survival. Moreover, the cohort was different from the surgical cohort in Paper IV.

5.6 Renal recovery

Renal recovery following AKI has not been well studied in the past, but was evaluated in Paper I and was the main focus of Paper III. In Paper I, one-third of AKI patients did not reach renal recovery during follow-up and the proportion of patients who recovered decreased with rising severity of AKI. Renal recovery in Paper I was defined as a return of SCr to within 1.5 x baseline using the average of the last three SCr measurements during follow-up. This is somewhat comparable to the non-recovery rate of 27% among patients with H-AKI reported by Ali *et al.* (Ali et al., 2007). A major limitation of this approach in determining renal recovery is that there is no fixed time point when recovery should be assessed. Moreover, the aforementioned definition of recovery had not been shown to have clinical relevance or prognostic value when the analyses for Paper III were performed. Prior studies have used many different definitions of renal recovery assessed at different time points, but before Paper III, no comparison of definitions with regards to long-term outcomes had been performed.

Several different definitions of renal recovery following AKI were subsequently examined in Paper III. The aim was to find a definition for renal recovery that would differentiate patients at increased risk of long-term mortality and/or the development of incident CKD or progression of preexisting CKD. The definition that had the strongest association with worse one-year survival was lack of return of SCr to below 1.5 x baseline within 30 days. In addition, lack of renal recovery defined as reduction in SCr to below 1.25 x baseline was associated with development of incident CKD and progression of preexisting CKD.

Studies on renal outcomes following AKI have been very heterogenous and, therefore, difficult to compare. Sawhney e*t al.* published a systematic review in 2015 that summarized the existing evidence from studies of AKI, focusing on outcomes with special regard to pre-AKI kidney function, post-AKI renal recovery and long-term outcomes (Sawhney et al., 2015). The main finding was that only three studies on mortality and two on CKD as outcomes of AKI stratified their analysis by pre-AKI and post-AKI kidney function. This means that other studies on outcomes following AKI did not adjust their analyses by either underlying kidney function or renal recovery, or both. Moreover, the few studies that stratified their analyses by pre-AKI and post-AKI kidney function all used different definitions of AKI, CKD, or renal recovery, making it difficult to compare the results. This highlights the importance of reaching a consensus on the definition of renal recovery to facilitate clinical

research on long-term outcomes of AKI. In 2004, ADQI suggested defining renal recovery as a return of SCr to below 1.5 x baseline, but, this definition has however not been validated as a predictor with prognostic value (Bellomo et al., 2004). Furthermore, there was no recommendation regarding the appropriate timing of the evaluation of recovery.

Before a consensus on the definition of renal recovery will be reached, certain factors should be considered. The definition of recovery should be relative to the patient's pre-AKI baseline kidney function rather than relative to the worst kidney function during the AKI episode or a predefined benchmark (Kellum, 2014). This would make the definition applicable to all patients irrespective of their pre-AKI kidney function. In addition, a critical dimension in the assessment of recovery is the timing of assessment. Recovery should be evaluated when recovery has been sustained long enough so it can be considered to be true and at the same time not require an unreasonably long timeframe for the assessment. A large study that was just published demonstrated that the time period from the peak SCr to recovery, defined as return of SCr to < 1.2 x baseline, is an important prognostic factor for the development of CKD and progression of preexisting CKD (Siew et al., 2019).

Based on the results of Paper III, it is proposed that the definition of renal recovery following postoperative AKI should be reduction of SCr to < 1.25 x baseline within 30 days, as this definition was found to be valuable for prediction of long-term outcomes. Hence, renal recovery could be assessed during outpatient follow-up with concurrent review of medications and risk factors, as well as evaluation of the need for further follow-up.

5.7 Duration of AKI and outcomes

The duration of AKI was examined in Paper III, included whether it associated with one-year survival, development of incident CKD or progression of preexisting CKD in the five years following AKI. There was no association between the duration of AKI and long-term outcomes, as long as the patients reached renal recovery, defined as return of SCr to < 1.5 x baseline within 30 days. Several reports have demonstrated an association between the duration of AKI and outcomes. One study of almost 5,000 patients undergoing cardiac surgery, where 39% of patients developed AKI based on the AKIN criteria, showed an association between the duration of AKI and both short-term and long-term mortality (Brown & Jeremiah R., 2010). In that study, there was considerable overlap of 95% confidence intervals of the adjusted hazard ratios between the groups with AKI duration of 1-2 days and 3-6 days and, therefore,

there was no significant difference between these groups. However, a duration of 7 days or longer, and also what the investigators termed as persistent AKI (defined as SCr > 26.5 μmol/L above baseline at hospital discharge), associated with worse outcomes. Compared with Paper III, this observation seems to be merely due to difference in terminology as it is similar to a finding in Paper III that would be classified as absence of renal recovery rather than long duration of AKI. Furthermore, all patients in the aformentioned study were included in the analysis of renal recovery, while in Paper III, in-hospital deaths within 30 days were excluded from the analysis of long-term survival. Thus, the association observed between duration of AKI and survival might be explained by short-term mortality.

Another large study by Coca *et al.* from 2011 demonstrated an association between the duration of AKI and long-term mortality in a non-cardiac surgical cohort of diabetic veterans (Coca et al., 2011). As opposed to the results of Paper III, when stratified by recovery status and three different AKI durations, this association remained significant both in those who experienced no recovery and those who recovered. Moreover, when patients were stratified by duration of AKI, there was minimal additional prognostic information offered by the magnitude of the SCr rise. The discrepancies in the results of the study by Coca *et al.* and Paper III are hard to pinpoint, but there were several methodological differences. In the study by Coca *et al.*, the cohort was larger and consisted predominantly of males with preoperative diabetes. Moreover, the studies used different definitions for estimating baseline SCr, for detecting AKI and for determining renal recovery.

5.8 Strengths and limitations

The strengths of the four papers that form the backbone of this thesis are several, with each of the papers making an important contribution to the rapidly growing literature of AKI. A major strength of all papers is the access to comprehensive data on the patients included in the studies. All SCr values measured at LUH from 1993 to 2016 (Papers I-IV) and all SCr measurements performed in the Iceland from 2008 to 2016 were available (Papers III-IV). This allowed a relatively accurate estimation of baseline SCr and baseline CKD status. Rather than relying on diagnostic codes, AKI was detected based on elevation in SCr from a measured baseline SCr, utilizing the SCr component of the currently accepted definition of AKI (KDIGO), with the exception that mild stage 1 AKI was not included in Paper I. Thus, no AKI episodes were identified based on diagnostic codes or SCr criteria that included estimated baseline SCr, thereby increasing the specificity of AKI diagnosis. Moreover, this

approach led to a precise estimation of the AKI duration, renal recovery, development of incident CKD and progression of preexisting CKD following AKI. The follow-up data on kidney function in Papers III-IV was nearly as complete as possible for a retrospective observational study. Additionally, mortality data was complete for all patients in the four papers.

A strength of Paper I was the large cohort comprising the majority of an entire nation during a long study period of 20 years. The major strength of Paper II was the assessment of AKI defined by the current KDIGO SCr criteria. Again, the occurrence of AKI could be studied in the great majority of patients undergoing abdominal surgery in a whole nation. Hence, the study adds to the previously limited literature on AKI following abdominal surgery, information on risk factors and outcome predictors that can aid in the risk stratification of patients undergoing abdominal surgery in the future.

A study design that allows precise timing of the insult causing AKI, e.g. surgery, is very important when studying various aspects of the disorder, such as the duration of AKI, definitions of renal recovery or when evaluating rapid, small changes in SCr. It makes the definition of AKI, duration of AKI and recovery of AKI more accurate and, therefore, can be viewed as a major strength of Papers II, III and IV. Furthermore, the availability of SCr measurements is a prerequisite for accurate estimation of pre-AKI and post-AKI kidney function.

There are several noteworthy limitations of the studies in this thesis. There was no available data on urine output, which is included in the KDIGO criteria for AKI and might have altered our results. However, most previous epidemiologic studies on AKI lack information on urine output (Ali et al., 2007; Wonnacott et al., 2014). It has previously been reported that AKI episodes detected solely by change in urine output are generally milder in nature (Kellum et al., 2015). Moreover, a study published in 2008 demonstrated that the SCr measurement determined the maximum stage of AKI, identified for 95% of patients with AKI (Lopes et al., 2008). Thus, while the lack of information on urine output is a considerable limitation to our study, it is unlikely to have a substantial impact on the principal findings. Another potential limitation is that all SCr measurements were obtained as a part of daily clinical practice which adds to an ascertainment bias towards AKI and its severity. In Paper I, the mild increase in SCr of 26.5 μmol/L within 48 hours was not included in the definition of AKI and, therefore, is likely to have resulted in underestimation of the true incidence of AKI. A relatively small sample size would also be considered a limitation of all four studies. Though large cohorts were examined in all the

studies, the group with AKI was not very large, especially when divided into groups for sub-analyses.

All four studies were observational cohort studies carried out retrospectively. Thus, there is always a possibility of residual confounding due to missing data of known and unknown variables that can alter the results of observational studies. While the availability of SCr measurements used to define AKI was excellent, some patients were without available baseline SCr measurement and, therefore, it was not possible to accurately detect AKI in those patients. The most important missing data in this thesis are SCr measurements that potentially may have been missed and diagnostic codes that were not properly recorded, leading to underestimation of comorbidities. This bias was minimized by carrying out multivariable analyses in the assessment of risk factors for AKI and its association with outcomes, together with careful propensity score matching. Finally, the retrospective design precludes drawing causal inference from the association pattern.

6 Conclusions

AKI is a common complication among postoperative patients, as well as in hospitalized patients in general, in whom the incidence of AKI is rising. A number of preoperatively obtainable risk factors can help predict the risk of AKI following abdominal surgery. This thesis demonstrates that both hospital-acquired and postoperative AKI are associated with decreased short-term and long-term survival, with a negative correlation with the severity of AKI. Furthermore, postoperative AKI associates with both incident CKD and progression of preexisting CKD within five-years of surgery. Renal recovery following AKI is far from certain and lack of recovery is associated with both decreased one-year survival and the development of CKD and progression of preexisting CKD. Currently, there is no consensus on how to define renal recovery following AKI, which is a major limiting factor regarding the comparison of epidemiologic studies on outcomes following AKI. This thesis indicates that lack of recovery of kidney function defined as decrease in SCr to below 1.25 x baseline within 30 days should be the reference for renal recovery. The duration of AKI was not associated with worse long-term outcomes as long as the patients achieved renal recovery defined as return of SCr to < 1.5 x baseline within 30 days. It is important to reach a consensus on how to evaluate progression of CKD in order to facilitate comparison of studies.

Patients who only fulfill the KDIGO criteria for AKI due to an absolute increase in SCr of 26.5 µmol/L within 48 hours, considered mild stage 1 AKI in the current studies, constitute one-third of all postoperative AKI patients. Interestingly, these patients have higher comorbidity burden than other AKI patients, particularly underlying CKD. Mild stage 1 AKI associates with incident CKD, progression of preexisting CKD and short-term mortality, but not with long-term mortality. It is likely that an episode of mild stage 1 AKI represents a different clinical scenario than other AKI episodes. Possibly it is merely an indicator of underlying early CKD with reduced renal functional reserve rather than a true injury to the kidney. These are only speculations that require further study. However, the association of mild stage 1 AKI with poor outcomes supports the inclusion of small absolute increase in SCr in the definition of AKI.

Currently, the treatment options for AKI are limited to supportive therapy, RRT and general measures to avoid further damage. This makes information on risk factors for AKI and factors associated with adverse outcomes of AKI patients especially important. Among these are independent risk factors for the

development of postoperative AKI following abdominal surgery. The preoperative access to information on the patient's age, sex, CKD status, ASA score and whether the surgery is a reoperation provides the treating physician with a tool for risk stratification of the patient and prepare the patient and himself accordingly. After AKI has developed, the physician managing the patient has several measures to facilitate assessment of the prognosis. Staging the severity of AKI accoring to the KDIGO classification system is useful as the severity has a negative correlation with survival. Monitoring of kidney function after an AKI episode to determine whether the patient achieves renal recovery defined as reduction in SCr to < 1.25 x baseline within 30 days can be used to assess long-term prognosis and also for evaluating the need for continued monitoring of kidney function.

Future studies should focus on elucidating the complex relationship between AKI and CKD. The interaction between changes in SCr and renal functional reserve and long-term renal outcomes requires further study. Moreover, the scientific community needs to reach a consensus on the definition of renal recovery. Subsequently, the focus of research can be placed on uncovering factors that promote renal recovery and improve long-term outcomes of AKI. A discovery of novel biomarkers or other measures to detect AKI at an earlier stage with concurrent introduction of preventive and supportive measures could possibly improve patient outcomes but this needs to be studied further.

Finally, the findings of this thesis highlight the importance of meticulous follow-up of patients with AKI, both immediately after the episode and in some cases for the remainder of their life. Additional studies on how AKI patients should be monitored and how they should be stratified according to risk of adverse outcomes are desperately needed to promote improvement in the care of these patients.

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Original publications

Paper I

Paper II

Paper III

Paper IV