European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Prospective study of risk factors for community-acquired acute kidney injury

Telma H Ragnarsdotttir [a,b], Margret Kristjansdottir [b], Gisli Gislason [b], Vicente Sanchez-Brunete [b], Margret O Tomasdottir [a,c], Olafur H Samuelsson [d], Runolfur Palsson [a,e], Olafur S Indridason [b,e,*]

[a] Faculty of Medicine, School of Health Sciences, University of Iceland, Iceland
[b] Internal Medicine Services, Landspitali University Hospital, Reykjavik, Iceland
[c] Primary Health Care of the Capital Area, Reykjavik, Iceland
[d] Section of Geriatrics, Landspitali University Hospital, Reykjavik, Iceland
[e] Section of Nephrology, Landspitali University Hospital, Reykjavik, Iceland

ARTICLE INFO

Keywords:
Acute kidney injury
Risk factors
Volume depletion
NSAID
Over-the-counter NSAID
ACE inhibitor
ARB
Diuretics

ABSTRACT

Background and hypothesis: Causes and risk factors for community-acquired acute kidney injury (CA-AKI) have not been thoroughly studied. The aim of this study was to examine the risk factors for CA-AKI.

Methods: In this prospective study, we examined serum creatinine from all individuals visiting a university hospital's emergency department (ED) over an 11-month period for the presence of AKI defined according to the KDIGO criteria. Patients with AKI were invited to participate. Randomly selected controls (1:2) were paired according to age, sex, and date of admission. Participants answered questions about their medical history and medication use, including over-the-counter (OTC) drugs. Conditional logistic regression was used to identify factors associated with AKI.

Results: Of 602 AKI cases identified, 512 participated in the study. AKI cases were significantly more likely than controls to have used nonsteroidal anti-inflammatory drugs (NSAIDs) (26.0 % vs 18.0 %, $p = 0{,}001$) in the week preceding the ED visit, particularly OTC NSAIDs (23.3 % vs 15.9 %, $p < 0.001$). AKI was associated with a recent history of vomiting (OR 2.52 [95 %CI 1.87–3.39]), diarrhea (1.30 [1.00–1.70]) and urinary retention (1.92 [1.36–2.72]), use of non-selective NSAIDs (1.84, [1.37–2.48]), RAAS blockers (1.63 [1.21–2.19]), and diuretics (1.53 [1.13–2.08]), and a history of diabetes (1.42 [1.04–1.94]), CKD (1.36 [1.01–1.83]) and smoking (1.72 [1.24–2.37]).

Conclusions: Events in the setting of acute illness and medication use, including OTC NSAIDs, may play a greater role in the development of CA-AKI than comorbid conditions. Frequent use of OTC NSAIDs is a concern and should be addressed in view of serious adverse effects.

1. Introduction

Acute kidney injury (AKI) is a common condition, both in hospital and outpatient settings, and is associated with increased mortality, prolonged hospital stay, progressive chronic kidney disease (CKD) and increased community costs[1–4]. Despite improved understanding of the pathophysiology of AKI, the incidence of the disorder seems to be on the rise[5,6].

While AKI has been thoroughly studied in the hospital setting, limited research has been conducted on community-acquired AKI (CA-AKI) encountered in the outpatient setting or the emergency department (ED)[5,7,8]. Clinical guidelines have emphasized risk factors for AKI in both hospital and community settings and recommended screening for AKI in adults with acute illness and the presence of risk factors[9]. Given that the majority of AKI cases originate in the community, recognizing patients who are at risk of developing CA-AKI may enable healthcare staff to implement preventive measures and minimize potential consequences[10]. Up to 30 % of severe AKI has been considered preventable through early recognition and simple management of risk factors[11]. Preventive measures include raising awareness among health care providers, advising high-risk patients to temporarily discontinue medications known to increase the risk of AKI, monitoring kidney function, and

* Corresponding author at: Section of Nephrology, Office 11-H, Landspitali University Hospital, Hringbraut, 101 Reykjavik, Iceland.
E-mail address: olasi@landspitali.is (O.S. Indridason).

https://doi.org/10.1016/j.ejim.2024.09.016
Received 4 May 2024; Received in revised form 18 September 2024; Accepted 21 September 2024

employing e-alerts in primary care for automatic detection of AKI, all of which could potentially result in better outcomes for patients [12–15].

In order to effectively implement measures that prevent or mitigate CA-AKI, a comprehensive understanding of its causes and risk factors is necessary[18,19]. These risk factors are believed to be comparable to those of hospital-acquired AKI[7], in which studies have demonstrated associations with older age, various comorbid conditions, and recent hospitalization[16] as well as variable association with commonly used medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and combination therapy with ACE inhibitors or angiotensin receptor blockers (ARBs) and diuretics together with NSAIDs[17–23]. However, risk factors may differ between hospital-acquired AKI and CA-AKI[24], and limited evidence currently exists regarding risk factors for CA-AKI as only a handful of mostly retrospective studies have been conducted[2,3,5,17,23,25].

The aim of this study was to prospectively examine the main causes and contributing factors for CA-AKI among individuals visiting the ED. We hypothesized that a prospective examination of risk factors may yield a different profile than has been observed in retrospective studies.

2. Methods

2.1. Ethical considerations

The study was approved by the Icelandic National Bioethics Committee (VSN-19-156), and all participants signed an informed consent.

2.2. Study design

This was a prospective case-control study in which all individuals admitted to the ED of Landspitali University Hospital in Reykjavik, Iceland were evaluated for the presence of AKI. The planned one year-study period was from January 1 to December 31, 2020. The study had to be paused repeatedly due to the COVID-19 pandemic and was eventually conducted from January 1 until March 3, 2020, May 19 until September 21, 2020 and February 1 until June 15, 2021, yielding a total study period of 11 months. All patients who had a rise in serum creatinine (SCr) consistent with AKI based on the KDIGO criteria[26] were invited to participate. Randomly selected control cases (1:2), paired according to age (± 5 years), sex, and time of ED admission (± 3 days), were also invited to participate.

2.3. Data collection

The investigators reviewed all SCr measurements in patients undergoing evaluation in the ED, using the laboratory information system of the hospital's electronic medical records. Participants answered a questionnaire about prior health and events leading to the admission, as well as use of medications, including over the counter (OTC) drugs, in the week preceding the ED visit. Other items included in the questionnaire were height, weight, smoking (including electronic cigarettes), alcohol use, illicit drug use, and history of vomiting, diarrhea, or urinary retention (defined as inability to empty the bladder despite feeling an urge to urinate) in the week preceding the ED visit. Finally, the questionnaire included the five items of the FRAIL scale[27]. Information on age, sex, chief complaint on admission and past-medical history was obtained from electronic medical records. Additional information on medication use was retrieved from the Directorate of Health Prescription Medicines Register that contains all drug prescriptions in Iceland. The use of the following medications was documented: loop diuretics, potassium-sparing diuretics, thiazide diuretics, ACE inhibitors, ARBs, NSAIDs, both non-selective NSAIDs and cyclooxygenase-2 inhibitors, beta blockers, calcium-channel blockers, diabetes drugs (all classes), statins and proton pump inhibitors (PPIs).

2.4. Definitions

AKI was defined and staged based on the SCr component of the KDIGO criteria using the initial SCr value obtained in the ED compared with a baseline SCr, determined by examining pre-existing SCr measurements. CKD stage 3 or above was defined and classified according to KDIGO CKD guidelines[28] as eGFR <60 mL/min/1.73 m^2. Baseline kidney function was determined for all participants by one of the authors who is a nephrologist using prior SCr measurements. The baseline kidney function was preferably determined from outpatient SCr measurements in the preceding one year [29]. If such a value was not available, inpatient SCr were used, or measurements performed more than one year before to the ED visit. If no pre-existing SCr measurements were available and AKI was strongly suspected the course of SCr during the hospital stay was closely monitored and AKI was deemed to have occurred if a continued rise and/or subsequent decline in SCr was observed. Information on follow-up after discharge was also sought to facilitate the determination of the baseline SCr in such cases. Same approach was used for individuals in the control group who did not have a pre-existing SCr. Estimated glomerular filtration rate (eGFR) was calculated from SCr using the 2009 CKD-EPI equation[26].

Comorbid conditions were classified using the International Classification of Diseases (ICD)−10 codes. The ICD-10 codes used in this study were diabetes (E08-E13), hypertension (I10-I16), ischemic heart disease (I21-I25), cerebrovascular diseases (I63, I65, I66, I69) and peripheral artery disease (I70).

2.5. Statistical considerations

Based on unpublished data on AKI at Landspitali University Hospital, we estimated that the number of AKI cases would be in the range of 500–700 during a one-year study period. This would provide over 80 % power to detect a 5–8 % difference in the presence of a risk factor.

For the statistical analyses, medications were further categorized into non-selective NSAIDs (including aspirin in doses equal to or higher than 500 mg per day), Cox-2 inhibitors, RAAS blockers (ACE inihibitors, ARBs and aldosterone blockers), diuretics (including loop diuretics and thiazides). Ischemic heart disease, cerebrovascular disease and peripheral artery disease were combined in a single group labeled vascular disease. Drugs used for diabetes were not included in the statistical analysis due to collinearity with diabetes.

Continuous data are presented as mean ±standard deviation (SD) and categorical data as numbers and percent (%). Groups were compared using the $\chi 2$ test for categorical variables and *t*-test for continuous variables. Conditional logistic regression was performed to identify risk factors associated with AKI. In a multivariable logistic regression analysis, three models were examined. Model 1 exclusively incorporated comorbid conditions. Model 2 added prescription medications, while model 3 included OTC medications and symptoms experienced in the 7 days preceding to the ED visit in addition to smoking history. A two-sided p-value <0.05 was considered statistically significant for all analyses.

The statistical analyses were carried out using the statistical software package RStudio 2023.03.1 (Integrated Development for R. Rstudio, PBC, Boston, MA. Available from http://www.rstudio.com).

3. Results

A total of 602 episodes of AKI were identified in 574 persons during the study period, 489 (85 %) of whom participated in the study. The 602 AKI episodes were present in 31,024 ED visits, yielding an incidence of CA-AKI of 19.4 per 1000 ED visits. Of those who did not participate, 33 died before consent was obtained, 23 declined participation (of those, 2 persons declined participation twice and 4 persons declined participation once but accepted at another time in the study), 19 could not be reached, 2 did not reside in Iceland and 8 could not participate for other

reasons. Of patients who participated, 20 (3.5 %) experienced AKI twice and 2 (0.3 %) experienced 3 episodes during the study period, resulting in 512 cases. The control group comprised 1017 persons, of whom 7 (0.6 %) participated twice, yielding 1024 control cases. Thirteen of the AKI cases participated as controls at another time during the study period. In 2 AKI cases no pre-existing SCr measurements were available but the diagnosis was determined based on high SCr (223 and 321 μmol/L) and baseline SCr was derived from stable post-discharge SCr values. Eight individuals in the control group did not have pre-existing SCr but a stable course and for those individuals, admission SCr was used as baseline. The mean (±SD) age of AKI cases and controls was 67.1 ± 16.6 years and 67.2 ± 16.2 years, respectively; 48 % of cases and controls were female. The mean baseline SCr of the AKI cases and controls was 92.6 ± 35.1 μmol/L and 87.6 ± 34.8 μmol/L, respectively. In the AKI group, 298 cases (58 %) were classified as stage 1 AKI, 134 (26 %) as stage 2 and 80 (16 %) as stage 3 (Table 1). Seven cases (1.3 %) who had SCr available from <48 h before admission with a rise of ≥27 mmol/L, were considered to have stage 1 AKI.

3.1. Events leading up to emergency department visit

In the AKI group, the most common chief complaints on ED admission were gastrointestinal symptoms (32.6 %), malaise (25.6 %) and neurological symptoms (12.3 %), while gastrointestinal symptoms (25.1 %), cardiovascular symptoms (25.1 %) and neurological symptoms (13.4 %) were most common in the control group (Table 2). In the 7 days prior to ED visit, 90 cases (18 %) experienced urinary retention, 168 (33 %) vomiting and 192 (38 %) diarrhea, compared to 102 (10 %), 173 (17 %) and 272 (27 %), respectively, in the control group ($p < 0.001$, Table 2).

3.2. Comorbid conditions

The AKI cases were significantly more likely to have a history of diabetes (23.6 % vs. 16.5 %, $p < 0.001$), hypertension (63.9 % vs. 55.0 %, $p < 0.001$) and cerebrovascular disease (11.9 % vs. 8,4 %, $p = 0.027$) than the controls. The AKI group was also more likely to have pre-existing CKD stage 3 or above (eGFR <60 mL/min/1.73 m^2) than the control cases (33.0 % vs. 26.2 %, $p = 0.005$). There was no significant difference between the two groups with respect to history of ischemic heart disease, peripheral artery disease or heart failure (Table 3).

3.3. Medication use

Non-selective NSAID use in the week preceding the ED visit was significantly more common among AKI cases than controls (26.6 % vs. 18.0 %, $p = 0.001$), particularly OTC NSAIDs (23.3 % vs 15.9 %, $p < 0.001$). No significant difference in the use of COX-2 inhibitors between the AKI and control groups was observed (Table 4). Treatment with an aldosterone blocker was significantly more common in AKI cases than controls (9.6 % vs. 5.1 %, $p < 0.001$) and this was also true for a combination of an ACE inhibitor and a thiazide (4.5 % vs. 1.7 %, $p < 0.001$) and an ARB with a thiazide (12.5 % vs. 6.6 %, $p < 0.001$). There was no significant difference in the use of loop diuretics, thiazide diuretics, ACE inhibitors or ARBs (Table 4). Use of medications for diabetes was more common in AKI cases than controls (18.6 % vs. 12.2 %, $p < 0.001$), while there was no significant difference in the use of beta blockers, calcium channel blockers, statins and PPIs (Table 4).

Table 1
Baseline characteristics of the acute kidney injury cases and controls

	AKI cases ($n = 512$)	Controls ($n = 1024$)
Age, years	67.1 ± 16.6	67.2 ± 16.2
Sex, male	265 (52)	530 (52)
Smoking history[a]	103 (20)	137 (13)
BMI[b], kg/m^2	28.0 ± 7.4	28.0 ± 5.8
Baseline SCr, μmol/L	92.6 ± 35.1	87.6 ± 34.8
ED SCr, μmol/L	210 ± 145	88.8 ± 37.7
AKI stage		
1	298 (58)	–
2	134 (26)	–
3	80 (16)	–

Data presented as mean ± standard deviation or number (%).
Abbreviations: AKI, acute kidney injury; BMI, body mass index; SCr, serum creatinine; ED, emergency department.
[a] Data available for 501 cases and 1022 controls.
[b] Data available for 464 cases and 985 controls.

Table 2
Presenting complaint and symptoms preceding the emergency department visit in the acute kidney injury and control groups.

	AKI cases ($n = 512$)	Controls ($n = 1024$)	P-value
Presenting complaint			
Gastrointestinal symptoms	167 (32.6)	257 (25.1)	**0.005**
Malaise	131 (25.6)	128 (12.5)	**<0.001**
Neurological symptoms	63 (12.3)	137 (13.4)	0.62
Fever	43 (8.4)	65 (6.3)	0.18
Respiratory symptoms	36 (7.0)	126 (12.3)	**0.002**
Cardiovascular symptoms	25 (4.9)	257 (25.1)	**<0.001**
Accidental injury	30 (4.9)	94 (9.2)	**0.04**
Urinary symptoms	19 (3.7)	15 (1.5)	**0.008**
Intoxication	17 (3.3)	9 (0.9)	**0.001**
Blood test abnormalities	27 (5.3)	15 (1.5)	**<0.001**
Other	34 (6.6)	96 (9.4)	0.09
Symptoms in the 7 days preceding the visit			
Urinary retention[a]	90 (18.2)	102 (10.0)	**<0.001**
Vomiting[b]	168 (33.5)	173 (17.0)	**<0.001**
Diarrhea[c]	192 (38.3)	272 (26.8)	**<0.001**

Data presented as number (%).
[a] Data available for 493 cases and 1016 controls.
[b] Data available for 501 cases and 1015 controls.
[c] Data available for 501 cases and 1014 controls.

Table 3
Comorbid conditions in the acute kidney injury and the control groups.

	AKI cases ($n = 512$)	Controls ($n = 1024$)	P-value
Diabetes	121 (23.6)	169 (16.5)	**<0.001**
Hypertension	327 (63.9)	563 (55.0)	**<0.001**
Ischaemic heart disease	141 (27.5)	304 (29.7)	0.38
Cerebrovascular disease	61 (11.9)	86 (8.4)	**0.03**
Peripheral artery disease	38 (7.4)	67 (6.5)	0.52
Vascular disease	185 (36.1)	367 (35.8)	0.91
Heart failure	108 (21.1)	205 (20.0)	0.62
Chronic kidney disease	169 (33.0)	268 (26.2)	**0.005**

Data presented as number (%).
Chronic kidney disease stage 3 or above defined as eGFR <60 mL/min/1.73 m^2.

3.4. Risk factors for acute kidney injury

In a multivariable logistic regression analysis including only comorbid conditions (model 1), a history of hypertension (odds ratio [OR] 1.43, 95 % confidence interval [CI], 1.11–1.85), diabetes (OR 1.46, 95 % CI, 1.10–1.94) or CKD (OR 1.40, 95 % CI, 1.07–1.83) were found to be associated with CA-AKI, whereas this was not the case for a history of vascular disease or heart failure (Table 5). When prescription medications were added to the model (model 2), AKI was associated with history of diabetes (OR, 1.52, 95 % CI, 1.14–2.01) or CKD (OR 1.39, 95 % CI, 1.06–1.82), and use of non-selective NSAIDs (OR 2.03, 95 % CI, 1.10–3.74), RAAS blockers (OR 1.35, 95 % CI, 1.04–1.76) and diuretics (OR, 1.41, 95 % CI, 1.06–1.87). When further adding OTC medications, symptoms experienced in the 7 days preceding the ED visit and smoking history (model 3), AKI was associated with a history of diabetes (OR 1.42 95 % CI, 1.04–1.94), CKD (OR 1.36, 95 % CI, 1.01–1.83) and

Table 4
Use of selected medications by the acute kidney injury and control groups in the week preceding the emergency department visit

Medications	AKI cases (n = 512)	Controls (n = 1024)	P-value
Non-steroidal anti-inflammatory drugs (NSAIDs)			
Non-selective NSAIDs and/or COX-2 inhibitors	156 (31.1)	232 (22.8)	**<0.001**
Non-selective NSAIDs only	132 (26.6)	183 (18.0)	**<0.001**
COX-2 inhibitors only	25 (4.9)	53 (5.2)	0.81
Non-selective NSAIDs and/or COX-2 inhibitors by prescription	49 (9.6)	77 (7.5)	0.16
Non-selective NSAIDs over the counter	117 (23.3)	162 (15.9)	**<0.001**
Diuretics and antihypertensive drugs, n (%)			
Loop diuretics	109 (21.3)	181 (17.7)	0.09
Aldosterone blockers	49 (9.6)	52 (5.1)	**<0.001**
Thiazides (without ACE inhibitor/ARB)	16 (3.1)	42 (4.1)	0.34
ACE inhibitors	62 (12.1)	100 (9.8)	0.16
ACE inhibitors with thiazides	23 (4.5)	17 (1.7)	**<0.001**
ARBs	96 (18.8)	184 (18.0)	0.71
ARBs with thiazides	64 (12.5)	68 (6.6)	**<0.001**
Beta blockers	195 (38.1)	365 (35.6)	0.35
Calcium channel blockers	112 (21.9)	205 (20.0)	0.40
Other medications			
Diabetes drugs	95 (18.6)	125 (12.2)	**<0.001**
Statins	144 (28.1)	316 (30.9)	0.27
PPIs	175 (34.2)	368 (35.9)	0.50

Data presented as number (%).
Abbreviations: COX-2, cyclooxygenase-2; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; PPI, proton pump inhibitor.

Table 5
| Risk factors for community-aquired acute kidney injury (logistic regression).

	Model 1[a]	Model 2[b]	Model 3[c]
Comorbid conditions, RR (95 % CI)			
Hypertension	**1.43 (1.11–1.85)**	1.18 (0.89–1.56)	1.08 (0.79–1.46)
Diabetes	**1.46 (1.10–1.94)**	**1.50 (1.12–1.99)**	**1.42 (1.04–1.94)**
Vascular disease	0.89 (0.69–1.15)	0.87 (0.67–1.13)	0.89 (0.67–1.18)
Heart failure	0.94 (0.70–1.26)	0.81 (0.59–1.11)	0.81 (0.58–1.14)
CKD	**1.40 (1.07–1.83)**	**1.36 (1.04–1.77)**	**1.36 (1.01–1.83)**
Smoking			**1.72 (1.24–2.37)**
Medications, RR (95 % CI)			
Non-selective NSAIDs		**2.03 (1.10–3.74)**	**1.84 (1.37–2.48)**
Cox-2 inhibitors		1.04 (0.63–1.72)	1.13 (0.65–1.96)
RAAS blockers		**1.35 (1.04–1.76)**	**1.63 (1.21–2.19)**
Diuretics		**1.43 (1.07–1.89)**	**1.53 (1.13–2.08)**
Symptoms preceding the ED visit, RR (95 % CI)			
Vomiting[d]			**2.52 (1.87–3.39)**
Diarrhea[d]			**1.30 (1.00–1.70)**
Urinary retention[d]			**1.92 (1.36–2.72)**

[a] Logistic regression, including comorbid conditions.
[b] Logistic regression, including comorbid conditions and prescription medications.
[c] Logistic regression, including comorbid conditions, prescription medications, OTC medications and symptoms preceding the ED visit.
[d] Symptoms during the 7 days preceding the ED visit.
Statistically significant findings are indicated using bold text.

smoking (OR 1.72, 95 % CI, 1.24–2.37), the use of non-selective NSAIDs (OR 1.84, 95 % CI, 1.37–2.48), RAAS blockers (OR 1.63, 95 % CI, 1.21–2.19) and diuretics (OR 1.53, 95 % CI, 1.13–2.08) as well as a recent history of vomiting (OR 2.52, 95 % CI, 1.87–3.39), diarrhea (OR 1.30, 95 % CI, 1.00–1.70) and urinary retention (OR 1.92, 95 % CI, 1.36–2.72). Use of COX-2 inhibitors, a history of hypertension, vascular disease, or heart failure was not associated with CA-AKI (Table 5).

4. Discussion

This study shows that vomiting and diarrhea play a major role in the development of CA-AKI, presumably by causing a state of volume depletion. However, even after accounting for volume depletion, the use of NSAIDs, ACE inhibitors or ARBs and/or diuretics also contributed significantly to CA-AKI. While comorbid conditions were important risk factors in limited multivariable models, their significance became less when adjusting for medication use and recent volume depletion events. These findings suggest that increased risk of AKI in patients with diabetes, hypertension or CKD is conferred by the vulnerability of these patients when faced with acute illness, often associated with volume depletion, and possibly in part related to use of medications such as NSAIDs, RAAS blockers and diuretics.

To our knowledge this is the first published prospective, comparative cohort study on CA-AKI. Prospective collection of data is particularly important in AKI research as accurate documentation of pertinent clinical information and diagnosis codes in medical records is often limited, thereby hampering retrospective studies. Nevertheless, our results do partly align with the findings of a recent retrospective study on the epidemiology of CA-AKI that included >5 million US veterans [17]. In that study, an association was identified between CA-AKI and various chronic diseases, including CKD, diabetes, liver disease, heart failure, and cancer [17]. However, when compared to our study the results differ in several ways. Firstly, the retrospective American study identified AKI based on 2 consecutive SCr values and defined the disorder as ≥1.5-fold relative increase in SCr from an index value within 12 months. Only 27 % of CA-AKI cases were detected upon hospital admission, so fluctuations in SCr occurring independently of AKI cannot be excluded since it was not possible to thoroughly examine each case separately. By contrast, our study employed SCr measurements upon arrival in the ED, defining AKI as ≥1.5-fold increase in SCr from a baseline value or an increase of ≥27 μmol/L over 48 hrs, with the baseline kidney function determined for each individual by an experienced nephrologist using all pre-existing SCr measurements. Thus, our study likely missed some cases of CA-AKI that were detected and treated in outpatient clinics. However, the current study did include patients who were excluded in the aforementioned retrospective study if they lacked outpatient SCr values within the past 12 months or had experienced more than 30 inpatient days during the same period. Secondly, the retrospective study differed from our work due to a much larger sample size, providing greater statistical power. Thirdly, the US study predominantly included males (92–93 % of the study sample), whereas our study had an even participation of both sexes. Lastly, the retrospective study lacked information on OTC medication usage and symptoms and events preceding hospital admission. The results of the current study highlight the importance of these factors.

Our results are also consistent with a prospective study published in 2017 [27], showing that a high percentage of CA-AKI patients had used NSAIDs, ACE inhibitors, ARBs or diuretics. This was an observational study that included all ED patients with a GFR <60 mL/min/1.73 m^2 during an 8 week period, and defined CA-AKI according to the KDIGO AKI creatinine based criteria. It must be noted that this study only included patients with a GFR <60 mL/min/1.73 m^2, thus potentially missing milder CA-AKI cases, and that the use of random control individuals in our study may have allowed for better adjustment of

potential confounding variables. Another retrospective study from 2016 compared hospital-acquired AKI and CA-AKI and showed CA-AKI to be associated with co-morbidities such as CHF, CVD, diabetes and CKD, as well as prior use of NSAIDs, ACE inhibitors, ARBs or diuretics. Interestingly, the co-morbidities did not display any associations with hospital-acquired AKI, challenging the conventional belief that hospital-acquired AKI shares similar risk factors with CA-AKI[24].

Use of prescription NSAIDs has been found to associate with AKI in previous studies [17,20,30]. It is noteworthy that a substantial proportion of NSAID use among both cases and controls in our study involved OTC NSAIDs, suggesting that prior studies may have underestimated the effect of NSAID use on AKI risk. In view of potential adverse effects, excessive use of NSAIDs is of concern. Despite recommendations from NICE to temporarily discontinue treatment with ACE inhibitors and ARBs in individuals with diarrhea, vomiting, or sepsis until their clinical condition improves and stabilizes[9], there are no published studies on the discontinuation of medication during an acute intercurrent illness in the community setting[18]. Given the insights gained from our study, which highlights the risks associated with volume depletion events and exposure to ACE inhibitors or ARBs, diuretics, and NSAIDs, it seems prudent to recommend avoidance of OTC NSAIDs during acute illness characterized by gastrointestinal symptoms and fluid loss or inadequate fluid intake.

Even though the sample size in our study is reasonably large, retrospective studies using electronic medical records and administrative databases have the potential to include a far greater number of patients. In the aforementioned retrospective study comprising 5 million US veterans [17], a multitude of risk factors were explored, including factors reflecting disease burden, such as utilization of health services and numerous chronic diseases. Thus, the investigators managed to detect more subtle risk factors, including uncommon conditions, such as HIV and sickle cell anemia. However, volume status and OTC medications use are likely to be missing confounders in retrospective studies. Both the aforementioned American study and our study identified smoking or other tobacco use as a significant risk factor but it is unclear whether this relates to tobacco use itself or socioeconomic or health-related factors associated with smoking.

The main advantage of the current study is its prospective design, which allowed for the direct inquiry of participants regarding recent adverse health events and usage of OTC medications. This information is often not adequately documented or readily available in medical records and therefore not captured by retrospective studies. The identification of AKI by changes in SCr measurements rather than by ICD-10 codes gives this study more weight as AKI tends to be underestimated when defined by ICD-10 codes alone[31,32].

The study also has several limitations. CA-AKI solely managed in an outpatient clinic or office setting was not detected by our study but is likely to have involved less severe cases. The control group was randomly selected from patients without AKI who were present in the ED at the same time as the AKI cases. However, it is important to note that the AKI group may have been more severely ill than the control groups as some AKI patients who were too sick to answer the questionnaire upon admission were followed-up during the hospital stay. In such cases, their next of kin was contacted to obtain information when it was unavailable. This approach might not have been as thorough for the control group. Finally, it should be noted that only SCr measurements were used to identify CA-AKI, according to the KDIGO guidelines, since information on urine output measurements was generally not available. While this shortcoming may have lead to missing some AKI cases it should be acknowledged that accurate monitoring of urine output is difficult to achieve outside of the ICU environment.

In conclusion, our findings provide valuable insights into the causes and risk factors of CA-AKI and address an existing knowledge gap in this area. The results confirm the importance of volume depletion events and the use of RAAS blockers, diuretics and NSAIDs as risk factors for developing CA-AKI. Hence, the awareness of healthcare providers is important for identifying individuals at risk for AKI and implementing preventive measures. In addition, the association between CA-AKI and the use of NSAIDs, particularly OCT NSAIDs, emphasizes the need for increased monitoring and regulation of these commonly available medications.

Acknowledgements

The study was funded in part by grants from the University of Iceland Research Fund and Landspitali University Hospital Science Fund (B-2020-010). Preliminary results were presented in abstract form at the American Society of Nephrology Kidney Week in 2020 and 2021 and the Nordic Society of Nephrology Biennial Congress 2022. We are indebted to the Landspitali University Hospital Emergency Department staff for their assistance in the conduction of the study. We are also grateful to the hospital's Information Technology Department staff for creating a SCr-based alert for acute kidney injury in the electronic medical record system.

References

[1] Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol 2017;13(4):241–57.
[2] Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013;8(9):1482–93.
[3] Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community-acquired acute kidney injury. Nephrology 2014;19(5):282–7.
[4] Leither MD, Murphy DP, Bicknese L, Reule S, dM Vock, Ishani A, et al. The impact of outpatient acute kidney injury on mortality and chronic kidney disease: a retrospective cohort study. Nephrol Dial Transplant 2019;34(3):493–501.
[5] Hsu CY, McCulloch CE, Fan D, Ordoñez JD, Chertow GM. Go AS. Community-based incidence of acute renal failure. Kidney Int 2007;72(2):208–12.
[6] Sawhney S, Fluck N, Fraser SD, Marks A, Prescott GJ, Roderick PJ, et al. KDIGO-based acute kidney injury criteria operate differently in hospitals and the community - findings from a large population cohort. Nephrol Dial Transplant 2016;31(6):922–9.
[7] Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired aki. Clin J Am Soc Nephrol 2014;9(6):1007–14.
[8] Berl T. American Society of Nephrology Renal Research Report. J Am Soc Nephrol 2005;16(7):1886–903.
[9] National Institute for Health and Care Excellence, Available from:. Acute kidney injury: prevention, detection and management:. NICE Guideline; 2019. p. 1–26. https://www.nice.org.uk/guidance/ng148/.
[10] Kashani K, Macedo E, Burdmann EA, Hooi LS, Khullar D, Bagga A, et al. Acute kidney injury risk assessment: differences and similarities between resource-limited and resource-rich countries. Kidney Int Rep 2017;2(4):519–29.
[11] Kanagasundaram NS. Assessment and management of acute kidney injury. Medicine (Baltimore) 2019;47(9):551–61.
[12] Sawhney S. Automated alerts for acute kidney injury warrant caution. BMJ 2015;350:h19.
[13] Porter CJ, Juurlink I, Bisset LH, Bavakunji R, Mehta RL. Devonald MAJ. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. Nephrol Dial Transplant 2014;29(10):1888–93.
[14] Lewington AJP, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int 2013;84(3):457–67.
[15] Holmes J, Rainer T, Geen J, Roberts G, May K, Wilson N, et al. Acute kidney injury in the era of the AKI e-alert. Clin J Am Soc Nephrol 2016;11(12):2123–31.
[16] Holmes J, Geen J, Phillips B, Williams JD, Phillips AO. Community acquired acute kidney injury: findings from a large population cohort. Q J Med 2017;110(11):741–6.
[17] Diamantidis CJ, Zepel L, Smith VA, et al. Epidemiology of community-acquired acute kidney injury among US veterans. Am J Kidney Dis 2023;82(3):1–11.
[18] Whiting P, Morden A, Tomlinson LA, Caskey F, Blakeman T, Tomson C, et al. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. BMJ Open 2017;7(4):1–9.
[19] Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 2005;45(3):531–9.
[20] Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis. Am J Epidemiol 2006;164(9):881–9.
[21] Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with

non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 2013;346(7890):1–11.

[22] Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int 2015;88(2):396–403.

[23] Stucker F, Ponte B, De La Fuente V, Alves C, Rutschmann O, Carballo S, et al. Risk factors for community-acquired acute kidney injury in patients with and without chronic kidney injury and impact of its initial management on prognosis: a prospective observational study. BMC Nephrol 2017;18(1):1–9.

[24] Hsu CN, Te Lee C, Su CH, Wang YCL, Chen HL, Chuang JH, et al. Incidence, outcomes, and risk factors of community-acquired and hospital-acquired acute kidney injury: a retrospective cohort study. Medicine (Baltimore) 2016;95(19):1–9.

[25] Wang Y, Wang J, Su T, Qu Z, Zhao M, Yang L. ISN AKF 0by25 China Consortium. Community-acquired acute kidney injury: a nationwide survey in China. Am J Kidney Dis 2017;69(5):647–57.

[26] Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. Chronic kidney disease epidemiology collaboration. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med 2021;385(19):1737–49.

[27] Yu R, Tong C, Leung G, Woo J. Assessment of the validity and acceptability of the online FRAIL scale in identifying frailty among older people in community settings. Maturitas 2021;145:18–23.

[28] Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving Global Outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2(1):1–138.

[29] Siew ED, Alp Ikizler T, Matheny ME, Shi Y, Schildcrout JS, Danciu I, et al. Estimating baseline kidney function in hospitalized patients with impaired kidney function. Clin J Am Soc Nephrol 2012;7(5):712–9.

[30] Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. Eur J Intern Med 2015;26(4):285–91.

[31] Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J. Performance and limitations of administrative data in the identification of AKI. Clin J Am Soc Nephrol 2014;9(4):682–9.

[32] Esposito P, Cappadona F, Marengo M, Fiorentino M, Fabbrini P, Quercia AD, et al. Recognition patterns of acute kidney injury in hospitalized patients. Clin Kidney J 2024;17(8):1–11.