RESEARCH ARTICLE

The incidence, mortality and renal outcomes of acute kidney injury in patients with suspected infection at the emergency department

Meriem Khairoun[1]*, **Jan Willem Uffen**[2], **Gurbey Ocak**[3], **Romy Koopsen**[2], **Saskia Haitjema**[4], **Jan Jelrik Oosterheert**[2], **Karin Kaasjager**[1,2]

1 Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, Netherlands,
2 Department of Acute Internal Medicine, University Medical Center Utrecht, Utrecht, Netherlands,
3 Department of Internal Medicine and Nephrology, Sint Antonius Hospital, Nieuwegein, Netherlands,
4 Department of Laboratory of Clinical Chemistry/Haematology, University Medical Center Utrecht, Utrecht, Netherlands

* m.khairoun@umcutrecht.nl

Abstract

Background

Acute kidney injury (AKI) is a major health problem associated with considerable mortality and morbidity. Studies on clinical outcomes and mortality of AKI in the emergency department are scarce. The aim of this study is to assess incidence, mortality and renal outcomes after AKI in patients with suspected infection at the emergency department.

Methods

We used data from the SPACE-cohort (SePsis in the ACutely ill patients in the Emergency department), which included consecutive patients that presented to the emergency department of the internal medicine with suspected infection. Hazard ratios (HR) were assessed using Cox regression to investigate the association between AKI, 30-days mortality and renal function decline up to 1 year after AKI. Survival in patients with and without AKI was assessed using Kaplan-Meier analyses.

Results

Of the 3105 patients in the SPACE-cohort, we included 1716 patients who fulfilled the inclusion criteria. Of these patients, 10.8% had an AKI episode. Mortality was 12.4% for the AKI group and 4.2% for the non-AKI patients. The adjusted HR for all-cause mortality at 30-days in AKI patients was 2.8 (95% CI 1.7–4.8). Moreover, the cumulative incidence of renal function decline was 69.8% for AKI patients and 39.3% for non-AKI patients. Patients with an episode of AKI had higher risk of developing renal function decline (adjusted HR 3.3, 95% CI 2.4–4.5) at one year after initial AKI-episode at the emergency department.

Conclusion

Acute kidney injury is common in patients with suspected infection in the emergency department and is significantly associated with 30-days mortality and renal function decline one year after AKI.

Introduction

Acute kidney injury (AKI) is a major health problem associated with considerable mortality and morbidity. Globally, AKI is associated with increased length of hospital stay, need for complex interventions (e.g., renal replacement therapy (RRT)) and use of critical care services, leading to a high financial burden [1–3]. Depending on what definition is used, the incidence of AKI ranges between 5–30% in hospitalized patients and 40–65% in patients at the intensive care unit (ICU) [4–6].

Although the etiology of AKI is multifactorial, sepsis of any cause, including infection is the most common cause of AKI in critically ill patients [7–9]. Sepsis as cause of AKI in adult intensive care units has been reported in about 50–70% [7, 10]. In addition, depending on AKI severity, 90-day mortality rates ranged from 16–50% in septic patients with AKI at the ICU [11]. Moreover, in uncomplicated community acquired pneumonia the incidence of AKI was high and associated with lower survival [12].
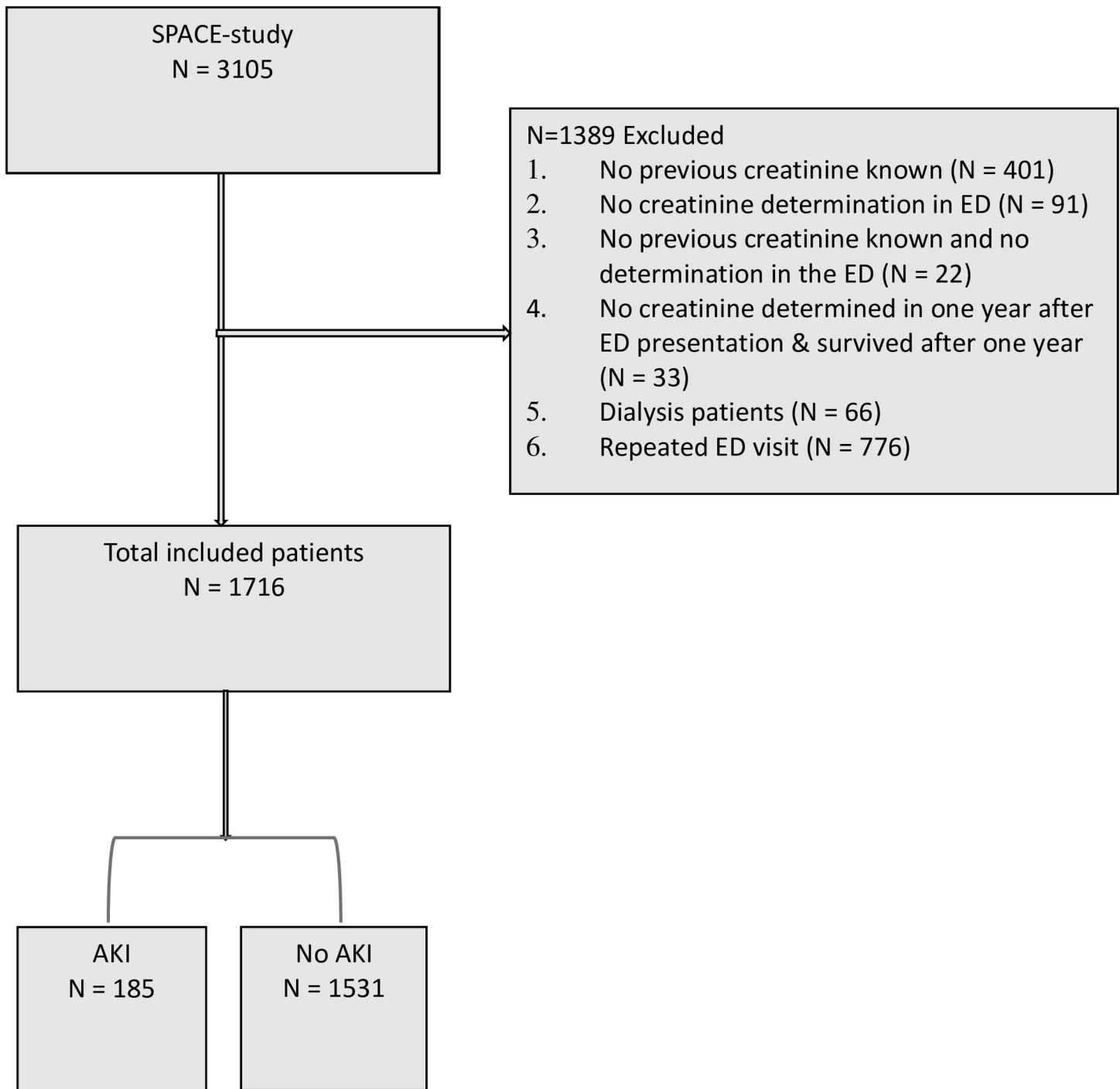
Given the complex pathophysiology of AKI and the various comorbidities of affected patients, recognition and management of AKI remains complicated [13, 14]. Inadequate recognition and treatment of AKI increases the susceptibility to chronic kidney disease (CKD) and end-stage renal disease (ESRD) with requirement for RRT and an increased mortality risk [15]. Moreover, recent studied have found that AKI was independently associated with an increased risk for a subsequent infection in different patient populations with and without sepsis and infection, up to 1 year after AKI [16].

The epidemiology of AKI in hospitalized and critically ill patients in the ICU with severe infection and sepsis has been well described, however data on mortality and clinical outcomes of AKI in the emergency department setting in patients with suspected infection are scarce [8, 17]. Since emergency departments are frequently the first site of care for patients with AKI, early identification may help to improve standards of care and patient outcomes [18, 19]. Therefore, we investigated the incidence, 30-days mortality and renal outcomes after AKI up to one year after initial AKI-episode in a unique cohort of patients with suspected infection at the emergency department of a tertiary care center.

Material and methods

Study design and setting

For the current study we used data from the SPACE-cohort (SePsis in the ACutely ill patients in the Emergency department) [20]. In short, this cohort consists of all consecutive patients presenting at the emergency department of the internal medicine with suspected infection in the University Medical Center Utrecht (UMCU). Analysis was performed on data collected prospectively from September 13rd 2016 until October 11th 2018 and included 1716 patients (Fig 1). The UMCU is one of the largest tertiary care centres in the Netherlands. The SPACE-cohort and current study were reviewed and approved by the Medical Ethical Committee of the UMCU under number 16/594 and registered in the Dutch Trial Register (NTR) under

SPACE-study
N = 3105

N=1389 Excluded
1. No previous creatinine known (N = 401)
2. No creatinine determination in ED (N = 91)
3. No previous creatinine known and no determination in the ED (N = 22)
4. No creatinine determined in one year after ED presentation & survived after one year (N = 33)
5. Dialysis patients (N = 66)
6. Repeated ED visit (N = 776)

Total included patients
N = 1716

AKI
N = 185

No AKI
N = 1531

ED: Emergency department

Fig 1. Flowchart of patients included in the analyses.

https://doi.org/10.1371/journal.pone.0260942.g001

Population and data collection

The SPACE-cohort consists of all consecutive patients who meet the following criteria: (1) $\geq$ 18 years or older; (2) presentation at the emergency department with the suspicion of an infection defined by the treating physician in the emergency department; (3) registration in the emergency department for the internal medicine department or its subspecialties (oncology, rheumatology, immunology, hematology, nephrology, endocrinology, gastro-enterology, infectious disease and vascular medicine). Patient data collected in this cohort consists of all clinical data upon presentation in the emergency department and, if applicable, hospital admission, laboratory data, treatment data and outcome data including mortality.

For all patients, SIRS and qSOFA and Modified Early Warning Score (MEWS) were automatically calculated in the emergency department based on the first complete available record. MEWS included blood pressure, pulse rate, respiratory rate, body temperature, consciousness. Each condition was given a score of 0–3, and the sum of the scores was calculated. A higher MEWS score indicates an increased disease severity. SIRS was considered present in case of two or more of the following criteria: heart rate $\geq$ 90 per minute, leukocyte count $\geq$ 12.0 or $\leq$ 4.0 (x10^9/l), respiratory rate $\geq$ 20 per minute or temperature $\geq$ 38.0 or $\leq$ 36.0˚C. qSOFA was considered positive in case of two or more of the following criteria: respiratory rate $\geq$ 22 per minute, Glasgow Coma Score (GCS) $\leq$14 or systolic blood pressure $<$ 100 mmHg.

Data on general patient information, vital signs, laboratory testing (including serum creatinine (SCr) and estimated glomerular filtration rate (eGFR)), immune status, medication use and mortality were automatically extracted from the Electronic Health Records.

Diagnosis at admission and diagnosis at discharge were retrieved from the emergency department record and hospital discharge letter, respectively. These diagnoses were reviewed on correctness and accuracy by a standardized independent review of the medical record by two principal investigators. This review was based on symptoms, vital signs, laboratory results, radiology and microbiology results and was standardized for most common infections.

Definitions acute kidney injury

The diagnosis and staging of AKI in adults were defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria [21]. Data on urinary output were not available in this SPACE-cohort and were not included in the definition of AKI. Baseline SCr was defined as the last available SCr level up to 12 months prior to presentation to the emergency department [22, 23]. The median period between baseline SCr and presentation at the emergency department was 28 days (IQR 13–73). Patients receiving RRT or without SCr value at baseline or during emergency department visit were excluded. Kidney transplant recipients were included in the current study and considered as immunocompromised for the analyses. Follow-up SCr and eGFR data were obtained of all patients if available, up to 12 months after initial AKI episode.

Outcomes

The primary outcomes of this study were 30-days all-cause mortality and renal function decline after AKI up to 1 year in patients with suspected infection at the emergency department, up to one year after presentation. Secondary outcomes were in-hospital mortality and association with AKI. Decline of renal function after AKI episode at emergency department visit was defined as SCr $\geq$30% above baseline [24]. For assessment of renal function after discharge, we included the latest available SCr value up to 12 months after initial presentation. Data on comorbidity was quantified using the Charlson Comorbidity Index (CCI).

Statistical analyses

Data are presented as median and interquartile range and compared using a Man-Whitney U tests. Categorical variables are presented as frequencies and percentages and compared using Chi-square tests. Survival curves of mortality were determined with the Kaplan–Meier method for the AKI and non-AKI group. Significant differences in survival curves were analyzed using Log-rank test. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression analysis to investigate the relationship between AKI and all-cause mortality and renal function decline. In addition, we adjusted HRs for potential confounders including age, gender, Charlson Comorbidity Index (including CKD), immune status, smoking status, medication use (diuretics, proton-pump inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin converting enzyme inhibitors (ACEi)), disease severity, diagnosis in the emergency department. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS-software version 25.0.

Results

Baseline characteristics

Of the 3105 patient in the SPACE-cohort, we included 1716 patients for this analysis after exclusion of the following patients from analyses: 401 patients had no baseline SCr, 91 patients had no SCr measurement at emergency department presentation, 22 patients missed both baseline and emergency department admission SCr value, 33 patients had no SCr determined in one year after emergency department presentation and survived after one year, 66 patients had renal replacement therapy at the time of emergency department visit and 776 patients had a repeated emergency department visit during the study period (Fig 1). The median age of the patients was 62 years (IQR 48–70) and 52.9% of the patients were male. The most common causes of infection at presentation of the emergency department were lower respiratory tract infections (20.6%), viral respiratory infections (17.9%), gastro-intestinal infections (16.3%), urinary tract infections (15.7%), and skin infections (6.6%). The most common comorbidities were hypertension (31.5%), chronic kidney disease (23.7%) and rheumatic diseases (20.5%) with a median Charlson Comorbidity Index of 4 (IQR 2–7). Of the included patients, 37.9% had an immunocompromised status (including kidney transplant recipients). Median baseline SCr at admission was 83 (IQR 65–123) umol/L (Table 1).

AKI patients at emergency department

Of the 1716 included patients, 185 (10.8%) patients had AKI at presentation at the emergency department. Most patients had AKI stage 1 (67%), followed by stage 2 (22.2%) and stage 3 (10.8%). The median age in AKI patients was 61 years (IQR 51–69) and 53.0% were male. In patients with AKI, hypertension (34.6%), diabetes mellitus (25.4%), and cerebral vascular disease (16.8%) were the most common comorbidities. The median Charlson Comorbidity Index was 5 (IQR 3–7) in the AKI patients versus 4 (IQR 2–7) in the non-AKI group. Of the 185 patients with AKI, 15.1% had a kidney transplantation. Furthermore, patients with AKI had higher disease severity scores (qSOFA 1 (IQR 0–1) and MEWS 2 (IQR 1–5)) as compared to the non-AKI patients (qSOFA 0 (IQR 0–1) and MEWS 2 (IQR 0–3)). The baseline SCr levels were not significantly different between the AKI and non-AKI group. Most common infections in the AKI patients at admission to the emergency department were a urinary tract infection (26.5%), a gastro-intestinal infection (21.6%) and a lower respiratory tract infection (17.3%).

Table 1. Baseline characteristics.

	Total (N = 1716)	No AKI (N = 1531)	AKI (N = 185)	p-value
Age median (IQR)	62 (48–70)	62 (48–70)	61 (51–69)	0.94
Male (%)	908 (52.9)	810 (52.9)	98 (53.0)	0.98
Comorbidities				
Hypertension (%)	540 (31.5)	476 (31.1)	64 (34.6)	0.33
Diabetes Mellitus (%)	316 (18.4)	269 (17.6)	47 (25.4)	< **0.01**
Severe Liver disease (%)	18 (1.0)	13 (0.8)	5 (2.7)	**0.02**
Heart failure (%)	93 (5.4)	80 (5.2)	13 (7.0)	0.31
Myocardial infarction (%)	148 (8.6)	132 (8.6)	16 (8.6)	0.99
Peripheral vascular disease (%)	138 (8.0)	112 (7.3)	26 (14.1)	< **0.01**
Cerebrovascular disease (%)	182 (10.6)	151 (9.9)	31 (16.8)	< **0.01**
Kidney Transplant (%)	186 (10.8)	158 (10.3)	28 (15.1)	0.05
CKD (%)	407 (23.7)	346 (22.6)	61 (33.0)	< **0.01**
Immunocompromised	651 (37.9)	576 (37.6)	75 (40.5)	0.44
Medication				
ACE- inhibitor	487 (28.4)	418 (27.3)	69 (37.3)	< **0.01**
Diuretics	342 (19.9)	290 (18.9)	52 (28.1)	< **0.01**
PPI	858 (50.0)	748 (48.9)	110 (59.5)	< **0.01**
NSAID	98 (5.7)	82 (5.4)	16 (8.6)	0.07
Disease severity in ED				
MEWS	2 (1–3)	2 (0–3)	2 (1–5)	< **0.01**
qSOFA	0 (0–1)	0 (0–1)	1 (0–1)	< **0.01**
Infectious diagnosis upon presentation in the ED				
Lower respiratory tract infection	354 (20.6)	322 (21.0)	32 (17.3)	0.24
Viral respiratory tract infection	307 (17.9)	293 (19.1)	14 (7.6)	< **0.01**
Urinary tract infection	270 (15.7)	221 (14.4)	49 (26.5)	< **0.01**
Gastro-intestinal infection	280 (16.3)	240 (15.7)	40 (21.6)	**0.04**
Skin infection	113 (6.6)	107 (7.0)	6 (3.2)	0.05
Stages of AKI				
Stage 1	-	-	124 (67.0)	-
Stage 2	-	-	41 (22.2)	-
Stage 3	-	-	20 (10.8)	-
Laboratory (IQR)				
Baseline serum creatinine (umol/L)	76 (63–105)	76 (63–105)	74 (58–118)	0.58
Baseline eGFR CKD-EPI (ml/min)	83 (58–100)	83 (58–100)	83 (51–100)	0.75

AKI: Acute Kidney Injury, any stage; IQR: Interquartile range; ACE: Angiotensin-converting-enzyme;PPI: Proton pump-inhibitor; ED: Emergency department; MEWS: Modified Early Warnings Score; quick Sepsis Related Organ Failure Assessment; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

https://doi.org/10.1371/journal.pone.0260942.t001

Mortality and AKI

Thirty days after the initial AKI episode, 1628 patient were still alive (survivors) and 88 patients passed away (non-survivors). In Fig 2, the Kaplan-Meier survival curve for patients with AKI and without AKI is shown. The cumulative 30-days mortality was 12.4% for the AKI group and 4.2 for the non-AKI group. The mortality rate of AKI in the survivor group was 1550 per 1000 person-years versus 530 in the non-AKI group. The association between AKI and 30 days mortality remained independently associated with a HR of 2.8 (95% CI 1.7–4.8), regardless of AKI stage AKI stage 1 HR of 3.0 (95% CI 1.6–5.5) and AKI stage 2 HR 2.6 (95%
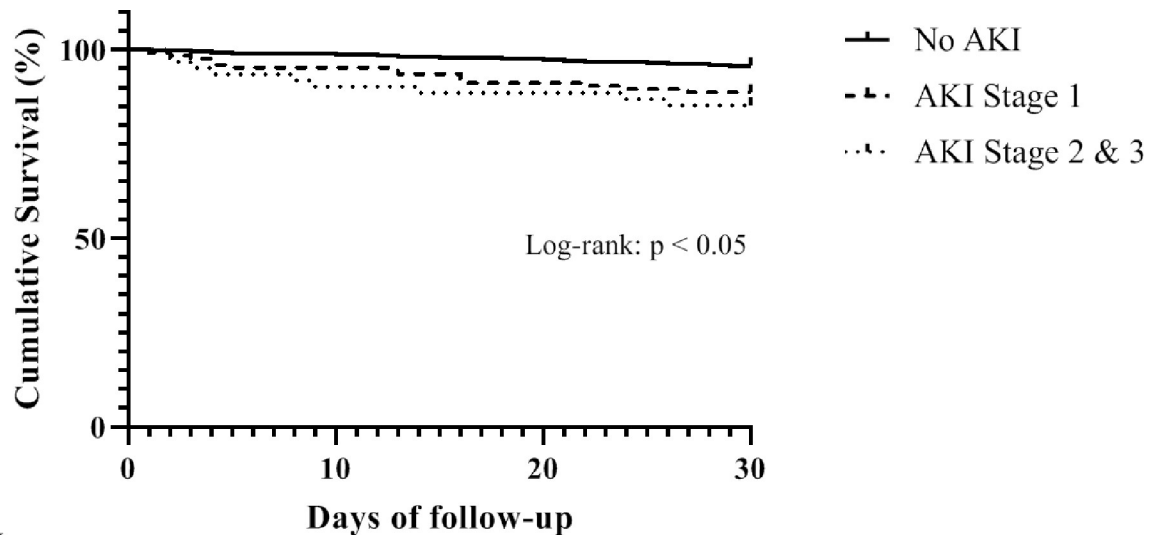
Fig 2. Kaplan Meijer curve for 30 days mortality comparing patients with and without acute kidney injury.

https://doi.org/10.1371/journal.pone.0260942.g002

CI 1.2–5.6), after adjustment for age, gender, comorbidities, immune status, smoking status, medication use, disease severity, diagnosis in the emergency department (Table 2). Consistently, adjusted in-hospital mortality was increased in patients with AKI compared to non-AKI (HR 4.0 (95% CI 2.2–7.4) (Table 3).

Long-term renal function in AKI and non-AKI patients

Of the 1716 patients that were included in our analyses, 1467 (85.5%) patients had a preserved renal function and 249 (14.5%) patients ended with an impaired renal function (defined as SCr ≥30% above baseline) up to one year after presentation at the emergency department. The cumulative incidence of renal function decline was 69.8% for the AKI group and 39.3% for the

Table 2. Association between acute kidney injury and 30-days mortality.

	N	Crude HR (95%CI)	Model 1[a] HR (95%CI)	Model 2[b] HR (95%CI)	Model 3[c] HR (95%CI)	Model 4[d] HR (95% CI)
No AKI	1531	1.0 (reference)	1.0	1.0	1.0	1.0
AKI	185	3.1 (1.9–5.0)	3.2 (2.0–5.1)	3.4 (2.1–5.5)	3.7 (2.2–6.0)	2.8 (1.7–4.8)
Subgroup analysis						
No AKI	1531	1.0 (reference)	1.0	1.0	1.0	1.0
AKI stage 1	124	2.7 (1.6–5.0)	2.8 (1.6–5.0)	3.3 (1.8–5.9)	3.6 (2.0–6.6)	3.0 (1.6–5.5)
Aki stage 2 & 3	61	3.8 (1.9–7.5)	3.8 (1.9–7.7)	3.5 (1.7–7.1)	3.8 (1.8–7.8)	2.6 (1.2–5.6)

a. Correction made for: age, gender.

b. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status.

c. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use

d. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use, disease severity (MEWS), diagnosis in the emergency department.

https://doi.org/10.1371/journal.pone.0260942.t002

Table 3. Association between acute kidney injury and in-hospital mortality.

	N	Crude HR(95%CI)	Model 1[a] HR (95%CI)	Model 2[b] HR (95%CI)	Model 3[c] HR (95%CI)	Model 4[d] HR (95% CI)
No AKI	1531	1.0 (reference)	1.0	1.0	1.0	1.0
AKI	185	4.9 (2.8–8.5)	4.9 (2.9–8.6)	5.0 (2.9–8.7)	5.2 (2.9–9.2)	4.0 (2.2–7.4)
Subgroup analysis						
No AKI	1531	1.0 (reference)	1.0	1.0	1.0	1.0
AKI stage 1	124	4.8 (2.5–9.0)	4.8 (2.6–9.1)	4.9 (2.6–9.3)	5.1 (2.7–10.0)	4.2 (2.1–8.3)
Aki stage 2 & 3	61	5.2 (2.3–11.7)	5.2 (2.3–11.8)	5.2 (2.3–11.8)	5.2 (2.3–12.0)	3.7 (1.5–9.0)

a. Correction made for: age, gender.

b. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status.

c. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use

d. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use, disease severity (MEWS), diagnosis in the emergency department.

non-AKI group. In our study, we observed an incidence rate for renal function decline of 641 cases per 1000 person-years over 1 year of follow-up in patients surviving an episode of AKI as compared to 212 cases per 1000 person-years in patients who did not have AKI. In addition, patients with an episode of AKI had higher risks of developing renal impairment (adjusted HR 3.3 (95% CI 2.4–4.5) up to one year after initial AKI-episode, even after adjustment for age, gender, comorbidities, immune status, smoking status, medication use, disease severity and diagnosis in the emergency department (Table 4).

Discussion

In this study of patients presented to the emergency department for the internal medicine with suspected infection, we found that 10.8% was suffering from an episode of AKI. Importantly, after adjustment for baseline characteristics, comorbidities and diagnosis at emergency department, occurrence of AKI on admission was independently associated with increased 30-days mortality as well as increased risk of renal function decline up to one year after AKI-episode at presentation to the emergency department. To our knowledge, this is the first study to describe the incidence of AKI and associated increased 30-days mortality and renal function decline up to one year after AKI-episode in patients presenting at the emergency department with different infections. Given the high incidence and associated worse outcomes, our study suggest that AKI is a common entity in patients in the emergency department and that awareness as well as early recognition will probably be of great importance and improve patient outcomes.

Table 4. Association between acute kidney injury and renal function decline up to one year after initial acute kidney injury episode.

	N	Incidence rate per 1000 person years	Crude HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 4[d] HR (95% CI)
No AKI	1531	212	1.0 (reference)	1.0	1.0	1.0	1.0
AKI	185	641	3.5 (2.6–4.7)	3.5 (2.6–4.7)	3.4 (2.6–4.6)	3.4 (2.6–4.5)	3.3 (2.4–4.5)

a. Correction made for: age, gender.

b. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status.

c. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use.

d. Correction made for: age, gender, comorbidities, baseline renal function, immune status, smoking status, medication use, disease severity in emergency department, diagnosis in the emergency department.

The epidemiology of AKI in hospitalized and critically ill patients with infection and sepsis has well been described with reported incidence rates that varies between 5–20% among hospitalized patients and 35–50% in critically ill patients [25]. However, studies about incidence rates for AKI and outcomes in patients admitted to the emergency department, which is frequently the first site of care for patients who develop AKI, are scarce and varies due to different patient populations and definitions of AKI used. The observed incidence for AKI in our study is in line with data reported in the study by Scheuermeyer et al. In this retrospective cohort study among 840 unselected patients admitted to the emergency department, they reported an incidence of 10.7% [8]. A study of Tollitt et al. among 17 287 patients with suspected community acquired infection, also showed an incidence rate of 11.9% [9]. Although, both studies included patients with and without baseline SCr, they used the KDIGO criteria for the definition of AKI, consistently with our study. In addition, two other studies found incidence rates of 16 (7) and 34% (8) in patients with (non-severe) community acquired pneumonia and severe pneumonia, respectively, presenting at the emergency department. However, the disparities in incidence rates could be explained by definition used in these studies (RIFLE-criteria) and our study (KDIGO) and severity of illness [12, 26]. Moreover, in the study of Murugan, they used in most of the patients estimated baseline SCr levels, while in our study we included patients with existing baseline SCr values [12].

There is increasing evidence that even a small decrease in renal function in AKI patients is associated with poor short-term and long-term outcomes. This association is extremely high in critically ill patients with infection and sepsis when compared to other causes for AKI [27–29]. In our study, we also found that AKI was associated with a higher 30-days mortality risk and renal function loss up to one year after initial AKI-episode in patients with suspected infection. These findings are consistent with other studies that showed higher mortality in AKI patients, even in non-critical ill patients with infection and in patients that were not admitted to the ICU [12, 30–32]. The study of Murugan et al. and Akram et al. showed that 30-days and 1-year mortality, respectively, were increased in patients with AKI in pneumonia and that the risk increases with increasing levels of renal dysfunction [12, 26]. In our study, we found that 30-days mortality in AKI-patients was 12.4%. In addition, we found an increased risk for mortality, with a HR of 2.8 in AKI patients. Consistently, previous studies have also shown an association between AKI episode and long-term renal dysfunction after hospital admission and discharge, but no studies reported on long-term renal function after AKI in patients at the emergency department, and especially in patients with suspected infection [33].

Severe infection in septic patients is the leading cause of AKI in critically ill patients. AKI in the setting of critically ill patients is associated with ICU admissions, greater hemodynamic complications and adverse outcomes, including cardiovascular events, chronic renal dysfunction, hospital readmission and high mortality [34–37]. Importantly, even studies in patients with early reversal of kidney function after AKI show a higher risk of mortality and progression to chronic kidney disease [38–40]. Although many studies proposed to explore the possible mechanisms between acute renal failure and progression to persistent renal dysfunction in patients with infection or sepsis, exact pathways are still poorly understood. Accumulating evidence in animal studies suggest that persistent renal injury in AKI is the result of an imbalance between pro-inflammatory and anti-inflammatory regulatory mechanisms, resulting in capillary rarefaction and myofibroblast activation with consequently development of fibrosis and scarring in the kidney tissue [37, 41, 42]. Although the kidney has the capacity to recover from acute and limited damage, critical illness, repeated injury, age and comorbidities can contribute to incomplete and maladaptive repair leading to chronic kidney injury and persistent renal dysfunction [35, 36, 41]. Targeted interventions in the early course of AKI, aiming at reducing

the transition from AKI to persistent chronic kidney damage, may prevent further damage and improve renal outcomes and reduce mortality rates.

Although there are no targeted therapies for AKI, initial management is crucial and involves recognition, therapy directed at the underlying cause, monitoring of renal function, prevention and adjustment of nephrotoxic medication and RRT if required. Because early AKI recognition might support timely and effective treatment, significant attention has been paid to the importance of early identification of patients with AKI, to limit progression to sustained renal impairment and improve long-term outcomes. However, prompt identification of AKI remains challenging due to a lack of awareness of the importance of early recognition, different care environments where AKI occurs (ICU, hospitalized patients, emergency department, primary care) and diversity of patient populations [43]. Recent studies have reported on the implementation of more specific tools to enhance the awareness and recognition with beneficial impact on long-term outcomes. Especially, the implementation of educational programs for healthcare workers with different backgrounds, electronic alerts for AKI and early nephrology consultation showed a positive effect on outcomes [15, 19, 44, 45]. A recent study of Connell et al. reported a significant improvement in AKI recognition and adjustment of nephrotoxic medication after implementation of a digitally-enabled care pathway for the recognition and management of AKI at the emergency department [46]. In addition, given the association between AKI and long-term renal dysfunction, nephrology consultation can also be of importance for the follow-up of renal function after discharge [44, 47–49]. Interestingly, the development of machine learning models and new biomarkers (e.g. Dickkopf-3) to predict AKI in different patient populations shows promising results, however, the impact of these tools on renal and patient outcomes in the long-term needs to be further evaluated [49, 50].

The current study has several strengths. To the best of our knowledge, this is the first study investigating the incidence, mortality and renal outcomes of AKI in patients with suspected infection presenting at the emergency department with a follow-up to one year. Although several studies reported on 30-days and 1-year outcomes after initial AKI episode at the emergency department, these studies did not include renal specific outcomes [8, 12, 26]. Another strength of our study is that, in contrast to other studies investigating AKI in patients with specific infections at the emergency department, we enrolled patients with different infections. Nevertheless, our study has also several limitations. First, this study is a single center study in an academic center with severely ill patients, which may limits the generalizability to other populations. Secondly, for the baseline SCr levels, we used the most recent SCr values up to 12 months before admission to the emergency department and included only patients with pre-admission baseline SCr from the SPACE-cohort, which may affect overall results by yielding a sicker cohort with predisposing comorbidities compared to healthier patients without these (outpatient) health records. However, we do not think that this has affected the association between AKI and mortality or renal function decline. Moreover, the median period between baseline SCr and presentation at the emergency department was short (28 days (IQR 13–73). Third, the definition of AKI was based only on KDIGO criteria with SCr levels only and did not include urine output. Since creatinine levels can be affected by different conditions (nutrition, infection, muscle mass, age), it could be that classification of AKI based on only SCr may not have captured all cases of AKI. Indeed, a recent study of Kaddourah et al. demonstrated differences in outcomes by using either SCr, urine output or both for the KDIGO definition of AKI [51]. Lastly, we did not perform routine SCr measurements at fixed time-points, therefore AKI episodes might remain undetected.

In conclusion, AKI is a common entity in patients with suspected infection presenting at the emergency department and is associated with 30-days mortality and renal function decline during 1-year follow-up. Our study underscores the importance of enhancing awareness of

AKI under treating physicians at the emergency department. More studies are needed to explore better tools for early detection of AKI and improve patient and renal outcomes early intervention.

Author Contributions

Conceptualization: Meriem Khairoun, Jan Willem Uffen, Romy Koopsen, Jan Jelrik Oosterheert, Karin Kaasjager.

Data curation: Jan Willem Uffen, Romy Koopsen, Saskia Haitjema.

Formal analysis: Jan Willem Uffen, Gurbey Ocak.

Investigation: Meriem Khairoun, Jan Willem Uffen, Romy Koopsen.

Methodology: Meriem Khairoun, Jan Willem Uffen, Gurbey Ocak, Romy Koopsen, Saskia Haitjema.

Supervision: Jan Jelrik Oosterheert, Karin Kaasjager.

Writing – original draft: Meriem Khairoun, Jan Willem Uffen.

Writing – review & editing: Meriem Khairoun, Jan Willem Uffen, Gurbey Ocak, Jan Jelrik Oosterheert, Karin Kaasjager.

References

1. Challiner R, Ritchie JP, Fullwood C, Loughnan P, Hutchison AJ. Incidence and consequence of acute kidney injury in unselected emergency admissions to a large acute UK hospital trust. BMC Nephrol. 2014; 15:84. https://doi.org/10.1186/1471-2369-15-84 PMID: 24885247

2. Silver SA, Long J, Zheng Y, Chertow GM. Cost of Acute Kidney Injury in Hospitalized Patients. J Hosp Med. 2017; 12(2):70–6. https://doi.org/10.12788/jhm.2683 PMID: 28182800

3. Foxwell DA, Pradhan S, Zouwail S, Rainer TH, Phillips AO. Epidemiology of emergency department acute kidney injury. Nephrology (Carlton). 2020; 25(6):457–66. https://doi.org/10.1111/nep.13672 PMID: 31654593

4. Argyropoulos A, Townley S, Upton PM, Dickinson S, Pollard AS. Identifying on admission patients likely to develop acute kidney injury in hospital. BMC Nephrol. 2019; 20(1):56. https://doi.org/10.1186/s12882-019-1237-x PMID: 30764796

5. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016; 37(2):85–98. PMID: 28303073

6. Teo SH, Lee KG, Koniman R, Tng ARK, Liew ZH, Naing TT, et al. A prospective study of clinical characteristics and outcomes of acute kidney injury in a tertiary care Centre. BMC Nephrol. 2019; 20(1):282. https://doi.org/10.1186/s12882-019-1466-z PMID: 31349813

7. Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int. 2019; 96(5):1083–99. https://doi.org/10.1016/j.kint.2019.05.026 PMID: 31443997

8. Scheuermeyer FX, Grafstein E, Rowe B, Cheyne J, Grunau B, Bradford A, et al. The Clinical Epidemiology and 30-Day Outcomes of Emergency Department Patients With Acute Kidney Injury. Can J Kidney Health Dis. 2017; 4:2054358117703985. https://doi.org/10.1177/2054358117703985 PMID: 28491339

9. Tollitt J, Bennett N, Darby D, Flanagan E, Chadwick P, Sinha S, et al. The importance of acute kidney injury in suspected community acquired infection. PLoS One. 2019; 14(5):e0216412. https://doi.org/10.1371/journal.pone.0216412 PMID: 31063508

10. Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM. Sepsis-associated acute kidney injury. Semin Nephrol. 2015; 35(1):2–11. https://doi.org/10.1016/j.semnephrol.2015.01.002 PMID: 25795495

11. Shum HP, Kong HH, Chan KC, Yan WW, Chan TM. Septic acute kidney injury in critically ill patients—a single-center study on its incidence, clinical characteristics, and outcome predictors. Ren Fail. 2016; 38 (5):706–16. https://doi.org/10.3109/0886022X.2016.1157749 PMID: 26981621

12. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. Kidney Int. 2010; 77(6):527–35. https://doi.org/10.1038/ki.2009.502 PMID: 20032961

13. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? Nat Rev Nephrol. 2011; 7(4):209–17. https://doi.org/10.1038/nrneph.2011.13 PMID: 21343898

14. Togel F, Westenfelder C. Recent advances in the understanding of acute kidney injury. F1000Prime Rep. 2014; 6:83. https://doi.org/10.12703/P6-83 PMID: 25343040

15. Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013; 84(3):457–67. https://doi.org/10.1038/ki.2013.153 PMID: 23636171

16. Gist KM, Faubel S. Infection Post-AKI: Should We Worry? Nephron. 2020:1–4. https://doi.org/10.1159/000508101 PMID: 32564024

17. Bernardo EO, Cruz AT, Buffone GJ, Devaraj S, Loftis LL, Arikan AA. Community-acquired Acute Kidney Injury Among Children Seen in the Pediatric Emergency Department. Acad Emerg Med. 2018; 25 (7):758–68. https://doi.org/10.1111/acem.13421 PMID: 29630763

18. Holmes J, Geen J, Phillips B, Williams JD, Phillips AO, Welsh AKISG. Community acquired acute kidney injury: findings from a large population cohort. QJM. 2017; 110(11):741–6. https://doi.org/10.1093/qjmed/hcx151 PMID: 29025142

19. Wilson FP, Shashaty M, Testani J, Aqeel I, Borovskiy Y, Ellenberg SS, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet. 2015; 385(9981):1966–74. https://doi.org/10.1016/S0140-6736(15)60266-5 PMID: 25726515

20. Uffen JW, Oomen P, de Regt M, Oosterheert JJ, Kaasjager K. The prognostic value of red blood cell distribution width in patients with suspected infection in the emergency department. BMC Emerg Med. 2019; 19(1):76. https://doi.org/10.1186/s12873-019-0293-7 PMID: 31795936

21. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012; 120(4): c179–84. https://doi.org/10.1159/000339789 PMID: 22890468

22. Bernier-Jean A, Beaubien-Souligny W, Goupil R, Madore F, Paquette F, Troyanov S, et al. Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values. BMC Nephrol. 2017; 18(1):141. https://doi.org/10.1186/s12882-017-0552-3 PMID: 28454562

23. Lumlertgul N, Amprai M, Tachaboon S, Dinhuzen J, Peerapornratana S, Kerr SJ, et al. Urine Neutrophil Gelatinase-associated Lipocalin (NGAL) for Prediction of Persistent AKI and Major Adverse Kidney Events. Sci Rep. 2020; 10(1):8718. https://doi.org/10.1038/s41598-020-65764-w PMID: 32457335

24. Xu J, Xu X, Shen B, Zhuang Y, Liu L, Wang Y, et al. Evaluation of five different renal recovery definitions for estimation of long-term outcomes of cardiac surgery associated acute kidney injury. BMC Nephrol. 2019; 20(1):427. https://doi.org/10.1186/s12882-019-1613-6 PMID: 31752748

25. Rosenqvist M, Bronton K, Hartmann O, Bergmann A, Struck J, Melander O. Proenkephalin a 119–159 (penKid)—a novel biomarker for acute kidney injury in sepsis: an observational study. BMC Emerg Med. 2019; 19(1):75. https://doi.org/10.1186/s12873-019-0283-9 PMID: 31779591

26. Akram AR, Singanayagam A, Choudhury G, Mandal P, Chalmers JD, Hill AT. Incidence and prognostic implications of acute kidney injury on admission in patients with community-acquired pneumonia. Chest. 2010; 138(4):825–32. https://doi.org/10.1378/chest.09-3071 PMID: 20435657

27. Doyle JF, Forni LG. Update on sepsis-associated acute kidney injury: emerging targeted therapies. Biologics. 2016; 10:149–56. https://doi.org/10.2147/BTT.S87385 PMID: 27853353

28. Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. Crit Care. 2016; 20(1):188. https://doi.org/10.1186/s13054-016-1353-y PMID: 27373891

29. Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S, et al. Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med. 2009; 37(7):2203–9. https://doi.org/10.1097/CCM.0b013e3181a03961 PMID: 19487937

30. Joslin J, Ostermann M. Care of the critically ill emergency department patient with acute kidney injury. Emerg Med Int. 2012; 2012:760623. https://doi.org/10.1155/2012/760623 PMID: 22145079

31. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010; 21(2):345–52. https://doi.org/10.1681/ASN.2009060636 PMID: 20019168

32. Macedo E, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikizler TA, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. Crit Care. 2010; 14(3):R82. https://doi.org/10.1186/cc9004 PMID: 20459609

33. Sawhney S, Marks A, Fluck N, Levin A, McLernon D, Prescott G, et al. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. Kidney Int. 2017; 92(2):440–52. https://doi.org/10.1016/j.kint.2017.02.019 PMID: 28416224

34. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney Int. 2019; 95(1):160–72. https://doi.org/10.1016/j.kint.2018.08.036 PMID: 30473140

35. Selby NM, Casula A, Lamming L, Stoves J, Samarasinghe Y, Lewington AJ, et al. An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial. J Am Soc Nephrol. 2019; 30(3):505–15. https://doi.org/10.1681/ASN.2018090886 PMID: 31058607

36. Zarbock A, Gomez H, Kellum JA. Sepsis-induced acute kidney injury revisited: pathophysiology, prevention and future therapies. Curr Opin Crit Care. 2014; 20(6):588–95. https://doi.org/10.1097/MCC.0000000000000153 PMID: 25320909

37. Vandijck DM, Reynvoet E, Blot SI, Vandecasteele E, Hoste EA. Severe infection, sepsis and acute kidney injury. Acta Clin Belg. 2007; 62 Suppl 2:332–6. https://doi.org/10.1179/acb.2007.075 PMID: 18283994

38. Bhandari S, Turney JH. Survivors of acute renal failure who do not recover renal function. QJM. 1996; 89(6):415–21. https://doi.org/10.1093/qjmed/89.6.415 PMID: 8758044

39. 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. https://doi.org/10.1038/nrneph.2017.2 PMID: 28239173

40. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis. 2012; 60(3):402–8. https://doi.org/10.1053/j.ajkd.2012.03.014 PMID: 22541737

41. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012; 2 (2):1303–53. https://doi.org/10.1002/cphy.c110041 PMID: 23798302

42. Kumar S. Cellular and molecular pathways of renal repair after acute kidney injury. Kidney Int. 2018; 93 (1):27–40. https://doi.org/10.1016/j.kint.2017.07.030 PMID: 29291820

43. Liu KD, Goldstein SL, Vijayan A, Parikh CR, Kashani K, Okusa MD, et al. AKI!Now Initiative: Recommendations for Awareness, Recognition, and Management of AKI. Clin J Am Soc Nephrol. 2020.

44. Al-Jaghbeer M, Dealmeida D, Bilderback A, Ambrosino R, Kellum JA. Clinical Decision Support for In-Hospital AKI. J Am Soc Nephrol. 2018; 29(2):654–60. https://doi.org/10.1681/ASN.2017070765 PMID: 29097621

45. Martinez DA, Levin SR, Klein EY, Parikh CR, Menez S, Taylor RA, et al. Early Prediction of Acute Kidney Injury in the Emergency Department With Machine-Learning Methods Applied to Electronic Health Record Data. Ann Emerg Med. 2020. https://doi.org/10.1016/j.annemergmed.2020.05.026 PMID: 32713624

46. Connell A, Montgomery H, Martin P, Nightingale C, Sadeghi-Alavijeh O, King D, et al. Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions. NPJ Digit Med. 2019; 2:67. https://doi.org/10.1038/s41746-019-0100-6 PMID: 31396561

47. Bhatraju PK, Zelnick LR, Chinchilli VM, Moledina DG, Coca SG, Parikh CR, et al. Association Between Early Recovery of Kidney Function After Acute Kidney Injury and Long-term Clinical Outcomes. JAMA Netw Open. 2020; 3(4):e202682. https://doi.org/10.1001/jamanetworkopen.2020.2682 PMID: 32282046

48. Harel Z, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. Kidney Int. 2013; 83(5):901–8. https://doi.org/10.1038/ki.2012.451 PMID: 23325077

49. Kellum JA, Bihorac A. Artificial intelligence to predict AKI: is it a breakthrough? Nat Rev Nephrol. 2019; 15(11):663–4. https://doi.org/10.1038/s41581-019-0203-y PMID: 31506607

50. Schunk SJ, Zarbock A, Meersch M, Kullmar M, Kellum JA, Schmit D, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. Lancet. 2019; 394(10197):488–96. https://doi.org/10.1016/S0140-6736(19)30769-X PMID: 31202596

51. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. N Engl J Med. 2017; 376(1):11–20. https://doi.org/10.1056/NEJMoa1611391 PMID: 27959707