Prognosis after acute kidney injury among intensive care patients

PhD dissertation

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Preface

This PhD dissertation is based on studies carried out during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

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I. Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. Critical Care. 2012 Jul 12;16(4):R124.

II. Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT. Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study. Critical Care. 2013 Jul 22;17(4):R145.

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List of abbreviations

ACE	Angiotensin-converting enzyme
ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AT II	Angiotensin II
BUN	Blood urea nitrogen
CABG	Coronary arterial bypass grafting
CI	Confidence interval
CKD	Chronic kidney disease
D-AKI	Dialysis-requiring acute kidney injury
DNRP	Danish National Registry of Patients
eGFR	estimated glomerular filtration rate
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD-10	International Classification of Diseases 10th revision
ICU	Intensive care unit
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcome
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NRDT	Danish National Registry on Regular Dialysis and Transplantation
NSAID	Non-steroidal anti-inflammatory drug
RIFLE	Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease
SCr	Serum creatinine
UO	Urine output

Content

1 Introduction

1.1 Intensive care

In Denmark, the specialty of intensive care began as a result of the challenge of the poliomyelitis epidemic in 1952.[1] On the initiative of the Danish anesthesiologist Bjørn Ibsen, patients with polio and respiratory failure were treated with tracheostomy and manual positive airway ventilation. Subsequently, the in-hospital mortality decreased from 87% to 40%.[1]

This improvement led to the recognition that critically ill patients should be observed and treated in special wards by medical doctors and nurses trained in restoring and/or maintaining the function of vital organs. In 1953, the first Danish intensive care unit (ICU) was established.[2]

Since then, the field of intensive care medicine has evolved dramatically. In Denmark, there were 48 ICUs and more than 30,000 ICU admissions in 2010.[3] These ICUs monitor and treat patients at a high risk of developing or with manifest organ dysfunction requiring close monitoring and potentially support from equipment and medication to maintain normal body functions, such as mechanical ventilation, renal replacement support, and hemodynamic support with vasopressors and/or inotropes.[4]

The definition of an intensive care patient usually includes a patient admitted to an ICU. Admission to an ICU is not characterized by well-defined criteria or by a single specific condition, and the decision about and timing of ICU admission depend on clinical judgment, the clinical setting, the actual capacity at the ICU, and that sufficient monitoring and treatment cannot be achieved at the referral department.[4] Thus, ICU patients comprise a heterogeneous cohort of acutely ill patients.

1.2 Acute kidney injury in intensive care settings

Kidney function plays a central role in critical illness because the kidneys help to regulate the composition and volume of extracellular fluid, play an essential role in acid-base balance, remove waste material, and

affect drug disposition.[5] The overall aim of this dissertation is to examine the prognostic implication of acute kidney injury (AKI) in ICU patients and within subgroups of ICU patients.

AKI is a clinical syndrome characterized by a rapid decline of kidney excretory function.[6] Typically, AKI is diagnosed by surrogate markers of decreased glomerular filtration rate (GFR), such as retention of nitrogen metabolism waste products like creatinine and/or decreased urine output.[6] The severity of AKI ranges from mild kidney dysfunction to complete failure of renal function with the need for acute dialysis (throughout this dissertation, the term dialysis is used for both dialysis and hemofiltration).[6]

AKI may be one of the contributing factors for ICU admission, but AKI may also develop after ICU admission and complicate the ICU stay. Hence, patients may be admitted to an ICU any time during the clinical course of AKI.

1.2.1 Definition and staging of acute kidney injury

In 2002, the Acute Dialysis Quality Initiative (ADQI), a group of experts in nephrology and intensive care medicine, identified more than 30 different definitions of AKI (previously known as acute renal failure).[7] To address this lack of a uniform definition of AKI, the ADQI formulated the Risk of renal failure, Injury of kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure (RIFLE) criteria, which were published in 2004.[7] The RIFLE criteria are based on GFR changes, serum creatinine (SCr) changes, and/or decreased urine output. To acknowledge the entire spectrum of AKI, the ADQI workgroup incorporated three stages of increased severity of AKI: 'AKI-risk', 'AKI-injury', and 'AKI-failure'. Two outcome classes – 'loss of kidney function' and 'end-stage kidney disease' – were also incorporated into these criteria (Table 1.1).

Table 1.1 Definition and staging of acute kidney injury according to creatinine criteria[a]

Stage	RIFLE criteria[7]	AKIN criteria[8]	KDIGO criteria[9]
Risk/stage 1	1.5 to 1.9 times baseline[b] OR GFR decrease > 25%	1.5 to 2.0 times baseline[c] OR ≥ 0.3 mg/dl (≥ 26.4 µmol/l) increase within 48 hours	1.5 to 1.9 times baseline[d] OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase within 48 hours
Injury/stage 2	2.0 to 2.9 times baseline[b] OR GFR decrease > 50%	>2.0 to 3.0 times baseline[c]	2.0 to 2.9 times baseline[d]
Failure/stage 3	≥ 3.0 times baseline[b] OR Increase in SCr to ≥ 4.0 mg/dl (≥ 354 µmol/l) with an acute increase ≥ 0.5 mg/dl (44 µmol/l) OR GFR decrease > 75%	> 3.0 times baseline[c] OR Increase in SCr to ≥ 4.0 mg/dl (≥ 354 µmol/l) with an acute increase ≥ 0.5 mg/d (44 µmol/l) OR Initiation of dialysis	≥ 3.0 times baseline OR Increase in SCr to ≥ 4.0 mg/dl (≥ 354 µmol/l) and satisfaction of any of the other criteria for AKI OR Initiation of dialysis
Loss	Need for dialysis for more than 4 weeks	ND	ND
ESRD	Need for dialysis for more than 3 months	ND	ND

[a] The urine output (UO) criteria are similar for the three classification systems: AKI-risk/stage 1: UO < 0.5 ml/kg/h for more than 6 hours; AKI-injury/stage 2: UO < 0.5 ml/kg/h for more than 12 hours; AKI-failure/stage 3: UO < 0.3 ml/kg/h for more than 24 hours OR anuria for 12 hours. Stage is based on the worse of either SCr/GFR or UO criteria.

[b] Baseline SCr defined as measured at baseline (not further defined) or estimated using the Modification of Diet in Renal Disease equation assuming eGFR of 75 ml/min per 1.73 m^2 in patients without a measured baseline SCr and without chronic kidney disease.

[c] Increased within 48-hour period.

[d] The baseline SCr should reflect the patient's premorbid SCr level, and the increase should presumably have occurred within 7 days.

Abbreviations: AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcome; ND, not defined; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine; UO, urine output

After the publication of the RIFLE criteria, evidence emerged that even SCr changes smaller than those included in the RIFLE criteria were associated with worsening prognosis.[10] In 2007, the Acute Kidney Injury Network (AKIN) suggested incorporating an absolute SCr increase criterion of [0.3 mg/dl (26.5 µmol/l)] for the definition of AKI.[8] In addition, the AKIN also suggested (1) the terms AKI stages 1, 2, and 3 instead of AKI-risk, AKI-injury, and AKI-failure; (2) removal of the GFR criteria and the two outcome classes; (3) that all patients who start acute dialysis be classified as AKI stage 3; and (4) that the SCr changes should emerge within a 48-hour period for AKI diagnosis (Table 1.1).[8] In 2012, the Kidney Disease Improving Global Outcome (KDIGO) collaboration combined the suggested criteria from the ADQI and the AKIN. The primary change compared to the AKIN criteria was that again, there was no requirement that the relative increase

should occur within 48 hours, but instead should be compared to a baseline value that should reflect the patient's premorbid SCr level, and the increase should presumably have occurred within 7 days (Table 1.1).[9]

Baseline serum creatinine

The original RIFLE criteria recommend the use of a measured baseline SCr, if available.[7] If measured baseline is unavailable and the patient is without known chronic kidney disease (CKD), the ADQI recommends estimating the baseline SCr from age, gender, and race by the four-variable Modification of Diet in Renal Disease (MDRD) equation assuming estimated GFR (eGFR) of 75 ml/min per 1.73 m^2.[7] Despite this, several different approaches to defining baseline SCr have been used in the literature, such as hospital admission creatinine,[11,12] lowest of hospital admission and MDRD estimated SCr,[13-15] lowest SCr during hospitalization,[16] and use of MDRD estimated assuming eGFR of 75 ml/min per 1.73 m^2 for all patients (also for those with known CKD).[17-20] In addition, multiple imputations have also been suggested as an alternative if baseline SCr is missing.[21]

Few studies have validated the different surrogate methods for defining baseline SCr if a premorbid SCr is unavailable.[21-23] Bagshaw and colleagues validated the suggested approach from the RIFLE criteria in a cohort of ICU patients with severe AKI[1] who had a measured pre-hospital SCr for comparison. They found that the assumption of an eGFR of 75 ml/min per 1.73 m^2 overestimated the proportion with AKI at ICU admission by 18.8 percentage points (55.1% vs. 36.3%). However, after excluding patients with known CKD (eGFR > 60 ml/min per 1.73 m^2), as suggested by the ADQI, this approach instead underestimated the proportion with AKI by 6.6 percentage points (45.1% vs. 51.7%).[24]

In a more recent study, Siew and colleagues validated how the use of (1) the minimum SCr during the first 7 days of hospitalization, (2) the first available SCr during hospitalization, or (3) the SCr estimated by the MDRD equation assuming eGFR of 75 ml/min per 1.73 m^2 affected the sensitivity and specificity of AKI diagnosis compared to the use of a preadmission outpatient measurement as the baseline measure. This

[1] Severe AKI defined as urine output of less than 200 ml in 12 hours, blood urea nitrogen level higher than 84 mg/dl (30 mmol/l, or need for acute dialysis during ICU admission)

validation study was conducted in a cohort of 1,241 adult hospitalized patients in the USA who had a known outpatient SCr measurement from 365 days to 7 days before hospitalization for comparison.[23] Table 1.2 shows the sensitivity and specificity of AKI defined by the use of these three different approaches compared with the use of measured baseline SCr to define AKI with the AKIN criteria.

Table 1.2 Sensitivity and specificity of AKI defined by the use of three different approaches to estimate baseline SCr[23]

	Sensitivity[a], %	Specificity[a], %
Minimum SCr during the first 7 days of hospitalization	81.7%	79.8%
First available SCr during hospitalization	38.9%	94.9%
Assuming eGFR of 75 ml/min per 1.73 m^2	84.2%	77.4%

[a] The reference standard was the most recent outpatient measurement between 7 and 365 days prior to hospitalization.
Abbreviations: eGFR, estimated glomerular filtration rate; SCr, serum creatinine

However, 34.7% of patients included in this validation study had CKD (defined by eGFR < 60 ml/min per 1.73 m^2 and/or by International Classification of Diseases (ICD) codes).[23] Therefore, these results cannot be generalized to indicate what the sensitivity and specificity for 'assuming eGFR of 75 ml/min per 1.73m^2' are in patients without known CKD, which was what was suggested by the ADQI.[7] The same research group also examined whether the use of multiple imputation could improve estimation of missing baseline SCr.[21] In patients without CKD (eGFR ≥ 60 ml/min per 1.73 m^2), various multiple imputation strategies were not superior to estimating the SCr assuming eGFR of 60 ml/min per 1.73 m^2.[21]

1.2.2 Prevalence of AKI in intensive care units

AKI is common among ICU patients. Previous large cohort studies (> 1,000 adult ICU patients) reported that the prevalence of patients with AKI at ICU admission ranges between 18% and 35%, and during the entire ICU stay, AKI prevalence ranges between 22% and 67% (Table 2.1).[11,12,15-19,25,26] The large differences in AKI occurrence may primarily be explained by differences in ICU settings and characteristics of ICU patients.

The maximum AKI stage during an ICU stay or at ICU admission was in most of these large cohort studies AKI-risk/stage 1,[12,16-19,25] whereas the proportion with AKI-injury/stage 2 and AKI-failure/stage 3 was similar,[15,25] or the proportion with AKI-failure/stage 3 was lower than the proportion with AKI-injury/stage

2.[12,16-19] In a combined German and English multicenter cohort study of 41,972 adult ICU patients, Ostermann and colleagues found a prevalence of AKI of 35.8% during the ICU stay; 17.2% had maximum AKI-risk, 11.0% had maximum AKI-injury, and 7.6% had maximum AKI-failure.[19] Similar results were found for AKI at ICU admission among 120,123 adult ICU patients from Australia and New Zealand: 36.1% had AKI at ICU admission. Among these, 16.2% had AKI-risk, 13.6% had AKI-injury, and 6.3% had AKI-failure.[17] The prevalence of severe AKI with a requirement for acute dialysis is in most studies reported to occur in 4% to 6% of ICU patients.[19,27,28]

1.2.3 Risk factors for AKI in the intensive care setting

The risk factors for AKI in ICU patients are many, and multiple factors contribute to AKI.[29,30] Sepsis is reported as one of the most commonly reported risk factors for AKI and is assumed to contribute to AKI in around 50% of ICU patients with AKI.[29,30] Major surgery, nephrotoxic drugs, and hypovolemia are other commonly reported risk factors for AKI.[29-31]

Traditionally, AKI has been grouped into pre-renal, renal (intrinsic), and post-renal AKI,[9] but the use of this traditional categorization, especially in ICU patients with sepsis, has been questioned.[32] Briefly, the arguments against this categorization are that (1) it is very difficult to define when pre-renal AKI results in structural changes in the kidney and thus in renal AKI; (2) the differentiation between pre-renal AKI and renal AKI due to pre-renal AKI may have limited implications for treatment; and (3) the assumption that prolonged pre-renal AKI causes structural changes in the kidney and thus renal AKI might not be valid because postmortem studies of patients with sepsis and AKI severe enough to cause death showed normal histopathological findings in more than 90% of the patients.[32]

1.2.4 Treatment of AKI

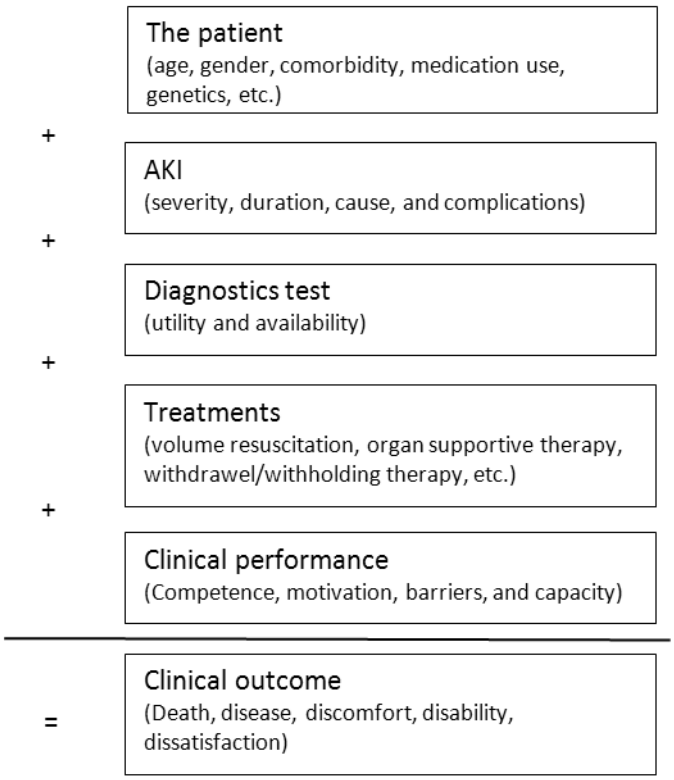
No specific treatment is available to reverse AKI.[9] Therefore, the primary treatment is focused on diminishing or treating potential contributing factors, ensuring sufficient volume status and perfusion pressure, avoiding drugs and procedures that might further worsen kidney function, and treatment of

complications of AKI, such as hyperkalemia, volume overload, and acidosis. Depending on AKI severity and complications, renal support with dialysis may be needed.[9]

1.3 Studying prognosis of AKI among ICU patients

The word prognosis arises from the Greek word *pro-gnosis*, meaning 'foreknowledge', and is defined as predicting or estimating the probability or risk of future outcomes over a specific time.[33] The estimated outcomes can be clinical events such as death or diseases/complication, or measures of discomfort, disability, and dissatisfaction.[34] Numerous factors that may influence the prognosis are shown in figure 1.1.[35]

Figure 1.1. Determinants of the outcome of AKI
(adapted from Sackett)[35]

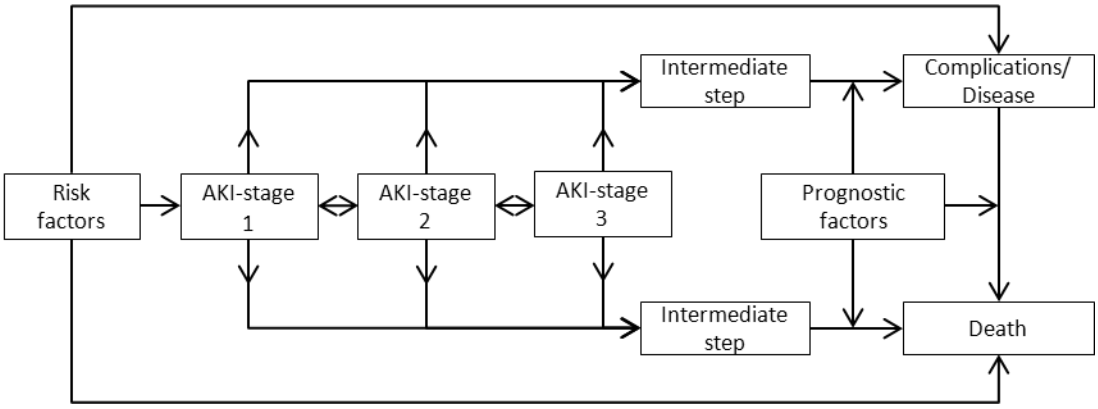


1.3.1 Conceptual model of AKI development and prognosis

Figure 1.2 illustrates a conceptual model of the development and prognosis of AKI. Factors that increase the risk of AKI are referred to as risk factors. Knowledge of these risk factors is important for developing primary prophylactic strategies to reduce the incidence of AKI. In contrast, factors that influence the prognosis after AKI onset are referred to as prognostic factors.

When evaluating the prognosis of AKI, several factors may be part of the causal pathway from AKI to the outcome of interest; these are referred to as intermediate steps. Thus, depending on the specific study and time of development, the same condition (e.g., CKD) can be a risk factor, a prognostic factor, and/or an intermediate step.

Figure 1.2. A conceptual model of risk and prognosis of AKI



Addressing effect measure modification by subgroup analysis

ICU patients are a heterogeneous population, and the prognostic implication of AKI may vary within subgroups of ICU patients. Such difference is referred to as 'effect measure modification'.[36] Knowledge of effect measure modification will improve our knowledge of the clinical course of AKI in different ICU groups. In this dissertation, we therefore also examine how prognosis after AKI is influenced by, e.g. age, comorbidity level, CKD, primary diagnosis during current hospitalization, and renal recovery before hospital discharge. This examination is performed by stratifying our analyses by these variables.

All three studies in this dissertation are prognostic studies that examine the prognostic implication of AKI in ICU patients overall and within subgroups of ICU patients. Understanding of prognosis and knowledge about prognostic factors may help improve our understanding of the disease process and help guide clinical decision making.

2 Background and existing literature

2.1 Long-term mortality after AKI in ICU patients (study I)

2.1.1 Background

Recent large cohort studies (> 1,000 ICU patients) have shown that AKI in ICU patients is associated with a relatively increased short-term mortality (in-hospital mortality or follow-up ≤ 90 days) compared with ICU patients without AKI (Table 2.1).[11,12,15-19,25,26] Most of these studies also reported an increased mortality by AKI severity. The reported adjusted relative risk estimates for short-term mortality range from 1.0 to 2.2 for patients with AKI-risk/stage 1; from 1.4 to 6.1 for patients with AKI-injury/stage 2; and from 1.59 to 8.6 for patients with AKI-failure/stage 3 (Table 2.1). However, AKI may also have adverse long-term implications for mortality.

Table 2.1 Short-term mortality (in-hospital mortality or follow-up ≤ 90 days) in ICU patients with RIFLE-equivalent defined AKI compared with ICU patients without AKI in large studies including more than 1,000 ICU patients

First author/ year	Design/setting	Study population	AKI definition and time of assessment	Prevalence of AKI	Outcome	Adjusted relative risk estimate for short-term mortality[a]
Bagshaw, 2008[17]	Multicenter cohort study, Australia and New Zealand	120,123 adult (age ≥ 18 years) ICU patients, 2000–2005	Maximum SCr or UO RIFLE stage at ICU admission	36.1% at ICU admission	In-hospital mortality	AKI-risk: 1.58 (1.5–1.7) AKI-injury: 2.54 (2.4–2.7) AKI-failure: 3.22 (3.0–3.4)
Bagshaw, 2008[18]	Multicenter cohort study, Australia and New Zealand	9,449 adult (age ≥ 18 years) ICU patients with a primary diagnosis of trauma, 2000–2005[c]	Maximum SCr or UO RIFLE stage at ICU admission	18.1% at ICU admission	In-hospital mortality	AKI-risk: 1.69 (1.3–2.1) AKI-injury: 1.88 (1.4–2.5) AKI-failure: 2.29 (1.5–3.7)
Clec'h, 2011[25]	Multicenter cohort study, French	8,639 adult (age ≥ 16 years) ICU patients without CKD, 1997–2009	Maximum eGFR RIFLE stage during ICU stay	32.9% during ICU stay	In-hospital mortality	AKI-risk: 1.58 (1.32–1.88) AKI-injury: 3.99 (3.43–4.65) AKI-failure: 4.12 (3.55–4.79)
Hoste, 2006[15]	Single-center cohort study, USA	5,383 adult (age ND) ICU patients without chronic hemodialysis, 2000–2001	Maximum eGFR or UO RIFLE stage during ICU stay	21.9% at ICU admission and additional 45.3% during ICU stay	In-hospital mortality	AKI-risk: 1.0 (0.68–1.56) AKI-injury: 1.4 (1.02–1.88) AKI-failure: 2.7 (2.03–3.55)
Joannidis, 2009[11]	Multicenter cohort study, multinational	16,784 adult (age ≥ 16) ICU patients without chronic renal failure, 2002	Maximum eGFR or UO RIFLE stage within 48 h of ICU admission	35.5% at ICU admission	In-hospital mortality	AKI-risk: 1.38 (1.17–1.63) AKI-injury: 1.90 (1.65–2.18) AKI-failure: 2.99 (2.66–3.36)
Mandelbaum, 2011[16]	Multicenter cohort study, USA	14,524 adult (age ≥ 15 years) ICU patients without ESRD, 2001–2007	Maximum AKI stage during ICU stay according to the SCr or UO AKIN criteria	57.0% during ICU stay	In-hospital mortality	AKI-stage 1: 1.38 (1.20–1.59) AKI-stage 2: 1.26 (1.06–1.50) AKI-stage 3: 2.48 (1.98–3.12)
Nisula, 2013[26]	Multicenter cohort study, Finland	2,901 adult (age ≥ 18 years) ICU patients without ESRD, 2011–2012	Maximum AKI stage during ICU stay according to the SCr or UO AKIN criteria	32.7% at ICU admission and additional 6.6% during ICU stay	90-day mortality	AKI-stage 1: 1.71 (1.31–2.23) AKI-stage 2: 1.78 (1.26–2.51) AKI-stage 3: 1.71 (1.28–2.29)
Ostermann, 2007[19]	Multicenter cohort study, UK and Germany	41,972 adult (age ND) ICU patient, 1989–1999	Maximum eGFR RIFLE stage during ICU stay	35.8% during ICU stay	In-hospital mortality	AKI-risk: 1.40 (1.28–1.53) AKI-injury: 1.96 (1.80–2.14) AKI-failure: 1.59 (1.43–1.76)
Thakar, 2009[12]	Multicenter cohort study, USA	325,395 adult (age ND) veteran affairs ICU patients without ESRD, 2001–2006	Maximum SCr AKI stage during ICU stay defined by the AKIN criteria	22.0% during ICU stay	In-hospital mortality	AKI-stage 1: 2.23 (2.17–2.30) AKI-stage 2: 6.08 (5.74–6.44) AKI-stage 3: 8.60 (8.07–9.15)

[a] Relative risk estimate is reported by hazard ratios or odds ratios and all compared with patients without AKI.
[b] Subgroup population from study population in the other study by Bagshaw and colleagues.[17]
Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; ND, not defined; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine; UO, urine output

2.1.2 Existing literature

In the literature search, we focused on the long-term prognosis (follow-up for more than 90 days) of AKI defined by RIFLE-equivalent criteria in ICU patients. We used the following query to search Medline (last search November 1, 2013):

("Critical Care"[MeSH] OR "Intensive Care Units"[MeSH] OR "Critical Illness"[MeSH])
AND
(("Acute Kidney Injury/mortality"[MeSH]) OR ("Acute Kidney Injury"[MeSH] AND "Mortality"[MeSH]))

The search was limited to English or Danish language articles and studies conducted in humans and resulted in 552 hits. After title review, 137 were found to be of relevance. Among these, 27 were selected for full article review. Two studies examined mortality after AKI with a follow-up period for more than 90 days.[13,37] Two additional studies were identified by cross references of these articles and review articles.[14,38] The four studies are summarized in Table 2.2.

In summary, all four studies found that patients with AKI had increased long-term mortality compared with patients without AKI.[13,14,37,38] In the two studies that examined the association between AKI severity and long-term mortality, taking into account potential confounding factors, mortality increased with AKI severity.[13,14]

2.1.3 Limitations of the existing literature

The existing literature on the long-term mortality after AKI in ICU settings is limited by recruitment at single centers,[13,14,37,38] including selected subpopulations of ICU patients (surgical or septic ICU patients),[13,14,38] lack of adjustment for confounders,[37] and loss to follow-up.[38] In addition, none of the existing studies examined whether the association varied in subgroups of ICU patients with different comorbidity levels, CKD status, surgical status, primary hospital diagnosis, treatment with mechanical ventilation, and treatment with inotropes/vasopressors.

Table 2.2 Studies of the association between AKI and long-term mortality (follow-up > 90 days) in ICU patients[a]

First Author/ Year	Design/Setting	Study population	AKI definition	Follow-up time	Results
Abosaif, 2005[37]	Single-center cohort study, UK	183 mixed medical and surgical ICU patients with admission SCr > 1.7 mg/dl (150 µmol/l) without CKD and 24 randomly selected patients admitted to the same ICU without having AKI at ICU admission, 2000–2003	AKI status at ICU admission using the RIFLE criteria (either change in eGFR or change in urine output)[b]	Up to 6 months from ICU admission	6-month mortality: – Without AKI: 25.0% – AKI-risk: 43.3% – AKI-injury: 53.6% – AKI-failure: 86.0%
Bihorac, 2009[13]	Single-center cohort study, USA	10,518 adult (age ND) surgical ICU patients without known CKD who survived to hospital discharge, 1992–2002	Maximum SCr RIFLE stage during hospitalization[c]	Up to 10 years from hospital discharge. Median or mean duration not reported	10-year mortality: – Without AKI: 35% – AKI-risk: 50% – AKI-injury: 56% – AKI-failure: 61% Adjusted HR (95% CI): – Without AKI: 1 (reference) – AKI-risk: 1.18 (1.08– 1.29) – AKI-injury: 1.43 (1.29–1.59) – AKI-failure: 1.57 (1.40–1.75) Adjusted HR (95% CI) stratified by renal recovery:[d] – Complete recovery: 1.20 (1.10–1.31) – Partial recovery: 1.45 (1.32–1.58) – No recovery: 2.67 (2.09–3.43)
Hobson, 2009[14]	Single-center cohort study, USA	2,973 adult (age ND) cardiothoracic surgical ICU patients without known CKD who survived to hospital discharge, 1992–2002	Maximum SCr RIFLE stage during hospitalization[c]	Up to 10 years from hospital discharge. Median or mean duration not reported	10-year mortality: – Without AKI: 37% – AKI-risk: 49% – AKI-injury: 58% – AKI-failure: 74% Adjusted HR (95% CI): – Without AKI: 1 (reference) – AKI-risk: 1.23 (1.06– 1.42) – AKI-injury: 1.45 (1.22–1.72) – AKI-failure: 2.14 (1.73–2.66) Adjusted HR (95% CI) stratified by renal recovery at hospital discharge:[d] – Complete recovery: 1.28 (1.11–1.48) – Partial recovery: 1.49 (1.27–1.74) – No recovery: 3.76 (2.46–5.76)

(Continues)

Table 2.2 Studies of the association between AKI and long-term mortality (follow-up > 90 days) in ICU patients[a] *(continued)*

Author/ Year	Design/Setting	Study population	AKI definition	Follow-up time	Results	
Lopes, 2010[38]	Single-center cohort study, Spain	304 adult (age ND) septic ICU patients without ESRD who survived to hospital discharge, 2002–2007	AKI as dichotomous variable defined by the RIFLE criteria using SCr measurement[e]	Mean follow-up was 21 months	6-month mortality:	
					− Without AKI:	2.2%
					− AKI:	8.3%
					1-year mortality:	
					− Without AKI:	6.0%
					− AKI:	16.9%
					2-year mortality:	
					− Without AKI:	8.9%
					− AKI:	34.2%
					Adjusted HR (95% CI):	
					− Without AKI:	1 (reference)
					− AKI:	1.4 (1.2–1.6)

[a] AKI defined by RIFLE-equivalent criteria.

[b] Baseline SCr was defined as preadmission SCr for up to 3 months before current admission. If not available, the lowest SCr during the current hospitalization was used as baseline.

[c] Baseline SCr defined as lowest of measured SCr at hospital admission or estimated by the MDRD equation assuming GFR of 75 ml/min/1.73 m^2.

[d] Complete recovery was considered if patient returned to their baseline RIFLE class; partial recovery if there was a persistent change in RIFLE class, but without persistent need for dialysis; no recovery defined by need for dialysis at time of hospital discharge.

[e] Pre-admission SCr was used as baseline SCr if available. If unavailable, baseline SCr was estimated by the MDRD equation assuming GFR of 75 ml/min/1.73 m^2.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MDRD, Modification of Diet in Renal Disease; ND, not defined; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine.

2.2 Risk of end-stage renal disease after dialysis-requiring AKI (study II)

2.2.1 Background

End-stage renal disease (ESRD) is a condition involving chronic impairment of kidney function that requires chronic need of dialysis or kidney transplantation.

Through the 1980s and 1990s, the incidence of ESRD has been rising in the developed world.[39,40] However, in the last decade, ESRD incidence seems to have stagnated, plateauing around 350 per million in the USA and 115 per million in Denmark.[39,40] The difference in ESRD incidence between the two countries may primarily by explained by ethnic differences, as African-Americans have four times the incidence rate of ESRD compared to Caucasians.[39] In 2012, almost 1 out 1,000 Danish residents was actively treated for ESRD.[40]

Patients with ESRD have impaired quality of life compared to both the general population and most other patients with various other chronic diseases.[41] In addition, ESRD is associated with considerable costs: In the USA, the annual treatment cost is estimated to be around $70,000.[39]

Animal studies suggest that AKI may have long-term implications for further renal function, also for those who initially recover their renal function after AKI.[42,43] Basile and colleagues found that ischemia induces AKI in rats with apparent initial complete renal recovery (creatinine clearance similar to sham-operated controls at post-injury weeks 2 and 4, and normal histology at post-injury weeks 4 and 8) had increased risk of proteinuria and intestinal fibrosis at post-injury week 40.[42] The possible long-term implications of AKI on renal function are further supported by a more recent animal study from Burne-Taney and colleagues. They found that transfer of lymphocytes from mice with renal ischemia can induce albuminuria in naive mice,[43] suggesting that AKI-induced activation of the immune system may predispose the patient to progressive renal dysfunction.

Several studies of ICU patients report dialysis dependency at hospital discharge in patients with dialysis-requiring AKI (D-AKI).[44-49] However, patients may become free of dialysis following hospital discharge, and

patients initially free of dialysis may still be at increased risk of ESRD. Therefore, studies on the long-term ESRD risk after D-AKI are needed to examine the potential need for systematic post-discharge follow-up of these patients to avoid further kidney damage and for development of prophylactic strategies.

2.2.2 Existing literature

We searched the existing literature for studies investigating the ESRD risk or dependency of dialysis after an episode of D-AKI among ICU patients using the following query in Medline (last search November 1, 2013):

("Critical Care"[MeSH] OR "Intensive Care Units"[MeSH] OR "Critical Illness"[MeSH])
AND
("Acute Kidney Injury"[MeSH])
AND
("Chronic Kidney Failure" [MeSH] OR "Renal Replacement Therapy" [MeSH] OR "Recovery of Function" [MeSH])

The following criteria were used to select relevant articles: (1) the study population consisted of ICU patients; (2) patients were defined by D-AKI; and (3) ESRD risk or dialysis dependency at a specified time point at 90 days or later after initiation of acute dialysis was reported.

This query resulted in 1,008 hits after restriction to studies in humans and English or Danish language articles. After titles were examined, 240 articles were identified as potentially relevant and selected for abstract review. Forty-six of these were selected for full article review, from which we identified 12 relevant articles. Finally, the reference list and articles citing the selected articles were reviewed, and one additional article was identified.[50] Table 2.3 outlines the findings on ESRD risk or dialysis-dependency of these 13 articles.

Table 2.3 Studies that report ESRD risk or dialysis dependency at 90 days or later after start of acute dialysis in adult ICU patients

Author/ year	Design/Country	Patients	D-AKI definition	Results on dialysis dependency or ESRD risk
Bagshaw, 2005[27]	Multicenter cohort study, Canada	240 adult (18 years or more) ICU patients with D-AKI without ESRD, 1999–2002	Acute requirement for dialysis with evidence of renal dysfunction (SCr ≥ 150 µmol/l)	Dialysis dependence among patients still alive at: – 90 days: 28% (27/96) – 1 year: 22% (19/87)
Bell, 2007[51]	Multicenter cohort study, Sweden	2,202 adult (age ND) ICU patients with D-AKI without ESRD, 1995–2004	Acute requirement for dialysis	ESRD risk among 90-day survivors: – 90 days: 9.4% (104/1102) – 91 days to 7 years: 3.4% (34/998)
Bellomo, 2009[52]	Multicenter randomized controlled trial, Australia and New Zealand	1,464 adult (18 years or more) ICU patients with D-AKI without ESRD, 2005–2008 assigned to low- or high-intensity continuous renal-replacement therapy	Acute requirement for dialysis with evidence of AKI by urine output < 100 ml/6 h, serum potassium > 6.5 mmol/l, pH < 7.2, plasma urea nitrogen level 25 mmol/l (70 mg/dl), SCr > 300 µmol/l (3.4 mg/dl), or clinically significant organ edema	Dialysis dependency among patients still alive at: – 28 days: 13.3% (121/912) (High intensity: 15.5%; low intensity: 12.2% – 90 days: 5.6% (45/810) (High intensity: 6.8%; low intensity: 4.4%)
Cartin-ceba, 2009[53]	Multicenter cohort study, USA, 2003–2006	1,065 adult (18 years or more) ICU patients with D-AKI without ESRD, 2003–2006	Acute requirement for dialysis with evidence of renal dysfunction according to the RIFLE criteria	Dialysis dependency of hospital survivors at: – 90 days: 37% (282/784)
Darmon, 2007[47]	Single-center cohort study, France	94 adult (age ND) cancer patients admitted to an ICU with D-AKI and without ESRD, 2000–2005	Acute requirement for dialysis	Among 180-day survivors treatment with dialysis for a minimum of: – 90 days: 22% (6/27)
Davies, 2010[54]	Single-center cohort study, UK	94 adult (age ND) ICU patients who underwent open surgical repair of ruptured abdominal aortic aneurysm, 2002–2008	Acute postoperative requirement for dialysis	Dialysis-dependency of patients still alive at: – 6 months: 33% (1/3)
Delannoy, 2009[55]	Multicenter cohort study, France	205 adult (18 years or more) ICU patients with D-AKI without ESRD, 2007–2008	Acute requirement for dialysis with evidence of renal dysfunction according to the RIFLE criteria	Dialysis dependency among patients still alive at: – 28 days: 27% (30/112) – 3 months: 13% (12/91) – 6 months: 12% (9/77)
Lin, 2009[56]	Multicenter cohort study, Taiwan	342 surgical (18 years or more) ICU patients with postoperative D-AKI without ESRD, 2002–2006	Acute requirement for dialysis	Dialysis dependency among hopspital patients still alive at: – 90 days: 15% (21/137)
McCarthy, 1996[57]	Multicenter cohort study, USA	142 adult (19 years or more) ICU patient with D-AKI without CKD, 1977–1979 and 1991–1992	Acute requirement for dialysis	Dialysis dependency of patients still alive at: – 1 year: 15% (9/60) (1977–1979: 4%; 1991–1992: 22%)
Saudan, 2006[31]	Single-center, randomized controlled trial, Switzerland	206 adult (age ND) ICU patients with D-AKI without ESRD randomly assigned to hemofiltration or hemodiafiltration, 2000–2003	Acute requirement for dialysis with evidence of AKI (UO < 200 ml/12 h and/or BUN > 30 mmol/l with UO < 1500 ml/12 h	Dialysis dependency among patients still alive at: – 90 days: 4.2% (4/95) (2.1% in both groups)

(Continues)

Table 2.3 Studies that report ESRD risk or dialysis-dependency at 90 days or later after start of acute dialysis in adult ICU patients (*Continued)*

Author/ year	Design/Country	Patients	D-AKI definition	Results on dialysis dependency or ESRD risk
Schiffl, 2013[58]	Multicenter cohort study, Germany	289 adult (age ND) ICU patients with clinically diagnosed of ischemic acute tubular necrosis and normal renal function prior to AKI (eGFR > 90 ml/min per 1.73 m^2) with D-AKI, 1996–2002	Acute requirement for dialysis	Dialysis dependency among patients and still alive at: - Hospital discharge: 0% (0/141) - 1 year: 0% (0/121)
Triverio, 2009[50]	Single-center randomized controlled trial, Switzerland[a]	206 adult (age ND) ICU patients with D-AKI without ESRD assigned hemofiltration or hemodiafiltration, 2000–2003	Acute requirement for dialysis with evidence of AKI (UO < 200 ml/12 h and/or BUN > 30 mmol/l with UO < 1500 ml/12 h	Dialysis dependency among patients and still alive at: - 3 years: 1.7% (1/60)
Yunos, 2012[59]	Single-center cohort study, Australia	1,533 ICU patients admitted to an ICU in part of 2008 and 2009. Among these, 83 ICU survivors were treated with dialysis	Acute requirement for dialysis	Dialysis dependency among ICU survivors with D-AKI at: - 90 days after discharge: 13.3% (11/83)

[a] Long-term follow-up study of the study by Saudan and colleagues[31]

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; D-AKI, dialysis-requiring AKI; ESRD, end-stage renal disease; h, hours; ICU, intensive care unit; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine; UO, urine output

In summary, Table 2.3 shows that ESRD risk and dialysis dependency after D-AKI vary largely in these 13 ICU studies. The most commonly reported measurement for long-term renal outcomes was 90-day dialysis dependency, or ESRD risk among 90-day survivors. The variation in ESRD risk and dialysis dependency at 90 days after initiating acute dialysis or after ICU discharge ranged between 4% and 37%.[27,31,47,51-53,55,56,59]

2.2.3 Limitations of the existing literature

The existing studies on the risk of ESRD or dialysis dependency for 90 days or more among ICU patients with D-AKI are all limited by a lack of a comparison cohort of ICU patients without D-AKI.[27,31,47,50-59] Most studies are hampered by inclusion of few ICU patients with D-AKI (< 350 patients).[27,31,47,50,54-58] In addition, only one ICU-based study reported the risk of ESRD among D-AKI patients who initially survived without developing ESRD.[51]

2.3 AKI and risk of cardiovascular diseases (study III)

2.3.1 Background

Cardiovascular morbidity following AKI may be one of the reasons for the increased mortality observed after AKI. In recent years, it has been recognized that AKI may have adverse effects on other organs than the kidney, such as the cardiovascular system.[60] This observation is supported by animal studies showing that AKI causes a systematic inflammatory response and activation of the renin–angiotensin system, which subsequently promotes apoptosis and interstitial/perivascular fibrosis in the myocardium, and ultimately cardiac dysfunction.[61,62] It has also been suggested that AKI can precipitate myocardial infarction (MI) and stroke.[63]

2.3.2 Existing literature

We searched the existing literature for studies investigating the risk of heart failure, MI, or stroke after AKI among ICU patients. We searched Medline for English and Danish language studies in humans using the following query (last search November 1, 2013):

("Critical Care"[MeSH] OR "Intensive Care Units"[MeSH] OR "Critical Illness" [MeSH])
AND
("Acute Kidney Injury"[MeSH])
AND
("Myocardial Infarction"[MeSH] OR "Heart Failure"[MeSH] OR "Stroke"[MeSH])

This search resulted in 32 articles. We used the following criteria to select relevant articles: (1) patients were defined by an episode of AKI defined by change in SCr and/or urine output, and (2) outcomes of interest were heart failure, MI, and/or cerebral stroke. None of these 32 articles were found to be relevant. We therefore expanded the search to include studies outside ICU settings, as follows:

("Acute Kidney Injury"[MeSH])
AND
("Myocardial Infarction"[MeSH] OR "Heart Failure"[MeSH] OR "Stroke"[MeSH])

A total of 575 additional articles were identified. After reading the titles, we collected and reviewed the abstracts of 50 potentially relevant articles. This review resulted in 10 articles for full article review. Of these, six were found to be relevant.[64-69] Two additional articles were identified in the references lists of the selected articles and articles citing these.[70,71] In this way, a total of eight studies were identified that examined heart failure, MI, and/or stroke risk after AKI. These eight studies are summarized in Table 2.4.

Table 2.4 Studies on the association between AKI and heart failure, myocardial infarction, and stroke

Author/ Year	Design/ Country	Study population	AKI definition	Follow-up time	Outcome[a]	Results[a]
Choi, 2010[70]	Multicenter cohort study, USA	17,325 HIV-infected patients from the Department of Veterans Affairs Clinical Case Registry, who survived at least 90 days after discharge from their first medical hospital admission, 1986–2006	Maximum AKI level during hospitalization classified according to the AKIN criteria.[b] AKI stage 2 and 3 were combined, and patients with dialysis-requiring AKI were examined separately.	Mean 5.7 years (SD: 4.8) from 90 days after current hospital admission	Heart failure hospitalization[c]	Adjusted HR (95% CI) for heart failure: − Without AKI: 1 (reference) − AKI stage 1: 1.17 (0.82–1.67) − AKI stage 2/3: 2.11 (1.07–4.16) − D-AKI: 4.20 (2.24-7.88) Adjusted HR (95% CI) for heart failure by recovery status: − Without AKI: 1 (reference) − AKI stage 1 ・with recovery: 1.00 (0.63–1.59) ・without recovery: 1.45 (0.90–2.34) − AKI stage 2/3 ・ with recovery: 1.90 (0.76–4.71) ・without recovery: 2.38 (0.88–6.42) − D-AKI: NA
Goldberg, 2009[71]	Single-center cohort study, Israel	1,957 patients admitted to a cardiac ICU with ST-segment MI who survived to hospital discharge, 2000–2007	Maximum AKI level during hospitalization defined by absolute change in SCr into five groups: No AKI, transient mild AKI, persistent mild AKI, transient moderate/severe AKI, and persistent moderate/severe AKI[d]	Median 36 months (range: 9–60) after hospital discharge	Heart failure [e] and recurrent MI hospitalization	Adjusted HR (95% CI) for heart failure: − Without AKI: 1 (reference) − Trans. mild AKI: 1.5 (0.8–2.8) − Pers. mild AKI: 1.7 (1.1–2.8) − Trans. moderate/severe AKI: 1.7 (1.1–2.9) − Pers. moderate/severe AKI: 2.0 (1.2–3.3) Adjusted HR (95% CI) for recurrent MI: − Without AKI: 1 (reference) − Trans. mild AKI: 0.6 (0.2–1.8) − Pers.mild AKI: 1.6 (0.9–1.8) − Trans.moderate/severe AKI: 1.4 (0.7–3.0) − Pers. moderate/severe AKI: 1.4 (0.7–2.8)
James, 2011[64]	Population-based cohort study, Canada	14,782 adult (≥ 18 years) residents in Alberta, Canada, who underwent CAG and survived to hospital discharge, 2004–2006	Maximum AKI level within 7 days from CAG or before potential subsequent CABG according to the AKIN criteria	Median 19.7 months (IQR: 10.8–28.8) from hospital discharge	Heart failure, MI, and stroke hospitalization[f]	Adjusted HR (95% CI) for heart failure: − Without AKI: 1 (reference) − AKI stage 1: 1.48 (1.16–1.91) − AKI stage 2/3 2.17 (1.49–3.15) Adjusted HR (95% CI) for MI: − Without AKI: 1 (reference) − AKI stage 1: 1.47 (1.12–1.91) − AKI stage 2/3: 1.19 (0.70–2.02) Adjusted HR (95% CI) for stroke: − Without AKI: 1 (reference) − AKI stage 1: 1.07 (0.61–1.89) − AKI stage 2/3: 1.18 (0.43–3.19)
Lindsay, 2003[65]	Single-center cohort study, USA.	4,882 patients who underwent successful PCI and who survive to hospital discharge, 1994–2000.[g]	SCr increase ≥ 50% from pre PCI to post PCI measurement during hospitalization	For up to one year[h]	MI[i]	Adjusted OR (95% CI) for MI: − Without AKI: 1 (reference) − AKI: 2.0 (1.3–3.2)

Table 2.4 Studies on the association between AKI and heart failure, myocardial infarction, and stroke *(continued)*

Author/ Year	Design/ Country	Study population	AKI definition	Follow-up time	Outcome[a]	Results[a]
Olsson, 2013[66]	Nationwide cohort study, Sweden	24,018 patients who underwent isolated CABG and survived the first 30 days after surgery, 2000–2008	Maximum AKI level during hospitalization, classified according to the AKIN criteria[b]	Mean 4.1 years (SD: 2.4) from hospital discharge	Heart failure hospitalization[f]	Adjusted HR (95% CI) for HF admission: – Without AKI: 1 (reference) – AKI stage 1: 1.69 (1.48–1.94) – AKI stage 2: 2.33 (1.69–3.22) – AKI stage 3: 1.87 (0.84–4.20)
Rihal, 2002[67]	Multicenter cohort study, USA	7,075 patients who had PCI and survived to hospital discharge at Mayo Clinic, 1996 to May 2000	AKI defined by absolute SCr increase ≥ 0.5 mg/dl (44.2 µmol/l) form pre-procedural values up to 48 hours after PCI	For up to 5 years after PCI	MI hospitalization	Cumulative incidence (No AKI vs. AKI) 6-month: 2.7% vs. 4.3% 1-year: 3.8% vs. 7.0% 5-year: 10.5% vs. 18.5%
Ryden, 2012[72]	Single-center cohort study, Sweden	7,594 who underwent first isolated CAGB and were alive 48 hours postoperatively, 1995–2006	Maximum AKI stage around second postoperative day according to the AKIN criteria[j]	From day of classification of AKI and for up to 60 days	Stroke[k]	Adjusted OR (95% CI) for stroke: – Without AKI: 1 (reference) – AKI stage 1: 2.34 (1.43–3.82) – AKI stage 2/3: 6.52 (2.97–14.3)
Zhou, 2012,[68]	Single-center cohort study, China	1,005 patients hospitalized in a coronary care unit with heart failure and survived to hospital discharge, 2003–2010.[l]	AKI during hospitalization classified according to the RIFLE criteria[m]	Up to one year; mean or median duration not available	Heart failure readmission[f]	Proportion of hospital survivors with readmission for HF: Patients with eGFR ≥ 60 ml/min/1.73 m^2 – Without AKI: 3.8% – AKI: 9.0% Patients with eGFR < 60 ml/min/1.73 m^2 – Without AKI: 2.9% – AKI: 14.0%

[a] Only results on outcomes similar to our outcomes of interest are included in the table.

[b] Baseline SCr was defined as most recent SCr before surgery[66] or hospitalization.[70]

[c] Defined by discharge diagnoses and procedural codes in Veteran Affairs (VA) and non-VA data sources.

[d] Transient mild AKI: Peak serum creatinine ≥ 0.30–0-49 mg/dl (26.5–44 µmol/l) higher than serum creatinine at any point during hospitalization and SCr return to a level that was < 0.30 mg/dl (26.5 µmol/l) higher than admission SCr before hospital discharge. Persistent mild AKI: Peak SCr ≥ 0.30–0-49 mg/dl (26.5–44 µmol/l) higher than SCr at any point during hospitalization and SCr did not return to a level that was < 0.30 mg/dl (26.5 µmol/l) higher than admission SCr before hospital discharge. Moderate/severe transient AKI: Peak SCr ≥ 0.50 mg/dl (44 µmol/l) higher than SCr at any point during hospitalization and SCr did return to a level that was < 0.50 mg/dl (44 µmol/l) higher than admission SCr before hospital discharge. Persistent moderate/severe AKI: Peak SCr ≥ 0.50 mg/dl (44 µmol/l) higher than SCr at any point during hospitalization and SCr did not return to a level that was < 0.50 mg/dl (44 µmol/l) higher than admission SCr before hospital discharge. All others defined as without AKI.

[e] Readmission for the management of HF (defined by presence of new symptoms of dyspnea with pulmonary venous congestion on X-ray with intestinal or alveolar edema.

[f] Assessed by ICD codes.

[g] Patient who had AMI < 48 hours prior to PCI or serum creatinine ≥ 1.2 mg/dl (106 µmol/l) were not included.

[h] One-year follow-up was obtained in 86% and 84% of patients with and without AKI, respectively.

[i] Follow-up performed by mail or telephone with the patient or physician. Report of MI was subsequently confirmed by medical chart, by presence of new pathologic Q-waves in electrocardiogram associated with an elevation of creatinine kinase MB at least two times upper limit of normal.

[j] Baseline SCr was defined as hospital admission SCr.

[k] Defined as central neurological symptoms persisting for at least 72 hours, presumably identified from medical records.

[l] Several exclusion criteria, e.g., no record of SCr within 6 months before hospital admission, eGFR < 30 ml/min/1.73 m^2, multiorgan failure, during current admission, etc.

[m] Baseline was defined as mean SCr level from 6 months before to hospital admission.

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney network; AMI, acute myocardial infarction; BUN, blood urea nitrogen; CABG, coronary arterial bypass grafting; CAG, coronary angiography; CI, confidence intervals; D-AKI, dialysis-requiring AKI; ESRD, end-stage renal disease; HR, hazard ratio; ICD, international classification of diseases; ICU, intensive care unit; IQR, interquartile range; NA, not available; OR, odds ratio; PCI, percutaneous coronary intervention, RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine; SD, Standard deviation; UO, urine output.

Heart failure

Five studies have examined the association of AKI with heart failure.[64,66,68,70,71] In summary, all of these studies reported that AKI as a complication of coronary angiography,[64] MI,[71] coronary arterial bypass grafting (CABG) surgery,[66] heart failure,[68] and human immunodeficiency virus (HIV)[70] increased the risk of subsequent hospitalization for heart failure. In addition, studies that divided AKI into stages of AKI severity found that the relative risk of hospitalization for heart failure increased with severity of AKI.[64,66,70,71] Furthermore, both studies that examined how renal recovery at hospital discharge influenced the risk of heart failure indicated that patients with renal recovery have a reduced risk of heart failure compared with patients without renal recovery at hospital discharge.[70,71]

Myocardial infarction

Four studies have examined the risk of MI after AKI, each in a different study population.[64,65,67,71] These authors found that coronary angiography, percutaneous coronary intervention, and MI complicated by AKI are associated with increased risk of subsequent MI hospitalization.[64,65,67,71]

Stroke

Only two studies have examined the risk of stroke after AKI.[64,72] In a single-center Swedish study, Rydèn and colleagues found that CABG complicated by AKI stage 1 was associated with a two-fold increased risk of stroke up to 60 days postoperatively, and for AKI stages 2–3, they found a six-fold increased risk.[72] In contrast, a more recent study by James and colleagues identified no marked association between AKI and hospitalization for stroke in patients who underwent coronary angiography and survived to hospital discharge.[64]

2.3.3 Limitations of the existing literature

Previous studies have primarily examined the association between AKI and cardiovascular diseases in patients with AKI secondary to an MI or coronary intervention.[64-68,71,72] No earlier study has focused on the

association between AKI and incident hospitalization for heart failure, MI, or stroke, and only one previous study was conducted among ICU patients (cardiac ICU patients). Therefore, it remains unknown if AKI is associated with incident hospitalization for heart failure, MI, and stroke in ICU patients.

3 Aims of the dissertation

The literature review revealed that only few ICU studies have examined the association of AKI and mortality with follow-up for more than 90 days. None of these examined if the association varied within subgroups of ICU patients with, e.g., different comorbidity level and CKD. In addition, the literature review also showed that no previous ICU study has compared ESRD risk after D-AKI in patients to ICU patients without D-AKI. Finally, our review revealed that previous studies on the association between AKI and cardiovascular diseases primarily examined AKI secondary to MI or coronary intervention in non-ICU patients, and no studies have focused on the association between AKI and first-time cardiovascular diseases.

To address these limitations in the existing literature, we conducted three studies with the following aims:

Study I: Examine (1) the association of AKI at ICU admission and mortality during one year of follow-up and (2) whether the influence of AKI varies in subgroups of ICU patients with different comorbidity levels, CKD status, surgical status, primary hospital diagnosis, and treatment with mechanical ventilation or inotropes/vasopressors.

Study II: Examine (1) the short-term risk of ESRD after D-AKI and (2) the long-term risk in those patients who initially recovered sufficient renal function to become dialysis independent. In addition, to examine (3) whether the association of D-AKI and ESRD risk varies across subgroups of ICU patients according to age, gender, presence of CKD, presence of diabetes, and surgical status.

Study: III: To (1) examine the association between AKI and the 3-year risk of first-time hospitalization for heart failure, MI, and stroke among ICU patients who survived to hospital discharge and (2) determine whether the association was modified by AKI recovery status at hospital discharge.

4 Patients and methods

4.1 Setting

We conducted study I and study III in Northern Denmark (former counties of Aarhus and North Jutland) with a mixed rural and urban area and approximately 1.15 million inhabitants. Study II was conducted within Denmark, with a population of approximately 5.4 million inhabitants.[73]

The Danish National Health Service provides tax-supported health care to all Danish residents, with universal access to public hospitals and general practitioners. All intensive care and associated treatments are provided at these public hospitals. In 2010, Denmark had 48 ICUs, including 37 multidisciplinary ICUs, four neurosurgical ICUs, three cardiothoracic ICUs, two multidisciplinary/cardiothoracic ICUs, one multidisciplinary/neurosurgical ICU, and one cardiac ICU. In Northern Denmark (study area for studies I and III), there are 12 ICUs, eight multidisciplinary, one cardiothoracic, one mixed cardiothoracic/multidisciplinary, one mixed neurosurgery/multidisciplinary, and one neurosurgical.[3]

4.2 Data sources

4.2.1 The Civil Registration System (studies I–III)

The Civil Registration System assigns a unique 10-digit civil registration number at birth or at immigration to all Danish residents. The Civil Registration System was established in 1968 and contains complete and daily updated information on residency, vital status and exact date of death for all residents. The unique civil registration number permits unambiguous linkage of all Danish medical and administrative registries.[74]

4.2.2 Danish National Registry of Patients (studies I–III)

The Danish National Registry of Patients (DNRP) includes data on all non-psychiatric hospitalizations in Denmark since 1977. Since 1995, the DNRP also has included data from outpatient clinic visits, emergency room visits, and psychiatric units. DNRP records contain each patient's civil registration number, hospital and department, dates of admission and discharge, type of admission (emergency vs. planned), surgical and

major procedures performed, and one primary and up to 19 secondary discharge diagnoses assigned by the discharging physician. According to Danish guidelines, the primary diagnosis represents the main reason for the admission. Diagnoses are assigned by the discharging physicians. Since 1994, discharge diagnoses have been coded using the *International Classification of Diseases, 10th revision* (ICD-10).[75] Information on ICU admissions and major treatments during the ICU stay, such as mechanical ventilation, acute dialysis, and treatment with inotropes/vasopressors, has been coded in the DNRP with a high degree of accuracy since 2005.[76]

4.2.3 The laboratory information systems database (studies I and III)

Computer-based laboratory information systems are a central tool for medical doctors at hospitals, private clinics, and general practices. All tests analyzed at hospital laboratories are immediately entered into these systems. Therefore, these systems hold laboratory test results from virtually all tests performed at hospitals, private specialists and at general practitioners (except tests for which analyses are usually performed at the offices of private specialists and general practitioners as point-of-care tests, such as C-reactive protein, hemoglobin, and blood glucose).

Data from these laboratory information systems started to be transferred to the laboratory information system database in 1990, but data were first considered complete in the North Jutland County in 1997 and Aarhus County in 2000. Data include each patient's civil registration number, date of the test, test name, test code (Nomenclature, Properties and Units in Laboratory Medicine codes and/or local Danish laboratory codes), and unit.[77]

Plasma creatinine measurement in the laboratory database

In Northern Denmark, the assay used for plasma creatinine (equivalent to SCr[78]) measurement varied between laboratories and also within laboratories during our study period. However, standardization of plasma creatinine measurement to an isotope dilute mass spectrometry reference was implemented in Northern Denmark from 2005 to 2011 (Table 4.1). Furthermore, the analytic method also changed in most

laboratories in this time period from an alkaline picrate method (Jaffe method) to enzymatic methods (Table 4.1) (personal communication with the departments of Clinical Biochemistry in Northern Denmark).

Table 4.1 Method for the measurement of plasma creatinine and date of start of standardization plasma creatinine measurements to isotope dilute mass spectrometry reference in Northern Denmark from 2004 to 2011

Laboratory	Analysis methods	Standardization
Sygehus Vendsyssel	Jaffe methods until 31 March 2007; enzymatic methods thereafter	Exact date unknown, but standardized methods are currently used.
Aalborg University Hospital	Enzymatic methods since 1 April 2004	1 April 2010
Himmerland Hospital	Enzymatic methods since 1 April 2004	1 April 2010
Dronninglund Hospital	Enzymatic methods since 1 April 2004	1 April 2010
Randers Hospital	Jaffe methods until 15 March 2005; enzymatic methods thereafter	19 January 2005
Silkeborg Hospital	Jaffe methods until 19 January 2005; thereafter, enzymatic methods	19 January 2005
Aarhus University Hospital, Skejby	Enzymatic methods throughout the study period	19 January 2005
Aarhus University Hospital, Nørrebrogade	Jaffe methods until 18 January 2005; thereafter, enzymatic methods	19 January 2005
Aarhus University Hospital, Tage Hansens Gade	Jaffe method until 15 June 2008; thereafter enzymatic	19 January 2005

4.2.4 The Danish National Registry of Patients in Regular Dialysis or Transplantation (study II)

The Danish National Registry on Regular Dialysis or Transplantation (NRDT) was established in 1990. This registry contains valid information on all Danish residents with CKD actively treated with either dialysis or kidney transplantation. Only patients with a chronic need for dialysis or a kidney transplant are included in the NRDT, thus excluding patients with reversible kidney failure.[79] One nephrologist at each of the 15 nephrological departments in Denmark is responsible for transferring the data to the NRDT. Registry data include, among others, the date of first active treatment, treatment modalities, and underlying kidney disease.[79]

4.2.5 The Aarhus University Prescription Database (study III)

Prescribed medication is fully or partly reimbursed by the Danish Health Care system. Community pharmacies collect data on all prescriptions filled by general practitioners and medical doctors at outpatient clinics at or outside hospitals when dispensed. These data are electronically transmitted to the regional subdivisions of the National Health Service for reimbursement. Data from these systems in the Central and North Denmark regions are transferred to the Aarhus University Prescription Database. Variables included in this database are each patient's civil registration number, type of drug according to the Anatomic Therapeutic Chemical Classification System, dosage, and prescription date.[80]

4.3 Study design

All three studies were designed as population-based cohort studies.

4.4 Study period

The study periods for all three studies were 1 January 2005 to 31 December 2010. We started the study period 1 January 2005 because information on ICU admissions and major treatments during the ICU stay, such as mechanical ventilation, acute dialysis, and treatment with inotropes/vasopressors, has been coded in the DNRP with a high degree of accuracy since 2005.[76]

4.5 Study population

The study populations in studies I and III were all adult (aged 15 or older) residents in Northern Denmark with a first-time ICU admission in Northern Denmark in the study period. The study area was chosen based on availability of laboratory date (i.e., plasma creatinine) to classify and stage AKI. We also required one year of residency in Northern Denmark before the index hospitalization. This requirement ensured availability of data on previous plasma creatinine from the laboratory database to identify baseline plasma creatinine used to both define AKI and estimate baseline renal function by eGFR to categorize CKD status.

In study III, we further restricted our study population to patients who survived to hospital discharge. This restriction was done to ensure our outcome of interest (i.e., hospital admission with heart failure, MI, and stroke) followed AKI.

In study II, we included all adult (aged 15 or older) Danish residents with a first-time ICU admission in Denmark in the study period. We only included patients who survived to 90 days after ICU admission because our outcome of ESRD was defined as the need for kidney transplant or chronic dialysis for more than 90 days. Therefore, patients would not be at risk of ESRD in the first 90 days after ICU admission.

In all three studies, we categorized the ICU patients into major disease groups by the primary ICD-10 diagnosis of the current hospitalization. In addition, we also categorized patients into five groups according to surgical status: non-surgical, elective non-cardiac surgery, elective cardiac surgery, acute non-cardiac surgery, and acute cardiac surgery. We used the Nordic Medico-Statistical Committee classification of surgical procedures in the DNRP to classify patients as cardiac and non-cardiac surgical based on whether they had any surgical procedure and on the type of surgical procedure up to 7 days before or on the day of ICU admission, respectively.[81] Surgical ICU patients were further divided into acute or elective, according to the hospital admission type registered in the DNRP.

4.6 Exposures

The exposure in study I was AKI stage at ICU admission according to the creatinine criteria in the RIFLE classification: AKI-risk, AKI-injury, and AKI-failure (Table 1.1). Patients who did not fulfill these criteria were classified as without AKI. The plasma creatinine measurements used to classify AKI status and stage were highest plasma creatinine at ICU admission compared to the baseline plasma creatinine level of the patient. We searched the laboratory database for the highest plasma creatinine measurement on the day of ICU admission. For patients with missing values on that day, we calculated the mean of the highest creatinine measurements available on the day before and the day after ICU admission. Baseline creatinine was defined as the most recent creatinine measurement from an outpatient clinic or general practitioner in the

period from one year to 7 days before the current hospitalization.[82] Creatinine assessments up to 7 days before the current hospitalization were not considered because the AKI process may have started before hospital admission. For patients lacking a measured baseline creatinine level and without CKD, we estimated baseline creatinine using the four-variable version of the MDRD equation based on age, race, and gender, as suggested in the RIFLE criteria. This assumes a normal GFR of 75 ml/min per 1.73 m^2.[7]

In study II, the exposure was D-AKI. D-AKI was defined as the need for acute dialysis from ICU admission to hospital discharge and maximum within 90 days from ICU admission. This information was retrieved from the DNRP using procedure codes for acute dialysis in the DNRP.

The exposure in study III was similar to study I AKI stage; however, now maximum AKI stage from ICU admission to hospital discharge was used, according to the later-suggested KDIGO criteria.[9] Maximum AKI stage was based on the highest plasma creatinine measurement from the day of ICU admission until hospital discharge compared to the baseline plasma creatinine level. Baseline plasma creatinine was identified by a similar method as that used for study I.

4.7 Outcomes

4.7.1 Mortality (study I)

The outcome in study I was time to death within 0–30 days and 31–365 days from ICU admission. We divided the follow-up period into two time periods to examine short- and long-term mortality. Data on mortality were gathered from the civil registration system.

4.7.2 End-stage renal disease (study II)

ESRD was the outcome of interest in study II. It was defined as a kidney transplant or need for dialysis for more than 90 days because chronic disease of the kidney is defined as impairment for more than 90 days.[83] We obtained data on ESRD from the NRDT.

4.7.3 Cardiovascular disease (study III)

Information on cardiovascular diseases, i.e., heart failure, MI, and stroke, were all obtained from the DNRP as a subsequent hospital admission with a primary or secondary diagnosis of heart failure, MI, or stroke. We were interested in studying first-time admission for our outcomes; therefore, prevalent cases were omitted by excluding all patients with any previous diagnosis of heart failure, MI, or stroke up to 10 years prior to or during the current hospital admission.

4.8 Covariates

We obtained information on age and gender from the civil registration system. Data on comorbidity were primarily obtained from the DNRP using inpatient and outpatient diagnoses up to 5 years (study I and study II) and 10 years (study III) prior to current hospital admission.

In studies I and III, we had access to laboratory data from the entire study area; therefore, we instead identified patients with CKD by an eGFR below 60 ml/min per 1.73 m^2 (CKD stage 3 or higher according to National Kidney Foundation guidelines).[83] The eGFR was estimated by the four-variable MDRD equation.[84] We used the most recent plasma creatinine measurement from an outpatient clinic or general practitioner one year to 7 days before the current hospitalization to compute eGFR.[82]

Some patients with diabetes might not have had an admission to the hospitals. Therefore, we used information from the prescription database and the laboratory database to obtain data on diabetes in addition to data from the DNRP in study III. Patients with a hemoglobin A1c level above 6.5% up to one year before the current admission[85] or a prescription for an anti-diabetic drug (insulin or oral anti-diabetic agent) up to 5 years before the current hospital admission were also defined as having diabetes. However, diabetes patients identified solely by a prescription of metformin and with co-existing polycystic ovary syndrome were classified as not having diabetes.

Information on preadmission use of cardiovascular drugs and non-steroidal anti-inflammatory drugs (NSAIDs) used in study III were retrieved from the Aarhus University Prescription Database.

In study III, information on renal recovery at hospital discharge was also obtained. Patients were considered to have achieved renal recovery at hospital discharge if they did not receive any type of dialysis up to 7 days before hospital discharge and their last plasma creatinine measurement before discharge was less than 50% above their baseline level, i.e., they no longer fulfilled the criteria for AKI.[7]

4.9 Statistical analysis

In study I, we followed patients from day of ICU admission. For study II, follow-up started 90 days after ICU admission, as our outcome of interest was ESRD, defined as a kidney transplant or need for dialysis for more than 90 days. In study III, follow-up started at hospital discharge to ensure that the outcomes (hospital admission with heart failure, MI, and stroke) succeeded AKI. Analyses were performed using the statistical software package Stata 11.1 (StataCorp LP, College Station, TX, USA).

All data were obtained from Danish registries, which are available to researchers, and their use does not require approval or informed consent. The studies were approved by the Danish Data Protection Agency (record number 2009-41-3987).

4.9.1 Cumulative incidence (studies I–III)

We used the Kaplan–Meier method to compute the cumulative mortality in study I. In study II and study III, we examined the risk of ESRD and cardiovascular diseases. Thus, patients who died during follow-up will no longer be at risk of the outcomes under study. We therefore used the cumulative incidence methods taking death into account as a competing risk to estimate the cumulative incidence in studies II and III.[86]

4.9.2 Cox proportional hazards regression models (studies I–III)

We used Cox proportional hazards regression models in all three studies to compute crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The assumptions of proportional hazards were for all models checked graphically using log(-log(survival probability)) and found to be appropriate.

In study I, we examined the one-year mortality risk for patients with AKI-risk, AKI-injury, and AKI-failure, all compared with ICU patients without AKI. We controlled for potential confounders by adjusting for age, gender, CKD, Charlson Comorbidity Index level, and surgical status.

In our ESRD risk study (study II), we compared ESRD risk for patients with and without D-AKI within two time periods: 90-day to 180-day and 181-day to 5-year. In the regression model, we adjusted for age group, gender, CKD, diabetes, MI, heart failure, peripheral vascular disease, cerebrovascular disease, malignant neoplasm, and surgical status.

In study III, we compared the 3-year risk of each outcome (heart failure, MI, and stroke) for patients with AKI stage 1 and AKI stages 2–3 with that of patients without AKI among hospital survivors. In the multivariate analyses, we adjusted for age, gender, ischemic heart disease except MI, cerebrovascular disease except stroke, hypertension, peripheral vascular disease, diabetes, CKD, cancer, surgical status, and current use of angiotensin-converting enzyme (ACE)/angiotensin II (ATII) inhibitors, beta blockers, calcium channel antagonists, aspirin, diuretics, nitrates, statins, and NSAIDs.

4.9.3 Subgroup analyses (studies I–III)

The association between an exposure and an outcome may vary in subgroups of ICU patients. We therefore stratified our overall analyses by age groups, Charlson Comorbidity Index level, surgical status, primary diagnosis during current hospitalization, CKD, and ICU treatments in study I. In study II, we stratified by age groups, gender, CKD, diabetes, and surgical status. Additionally, the prognosis after AKI may vary in patients who do or do not recover their renal function at hospital discharge, so we stratified by renal recovery status at hospital discharge (study III).

4.9.4 Sensitivity analyses (studies I–III)

To examine the robustness of our results, we conducted two sensitivity analyses.[87]

Multiple imputation (studies I and III)

We excluded patients without a plasma creatinine measurement at ICU admission in study I and without a plasma creatinine measurement from ICU admission to hospital discharge in study III. This exclusion could potentially lead to selection bias if the association between exposure and outcome is different for those excluded compared to those who participated in the study.[88] We therefore conducted a sensitivity analysis to examine the potential influence of excluding these patients using multiple imputations in study I and study III. We estimated AKI levels for patients with missing plasma creatinine using multiple imputations,[89-91] generating five imputed datasets. HRs were calculated as the average HRs of the five datasets, corrected for between- and within-imputation variation.[89-91] The imputation model included all measured covariates in Table 1 in article 1 (study I) and Table 1 in article 3 (study III), the outcomes of interest, and the Nelson-Aalen estimator of the cumulative baseline hazard evaluated at the observed survival time.[92]

Potential residual confounding due to incomplete data on CKD and CKD severity (study II)

CKD is known to be associated with both AKI and ESRD. Therefore, CKD is a potentially important confounder when examine the ESRD risk after D-AKI (study II). Data on CKD in study II were retrieved from the DNRP. However, data on CKD might be incomplete, and our results may therefore be prone to residual confounding of CKD. To examine this possible limitation, we repeated the overall analysis after restricting the study population to residents in Northern Denmark. In Northern Denmark, we had access to data on plasma creatinine measurements. In this way, we could define CKD by eGFR level.[83]

5 Results

5.1 Study I (Mortality risk)

5.1.1 Characteristics

The study population comprised 30,762 adults admitted to an ICU in Northern Denmark during the 6-year observation period, after excluding 192 (0.6%) patients receiving chronic dialysis or with a previous kidney transplant, and 1,578 (4.9%) patients lacking information on plasma creatinine level at ICU admission.

Patients without a plasma creatinine measurement were younger and had less comorbidity and shorter hospital stays compared with patients with a plasma creatinine measurement (Appendix to Article 1). Total time of follow-up was 23,850 person years (median duration = 365 days (interquartile range (IQR): 258–365)).

The median age in the study population was 65 years, and 13,352 (43%) patients were female. At ICU admission, a total of 4,793 (15.6%) patients had AKI; these included 1,986 (6.5%) patients with AKI-risk, 1,311 (4.3%) with AKI-injury, and 1,496 (4.9%) with AKI-failure. Preadmission baseline plasma creatinine results were available for 21,028 (68.4%) patients and were estimated using the MDRD equation for the remaining 9,734 (31.6%).

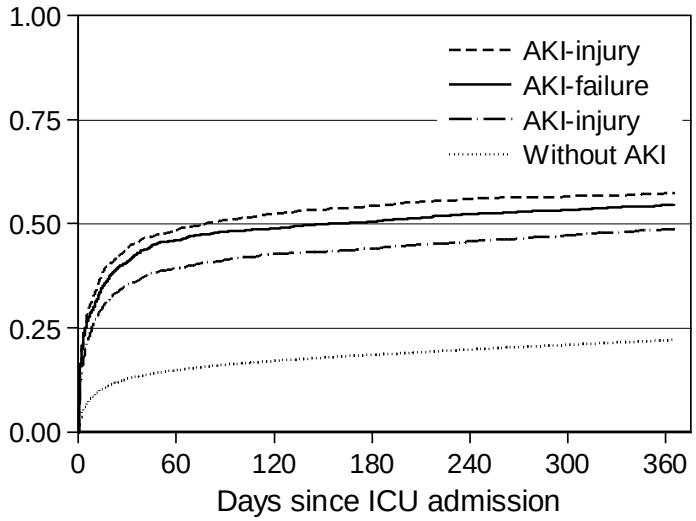
Patients with AKI were older and had more comorbidity, including CKD, than other ICU patients. The most frequent diagnoses among AKI patients were other infectious disease, gastrointestinal/liver disease, and cardiovascular disease. AKI was less frequent in elective surgical patients (cardiac and non-cardiac) compared with both non-surgical and acute surgical patients (cardiac and non-cardiac). In addition, patients with AKI were more often treated with mechanical ventilation, inotropes/vasopressors, and, as expected, dialyses during their ICU stay compared to patients without AKI (Table 1 in Article 1).

During the time between ICU admission and hospital discharge (median duration = 8 days (IQR: 3–17)), another 3,099 (10.1%) patients developed AKI.

5.1.2 Mortality

The one-year mortality was 22.1% for patients without AKI, 48.7% for patients with AKI-risk, 57.4% for patients with AKI-injury, and 54.7% for patients with AKI-failure (Figure 5.1).

Figure 5.1 Cumulative 1-year mortality by AKI-stage, Northern Denmark, 2005–2010



Abbreviations: AKI: acute kidney injury; ICU: intensive care unit

0–30-day overall mortality

Thirty-day mortality was 35.5% for the AKI-risk group, 44.2% for the AKI-injury group, and 41.0% for the AKI-failure group, compared with 12.8% for patients without AKI. This corresponded to adjusted HRs of 1.96 (95% CI: 1.80–2.13), 2.60 (95% CI: 2.38–2.85), and 2.41 (95% CI: 2.21–2.64), respectively, all compared with ICU patients without AKI (Table 5.1).

31–365-day overall mortality

Among patients surviving 30 days (n = 25,539), mortality between 31 days and 365 days was 20.5% for the AKI-risk group, 23.8% for the AKI-injury group, and 23.2% for the AKI-failure group compared with 10.7% for patients without AKI. The adjusted HRs were 1.33 (95% CI: 1.17–1.51), 1.60 (95% CI: 1.37–1.87), and 1.64 (95% CI: 1.42–1.90), respectively, compared with ICU patients without AKI (Table 5.1).

Table 5.1 Cumulative 30-day and 31–365-day mortality and corresponding hazard ratios by AKI status

	Dead (n)	N at period start	Cumulative mortality % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
0–30 day					
Without AKI	3,327	25,969	12.8 (12.4–13.2)	1 (reference)	1 (reference)
AKI-risk	704	1,986	35.5 (33.4–37.6)	3.17 (2.93–3.45)	1.96 (1.80–2.13)
AKI-injury	579	1,311	44.2 (41.5–46.9)	4.21 (3.86–4.60)	2.60 (2.38–2.85)
AKI-failure	613	1,496	41.0 (38.5–43.5)	3.83 (3.52–4.18)	2.41 (2.21–2.64)
31–365 day					
Without AKI	2,421	22,642	10.7 (10.3–11.1)	1 (reference)	1 (reference)
AKI-risk	263	1,282	20.5 (18.4–22.8)	2.04 (1.80–2.32)	1.33 (1.17–1.51)
AKI-injury	174	732	23.8 (20.9–27.0)	2.46 (2.11–2.87)	1.60 (1.37–1.87)
AKI-failure	205	883	23.2 (20.6–26.1)	2.38 (2.06–2.75)	1.64 (1.42–1.90)

[a] Adjusted for age, gender, Charlson Comorbidity Index score, surgical status, and chronic kidney disease.
Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit

Subgroup analyses

The association between AKI and 30-day mortality was evident in all subgroups of the ICU population. The relative impact of AKI was most pronounced in patients aged 15–40 years; the mortality of patients without AKI in this subgroup was 2.5%, compared to 16.8% for patients with any degree of AKI. This corresponds to an adjusted HR of 4.87 (95% CI: 3.33–7.13). The relative impact of AKI was also more pronounced among both elective cardiac and non-cardiac surgical patients and among acute cardiac surgical patients with adjusted HR values of 3.76 (95% CI: 1.62–8.77), 3.43 (95% CI: 2.65–4.45), and 3.27 (95% CI: 2.48–4.31), respectively, and among patients with low Charlson Comorbidity Index level (adjusted HR = 2.55 (95% CI: 2.31–2.81)) because of a low baseline hazard. By diagnostic category, the adjusted HRs ranged from 1.53 (95% CI: 1.19–1.96) among patients with a primary registry diagnosis of septicemia to 2.54 (95% CI: 2.20–2.93) for patients with a primary diagnosis of gastrointestinal/liver disease and 2.59 (95% CI: 2.12–3.16) for cancer patients. The association between AKI and 30-day mortality was also evident in patients treated with mechanical ventilation (adjusted HR = 1.60 (95% CI: 1.48–1.72)) and inotropes/vasopressors (adjusted HR = 1.77 (95% CI: 1.63–1.91)), and in patients with CKD (adjusted HR = 1.80 (95% CI: 1.60–2.02)).

After 30 days of follow-up, AKI still was associated with increased mortality in most subgroups, although to a less pronounced degree than in the 30-day period after ICU admission (Table 5.2).

Table 5.2 Cumulative 31–365 day mortality and corresponding adjusted hazard ratios within subgroups

	N	Without AKI	With AKI	
		Cumulative mortality % (95% CI)	Cumulative mortality % (95% CI)	Adjusted HR[a] (95% CI)
Overall	25,539	10.7 (10.3–11.1)	22.2 (20.7–23.7)	1.49 (1.36–1.63)
Age group				
15–39	4,516	1.7 (1.4–2.1)	5.1 (2.8–8.9)	1.52 (0.79–2.94)
40–59	6,627	7.5 (6.9–8.2)	15.4 (12.9–18.3)	1.58 (1.27–1.97)
60–79	11,561	13.8 (13.2–14.5)	23.8 (21.7–26.0)	1.41 (1.25–1.59)
≥80	2,835	21.8 (20.2–23.6)	34.2 (30.1–38.5)	1.46 (1.22–1.74)
Charlson Comorbidity Index Score				
Low (score: 0)	13,834	5.5 (5.1–5.9)	15.3 (13.4–17.4)	1.88 (1.59–2.22)
Medium (score: 1–2)	8,403	14.5 (13.7–15.4)	25.8 (23.3–28.5)	1.60 (1.40–1.83)
High (score ≥ 3)	3,302	24.6 (23.0–26.2)	29.6 (26.1–33.5)	1.12 (0.94–1.34)
Surgical status[b,c]				
Non-surgical	9,234	10.3 (9.6–10.9)	22.1 (20.0–24.5)	1.42 (1.24–1.63)
Surgical				
Acute non-cardiac	8,038	13.1 (12.4–13.9)	24.0 (21.5–26.5)	1.46 (1.27–1.68)
Acute cardiac	873	5.6 (4.2–7.4)	21.4 (14.5–30.9)	4.44 (2.63–7.51)
Elective non-cardiac	4,039	14.3 (13.2–15.4)	19.1 (15.2–23.9)	1.28 (0.98–1.67)
Elective cardiac	3,355	3.8 (3.2–4.5)	12.0 (6.4–21.8)	2.96 (1.50–5.85)
Primary diagnosis during current hospitalization				
Septicemia	340	21.8 (15.9–29.6)	17.7 (13.0–23.7)	0.81 (0.49–1.32)
Other infectious diseases	2,380	10.0 (8.8–11.4)	19.8 (16.2–24.0)	1.28 (1.02–1.61)
Endocrinology diseases	498	10.2 (7.4–14.0)	12.1 (8.0–18.2)	0.85 (0.48–1.50)
Cardiovascular diseases	6,829	6.2 (5.7–6.9)	20.9 (17.5–24.8)	2.21 (1.76–2.78)
Respiratory diseases	1,202	22.0 (19.6–24.7)	31.6 (25.2–39.1)	1.27 (0.94–1.73)
Gastrointestinal or liver diseases	2,486	14.0 (12.6–15.6)	25.3 (21.7–29.4)	1.75 (1.41–2.17)
Cancer or other neoplasm	3,350	24.5 (23.0–26.0)	32.0 (26.9–37.7)	1.17 (0.93–1.46)
Trauma or poisoning	4,560	5.3 (4.6–6.0)	20.7 (16.2–26.2)	1.85 (1.36–2.53)
Other	3,894	8.1 (7.3–9.1)	19.0 (15.7–22.9)	1.37 (1.08–1.75)
Chronic kidney disease[d]				
Yes	3,084	19.5 (18.0–21.1)	28.7 (25.2–32.5)	1.43 (1.19–1.71)
No	22,455	9.6 (9.2–10.0)	20.5 (18.9–22.2)	1.48 (1.33–1.64)
ICU treatments				
Mechanical ventilation	8,976	10.6 (10.0–11.4)	24.6 (22.3–27.0)	1.49 (1.30–1.70)
Inotropes/vasopressors	7,691	12.3 (11.5–13.2)	24.7 (22.5–27.1)	1.46 (1.27–1.66)

[a] Compared to patents without AKI within subgroups and adjusted for age, gender, Charlson Comorbidity Index score, surgical status, and chronic kidney disease.

[b] Surgical status and cardiac surgical status identified by surgery and surgical type on or up to 7 days before ICU admission, respectively.

[c] Acute and elective status classified according to hospital admission type.

[d] Known eGFR < 60 ml/min per 1.73 m^2.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit

5.1.3 Sensitivity analysis

The associations between AKI and mortality were similar after imputation of AKI level in patients missing a plasma creatinine measurement at ICU admission. The adjusted 30-day HRs were 1.95 (95% CI: 1.80–2.12) for the AKI-risk group, 2.62 (95% CI: 2.39–2.86) for the AKI-injury group, and 2.42 (95% CI: 2.22–2.64) for the AKI-failure group. In the period 31–365 days following ICU admission, the adjusted HRs were 1.36 (95%

CI: 1.19–1.54), 1.61 (95% CI: 1.38–1.88), and 1.66 (95 % CI 1.43–1.92) for the AKI-risk, AKI-injury, and AKI-failure groups, respectively.

5.2 Study II (End-stage renal disease risk)

5.2.1 Characteristics

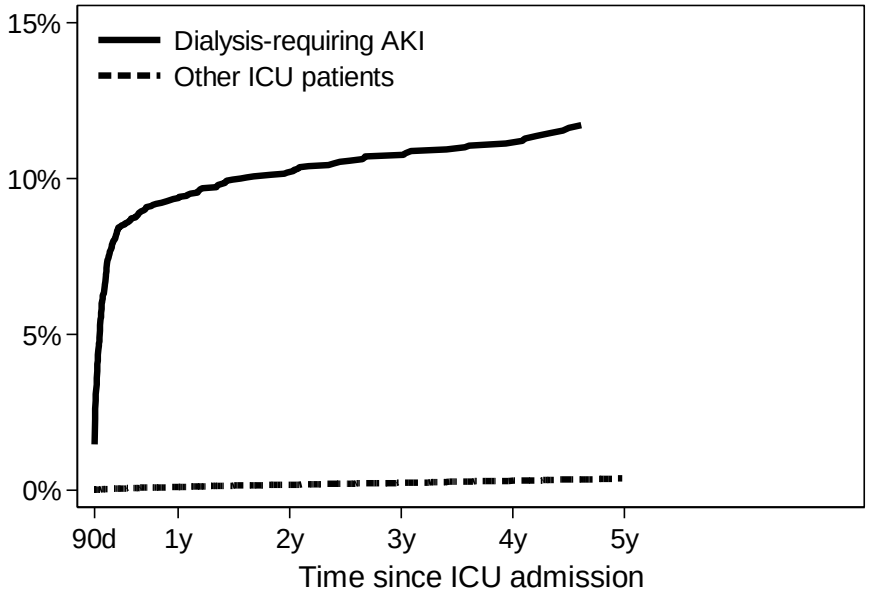
The study population consisted of 107,937 adult ICU patients. Patients who died during the first 90 days after ICU admission (n = 33,367) and patients with ESRD or any previous dialysis treatment (n = 1,697) were not considered for the study. Total follow-up time was 230,278 person-years, with a median duration of 3.1 years (IQR: 1.6–4.8).

We found that 3,062 (2.8%) patients who survived for 90 days or more had an episode of D-AKI following ICU admission. Compared to other ICU patients, patients with D-AKI were slightly older (median age = 65 years (IQR: 55–73) vs. median age = 62 years (IQR: 46 to 72)), more often male, and in general with more comorbidity, in particularly CKD, diabetes, and hypertension. They also had longer hospital stays, were more often treated with mechanical ventilation or inotropes/vasopressors, and more often had a primary diagnosis of septicemia.

5.2.2 Risk of end-stage renal disease

The overall 5-year ESRD risk was 11.7% (95% CI: 10.5–13.0) for ICU patients with an episode of D-AKI, compared with 0.4% (95% CI: 0.3%–0.4%) for other ICU patients (Figure 5.2).

Figure 5.2 Cumulative 5-year risk curve of ESRD by D-AKI status, Denmark, 2005–2010



Abbreviations: D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit

Risk of ESRD within 90 to 180 days

Of the 3,062 ICU patients with D-AKI who survived for 90 days after ICU admission, 260 developed ESRD within 180 days following ICU admission (cumulative risk = 8.5% (95% CI: 7.5%–9.5%)) compared with 57 patients out of 104,875 other ICU patients (cumulative risk = 0.1% (95% CI: 0.0%–0.1%)). This corresponds to an unadjusted HR for ESRD of 165.9 (95% CI: 124.6–221.0) for D-AKI patients compared with other ICU patients. After adjusting for potential confounders, with CKD being the most important, the adjusted HR was 105.6 (95% CI: 78.1–142.9) (Table 5.3).

Risk of ESRD within 181 days to 5 years

Among ICU patients who survived 180 days after ICU admission without developing ESRD, the 181-day to 5-year ESRD risk for patients with D-AKI was 3.8% (95% CI: 3.0%–4.8%), compared with 0.3% (95% CI: 0.3%–0.4%) for other ICU patients. This result corresponds to an unadjusted HR of 13.5 (95% CI: 10.5–17.5) and an adjusted HR of 6.2 (95% CI: 4.7–8.1) (Table 5.3). Again, CKD was the most important confounder in the adjusted model.

Table 5.3 Cumulative risk and hazard ratios of ESRD for ICU patients with D-AKI compared to other ICU patients

Follow-up/cohort	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
90 to 180 days					
D-AKI	3,062	260	8.5 (7.5–9.5)	165.9 (124.6–221.0)	105.6 (78.1–142.9)
Other ICU patients	104,875	57	0.1 (0.0–0.1)	1 (reference)	1 (reference)
181 days to 5 years					
D-AKI	2,579	76	3.8 (3.0–4.8)	13.5 (10.5–17.5)	6.2 (4.7–8.1)
Other ICU patients	101,417	249	0.3 (0.3–0.4)	1 (reference)	1 (reference)

[a] Adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer, and surgical status

Abbreviations: CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; HR, hazard ratio; ICU, intensive care unit; n, number

Subgroup analyses

The association between D-AKI and ESRD was evident within all subgroups of ICU patients in the 90- to 180-day period (Table 5.4). Within the 181-day to 5-year follow-up period, we found that the association between D-AKI and risk of ESRD was higher for patients without CKD (adjusted HR = 11.9 (95% CI: 8.5–16.8)) than for patients with CKD (adjusted HR = 2.8 (95% CI: 1.8–4.3)) due to a high risk of ESRD even without AKI (cumulative risk = 7.2% (95% CI: 5.9%–8.8%)). Nonetheless, the absolute risk difference between D-AKI patients and other ICU patients was higher for patients with CKD compared to patients without CKD. The relative impact of D-AKI on risk of future ESRD was also most pronounced in the youngest age group, in females, and among elective surgical patients, but similar among diabetic and non-diabetic patients (Table 5.5).

Table 5.4 ESRD risk and adjusted HR between 90 and 180 days after ICU admission within subgroups

	Other ICU patients			D-AKI			
	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Adjusted HR[a] (95% CI)
Age, years							
15–49	30,629	9	0.03 (0.01–0.06)	533	30	5.6 (3.9–7.8)	121.6 (54.2–272.9)
50–69	42,078	26	0.06 (0.04–0.09)	1,444	120	8.3 (7.0–9.8)	91.6 (58.7–143.0)
≥ 70	32,159	22	0.07 (0.04–0.10)	1,085	110	10.1 (8.4–12.0)	109.0 (67.6–175.6)
Gender							
Female	45,441	21	0.05 (0.03–0.07)	1,116	89	8.3 (6.8–9.9)	117.3 (70.8–194.5)
Male	59,435	36	0.06 (0.04–0.08)	1,946	171	8.4 (6.9–10.1)	98.7 (67.7–143.9)
Chronic kidney disease							
Yes	1,961	38	1.94 (1.40–2.62)	325	90	27.7 (22.9–32.6)	17.4 (11.8–25.7)
No	102,914	19	0.02 (0.01–0.03)	2,737	170	6.2 (5.3–7.2)	313.0 (193.4–506.4)
Diabetes							
Yes	8,715	15	0.17 (0.10–0.28)	547	62	11.3 (8.8–14.2)	52.4 (29.0–94.8)
No	96,160	42	0.04 (0.03–06)	2,515	198	7.9 (6.8–9.0)	122.6 (86.5–173.8)
Surgical status							
No surgery	38,406	32	0.08 (0.06–0.12)	1,250	129	10.3 (8.7–12.1)	83.1 (55.2–125.0)
Surgery							
Acute non-cardiac	30,559	11	0.04 (0.02–0.06)	1,126	83	7.3 (5.9–9.0)	145.3 (76.4–276.2)
Acute cardiac	2,510	4	0.16 (0.06–0.40)	162	8	4.9 (2.3–9.0)	25.2 (6.7–94.9)
Elective non-cardiac	19,320	7	0.04 (0.02–0.07)	276	28	10.1 (6.9–14.0)	218.9 (91.1–521.1)
Elective cardiac	14,080	3	0.02 (0.00–0.06)	248	12	4.8 (2.6–8.0)	136.2 (33.1–561.3)

[a] Compared to ICU patents not treated with dialysis within the same subgroup and adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer, and surgical status.

Abbreviations: CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit; HR, hazard ratio; n, number

Table 5.5 ESRD risk and adjusted HR between 181 days and 5 years after ICU admission within subgroups

	Other ICU patients			D-AKI			
	Total n	ESRD n	Cumulative risk % (95% CI)	Total n	ESRD n	Cumulative risk % (95% CI)	Adjusted HR[a] (95% CI)
Age, y							
15–49	30,299	38	0.18 (0.13–0.24)	484	14	3.4 (1.9–5.5)	12.8 (6.5–25.4)
50–69	40,750	129	0.44 (0.37–0.53)	1,227	33	3.9 (2.6–5.4)	5.3 (3.6–8.0)
≥ 70	30,330	82	0.35 (0.28–0.43)	864	29	4.0 (2.7–5.7)	6.9 (4.4–10.9)
Gender							
Female	43,955	99	0.30 (0.24–0.37)	952	34	5.0 (3.2–7.5)	7.3 (4.8–11.1)
Male	57,462	150	0.36 (0.30–0.42)	1,627	42	3.3 (2.3–4.6)	5.5 (3.9–8.0)
Chronic kidney disease							
Yes	1,795	102	7.23 (5.94–8.81)	218	28	18.4 (12.2–25.6)	2.8 (1.8–4.3)
No	99,622	147	0.21 (0.18–0.25)	2,361	48	2.7 (2.0–3.6)	11.9 (8.5–16.8)
Diabetes							
Yes	8,232	83	1.51 (1.20–1.88)	434	29	10.3 (6.7–14.7)	6.0 (3.9–9.4)
No	93,102	166	0.23 (0.20–0.27)	2,145	47	2.7 (2.0–3.6)	6.7 (4.7–9.4)
Surgical status							
No surgery	36,986	100	0.35 (0.28–0.42)	1,033	33	4.3 (2.9–6.1)	6.0 (4.0–9.2)
Surgery							
Acute non-cardiac	29,341	73	0.35 (0.27–0.44)	960	23	3.0 (1.9–4.5)	5.8 (3.5–9.5)
Acute cardiac	2,478	5	0.27 (0.10–0.62)	143	1	1.0 (0.1–5.9)	3.9 (0.4–39.9)
Elective non-cardiac	18,640	34	0.25 (0.17–0.36)	226	5	2.8 (1.0–6.1)	8.7 (3.2–23.3)
Elective cardiac	13,972	37	0.39 (0.28–0.54)	217	14	8.2 (4.6–13.2)	10.8 (5.3–22.3)

[a] Compared to ICU patents not treated with dialysis within the same subgroup and adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer, and surgical status.

Abbreviations: CI, confidence interval; D-AKI, dialysis requiring acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit; HR, hazard ratio; n, number

5.2.3 Sensitivity analyses

In Northern Denmark, we had access to complete laboratory data. The use of eGFR (eGFR < 60 ml/min per 1.73 m^2) to identify patients with CKD did not change the overall results compared to the use of ICD-10 codes to retrieve information on CKD status. However, the results were slightly lower when CKD stages were included in the regression model compared to CKD as a dichotomous variable (Table 5.6).

Table 5.6 Adjusted hazard ratio for ESRD risk after D-AKI by different approaches for the definition of CKD, Northern Denmark, 2005–2010

Follow-up/cohort	Adjusted HR[a] (95% CI)
90 to 180 days	
CKD defined by ICD-10 codes	86.1 (54.8–135.3)
CKD defined as known eGFR < 60 ml/min per 1.73 m^2	87.4 (56.0–136.3)
CKD stages[b]	71.1 (44.8–113.0)
181 days to 5 years	
CKD defined by ICD-10 codes	8.3 (5.2–13.1)
CKD defined as known eGFR < 60 ml/min per 1.73 m^2	7.8 (5.0–12.1)
CKD stages[b]	5.8 (3.6–9.2)

[a] Adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer, and surgical status

[b] No CKD (unknown eGFR or eGFR ≥ 60 ml/min per 1.73 m^2), CKD stage 3 (eGFR: 30–59 ml/min per 1.73 m^2), CKD stage 4–5 (eGFR < 30 ml/min per 1.73 m^2)

Abbreviations: CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; ICD-10, International Classification of Diseases 10th revision; ICU, intensive care unit; n, number

5.3 Study III (Cardiovascular risk)

5.3.1 Characteristics

The study population comprised 21,556 ICU patients who survived to hospital discharge after exclusion of those with a previous kidney transplant or chronic dialysis treatment (n = 314), those with a previous or concurrent diagnosis of heart failure, MI, or stroke (n = 6,702), and those lacking a plasma creatinine measurement at or after ICU admission (n = 1,846). Compared to patients with a plasma creatinine measurement, patients lacking this measurement were younger, had less comorbidity, and had a markedly shorter hospital stay (Appendix to Article 1).

We found that 4,792 (22.2%) of the 21,556 ICU patients had an episode of AKI, with 2,666 (12.4%) having AKI stage 1 and 2,126 (9.9%) AKI stages 2–3. Patients with AKI were older and more often male and had a

higher degree of comorbidity than other ICU patients. AKI patients also were more frequently current users of cardiovascular drugs and NSAIDs. The primary diagnosis during the current hospitalization was most frequently cardiovascular disease for patients with AKI stage 1, infectious disease for patients with AKI stages 2–3, and trauma and poisoning for patients without AKI. Patients with AKI were more frequently treated with mechanical ventilation and inotropes/vasopressors and had longer hospital stays (Table 1 in article 3). Median duration of follow-up was 2.7 years for all three outcomes.

5.3.2 Risk of heart failure

During the 3 years after hospital discharge, 2.2% of patients without AKI, 5.0% with AKI stage 1, and 5.0% with AKI stages 2–3 were hospitalized with first-time heart failure. Compared to patients without AKI, the adjusted HR was 1.35 (95% CI: 1.08–1.69) for patients with AKI stage 1 and 1.46 (95% CI: 1.15–1.87) for patients with AKI stages 2–3, both compared to patients without AKI (Figure 5.3 and Table 5.7).

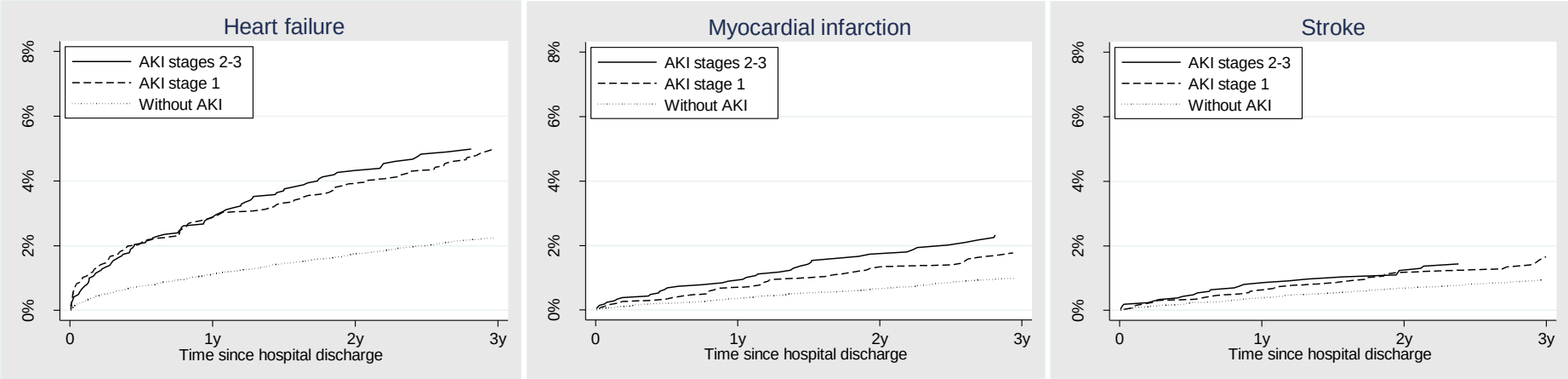
5.3.3 Risk of myocardial infarction

The 3-year cumulative risk of MI was 1.0% for patients without AKI, 1.8% for patients with AKI stage 1, and 2.3% for patients with AKI stages 2–3. The adjusted HR was 1.05 (95% CI: 0.72–1.52) for patients with AKI stage 1 and 1.49 (95% CI: 1.04–2.15) for patients with AKI stages 2–3 (Figure 5.3 and Table 5.7).

5.3.4 Risk of stroke

Stroke risk within the first 3 years after hospital discharge was 0.9% for patients without AKI, 1.7% for patients with AKI stage 1, and 1.4% for patients with AKI stages 2–3. The adjusted HRs were 1.09 (95% CI: 0.74–1.60) for patients with AKI stage 1 and 1.08 (95% CI: 0.70–1.65) for patients with AKI stages 2–3 (Figure 5.3 and Table 5.7).

Figure 5.3 Three-year cumulative incidence of heart failure, myocardial infarction, and stroke by AKI stages



Abbreviations: AKI, acute kidney injury; y, year

Table 5.7 Three-year risk of cardiovascular diseases according to AKI stages, Northern Denmark, 2005–2010

	Without AKI		AKI stage 1				AKI stages 2–3			
	Events, n	Cumulative risk % (95% CI)	Events, n	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Events, n	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Heart failure	320	2.2 (2.0–2.5)	114	5.0 (4.2–6.0)	2.43 (1.96–3.01)	1.35 (1.08–1.69)	91	5.0 (4.0–6.1)	2.53 (2.01–3.01)	1.46 (1.15–1.87)
MI	135	1.0 (0.8–1.2)	38	1.8 (1.3–2.4)	1.93 (1.35–2.76)	1.05 (0.72–1.52)	40	2.3 (1.7–3.1)	2.68 (1.88–3.82)	1.49 (1.04–2.15)
Stroke	131	0.9 (0.8–1.1)	35	1.7 (1.2–2.4)	1.83 (1.26–2.65)	1.09 (0.74–1.60)	26	1.5 (1.0–2.1)	1.79 (1.17–2.72)	1.08 (0.70–1.65)

[a] Adjusted for age, gender, ischemic heart disease, cerebrovascular disease, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status, and use of ACE inhibitors/AT2 antagonists, beta blockers, calcium channel antagonists, acetylsalicylic acid, diuretics, nitrates, statins, and NSAIDs.

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; AT2, angiotensin 2; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MI, myocardial infarction; NSAIDs, Non-steroidal anti-inflammatory drugs; n, number

5.3.5 Renal recovery

Of the 4,792 ICU patients with AKI who survived to hospital discharge, a total of 3,888 (81.1%) recovered renal function by the time of discharge. The increased risk of heart failure following any stage of AKI and of MI following AKI stages 2–3 persisted in patients who recovered their renal function, although with less pronounced risk compared to most patients without renal recovery (Table 5.8).

Table 5.8 Risk of cardiovascular diseases according to renal recovery status among AKI patients at hospital discharge

	Recovery (n = 3,888)		Non-recovery (n = 904)	
	Events, n	Adjusted HR[a] (95% CI)	Events, n	Adjusted HR[a] (95% CI)
AKI stage 1				
Heart failure	98	1.29 (1.02–1.63)	15	1.80 (1.07–3.04)
MI	35	1.06 (0.72–1.55)	3	0.81 (0.26–2.57)
Stroke	32	1.12 (0.75–1.67)	3	0.99 (0.31–3.13)
AKI stages 2–3				
Heart failure	62	1.49 (1.13–1.96)	30	1.55 (1.06–2.27)
MI	23	1.27 (0.81–2.00)	17	1.02 (1.20–3.40)
Stroke	19	1.17 (0.78–1.90)	7	0.91 (0.42–1.97)

[a] Adjusted for age, gender, ischemic heart disease except MI, cerebrovascular disease except stroke, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status, and current use of ACE inhibitors/AT2 antagonists, beta blockers, calcium channel antagonists, acetylsalicylic acid, diuretics, nitrates, statins, and NSAIDs.

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; AT2, angiotensin 2; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NSAIDs, Non-steroidal anti-inflammatory drugs; n, number

5.3.6 Sensitivity analysis

The associations between AKI and mortality were similar after imputation of AKI level in patients missing a plasma creatinine measurement at ICU admission (Table 5.9).

Table 5.9 Adjusted HR of cardiovascular diseases after multiple imputation of AKI stages in patients without measured plasma creatinine from ICU admission to hospital discharge, Northern Denmark, 2005–2010[a]

	AKI stage 1 Adjusted HR[b] (95% CI)	AKI stages 2–3 Adjusted HR[b] (95% CI)
Heart failure	1.34 (1.07–1.65)	1.45 (1.15–1.84)
MI	1.08 (0.74–1.58)	1.53 (1.07–2.20)
Stroke	1.11 (0.76–1.64)	1.10 (0.71–1.69)

[a] Compared with patients without AKI.

[b] Adjusted for age, gender, ischemic heart diseases except MI, cerebrovascular diseases except stroke, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status, and use of ACE inhibitors/AT2 antagonists, beta blockers, calcium channel antagonists, acetylsalicylic acid, diuretics, nitrates, statins, and NSAIDs.

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ; AT2, angiotensin 2; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MI, myocardial infarction; NSAIDs, Non-steroidal anti-inflammatory drugs

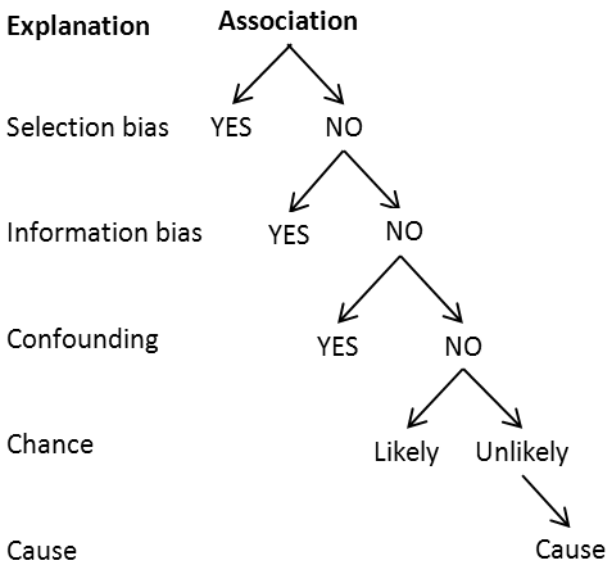
6 Discussion

6.1 Methodological considerations

All three studies in this dissertation are etiological prognostic studies in which the aim was to examine if AKI was causally related to time to death, ESRD, and cardiovascular disease. This approach is in contrast to prediction studies, which aim is to develop a score model of available variables that predicts the outcome of future patients.[33] In ICU settings, the acute physiology and chronic health evaluation and the simplified acute physiology score are examples of commonly used prediction score models that predict in-hospital mortality.[81,93]

Several factors may influence the validity and robustness of our results, and the association identified can therefore have several explanations that require consideration before inferring a causal relationship. We consider here how problems in selection and information of participants, confounders, and chance may have affected our results (Figure 6.1).[94]

Figure 6.1. Association and cause
(adapted from Fletcher)[94]



6.1.1 Selection bias

Selection bias can occur in studies due to methods for participant inclusion and factors that influence loss to follow-up, if the association between exposure and outcome varies among those who participate and those who do not participate in the study.[88]

All three studies in this dissertation were conducted in well-defined populations with uniform access to health care, using high-quality administrative and medical databases. These features together with virtually complete follow-up data minimized the risk of selection bias. Nevertheless, exclusion of patients without a plasma creatinine measurement at ICU admission (study I) and without a plasma creatinine measurement from ICU admission until hospital discharge (study III) might have introduced selection bias. However, the overall result for mortality did not change after imputation of AKI level in patients without plasma creatinine measurement at or following ICU admission in study I and study III.

6.1.2 Information bias

Erroneous information about exposure or outcome may introduce information bias. In this dissertation, exposures and outcome are either dichotomous or on a categorical scale; thus, misclassification of these variables might lead to information bias.[88]

Misclassification can be divided into differential and non-differential misclassification. When the misclassification of the exposure depends on the status of the outcome, or the misclassification of the outcome depends on the exposure status, the misclassification is differential. Differential misclassification can both underestimate and overestimate an effect. In contrast, if the misclassification of dichotomous exposures and outcomes is each independent of the other, the misclassification is non-differential and will most likely bias the result towards a null effect or not bias the result at all.[88,95] However, when the exposure variable has more than two levels (studies I and III), non-differential misclassification between two of the exposure levels will make the relative risk estimate come together. Therefore, only for the exposure group with the highest risk estimate can we assume, that the results are biased towards a null effect.[88,95]

AKI

In studies I and III, the exposure was AKI as defined and staged by change in plasma creatinine according to the creatinine criteria in the RIFLE and KDIGO classifications, respectively.[7,9] Unfortunately, it is difficult to examine the extent of any misclassification because no gold standard for AKI exists. Still, we presumably misclassified some patients because of (1) estimation of baseline plasma creatinine assuming eGFR of 75 ml/min per 1.73 m^2 in patients without an outpatient plasma creatinine measurement and without known CKD; (2) non-renal factors that influence plasma creatinine level; and/or (3) bias and impression of the plasma creatinine measurements.[24,96,97]

Dialysis-requiring AKI

The exposure in study II was D-AKI. D-AKI was defined as a procedure of acute dialysis following ICU admission in the DNRP. A previous validation study has shown that the positive predictive value of the procedure code 'acute dialysis' among ICU patients is 98.0% (95% CI: 91.0–99.8%).[76] In addition, we expect the completeness of this code to be high because the code for acute dialysis is used in the Diagnostic Related Group system, which is employed for reimbursement of health care costs to the hospital owners (the regions) from the state and municipality of the patient.[98] Therefore, misclassification of D-AKI is expected to be limited.

Death

In study I, the outcome was time to death. This information was obtained from the Civil Registration System, which is updated daily and contains complete information on all Danish residents since 1968 on among others migration and exact date of death.[74] Therefore, misclassification of death is unlikely.

ESRD

ESRD was the outcome of interest in study II. Information on ESRD was retrieved from the NRDT, and ESRD data in this database were found to be highly valid in a recent study.[79] The completeness of ESRD status in the NRDT was 97.2% (2,934/3,020) when compared to data in the DNRP, and the positive predictive value

of the ESRD diagnosis was 100% (108/108) for those who survived more than 90 days after first active treatment with dialysis, using the medical chart as the reference standard.[79] Thus, misclassification of ESRD is also expected to be limited.

Heart failure, MI, and stroke

In study III, information bias may have occurred as a result of misclassification of our outcome variables of heart failure, MI, and/or stroke. These data were obtained from the DNRP as any inpatient diagnosis. Previous validation studies have found that the positive predictive values of diagnoses recorded in the DNRP for heart failure, MI, and stroke are 81%, 92%, and 84%, respectively.[99-101] Thus, it is possible that some patients diagnosed with one of the three diseases did not fulfill the strict diagnostic criteria for the registered diagnosis. This misclassification is not thought to be related to AKI and thus should be non-differential. A false-positive registration of these variables in the DNRP would therefore bias our results towards a null association.

To the best of our knowledge, no studies have examined the sensitivity (as an estimate of the completeness) of MI and stroke diagnosis in the DNRP. Although patients with sudden death due to MI or stroke outside hospitals would not be included in the DNRP, we expect the sensitivity to be high because of the mainly acute symptomatic nature of MI and stroke. In contrast, the overall sensitivity of heart failure diagnosis registration in the DNRP has been reported to be as low as 29% after any single hospital admission using a combination of clinical symptoms and echocardiographic findings as the reference standard.[99] However, patients wrongly classified as not having heart failure, MI, or stroke during follow-up will presumably not bias HR estimates because such misclassifications are expected to be non-differential.[95]

The lack of sensitivity of a heart failure diagnosis limits our ability to exclude all patients with heart failure prior to AKI. Therefore, some of the found associations might be explained by an increased risk of AKI among patients with heart failure. Despite this limitation, we believe it is unlikely that misclassification of heart failure can explain the entire association found between AKI and heart failure. In addition, we cannot

rule out that the observed null result between the association of AKI and stroke could partly be explained by non-differential misclassification of stroke.

6.1.3 Confounding

Confounding is study specific and thus occurs only in the context of a particular study. Confounding may be considered as a mixing of effect, which implies that the effect of the exposure is mixed together with the effect of another risk factor.[95] Three criteria have to be fulfilled before a variable can be considered as a confounder. The variable must be (1) an extraneous risk factor for the outcome or a proxy or marker of the cause; (2) imbalanced in the exposure categories; and (3) not part of the causal pathway.[95]

Potential confounding in observational studies can be handled in the study design by restriction and matching or in the analysis by stratification, standardization, and adjustment. In this dissertation, we handled confounding by restriction (studies I to III), adjustment (studies I to III), and stratification (studies I and II).

In general, misclassification of confounders will result in residual confounding because of incomplete adjustment in the regression analysis. Information on comorbidities was primarily obtained from the hospital registry, the DNRP. Some of these comorbidities might be especially prone to lack of sensitivity, e.g., diseases that primarily are treated and/or followed in the primary care setting by general practitioners. Therefore, we tried to increase the sensitivity of potential confounders such as diabetes by the use of additional information on medical use and laboratory values (study III), and defining CKD by eGFR using data on plasma creatinine from the laboratory database (studies I and III).

In study I, we handled confounding by both stratification and adjustment for age, gender, surgical status, Charlson Comorbidity Index level, and CKD. We did not have detailed information on severity of illness at ICU admission. However, the physiological variables included in these scores may be part of the causal pathway and adjustment may thus attenuate any true effect.[95] Nevertheless, the association between AKI

and mortality was evident in patients treated with mechanical ventilation and inotropes/vasopressors, which may be indicators of more severe illness.

In our ESRD risk study (study II), we stratified on and adjusted for several potential confounding factors. Data on all these potential confounders including CKD were obtained from the DNRP. Patients with CKD could be underreported in the DNRP, reducing the ability to sufficiently control for CKD.[95] After restricting our study population to patients admitted to an ICU in Northern Denmark, where we had access to virtually all conducted plasma creatinine measurements, we found similar results when data on CKD were retrieved from DNRP or defined by eGFR below 60 ml/min per 1.73 m^2. However, categorization by CKD severity (unknown or eGFR ≥ 60 ml/min per 1.73 m^2, eGFR 30–59 ml/min per 1.73 m^2, and eGFR < 30 ml/min per 1.73 m^2) revealed that some of the identified association appeared to be caused by residual confounding arising from a lack of nationwide data on CKD severity (Table 5.6). In addition, because both our exposure and outcome were disease of the kidney, we cannot exclude that our results could be attributable to an unknown common risk factor for both AKI and ESRD, such as genetics that predispose to both.

In study III, despite the control for a wide range of potential confounders by adjustment using highly valid data for patient characteristics, comorbidities, and preadmission drug use, we cannot exclude that our results were influenced by unknown and residual confounding, e.g., residual confounding by lack of severity of various comorbidities, together with possible incomplete registrations of cardiovascular diseases in the DNRP.

6.1.4 Chance

The precision of the associations was reflected by 95% CI in all three studies. The statistical precision was high in most main analyses. However, in some subgroup analyses and in studying MI and stroke risk in study III, our results were prone to imprecision and therefore more sensitive to chance.

6.2 Comparison with the existing literature

The following section will discuss the findings of the studies in this dissertation in relation to the existing literature.

6.2.1 Study I: Mortality risk

Previous studies reported a higher prevalence of RIFLE-equivalent defined AKI at the time of ICU admission (18%–36%) compared to our findings (Table 2.1).[11,15,17,18] This difference may stem from heterogeneity in study cohorts and the fact that some of these previous studies estimated baseline creatinine by assuming GFR of 75 ml/min per 1.73 m^2 in cohorts that included patients with CKD.[11,17,18] The latter will overestimate the prevalence of AKI.[24]

In accordance with our findings of increased 30-day mortality, eight recent large cohort studies with between 5,000 and 325,000 ICU patients all reported increased in-hospital mortality among patients with RIFLE-equivalent defined AKI at ICU admission or during an ICU stay than in ICU patients without AKI (Table 2.1).[11,12,15-19,25] In these studies, the relative risk of in-hospital mortality ranged from 1.0 to 2.2 among patients with AKI-risk/AKI-stage 1; from 1.4 to 6.0 among patients with AKI-injury/AKI-stage 2; and from 1.6 to 8.6 among patients with AKI-failure/AKI-stage 3. In addition, a Finnish study of 2,901 ICU patients also reported increased 90-day mortality for patients with AKI compared with patients without AKI.[26]

Four ICU studies have examined the association between AKI defined by the RIFLE-equivalent criteria and mortality beyond 90 days (Table 2.2).[13,14,37,38] Our finding of increased 31–365 day mortality among both acute and elective surgical ICU patients is in line with the work of Bihorac and colleagues, who examined a cohort of 10,518 elective and acute surgical ICU patients who were discharged alive. They reported the following 10-year adjusted HRs after hospitalization: 1.18 (95% CI: 1.08–1.29) for patients with AKI-risk; 1.43 (95% CI: 1.29–1.59) for AKI-injury; and 1.57 (95% CI: 1.40–1.75) for AKI-failure, all compared to patients without AKI.[13] Similar relative estimates were found in another study from the same research group, after restriction of the initial cohort of patients to cardiothoracic surgical ICU patients.[14] The slight

difference in results from these two studies and our results may primarily be because of the different composition of elective and acute surgeries as well as the type of surgical procedures performed. A Spanish study of 234 septic ICU patients who survived to hospital discharge found a relative 2-year mortality risk of 3.2 (95% CI: 1.6–6.5) in patients with AKI during the ICU stay compared to patients without AKI.[20] However, data on mortality were not available for 23% of the initial cohort, and this cohort of septic ICU patients may not be directly comparable with our subgroup of patients with a primary hospital diagnosis of septicemia in which we found no impact of AKI on 31–365 day mortality. In a UK cohort study of 153 patients with AKI at ICU admission, Abosaif and colleagues observed 6-month mortality values of 43.3%, 53.6%, and 86.0% for patients with AKI-risk, AKI-injury, and AKI-failure, respectively.[37] The crude 6-month mortality risk for patients with AKI-risk and AKI-injury corresponds well with our findings.

6.2.2 Study II: End-stage renal disease risk

In line with our observations on the short-term risk of ESRD, a Swedish cohort study reported that 9.4% (104/1,102) of ICU patients with D-AKI alive 90 days after commencement of acute dialysis had started active treatment for ESRD.[51] Slightly lower estimates were reported by Bellomo and colleagues from their randomized trial that examined the optimal intensity of dialysis. They found that 5.6% (45/810) of patients with D-AKI still were dependent on dialysis 90 days after initiating acute dialysis.[52] However, in contrast, Cartin-Ceba and colleagues found that as many as 37.0% (282/784) of ICU patients who survived and were discharged from the hospital needed dialysis for more than 90 days.[53] Furthermore, smaller studies that included between 27 and 137 surviving ICU patients reported dialysis dependency among surviving ICU patients at 90 days after initiating acute dialysis to range from 4% (4/95) to 28% (27/96);[27,31,47,55,56,59] 12% (9/77) to 33% (1/3) at 6 months;[54,55] 0% (0/121) to 22% (19/87) at 1 year;[27,57,58] and 1.7% (1/60) at 3 years after initiating acute dialysis (Table 2.3).

Our estimates of long-term ESRD risk among patients with D-AKI who survived 180 days without developing ESRD are also consistent with the Swedish study by Bell and colleagues.[51] They found that 3.4% (34/998) of

ICU patients with D-AKI developed ESRD in the period from 90 days up to 7 years after initiating dialysis.[51] Our results of long-term ESRD risk are also consistent with recent studies in non-ICU settings. A Canadian study and a US study of hospitalized patients found an increased risk of ESRD in patients requiring acute dialysis who initially recovered enough renal function to discontinue dialysis.[102,103] The Canadian study by Wald and colleagues reported an adjusted HR of 3.23 (95% CI: 2.70–3.86) for ESRD after D-AKI among hospitalized patients who did not develop ESRD in the first month after hospital discharge compared to a matched cohort of patients without D-AKI.[102] Results were similar for a subgroup analysis of 1,716 mechanically ventilated patients.[102] The US study, by Hsu and colleagues, examined patients with known CKD (eGFR below 45 ml/min per 1.73 m^2) with D-AKI during hospitalization who did not develop ESRD within the first month after hospital discharge. The authors reported an adjusted HR of 1.47 (95% CI: 0.95–2.28) for ESRD.[103]

6.2.3 Study III: Cardiovascular risk

To the best of our knowledge, we are the first to examine the association between AKI and the incidence of hospitalization for heart failure, MI, and stroke.

Five previous studies examined the impact of AKI on heart failure (Table 2.4). They reported that AKI, as a complication of coronary angiography,[64] CABG surgery,[66] MI,[71] heart failure,[68] and HIV infection,[70] increased the risk of subsequent admission for heart failure. This is similar to our finding for ICU patients with AKI. In a cohort of 14,782 patients who underwent coronary angiography in Canada and survived to hospital discharge, James and colleagues found that procedures complicated by AKI were associated with an increased risk of subsequent hospital admission for heart failure after a median follow-up of 20 months. The adjusted HRs ranged from 1.48 (95% CI: 1.16–1.91) for patients with AKI stage 1 to 2.17 (95% CI: 1.49–3.15) for patients with AKI stages 2–3.[64] Similarly, a single-center Israeli study including 1,957 patients admitted for ST-elevation MI found that during a median follow-up of 36 months, AKI was associated with a subsequent risk of heart failure among hospital survivors. This study also found that the association

persisted in patients who recovered renal function before hospital discharge, which our findings confirmed.[71] A Swedish study of 24,018 patients who underwent CABG surgery found that among 30-day survivors, the adjusted HR values for heart failure during a mean follow-up of 4.1 years were 1.69 (95% CI: 1.48–1.94), 2.33 (95% CI: 1.69–3.22), and 1.87 (95% CI: 0.84–4.20) for AKI stages 1, 2, and 3, respectively. The association between AKI and a subsequently increased risk of heart failure was also evident in a cohort of US veterans with HIV who survived the first 3 months after hospital discharge. Choi et al. reported an adjusted HR of subsequent heart failure of 1.17 (95% CI: 1.34–2.35) in patients with stage 1 AKI; 2.11 (95% CI: 1.07–2.35) in patients with AKI stages 2–3 not requiring dialysis; and 4.20 (95% CI, 2.24–7.88) in patients with AKI requiring dialysis, during a mean follow-up of 5.7 years.[70] In addition, a Chinese single-center study including 1,005 patients admitted with heart failure who survived to hospital discharge showed that both patients with and without CKD complicated by AKI more frequently were readmitted for heart failure up to 1 year after admission.[68]

Four studies have examined risk for MI after AKI, each in a different study population (Table 2.4). Like our study, these four studies showed that AKI was associated with MI.[64,65,67,71] James and colleagues found that the adjusted HRs of MI complicated by AKI stage 1 and AKI stages 2–3 were 1.47 (95% CI: 1.12–1.91) and 1.19 (95% CI: 0.70–2.02), respectively, compared with patients without AKI.[64] An Israeli study by Goldberg and colleagues found that the adjusted HR for recurrent MI after initial MI complicated by AKI was 1.6 (95% CI: 0.9–1.8) for patients with mild AKI who did not regain renal function by hospital discharge; 1.4 (95% CI: 0.7–3.0) for patients with moderate/severe AKI who did regain renal function by hospital discharge; and 1.4 (95% CI: 0.7–2.8) for those with moderate/severe AKI who did not recover renal function. However, these authors found no increased risk of MI for patients with mild AKI who regained renal function (adjusted HR = 0.6; 95% CI: 0.2–1.8).[71] In a single-center study, Lindsay and colleagues found that AKI after percutaneous intervention was associated with a two-fold increased risk of MI among hospital survivors (adjusted odds ratio = 2.0; 95% CI: 1.3–3.2).[65] The reported cumulative incidence of MI hospitalization was also higher for

patients who had percutaneous coronary intervention complicated by AKI compared to those without AKI throughout a 5-year follow-up period in a US study by Rihal and colleagues.[67]

In line with our results, James and colleagues did not find marked evidence for an association between a coronary angiography procedure complicated by AKI and hospitalization for stroke compared to procedures not complicated by AKI in hospital survivors during a median follow-up of 20 months (Table 2.4).[64] These findings in hospital survivors are in contrast to those for short-term risk of stroke in CABG patients complicated by AKI. A Swedish study by Ryden and colleagues found that patients with AKI stage 1 and AKI stages 2–3 as a complication of CABG had a two-fold and six-fold 60-day increased risk of stroke, respectively, compared to patients with CABG not complicated by AKI.[72] This difference between our results and the findings by Ryden and colleagues may be due to differences in the start of follow-up, together with the fact that this Swedish study was limited by a lack of adjustment for any factor related to the CABG surgical procedure.[72]

7 Main conclusions

7.1 Study I: Mortality risk

AKI was present at ICU admission in 15% of adult ICU patients. Any degree of AKI at ICU admission was associated with markedly increased 30-day mortality, and the association was still evident in the 31- to 365-day period. The association was also robust in most subgroups of ICU patients, with only a slight variation.

7.2 Study II: End-stage renal disease risk

One out of 10 ICU patients who survived 90 days after ICU admission with D-AKI developed ESRD during the 5 years of follow-up, compared with less than one out of 200 in other ICU patients. Thus, an episode of D-AKI among ICU patients is an important risk factor for subsequent ESRD up to 5 years after ICU admission. Although the increased risk compared with other ICU patients was evident within all subgroups of ICU patients, it was highest within subgroups with a low baseline risk of ESRD, such as young patients and patients without CKD.

7.3 Study III: Cardiovascular risk

ICU patients who survive an AKI stage 2–3 episode are at increased 3-year risk of heart failure and MI after hospital discharge. The increased risk of heart failure is even evident among patients with AKI stage 1. These outcomes were less pronounced but persisted among patients who recovered renal function by hospital discharge. We found no association between AKI and stroke.

8 Perspective

This dissertation adds to knowledge about the short- and long-term prognostic implications of AKI in ICU patients. Results from study I showed that ICU patients with AKI have increased short- and long-term mortality. To better understand the clinical course, we successively explored the potential risk for intermediate steps from AKI to mortality in studies II and III. These results revealed that AKI was associated with an increased risk of ESRD and cardiovascular diseases, including heart failure and MI.

We can diminish the clinical burden of AKI by preventing AKI development and/or improving the prognosis. To prevent AKI development, knowledge about modifiable risk factors for AKI is essential in order to enact prevention precautions. Similarly, knowledge of prognostic factors for AKI is needed to be able to modify their influence on the clinical course of AKI.

The Danish health care system provides an important source for generating large population-based studies for examining both risk and prognostic factors of AKI by linking medical and administrative registries. The available registries include, among others, complete data on residency and vital status, information from hospital contacts, information on reimbursed drugs from outpatient pharmacies, laboratory test results, and clinical data from clinical databases such the NRDT, which contains information on all patients actively treated with regular dialysis or transplantation. However, to examine both risk and prognostic factors, additional detailed clinical data from the hospital stays are wanted, such as information on in-hospital complications, severity of illness scores, hemodynamic parameters, volume resuscitation, type and intensity of dialysis, and detailed data on vasopressor/inotropes treatment. With the introduction of the electronic patient journal in Denmark, these data will be increasingly available in the future. The work of retrieving these highly valuable data from the electronic patient journals has been initiated by the Department of Clinical Epidemiology. Similarly, in further studies of potentially modifiable risk and prognostic factors for AKI such as medication, data on in-hospital medication use are also wanted. Currently, we have access to prescribed medication from outpatient pharmacies, but preadmission

medication use may be discontinued or withheld, and other medication may be initiated. Data on in-hospital medication use will also be available from the medicine module in the electronic patient journal in the future.

Risk and prognostic factors for AKI in ICU patients may vary within groups of ICU patients because of the large heterogeneity of this patient group. To explore any differential effect in ICU patient, restrictions or stratification to specific subgroups of ICU patients is needed. Therefore, large study samples must be gathered to ensure precise estimates. At present, we have access to laboratory data to classify and stage AKI by the SCr consensus criteria in around one fifth to one third of the Danish population, depending on the study period of interest. However, the State Serum Institute is currently working on the establishment of a nationwide database of all measured laboratory results from all clinical biochemistry departments in Denmark. This information will allow even larger study sizes, and this will further increase the precision of our findings and thereby enable further examination of the risk and prognostic factors for AKI in specific subgroups of ICU patients.

9 Summary

Acute kidney injury (AKI) is characterized by an abrupt decline in kidney function from mild kidney dysfunction to complete failure with the need for acute dialysis.

AKI complicates around one third of intensive care unit (ICU) admissions, and 4% to 6% of ICU patients will need dialysis. Thus, knowledge about both the short- and long-term prognostic implications of AKI is important to guide clinical decision making, plan post-discharge follow-up, and develop potential prophylactic strategies.

This dissertation relies on three population-based cohort studies among ICU patients admitted from 2005 through 2010. We conducted the studies in Northern Denmark (studies I and III) and in Denmark (study II), using data from Danish population-based administrative and medical registries.

The aims of this dissertation were to examine (1) the prognostic implications of AKI at ICU admission in terms of the 1-year mortality risk; (2) the risk of end-stage renal disease (ESRD) after dialysis-requiring AKI (D-AKI) during 5 years of follow-up; and (3) the association between AKI and the 3-year risk of first-time hospitalization for heart failure, myocardial infarction (MI), and stroke, and whether this association was modified by AKI recovery at hospital discharge.

In study I, we included 30,762 adults admitted to an ICU in Northern Denmark. Thirty-day mortality was 35.5% for patients with mild AKI, 44.2% for patients with moderate AKI, and 41.0% for patients with severe AKI, whereas it was 12.8% for patients without AKI. This corresponded to adjusted HRs of 1.96 (95% confidence interval (CI): 1.80–2.13), 2.60 (95% CI: 2.38–2.85), and 2.41 (95% CI: 2.21–2.64), respectively, compared to patients without AKI. Among patients surviving 30 days (n = 25,539), 31- to 365-day mortality was 20.5% for patients with mild AKI, 23.8% for patients with moderate AKI, and 23.2% for patients with severe AKI, compared with 10.7% for patients without AKI, corresponding to adjusted HRs (hazard ratios) of 1.33 (95% CI: 1.17–1.51), 1.60 (95% CI: 1.37–1.87), and 1.64 (95% CI: 1.42–1.90), respectively. The association between AKI and 30-day mortality was evident in subgroups of the ICU population, with

associations persisting in most subgroups during the 31- to 365-day follow-up period, although to a lesser extent than for the 30-day period.

In study II, we identified 107,937 patients who survived for 90 days after ICU admission. Of these, a total of 3,062 (2.8%) had an episode of D-AKI within 90 days of ICU admission. The subsequent risk of ESRD up to 180 days after ICU admission was 8.5% for patients with D-AKI compared with 0.1% for other ICU patients. This corresponds to an adjusted HR of 105.6 (95% CI: 78.1–142.9). Among patients who survived 180 days after ICU admission without developing ESRD (n = 103,996), the 181-day to 5-year ESRD risk was 3.8% for patients with D-AKI compared with 0.3% for other ICU patients, corresponding to an adjusted HR of 6.2 (95% CI: 4.7–8.1).

Study III included 21,556 ICU patients who survived to hospital discharge without a previous or concurrent diagnosis of heart failure, MI, and/or stroke. The 3-year cumulative risk of heart failure was 2.2% in patients without AKI, 5.0% for mild AKI, and 5.0% for moderate/severe AKI. The corresponding adjusted HRs were 1.35 (95% CI: 1.08–1.69) for patients with mild AKI and 1.46 (95% CI: 1.15–1.87) for moderate/severe AKI compared to patients without AKI. Patients without AKI, with mild AKI, and with moderate/severe AKI had a 3-year cumulative MI risk of 1.0%, 1.8%, and 2.3%, respectively. The adjusted HR for MI was 1.05 (95% CI: 0.72–1.52) for patients with mild AKI and 1.49 (95% CI: 1.04–2.15) for patients with moderate/severe AKI. We found no association between AKI and stroke. Increased risk of heart failure and MI persisted in patients who regained renal function by hospital discharge, although it was less pronounced.

In conclusion, the work described in this dissertation shows that AKI in ICU patients is associated with a worse prognosis with regard to risk of death, ESRD, and some cardiovascular diseases compared with ICU patients without AKI.

10 Dansk resume

Akut nyresvigt (AKI) er karakteriseret ved et pludselig fald i nyrefunktionen. Sværhedsgraden varierer lige fra et subklinisk fald til svær nyrefunktionsnedsættelse der påkræver understøttede behandling med dialyse.

Blandt patienter indlagt på intensiv afdelinger har cirka en tredjedel AKI under deres intensiv forløb, og fire til seks procent i en sådan grad at behandling med dialyse er påkrævet. Derfor er kendskab til den prognostiske betydning af AKI vigtig i den kliniske beslutningstagning, i planlægningen af eventuel efterfølgende opfølgning, og i udvikling af profylaktiske tiltag.

Denne afhandling er baseret på tre studier blandt patienter indlagt på intensivafdelinger i perioden 2005 til 2010 i det tidligere Aarhus og Nordjyllands Amt (studie 1 og 3) og hele Danmark (studie 2). Informationen der er brugt er indhentet fra adskillige danske registre.

Formålet med afhandlingen er: (1) undersøge den prognostiske betydning af AKI ved intensiv indlæggelsen på et års overlevelsen, (2) undersøge risikoen for terminalt nyresvigt i op til fem år efter dialysekrævende AKI, og (3) undersøge sammenhængen mellem AKI og efterfølgende risiko for hjertevigt, blodprop i hjertet og slagtilfælde i op til tre år efter hospitalsudskrivelsen, samt om denne sammenhæng påvirkes af om nyrefunktionen er genvundet ved hospitalsudskrivelsen.

I studie 1 fandt vi at 30-dages dødeligheden var 12,8 % blandt dem uden AKI, 35,5 % for dem med let AKI, 44,2 % for dem med middelsvær AKI og 41,0 % for dem med svær AKI. Efter justering svarede dette til en hazard ratio (HR) på 1,96 (95 % konfidence interval(KI): 1,80–2,13) , 2,60 % (95 % KI: 2,38–2,85) og 2,41 (95 % KI: 2,21–2,61) for henholdsvis dem med let, middelsvær og svær AKI sammenlignet med dem uden AKI. Dødeligheden hos patienter med AKI forblev forøget også efter de første 30 dage, men i mindre omfang. Den 31-365 dags justeret HR for at død var 1,33 (95 % KI: 1,17–1,51) for dem med mild AKI, 1,60 (95 % KI: 1,37–1,87) for dem med middelsvær AKI og 1,64 (95 % KI: 1,42–1,90) for dem med svær AKI.

In studie 2 fandt vi blandt 107.937 intensivpatienter der overledede de først 90 dage efter indlæggelsen på intensiv, at 3062 (2,8 %) havde dialyse krævende AKI. Blandt dem der havde dialyse-krævende AKI endte 8,5 % med terminalt nyresvigt (vedvarende behov for dialyse i mere end 90 dage eller behov for nyretransplantation) inden for det første halve år. Blandt dem der levede mere end et halvt år efter indlæggelsen og ikke havde udviklet terminalt nyresvigt udviklede yderligere 3,8 % af dem der havde haft dialyse krævende AKI terminalt nyresvigt i perioden et halvt år til fem år efter indlæggelsen. Dette svare til en justeret HR på 6,2 (95 % KI: 4,7–8,1) for terminalt nyresvigt i denne periode sammenlignet med intensivpatienter der ikke havde haft en episode med dialyse-krævende AKI.

I studie 3 fandt vi at intensivpatienter der overlevede hospitalsforløbet havde en justeret HR på 1,35 (95% KI: 1,08–1,69) og 1,46 (95% KI: 1,15-1,87) for efterfølgende indlæggelse med hjertesvigt hvis deres intensivforløb havde været kompliceret med henholdsvis let AKI eller middel/svær AKI sammenlignet med dem der ikke havde haft AKI. Ligeledes fandt vi også at middel/svær AKI var associeret med en relativ øget risiko for blodprop i hjertet i forhold til dem uden AKI (justeret HR = 1,49 (95 % KI: 1.04–2.15). Modsat fandt vi ikke nogen sammenhæng mellem let AKI og blodprop i hjertet. Vi fandt heller ingen sammenhæng mellem AKI og slagtilfælde.

Samlet set har studierne vist at der er en association mellem AKI og sværhedsgraden af AKI og efterfølgende prognose hvad angår død, terminalt nyresvigt og visse kardiovaskulære sygdomme.

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Study I

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One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study

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Abstract

Introduction: There are few studies on long-term mortality among intensive care unit (ICU) patients with acute kidney injury (AKI). We assessed the prevalence of AKI at ICU admission, its impact on mortality during one year of follow-up, and whether the influence of AKI varied in subgroups of ICU patients.

Methods: We identified all adults admitted to any ICU in Northern Denmark (approximately 1.15 million inhabitants) from 2005 through 2010 using population-based medical registries. AKI was defined at ICU admission based on the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) classification, using plasma creatinine changes. We included four severity levels: AKI-risk, AKI-injury, AKI-failure, and without AKI. We estimated cumulative mortality by the Kaplan-Meier method and hazard ratios (HRs) using a Cox model adjusted for potential confounders. We computed estimates for all ICU patients and for subgroups with different comorbidity levels, chronic kidney disease status, surgical status, primary hospital diagnosis, and treatment with mechanical ventilation or with inotropes/vasopressors.

Results: We identified 30,762 ICU patients, of which 4,793 (15.6%) had AKI at ICU admission. Thirty-day mortality was 35.5% for the AKI-risk group, 44.2% for the AKI-injury group, and 41.0% for the AKI-failure group, compared with 12.8% for patients without AKI. The corresponding adjusted HRs were 1.96 (95% confidence interval (CI) 1.80-2.13), 2.60 (95% CI 2.38 to 2.85) and 2.41 (95% CI 2.21 to 2.64), compared to patients without AKI. Among patients surviving 30 days (n = 25,539), 31- to 365 day mortality was 20.5% for the AKI-risk group, 23.8% for the AKI-injury group, and 23.2% for the AKI-failure group, compared with 10.7% for patients without AKI, corresponding to adjusted HRs of 1.33 (95% CI 1.17 to 1.51), 1.60 (95% CI 1.37 to1.87), and 1.64 (95% CI 1.42 to 1.90), respectively. The association between AKI and 30-day mortality was evident in subgroups of the ICU population, with associations persisting in most subgroups during the 31- to 365-day follow-up period, although to a lesser extent than for the 30-day period.

Conclusions: AKI at ICU admission is an important prognostic factor for mortality throughout the subsequent year.

Introduction

Acute Kidney Injury (AKI) is defined as an abrupt decline of kidney function, primarily described in recent years using the widely accepted risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) classification based on changes in serum creatinine level and/or urine output [1,2].

Former studies have reported a prevalence of AKI at ICU admission between 22% and 36% [3-5]. It is associated with 1.4- to 3.2-fold increased in-hospital mortality compared with ICU patients without AKI, depending on the ICU study population and AKI severity [4,5]. ICU studies of the association between maximum AKI level during ICU or hospital stay and hospital mortality have shown similar results [3,6,7]. To date only four ICU studies, with sample sizes from 183 to 10,518 ICU patients with or without AKI, have examined the association between AKI defined by the RIFLE criteria and mortality beyond 90 days [8-11]. These studies have a number of limitations, including patient recruitment at a single center [8-11], inclusion of selected subpopulations of ICU patients (surgical or

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septic ICU patients) [9-11], lack of adjustment for confounders [8], and loss to follow-up [11].

A large study within a population-based hospital setting with complete history of preadmission comorbidity and complete follow-up is needed to quantify the impact of AKI on long-term mortality, including differential impacts in subgroups of the heterogeneous ICU population. Such information would improve understanding of the clinical course of AKI and identify potentially preventable post-discharge deaths.

We therefore conducted a cohort study to (1) examine the prevalence of AKI at ICU admission, (2) examine its impact on mortality during one year of follow-up, and (3) examine whether the influence of AKI varied in subgroups of ICU patients with different comorbidity levels, chronic kidney disease status, surgical status, primary hospital diagnosis, and treatment with mechanical ventilation, or inotropes/vasopressors.

Materials and methods

Setting

We conducted this cohort study using prospectively collected data from medical and administrative registries in Northern Denmark (the former counties of Aarhus and North Jutland, with approximately 1.15 million inhabitants) from 1 January 2005 to 31 December 2011. The Danish National Health Service provides tax-supported health care to all Danish residents, with universal access to public hospitals and general practitioners. All intensive care in Denmark is provided at these public hospitals. The unique 10-digit civil registration number assigned to all Danish residents since 1968 permits unambiguous linkage between medical databases [12].

Nearly all medical treatments, except very few highly specialized treatments (for example, liver transplantation and lung transplantation) are provided in the study region, which has twelve ICUs, eight at university hospitals and four at regional hospitals.

ICU patients

We identified all adult residents (aged 15 years or older) with a first-time ICU admission from 1 January 2005 to 31 December 2010 using the Danish National Registry of Patients (DNRP) [13]. We required one-year residency in the study region before the index hospitalization to ensure availability of data on previous laboratory measurements from the laboratory database. It is mandatory for hospitals in Denmark to electronically report information on all hospital contacts to the DNRP. The DNRP includes data from non-psychiatric hospital admissions since 1977. Since 1995, the registry has also covered all emergency room and outpatient clinic visits. Data in the registry include civil registration numbers, emergency vs. planned hospital admission, dates of hospital admission and discharge, hospital and department, surgical procedures and major treatments performed, one primary discharge diagnosis (main reason for hospitalization) and up to 19 secondary discharge diagnoses. Since 1994, diagnoses have been coded using the *International Classification of Diseases*, 10th revision (ICD-10) [14]. Information on ICU admissions and major treatments during the ICU stay, such as mechanical ventilation, acute renal replacement therapy, and treatment with inotropes/vasopressors, have been coded in the DNRP with a high degree of accuracy since 2005 [13].

We used the primary ICD-10 diagnosis for the current hospitalization to classify patients into nine disease categories as a proxy for reason for ICU admission, which is not recorded in the DNRP. In addition, we specified five types of ICU admission: non-surgical, elective non-cardiac surgical, elective cardiac surgical, acute non-cardiac surgical and acute cardiac surgical. We used the Nordic Medico-Statistical Committee classification of surgical procedures in the DNRP to classify patients as cardiac and non-cardiac surgical based on whether they had any surgical procedure and on type of surgical procedure up to 7 days before or on the day of ICU admission, respectively [15]. Surgical ICU patients were further divided into acute or elective, according to the hospital admission type registered in the DNRP. Admission type is recorded with high accuracy in the DNRP [14].

Acute kidney injury

The laboratory database covering the study area contains laboratory tests from all inpatient stays, outpatient clinic visits, and visits to general practitioners [16]. We searched the laboratory database for the highest measurement of plasma creatinine, which is equivalent to serum creatinine [17], on the day of ICU admission. For patients with missing values on that day, we calculated the mean of the highest creatinine measurements available on the day before and the day after ICU admission [18]. We used the creatinine level to classify each patient into one of three AKI severity levels based on the RIFLE criteria: AKI-risk defined as a 50% to 100% increase in creatinine from the baseline level, AKI-injury defined as a 100% to 200% increase, and AKI-failure defined as an increase of 200% or more or creatinine values ≥ 354 μmol/l, with an acute rise > 44 μmol/l up to seven days before ICU admission [1]. All other ICU patients were classified as without AKI. Baseline creatinine was defined as the most recent creatinine measurement from an outpatient clinic or general practitioner in the period from one year to seven days before the current hospitalization [19]. Creatinine assessments up to seven days before the current hospitalization were not considered, because the AKI process may have started

before hospital admission. For patients lacking a measured baseline creatinine level and without chronic kidney disease (CKD), we estimated baseline creatinine using the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation based on age, race, and gender assuming a normal glomerular filtration rate (GFR) of 75 ml/min, as suggested in the RIFLE criteria [1]. We assumed that all patients were Caucasians. Patients receiving chronic dialysis treatment, those with a previous kidney transplant, and those lacking information on creatinine level on the day of ICU admission, and on the day before and the day after admission were excluded from the study.

Covariates

We obtained data on preexisting comorbidity based on inpatient and outpatient diagnoses five years before the current hospitalization and used these to compute the Charlson Comorbidity Index (CCI) scores [20]. Patients were categorized as having low (score = 0), medium (score 1 to 2) and high (score ≥ 3) levels of comorbidity [21,22]. Kidney diseases were excluded from the CCI and addressed separately because the exposure under study was kidney dysfunction. CKD was included as a covariate, defined as an estimated GFR (eGFR) below 60 ml/min per 1.73 m^2 using the four-variable MDRD equation (stage 3 or higher CKD according to National Kidney Foundation guidelines) [23]. We used the most recent plasma creatinine measurement from an outpatient clinic or general practitioner one year to seven days before the current hospitalization to compute eGFR [19]. In addition, we also computed the length of the entire hospital stay, including continuous hospitalizations with inter-hospital transfer. All relevant codes are provided in Additional file 1.

Follow-up for mortality

Deaths and migration were identified from the Danish Civil Registration System through 31 December 2011. This registration system is updated daily and contains complete information since 1968 on migration, vital status, and the exact date of death (when relevant) for all Danish citizens [24].

Statistical analysis

Patient characteristics, including demographic characteristics, preexisting comorbidity level, and information from the current hospitalization, were tabulated by RIFLE group.

We followed patients from ICU admission until death or emigration, or for up to one year, whichever came first. The Kaplan-Meier method was used to compute mortality function curves (1 - survival function) and to estimate cumulative mortality for three time periods: 0 to 30 days, 31 to 365 days, and 0 to 365 days following ICU admission. We computed hazard ratios (HRs) within 0- to 30-day and 31- to 365-day periods using Cox proportional hazards regression, controlling for age, gender, CKD, CCI level, and surgical status. The assumption of proportional hazards was checked graphically using log(-log(survival probability)) plots and was found appropriate.

To examine potentially differing effects of AKI on mortality in subgroups of ICU patients (effect measure modification) [25], we stratified the analyses by age groups, CCI levels, surgical status, CKD, primary hospital diagnosis, and treatment with mechanical ventilation or inotropes/vasopressors. In these subgroup analyses we combined patients with any degree of AKI into one group.

We conducted a sensitivity analysis to examine the potential influence of excluding patients lacking a creatinine measurement at ICU admission. In this analysis we estimated AKI levels for patients with missing creatinine using multiple imputations [26-28], generating five imputed datasets. HRs were calculated as the average HRs of the five datasets, corrected for between- and within-imputation variation [26-28]. The imputation model included all measured covariates in Table 1, the outcome, and the Nelson-Aalen estimator of the cumulative baseline hazard evaluated at the observed survival time [29].

Analyses were performed using the statistical software package Stata version 11.0 (StataCorp LP, College Station; TX, USA). All data were obtained from Danish registries, which are generally available to researchers, and their use does not require ethical approval or informed consent. The study was approved by the Danish Data Protection Agency (record number 2009-41-3987).

Results

Descriptive data

The study population comprised 30,762 adults admitted to an ICU in Northern Denmark during the six-year observation period, after excluding 192 (0.6%) patients receiving chronic dialysis or with a previous kidney transplant, and 1,578 (4.9%) patients lacking information on plasma creatinine level at ICU admission. Patients without a creatinine measurement were younger and had less preexisting comorbidity and shorter hospital stays compared with patients with a creatinine measurement (Additional file 2). The total time of follow up was 23,850 person years (median duration 365 days, interquartile range 258 to 365).

The median age in the study population was 65 years and 13,352 (43%) patients were female. At ICU admission, 4,793 (15.6%) patients had AKI; these included 1,986

Table 1 Characteristics by AKI level among 30,762 ICU patients, Northern Denmark, 2005 to 2010

	Without AKI *n* = 25,969 (84.4%)	AKI-risk *n* = 1,986 (6.5%)	AKI-injury *n* = 1,311 (4.3%)	AKI-failure *n* = 1,496 (4.9%)
Age				
Median age (IQR)	64 (49, 75)	72 (61, 80)	71 (59, 80)	69 (59, 78)
Gender				
Female	11,172 (43.0%)	878 (44.2%)	645 (49.2%)	657 (43.9%)
Male	14,797 (57.0%)	1,108 (55.8%)	666 (50.8%)	839 (56.1%)
Charlson comorbidity index score[a]				
Low (score 0)	13,862 (53.4%)	798 (40.2%)	510 (38.9%)	556 (37.2%)
Medium (score 1 to 2)	8,654 (33.3%)	804 (40.5%)	507 (38.7%)	579 (38.7%)
High (score ≥ 3)	3,453 (13.3%)	384 (19.3%)	294 (22.4%)	361 (24.1%)
Chronic kidney disease[b]				
Yes	3,283 (12.6%)	395 (19.9%)	199 (15.2%)	470 (31.4%)
No	22,686 (87.4%)	1,591 (80.1%)	1,112 (84.8%)	1,026 (68.6%)
Surgical status[c, d]				
Non-surgical	9,495 (36.6%)	892 (44.9%)	593 (45.2%)	786 (52.5%)
Surgical				
Acute non-cardiac	8,271 (31.8%)	752 (37.9%)	564 (43.0%)	554 (37.0%)
Acute cardiac	920 (3.5%)	102(5.1%)	40 (3.1%)	34 (2.3%)
Elective non-cardiac	3,939 (15.2%)	188 (9.5%)	101 (7.7%)	106 (7.1%)
Elective cardiac	3,344 (12.9%)	52 (2.6%)	13 (1.0%)	16 (1.1%)
Primary diagnosis during current hospitalization				
Septicemia	232 (0.9%)	100 (5.0%)	127 (9.7%)	187 (12.5%)
Other infectious diseases	2,329 (9.0%)	254 (12.8%)	182 (13.9%)	194 (13.0%)
Endocrinology diseases	359 (1.4%)	65 (3.3%)	52 (4.0%)	82 (5.5%)
Cardiovascular diseases	7.377 (28.4%)	464 (23.4%)	196 (15.0%)	183 (12.2%)
Respiratory diseases	1,427 (5.5%)	180 (9.1%)	77 (5.9%)	66 (4.4%)
Gastrointestinal or liver diseases	2,416 (9.3%)	322 (16.2%)	266 (20.3%)	239 (16.0%)
Cancer or other neoplasm	3.410 (13.1%)	175 (8.8%)	139 (10.6%)	130 (8.7%)
Trauma or poisoning	4,651 (17.9%)	168 (8.5%)	110 (8.4%)	96 (6.4%)
Other	3,758 (14.5%)	258 (13.0%)	162 (12.4%)	319 (21.3%)
Laboratory information				
Baseline creatinine measured	17,384 (66.9%)	1,530 (77.0%)	950 (72.5%)	1.164 (77.8%)
ICU admission creatinine, μmol/L (IQR)	75 (61, 92)	137 (112, 168)	190 (153, 230)	375 (280, 516)
ICU treatments				
Acute renal replacement therapy	482 (1.9%)	206 (10.4%)	220 (16.8%)	561 (37.5%)
Mechanical ventilation	9,673 (37.2%)	965 (48.6%)	697 (53.2%)	719 (48.1%)
Inotropes/vasopressors	7,823 (30.1%)	939 (47.3%)	756 (57.7%)	864 (57.8%)
Length of admission				
In-hospital days, median (IQR)	10 (4, 19)	13 (5, 26)	14 (5, 30)	16 (6, 33)
In-hospital days before ICU admission, median (IQR)	1 (0, 2)	1 (0, 3)	1 (0, 3)	1 (0, 3)

Results are presented as number (percent) of patients unless stated otherwise.

[a]Charlson comorbidity index score after exclusion of kidney diseases.

[b]eGFR < 60 ml/min per 1.73 m^2.

[c]Surgical status and cardiac surgical status identified by surgery and type of surgery on or up to 7 days before ICU admission.

[d]Acute and elective status classified according to hospital admission type.

AKI, acute kidney injury; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.

(6.5%) patients with AKI-risk, 1,311 (4.3%) with AKI-injury, and 1,496 (4.9%) with AKI-failure. Preadmission baseline plasma creatinine results were available for 21,028 (68.4%) patients, and were estimated using the MDRD equation for the remaining 9,734 (31.6%) patients.

Patients with AKI were older and had more preexisting comorbidity, including CKD, than other ICU patients (Table 1). The most frequent diagnoses among AKI patients were other infectious disease, gastrointestinal or liver disease, and cardiovascular disease. AKI was

less frequent in elective surgical patients (cardiac and non-cardiac) compared with both non-surgical and acute surgical patients (cardiac and non-cardiac). In addition, patients with AKI were more often treated with mechanical ventilation, inotropes/vasopressors, and as expected, with dialysis during their ICU stay compared to patients without AKI (patients without AKI 1.9%, patients with AKI-risk 10.4%, patients with AKI-injury 16.8%, and patients with AKI-failure 37.5%) (Table 1).

During the time between ICU admission and hospital discharge (median duration 8 days, interquartile range 3 to 17), another 3,099 (10.1%) patients developed AKI.

Mortality

The one-year mortality was 48.7% (95% confidence interval (CI) 46.5% to 50.9%) for the AKI-risk group, 57.4% (95% CI 54.8% to 60.1%) for the AKI-injury group and 54.7% (95% CI 52.1% to 57.2%) for the AKI-failure group, compared with 22.1% (95% CI 21.6% to 22.7%) for the patients without AKI (Figure 1).

Overall 0- to 30-day mortality

Thirty-day mortality was 35.5% (95% CI 33.4% to 37.6%) for the AKI-risk group, 44.2% (95% CI 41.5% to 46.9%) for the AKI-injury group, and 41.0% (95% CI 38.5% to 43.5%) for the AKI-failure group, compared with 12.8% (95% CI 12.4% to 13.2%) for patients without AKI. This corresponded to adjusted HRs of 1.96 (95% CI 1.80 to 2.13), 2.60 (95% CI 2.38 to 2.85), and 2.41 (95% CI 2.21 to 2.64), respectively, all compared with ICU patients without AKI (Table 2).

Overall 31- to 365-day mortalitys

Among patients surviving 30 days (n = 25,539), mortality between 31 days and 365 days was 20.5% (95% CI 18.4% to 22.8%) for the AKI-risk group, 23.8% (95% CI 20.9% to 27.0%) for the AKI-injury group, and 23.2% (95% CI 20.6% to 26.1%) for the AKI-failure group compared with 10.7% (95% CI 10.3% to 11.1%) for patients without AKI. The adjusted HRs were 1.33 (95% CI 1.17 to 1.51), 1.60 (95% CI 1.37 to 1.87), and 1.64 (95% CI 1.42 to 1.90), respectively, compared with ICU patients without AKI (Table 2).

Subgroup analyses

The association between AKI and 30-day mortality was evident in all subgroups of the ICU population (Table 3). The relative impact of AKI was most pronounced in patients aged 15 to 40 years; the mortality of patients without AKI in this subgroup was 2.5%, compared to 16.8% for patients with any degree of AKI. This corresponds to an adjusted HR of 4.87 (95% CI 3.33 to 7.13) (Table 3). The relative impact of AKI was also more pronounced among both elective cardiac and non-cardiac surgical patients and among acute cardiac surgical patients, with adjusted HRs (95% CIs) of 3.76 (1.62 to 8.77), 3.43 (2.65 to 4.45), and 3.27 (2.48 to 4.31), respectively, and among patients with low CCI scores (adjusted HR 2.55, 95% CI 2.31 to 2.81), due to a low baseline hazard. By diagnostic category, the adjusted

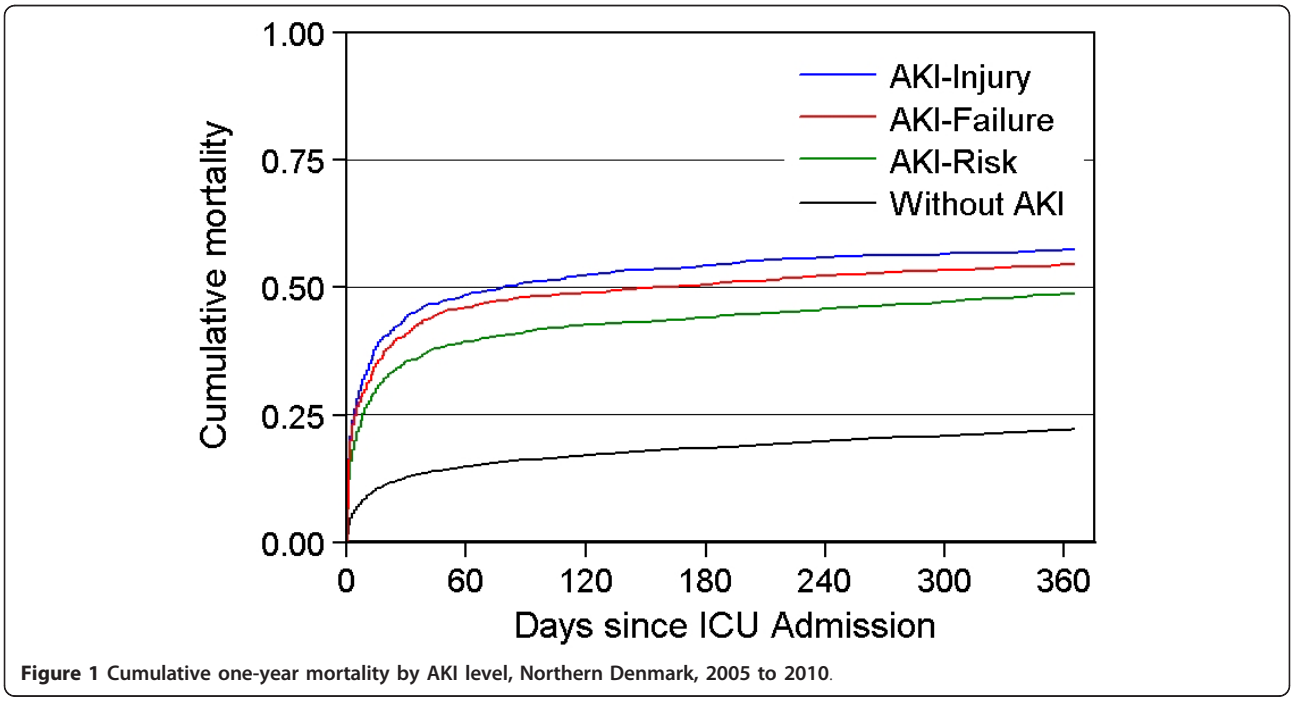

Figure 1 Cumulative one-year mortality by AKI level, Northern Denmark, 2005 to 2010.

Table 2 Cumulative 30-day and 31-365 day mortality and corresponding hazard ratios (HRs) by AKI status

	Number of deaths	Number at period start	Cumulative mortality % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
0 to 30 days					
Without AKI	3,327	25,969	12.8% (12.4-13.2)	1(ref.)	1(ref.)
AKI-risk	704	1,986	35.5% (33.4-37.6)	3.17 (2.93-3.45)	1.96 (1.80-2.13)
AKI-injury	579	1,311	44.2% (41.5-46.9)	4.21 (3.86-4.60)	2.60 (2.38-2.85)
AKI-failure	613	1,496	41.0% (38.5-43.5)	3.83 (3.52-4.18)	2.41 (2.21-2.64)
31 to 365 days					
Without AKI	2,421	22,642	10.7% (10.3-11.1)	1 (reference)	1 (reference)
AKI-risk	263	1,282	20.5% (18.4-22.8)	2.04 (1.80-2.32)	1.33 (1.17-1.51)
AKI-injury	174	732	23.8% (20.9-27.0)	2.46 (2.11-2.87)	1.60 (1.37-1.87)
AKI-failure	205	883	23.2% (20.6-26.1)	2.38 (2.06-2.75)	1.64 (1.42-1.90)

[a]Adjusted for age, gender, Charlson comorbidity index score, surgical status, and chronic kidney disease.

AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

HRs ranged from 1.53 (95% CI 1.19 to 1.96) among patients with a primary registry diagnosis of septicemia to 2.54 (95% CI 2.20 to 2.93) for patients with a primary diagnosis of gastrointestinal or liver disease and 2.59 (95% CI 2.12 to 3.16) for cancer patients. The association between AKI and 30-day mortality was also evident in patients treated with mechanical ventilation (adjusted HR 1.60, 95% CI 1.48 to 1.72) or inotropes/vasopressors (adjusted HR 1.77, 95% CI 1.63 to 1.91) and in patients with CKD (adjusted HR 1.80, 95% CI 1.60 to 2.02).

After 30 days of follow-up, AKI still was associated with increased mortality in most subgroups, although to a less pronounced degree than in the 30-day period after ICU admission (Table 4).

Sensitivity analysis

The associations between AKI and mortality were similar after imputation of missing creatinine measurement at ICU admission. The adjusted 30-day HRs were 1.95 (95% CI 1.80 to 2.12) for the AKI-risk group, 2.62 (95% CI 2.39 to 2.86) for the AKI-injury group and 2.42 (95% CI 2.22 to 2.64) for the AKI-failure group. In the period 31 to 365 days following ICU admission, the adjusted HRs were 1.36 (95% CI 1.19 to 1.54), 1.61 (95% CI 1.38 to 1.88), 1.66 (95% CI 1.43 to 1.92) for the AKI-risk, AKI-injury, and AKI-failure groups, respectively.

Discussion

In this large cohort study conducted within a population-based hospital setting, we found that 15% of ICU patients had AKI at ICU admission. AKI at ICU admission was associated with a two-fold increased 30-day mortality for patients in the AKI-risk group and two-and-a-half-fold increased 30-day mortality in the AKI-injury and AKI-failure groups. Relative mortality in AKI patients remained elevated, with 33% to 64% increased mortality during the 31- to 365-day period following ICU admission. The relative impact of AKI on 30-day mortality was most pronounced in younger age groups and among elective surgical and acute cardiac surgical ICU patients.

Existing studies

Our study extends current knowledge by providing complete one-year mortality information and by examining the differential impact of AKI on mortality in subgroups of the ICU population in a population-based setting.

Previous studies reported a higher prevalence of RIFLE-defined AKI at the time of ICU admission (22% to 36%) compared to our findings [3-5]. This may stem from heterogeneity in study cohorts and from estimation of baseline creatinine by assuming GFR of 75 ml/min in cohorts including patients with CKD [4,5], which may overestimate the prevalence of AKI [30].

In accordance with our findings of increased short-term mortality, five recent large studies with between 5,000 and 120,000 ICU patients all reported increased in-hospital mortality among patients with RIFLE-defined AKI at ICU admission or during an ICU stay, compared with ICU patients without AKI [3-7]. In these studies, relative risk of in-hospital mortality ranged from 1.0 to 1.6 among patients with AKI-risk, from 1.4 to 4.0 among patients with AKI-injury, and from 1.6 to 4.1 among patients with AKI-failure.

None of these studies included follow-up after hospital discharge. Similar to our results, two studies found that the impact of AKI on short-term mortality was similar in the AKI-injury and AKI-failure groups [6,7]. The variation found in the relative impact of AKI on short-term mortality in our study vs. and among previous studies may be explained by the heterogeneity of study cohorts, use of estimated vs. measured baseline creatinine levels, examination of the most advanced AKI stage during an ICU stay vs. AKI level at ICU admission, availability of

Table 3 Cumulative 30-day mortality and corresponding adjusted hazard ratios (HRs)

		Without AKI		With AKI	
	Number	Cumulative mortality % (95% CI)	Adjusted HR (95% CI)	Cumulative mortality % (95% CI)	Adjusted HR[a] (95% CI)
Overall	30,762	12.8 (12.4-13.2)	1 (reference)	39.6 (38.2-41.0)	2.27 (2.14-2.40)
Age group, years					
≥ 15 < 40	4,670	2.5 (2.1-3.0)	1 (reference)	16.8 (12.8-21.9)	4.87 (3.33-7.13)
≥ 40 < 60	7,397	7.6 (7.0-8.3)	1 (reference)	29.2 (26.4-32.2)	3.18 (2.72-3.70)
≥ 60 < 80	14,184	14.1 (13.5-14.8)	1 (reference)	39.1 (37.2-41.1)	2.28 (2.11-2.47)
≥ 80	4,511	31.4 (29.9-33.0)	1 (reference)	55.1 (52.2-58.1)	1.83 (1.65-2.02)
Charlson comorbidity index score[a]					
Low (score 0)	15,726	9.0 (8.5-9.4)	1 (reference)	35.0 (32.9-37.2)	2.55 (2.31-2.81)
Medium (score 1 to 2)	10,544	15.7 (15.0-16.5)	1 (reference)	41.4 (39.2-43.6)	2.17 (1.99-2.38)
High (score ≥ 3)	4,492	21.1 (19.8-22.5)	1 (reference)	44.5 (42.0-47.5)	1.96 (1.74-2.20)
Surgical status[c, d]					
Non-surgical	11,766	16.7 (16.0-17.5)	1 (reference)	41.7 (39.7-43.7)	2.01 (1.85-2.18)
Surgical					
Acute non-cardiac	10,141	15.9 (15.2-16.7)	1 (reference)	42.0 (40.8-44.3)	2.40 (2.20-2.63)
Acute cardiac	1,096	15.8 (13.6-18.3)	1 (reference)	44.3 (37.3-52.0)	3.27 (2.48-4.31)
Elective non-cardiac	4,334	5.4 (4.8-6.2)	1 (reference)	20.5 (16.9-24.8)	3.43 (2.65-4.45)
Elective cardiac	3,425	1.9 (1.5-2.4)	1 (reference)	7.4 (3.4-5.8)	3.76 (1.62-8.77)
Primary diagnosis during current hospitalization					
Septicemia	646	38.8 (32.9-45.4)	1 (reference)	52.2 (47.5-57.1)	1.53 (1.19-1.96)
Other infectious diseases	2,959	15.0 (13.6-16.5)	1 (reference)	36.5 (32.9-40.4)	1.97 (1.66-2.33)
Endocrinology diseases	558	7.2 (5.0-10.5)	1 (reference)	17.1 (12.5-23.1)	1.89 (1.11-3.19)
Cardiovascular diseases	8,220	13.8 (13.0-14.6)	1 (reference)	44.3 (41.0-47.7)	2.14 (1.89-2.41)
Respiratory diseases	1,750	27.8 (25.5-30.2)	1 (reference)	47.1 (41.8-52.7)	1.76 (1.46-2.13)
Gastrointestinal or liver diseases	3,243	17.1 (15.6-18.6)	1 (reference)	41.7 (38.4-45.2)	2.54 (2.20-2.93)
Cancer or other neoplasm	3,854	10.3 (9.3-11.4)	1 (reference)	34.5 (30.2-39.1)	2.59 (2.12-3.16)
Trauma or poisoning	5,035	7.6 (6.9-8.4)	1 (reference)	32.6 (28.1-37.6)	2.41 (1.95-2.99)
Other	4,497	8.8 (8.0-9.8)	1 (reference)	36.7 (33.3-40.3)	2.62 (2.22-3.09)
Chronic kidney disease[b]					
Yes	4,347	24. 1 (22.7-25.6)	1 (reference)	44.3 (41.3-47.3)	1.80 (1.60-2.02)
No	26,415	11.2 (10.7-11.6)	1 (reference)	38.2 (36.7-39.8)	2.45 (2.30-2.63)
ICU treatments					
Mechanical ventilation	12,054	20.5 (19.5-21.6)	1 (reference)	46.2 (44.2-48.2)	1.60 (1.48-1.72)
Inotropes/vasopressors	10,382	19.3 (18.4-20.2)	1 (reference)	46.2 (44.3-48.2)	1.77 (1.63-1.91)

[a]Compared to patients without AKI within subgroups and adjusted for age, gender, Charlson comorbidity index score, surgical status, and chronic kidney disease.
[b]eGFR < 60 ml/min per 1.73 m^2.
[c]Surgical status and cardiac surgical status identified by surgery and type of surgery on or up to 7 days before ICU admission, respectively.
[d]Acute and elective status classified according to hospital admission type
AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

data on urine output for the RIFLE classification, different approaches to adjusting for potential confounders, and examination of in-hospital mortality compared to mortality at 30 days or another fixed time point [30-32]. None of the five large earlier studies reported results from subgroups of the ICU population [3-7].

To our knowledge, only four studies have examined the association of AKI defined by the RIFLE criteria and long-term mortality (beyond 90 days) in ICU patients. All were single center studies [8-11]. These studies also observed increased long-term mortality among ICU patients with AKI compared with patients without AKI. Our finding of increased 30- to 365-day mortality among both acute and elective surgical ICU patients is in line with the work of Bihorac *et al.* who examined a cohort of 10,518 elective and acute surgical ICU patients discharged from an American hospital [9]. They reported the following 10-year adjusted HRs after hospitalization: 1.18 (95% CI 1.08 to 1.29) for patients with AKI-risk, 1.43 (95% CI 1.29 to 1.59) for patients with AKI-injury, and 1.57 (95% CI 1.40 to 1.75) for patients with AKI-failure, compared to patients without AKI [9].

Table 4 Cumulative 31- to 365-day mortality and corresponding adjusted hazard ratios (HRs)

	Number	Without AKI		With AKI	
		Cumulative mortality % (95%CI)	Adjusted HR (95%CI)	Cumulative mortality % (95%CI)	Adjusted HR[a] (95%CI)
Overall	25,539	10.7 (10.3-11.1)	1 (reference)	22.2 (20.7-23.7)	1.49 (1.36-1.63)
Age group, years					
≥ 15 < 40	4,516	1.7 (1.4-2.1)	1 (reference)	5.1 (2.8-8.9)	1.52 (0.79-2.94)
≥ 40 < 60	6,627	7.5 (6.9-8.2)	1 (reference)	15.4 (12.9-18.3)	1.58 (1.27-1.97)
≥ 60 < 80	11,561	13.8 (13.2-14.5)	1 (reference)	23.8 (21.7-26.0)	1.41 (1.25-1.59)
≥ 80	2,835	21.8 (20.2-23.6)	1 (reference)	34.2 (30.1-38.5)	1.46 (1.22-1.74)
Charlson comorbidity index score					
Low (score 0)	13,834	5.5 (5.1-5.9)	1 (reference)	15.3 (13.4-17.4)	1.88 (1.59-2.22)
Medium (score 1 to 2)	8,403	14.5 (13.7-15.4)	1 (reference)	25.8 (23.3-28.5)	1.60 (1.40-1.83)
High (score ≥ 3)	3,302	24.6 (23.0-26.2)	1 (reference)	29.6 (26.1-33.5)	1.12 (0.94-1.34)
Surgical status[c, d]					
Non-surgical	9,234	10.3 (9.6-10.9)	1 (reference)	22.1 (20.0-24.5)	1.42 (1.24-1.63)
Surgical					
Acute non-cardiac	8,038	13.1 (12.4-13.9)	1 (reference)	23.97 (21.5-26.5)	1.46 (1.27-1.68)
Acute cardiac	873	5.6 (4.2-7.4)	1 (reference)	21.4 (14.5-30.9)	4.44 (2.63-7.51)
Elective non-cardiac	4,039	14.3 (13.2-15.4)	1 (reference)	19.1 (15.2-23.9)	1.28 (0.98-1.67)
Elective cardiac	3.355	3.8 (3.2-4.5)	1 (reference)	12.0 (6.4-21.8)	2.96 (1.50-5.85)
Primary diagnosis during current hospitalization					
Septicemia	340	21.8 (15.9-29.6)	1 (reference)	17.7 (13.0-23.7)	0.81 (0.49-1.32)
Infectious diseases	2,380	10.0 (8.8-11.4)	1 (reference)	19.8 (16.2-24.0)	1.28 (1.02-1.61)
Endocrinology diseases	498	10.2 (7.4-14.0)	1 (reference)	12.1 (8.0-18.2)	0.85 (0.48-1.50)
Cardiovascular diseases	6,829	6.2 (5.7-6.9)	1 (reference)	20.9 (17.5-24.8)	2.21 (1.76-2.78)
Respiratory diseases	1,202	22.0 (19.6-24.7)	1 (reference)	31.6 (25.2-39.1)	1.27 (0.94-1.73)
Gastrointestinal or liver diseases	2,486	14.0 (12.6-15.6)	1 (reference)	25.3 (21.7-29.4)	1.75 (1.41-2.17)
Cancer or other neoplasm	3,350	24.5 (23.0-26.0)	1 (reference)	32.0 (26.9-37.7)	1.17 (0.93-1.46)
Trauma or poisoning	4,560	5.3 (4.6-6.0)	1 (reference)	20.7 (16.2-26.2)	1.85 (1.36-2.53)
Other	3,894	8.1 (7.3-9.1)	1 (reference)	19.0 (15.7-22.9)	1.37 (1.08-1.75)
Chronic kidney disease[b]					
Yes	3,084	19.5 (18.0-21.1)	1 (reference)	28.7 (25.2-32.5)	1.43 (1.19-1.71)
No	22,455	9.6 (9.2-10.0)	1 (reference)	20.5 (18.9-22.2)	1.48 (1.33-1.64)
ICU treatments					
Mechanical ventilation	8,976	10.6 (10.0-11.4)	1 (reference)	24.6 (22.3-27.0)	1.49 (1.30-1.70)
Inotropes/vasopressors	7,691	12.3 (11.5-13.2)	1 (reference)	24.7 (22.5-27.1)	1.46 (1.27-1.66)

[a]Compared to patients without AKI within subgroups and adjusted for age, gender, Charlson comorbidity index score, surgical status, and chronic kidney disease.
[b]eGFR < 60 ml/min per 1.73 m^2.
[c]Surgical status and cardiac surgical status identified by surgery and surgical type on or up to 7 days before ICU admission, respectively.
[d]Acute and elective status classified according to hospital admission type.
AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

They reported similar relative estimates in a study restricted to elective and acute cardiothoracic surgical ICU patients [10]. The slight difference between the results from these two studies and our results may primarily be a result of a different composition of elective and acute surgery as well as type of surgical procedures in the cohorts of ICU patients. A Spanish study of 234 ICU patients with sepsis who survived to hospital discharge, found a relative risk of two-year mortality of 3.2 (95% CI 1.6 to 6.5) in patients with AKI during the ICU stay compared to patients without AKI. However, data on mortality were not available for 23% of the initial cohort [11], and may not be directly comparable with our subgroup of patients with a primary hospital diagnosis of septicemia in which we found no impact of AKI on 31- to 365-day mortality. In a UK cohort study of 153 patients with AKI at ICU admission, Abosaif *et al.* observed 6-month mortality of 43.3%, 53.6% and 86.0% for patients with AKI-risk, AKI-injury, and AKI-failure, respectively [8]. The crude 6-month mortality risk for patients with AKI-risk and AKI-injury corresponds well with our findings.

Strengths and limitations

The main strengths of our study include its large size, well-defined study population, uniform access to health care in Denmark, comprehensive laboratory data including baseline measurements from outpatient clinics and general practitioners, and complete follow-up data. However, several additional issues should be considered when interpreting our results.

First, we used routine laboratory data to assess AKI at ICU admission, and some creatinine measurements (that is, those measured only with an arterial blood gas analyzer in the ICU) may not be transferred to the laboratory database. We excluded patients without a creatinine measurement at ICU admission. However, the overall results did not change after imputation of AKI level. Second, as our routine data did not include information about urine output we could not utilize urine criteria in the RIFLE classification of AKI. However, urine output criteria are affected by diuretics, which are commonly used in ICU patients. Third, we assessed AKI severity at ICU admission, when follow-up commenced. We thereby avoided including follow-up time before fulfilment of AKI criteria, that is, immortal person-time [33,34]. However this limits the generalization to patients with AKI at ICU admission. Fourth, we did not have detailed data on severity of illness scores at ICU admission or during the ICU stay. The physiological variables included in these scores may be part of the causal pathway and adjustment may thereby attenuate any true association [35]. Still, the impact of AKI on mortality was evident in subgroups of ICU patients treated with mechanical ventilation and inotropes/vasopressors, which may be indicators of more severe illness. In general, correct selection of confounders in prognostic studies of cohorts of ICU patients is challenging. Many covariates may be part of the causal pathway from exposure to outcome. Finally, despite adjustment for potential confounders, we cannot rule out unmeasured and residual confounding.

Conclusions

In this large cohort study, AKI was present at ICU admission in 15% of adult ICU patients. Any degree of AKI at ICU admission was associated with markedly increased 30-day mortality and the association was still evident in the 31- to 365-day period. The association was also robust in subgroups of ICU patients, with only slight variation.

Key messages

- The increased risk of death in patients with AKI at ICU admission was evident throughout the first year after ICU admission.
- The association was evident regardless of age, CKD, preexisting comorbidity, diagnostic category, and surgical status.
- The relative 30-day mortality was highest in younger age groups, elective surgical ICU patients, and acute cardiac surgical ICU patients.

Additional material

Additional file 1: List of relevant codes used in the current study.

Additional file 2: Table describing the characteristics of patients with and without a creatinine measurement on the day of ICU admission, and on the day before and the day after admission.

Abbreviations

AKI: acute kidney injury; CCI: Charlson comorbidity index; CI: confidence interval; CKD: chronic kidney disease; DNRP: Danish National Registry of Patients; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ICD: International Classification of Diseases; ICU: intensive care unit; IQR: inter quartile range; RIFLE: risk, injury, failure, loss of kidney function, and end-stage kidney disease.

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Authors' contributions

HTS, CFC, and HG conceived the study idea. HG, CFC, BJ, MBJ and HTS designed the study. MBJ and HTS collected the data. HG and MBJ analyzed the data. All authors interpreted the findings. HG and CFC reviewed the literature. HG wrote the first draft, and all authors critically reviewed and edited the manuscript and approved the final version.

Competing interests

The authors declare that they have no competing interests.

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Additional file 1

Relevant codes used in the current study

Danish treatment codes defining ICU admission:

- Intensive observation: NABE
- Intensive therapy: NABB

Nomenclature, Properties and Units in Laboratory Medicine (NPU) codes and local Danish laboratory codes used to identify creatinine measurements in the laboratory database:

- NPU18016; NPU01807; NPU04998; ASS00356; ASS00354; ASS00355

International Classification of Diseases (ICD)-10 codes defining primary diagnosis during current hospitalization:

- Septicemia: A02.1, A32.7, A39.2, A40-A41, A.42.7, B37.7
- Other infectious diseases :A00-B99 (except: A02.1, A32.7, A39.2, A40-A41, A.42.7, B37.7),, G00-G07, I00-I02, I30.1, I32.0, I33, I38, I40.0, J00-J06, J36, J39.0, J10-J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00-L03, L05-L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70-N77
- Cancer or other neoplasm: C00-D89
- Endocrine diseases E00-E90
- Cardiovascular diseases: I00-I99 without I00-I02, I30.1, I32.0, I33, I38, and I40.0
- Respiratory diseases: J00-J99 without J00-J06, J36, J39.0, J10-J22, J85.1, and J86
- Gastrointestinal or liver diseases: K00-K99 without K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, and K83.0
- Trauma or poisoning: S00-T98
- Other: all codes not included in other categories

ICD-10 disease categories included in non-renal Charlson Comorbidity Index score

Charlson score of 1:

- Myocardial infarction: I21, I22, I23;
- Congestive heart failure: I50, I11.0, I13.0, I13.2;
- Peripheral vascular disease: I70, I71, I72, I73, I74, I77;
- Cerebrovascular disease: I60-I69, G45, G46;
- Dementia: F00-F03, F05.1, G30;
- Chronic pulmonary disease: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3;
- Connective tissue disease: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86;
- Ulcer disease: K22.1, K25-K28;

- Mild liver disease: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0;
- Diabetes mellitus: E10.0-E10.2, E10.9, E11.0-E11.1, E11.9

Charlson score of 2:

- Hemiplegia: G81, G82;
- Diabetes with end organ damage: E10.2-E10.8, E11.2-E11.8;
- Any tumor: C00-C75;
- Leukemia: C91-C95;
- Lymphoma: C81-C85, C88, C90, C96

Charlson score of 3:

- Moderate to severe liver disease: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85

Charlson score of 6:

- Metastatic solid tumor: C76-C80;
- AIDS: B21-B24

Danish treatment codes for intensive care unit treatments

- Acute dialysis: JFD0
- Mechanical ventilation: GDA0
- Treatment with inotropics or vasopressors:FHC92, FHC93, FHC95

Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP) codes for cardiac surgery

- Heart and major thoracic vessels: KF

ICD-10 codes and Danish treatment codes for chronic renal replacement therapy and kidney transplantation

- Chronic renal replacement therapy: JFD2
- Kidney transplant status: KKAS, Z94.0

Additional file 2

Characteristics of patients with and without a creatinine measurement at ICU admission

	Missing creatinine n = 1,578	Available creatinine n = 30,762
Age		
Median age (IQR)	44 (30 ; 63)	65 (50 ; 75)
Gender		
Female	886 (56.1%)	13.352 (43.4%)
Male	692 (43.9%)	17,410 (56.6%)
Charlson Comorbidity Index score[a]		
Low (score: 0)	1,153 (73.1%)	15,726 (51.1%)
Medium (score: 1-2)	264 (16.7%)	10,544 (34.3%)
High (score ≥3)	161 (10.2%)	4,492 (14.6%)
Chronic kidney disease[b]		
Yes	100 (6.3%)	4.347 (14.1%)
No	1,478 (93.7)	26,415 (85.9%)
Primary diagnose during current hospitalization		
Septicemia	8 (0.5%)	646 (2.1%)
Other infectious diseases	162 (10.3%)	2.959 (9.6%)
Endocrine diseases	46 (2.9%)	558 (1.8%)
Cardiovascular diseases	141 (8.9%)	8,220 (26.7%)
Respiratory diseases	57 (3.6%)	1,750 (5.7%)
Gastrointestinal or liver diseases	79 (5.0%)	3,243 (10.5%)
Cancer or other neoplasm	126 (8.0%)	3,854(12.5%)
Trauma or poisoning	274 (17.4%)	5,035 (16.4%)
Other	685 (43.4%)	4.497 (14.6%)
Surgical status[c,d]		
Non-surgical	497 (31.5%)	11,766 (38.2%)
Surgical		
Acute non-cardiac	693 (43.9%)	10,141 (33.0%)
Acute cardiac	18 (1.1%)	1,096 (3.6%)
Elective non-cardiac	349 (22.1%)	4,334 (14.1%)
Elective cardiac	21 (1.3%)	3.425 (11.1%)
Laboratory information		
Measured baseline creatinine n (%)	744 (47.2)	21,028 (68.4%)
ICU treatments		
Acute renal replacement rherapy	16 (1.0%)	1,469 (4.8%)
Mechanical ventilation	180 (11.4%)	12,054 (39.2%)
Inotropes/vasopressors	106 (6.7%)	10,382 (33.7%)
Length of admission		
In-hospital days – median (IQR)	3 (1 ; 7)	10 (4 ; 21)
In-hospital days before ICU admission – median (IQR)	0 (0 ; 2)	1 (0 ; 3)

[a] Non-renal Charlson Comorbidity Index score

[b] eGFR < 60 ml/min per 1.73m^2

[c] Surgical status and cardiac surgical stutus identified by surgery and type of surgery on or up to 7 days before ICU admission

[d] Acute and elective status classified according to hospital admission type

AKI, acute kidney injury; CI, confidence interval; ICU, intensive care unit; IQR, inter quartile range; NA, not available

Study II

CRITICAL CARE

RESEARCH Open Access

Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study

Henrik Gammelager[1*], Christian Fynbo Christiansen[1], Martin Berg Johansen[1], Else Tønnesen[2], Bente Jespersen[3] and Henrik Toft Sørensen[1]

Abstract

Introduction: Dialysis-requiring acute kidney injury (D-AKI) is common among intensive care unit (ICU) patients. However, follow-up data on the risk of end-stage renal disease (ESRD) among these patients remain sparse. We assessed the short-term and long-term risk of ESRD after D-AKI, compared it with the risk in other ICU patients, and examined the risk within subgroups of ICU patients.

Methods: We used population-based medical registries to identify all adult patients admitted to an ICU in Denmark from 2005 through 2010, who survived for 90 days after ICU admission. D-AKI was defined as needing acute dialysis at or after ICU admission. Subsequent ESRD was defined as a need for chronic dialysis for more than 90 days or a kidney transplant. We computed the cumulative ESRD risk for patients with D-AKI and for other ICU patients, taking into account death as a competing risk, and computed hazard ratios (HRs) using a Cox model adjusted for potential confounders.

Results: We identified 107,937 patients who survived for 90 days after ICU admission. Of these, 3,062 (2.8%) had an episode of D-AKI following ICU admission. The subsequent risk of ESRD up to 180 days after ICU admission was 8.5% for patients with D-AKI, compared with 0.1% for other ICU patients. This corresponds to an adjusted HR of 105.6 (95% confidence interval (CI): 78.1 to 142.9). Among patients who survived 180 days after ICU admission without developing ESRD (n = 103,996), the 181-day to 5-year ESRD risk was 3.8% for patients with D-AKI, compared with 0.3% for other ICU patients, corresponding to an adjusted HR of 6.2 (95% CI: 4.7 to 8.1). During the latter period, the impact of AKI was most pronounced in the youngest patients, aged 15 to 49 years (adjusted HR = 12.8, 95% CI: 6.5 to 25.4) and among patients without preexisting chronic kidney disease (adjusted HR = 11.9, 95% CI: 8.5 to 16.8).

Conclusion: D-AKI is an important risk factor for ESRD for up to five years after ICU admission.

Keywords: acute kidney injury, cohort studies, critical care, end-stage renal disease, intensive care units, prognosis, renal dialysis

Introduction

Acute kidney injury is a common organ dysfunction that may lead to or complicate intensive care unit (ICU) admission [1]. Among ICU patients, 4% to 6% have dialysis-requiring AKI (D-AKI) [2-4], which is associated with increased short-term and long-term mortality compared to ICU patients without this condition [5,6].

End-stage renal disease (ESRD), including need for chronic dialysis or kidney transplantation, is associated with considerable costs and impaired quality of life [7]. Studies of hospitalized patients found that D-AKI is an important risk factor for ESRD [8,9]. However, as AKI is often secondary to other diseases [1], its impact on subsequent ESRD may differ in ICU patients compared to other hospitalized patients in general and within subgroups of ICU patients. Knowledge of the long-term risk of ESRD after D-AKI in ICU patients, both overall and within subgroups, remains sparse, especially for patients

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who regain sufficient renal function to discontinue dialysis after an episode of D-AKI.

Previous studies have primarily reported dependency on dialysis at hospital discharge, or up to 180 days after initiating acute dialysis in the ICU [10-18]. However, few studies have followed patients beyond 180 days to examine the long-term ESRD risk after D-AKI in an ICU [3,11,19-21].

These studies are all limited by lack of a comparison cohort of ICU patients without D-AKI [3,11,19-21]. None examined potentially different impacts in subgroups of ICU patients [3,11,19-21], and only one ICU-based study reported the risk of ESRD among D-AKI patients who initially survived without developing ESRD [11].

We, therefore, conducted a nationwide cohort study among all ICU patients who survived 90 days or more after ICU admission, in order to examine the risk of ESRD among patients with D-AKI compared with other ICU patients. We examined short-term ESRD risk up to 180 days after ICU admission, and long-term ESRD risk from 181 days to 5 years for those who did not develop ESRD within the first 180 days after ICU admission. Thereby, we were able to both examine the short-term risk of ESRD after D-AKI, and the long-term risk in those patients who initially recovered sufficient renal function to become dialysis independent. In addition, we examined whether the impact of D-AKI on risk of ESRD varied across subgroups of ICU patients according to age, gender, chronic kidney disease, diabetes and surgical status.

Methods

Setting

We conducted this cohort study using prospectively collected data from medical registries in Denmark from 1 January 2005 to 31 December 2010 (Denmark had 5,411,405 inhabitants on 1 January 2005). The Danish National Health Service provides tax-supported health care to all Danish residents, including unfettered access to public hospitals. All intensive care and associated treatments are provided at public hospitals [22]. Denmark has 48 ICUs, including 37 multidisciplinary ICUs, four neurosurgical ICUs, three cardiothoracic ICUs, two multidisciplinary/cardiothoracic ICUs, one multidisciplinary/neurosurgical ICU, and onecardiac ICU.

In Denmark, unambiguous linkage of all registries is possible using a unique civil registration number assigned to all Danish residents by the Danish Civil Registration System (CRS). This registry contains complete information on migration, vital status and exact date of death for all residents [23].

ICU patients

We used the Danish National Registry of Patients (DNRP) to identify all adult Danish residents (aged 15 years or older) with a first-time ICU admission from 1 January 2005 to 31 December 2010. Since 1977, it has been mandatory for hospitals in Denmark to report information on all in-hospital contacts to the DNRP. Since 1995, this registry has also included all emergency room and outpatient clinic visits. Variables in the registry include civil registration number, hospital and hospital department, date of hospital admission and discharge, emergency vs. planned hospital admission, surgical procedures, major treatments, and one primary diagnosis (the main reason for current hospitalization assigned by the discharging physician) and up to 19 secondary diagnoses. Since 1994, diagnoses have been coded according to the *International Classification of Diseases*, 10th revision (ICD-10) [24]. Data on ICU admissions have been coded in the DNRP with a high level of accuracy since 2005 [25].

We used the primary ICD-10 diagnosis of the hospitalization to categorize patients into nine major disease groups: septicemia, other infectious disease, endocrine disease, cardiovascular disease, respiratory disease, gastrointestinal or liver disease, cancer, trauma or poisoning and other (please see Additional file 1 for the ICD-10 codes). In addition, we categorized patients into five groups according to surgical status: no surgery, acute cardiac surgery, acute non-cardiac surgery, elective cardiac surgery and elective non-cardiac surgery [26].

Acute kidney injury

D-AKI was defined as the need for acute dialysis at or within 90 days after ICU admission, based on a Danish procedure code for acute dialysis in the DNRP. Acute dialysis includes dialysis and hemofiltration. All ICU patients not receiving acute dialysis were defined as 'other ICU patients'.

End-stage renal disease

Data on ESRD were obtained from the Danish National Registry on Regular Dialysis and Transplantation (NRDT). The NRDT, established in 1990, contains highly valid information on all Danish residents with chronic kidney disease actively treated with either dialysis or kidney transplantation. Only patients with a permanent need of dialysis or need of a kidney transplant are included in the NRDT, thereby excluding patients with reversible kidney failure [27]. Registry data include date of first active treatment, treatment modality and underlying kidney disease. We defined date of ESRD diagnosis as 90 days after first active treatment registered in the NRDT, because chronic disease of the kidney is defined as impairment for more than 90 days [28]. Patients who died within 90 days after the first treatment were consequently not considered ESRD patients (n = 25). Patients with preexisting ESRD or any

previous dialysis treatment were not included in the study.

Covariates

Data on age, gender and comorbidity were obtained from the CRS and the DNRP. We obtained data on comorbidities that are associated with D-AKI and also are potential risk factors for ESRD. Using the DNRP, we identified all previous inpatient or outpatient clinic diagnoses up to five years before the current hospitalization. We thus included previous diagnoses of chronic kidney diseases, diabetes, hypertension, congestive heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease and malignant neoplasms. (Please see Additional file 1 for relevant codes used in the current study).

Statistical analyses

Patient characteristics, including demographic characteristics, comorbidity and information from the current hospitalization, were tabulated for ICU patients with and without D-AKI. We followed patients who survived the first 90 days after ICU admission until ESRD, death, emigration, five years from ICU admission or until 31 December 2011, whichever came first.

We plotted a 5-year cumulative risk curve for ESRD and calculated 90-day to 180-day, 181-day to 5-year, and overall 5-year risk of ESRD, using the cumulative risk method, which takes into account death as a competing risk [29]. We computed hazard ratios (HRs) for ESRD as a measure of relative risk, using a Cox proportional hazards regression model controlling for age group, gender, preexisting chronic kidney disease, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, malignant neoplasms and surgical status. The assumptions of proportional hazards were checked graphically by log(-log) plots and found appropriate.

We examined the potentially different impact in subgroups of ICU patients, by stratifying the analyses by age groups, gender, presence chronic kidney disease, presence diabetes and surgical status. Analyses were performed using the statistical software package Stata version 11.1 (StataCorp LP, College Station, TX, USA).

All data were obtained from Danish registries, which are available to researchers, and their use does not require ethical approval or informed consent. The study was approved by the Danish Data Protection Agency (record number 2009-41-3987).

Results

Characteristics of the study population

The study population consisted of 107,937 adult ICU patients. Patients who died during the first 90 days after ICU admission (n = 33,367), and patients with preexisting ESRD or any previous dialysis treatment (n = 1,697) were not considered for the study. Total follow-up time was 230,278 person-years, with a median duration of 3.1 years (inter-quartile range (IQR): 1.6 to 4.8).

We found that 3,062 (2.8%) patients who survived for 90 days or more had an episode of D-AKI following ICU admission. Compared to other ICU patients, patients with D-AKI were slightly older (median age = 65 years (IQR: 55 to 73) vs. median age 62 = years, (IQR: 46 to 72)), more often male and, in general, with more preexisting comorbidity, in particularly chronic kidney disease, diabetes and hypertension. They also had longer hospital stays, were more often treated with mechanical ventilation or inotropes/vasopressors, and more often had a primary diagnosis of septicemia (Table 1).

Risk of end-stage renal disease

The five-year ESRD risk was 11.7% (95% CI: 10.5 to 13.0) for ICU patients with an episode of D-AKI, compared with 0.4% (95% CI: 0.3% to 0.4%) for other ICU patients (Figure 1).

Risk of ESRD within 90 to 180 Days

Out of the 3,062 ICU patients with D-AKI who survived for 90 days after ICU admission, 260 developed ESRD within 180 days following ICU admission (cumulative risk = 8.5% (95% CI: 7.5% to 9.5%)) compared with 57 patients out of 104,875 other ICU patients (cumulative risk = 0.1%, 95% CI: 0.0% to 0.1%). This corresponds to an unadjusted HR for ESRD of 165.9 (95% CI: 124.6 to 221.0) for D-AKI patients compared with other ICU patients. After adjusting for potential confounders, with chronic kidney disease being the most important, the adjusted HR was 105.6 (95% CI: 78.1 to 142.9) (Table 2).

Risk of ESRD within 181 days to 5 years

Among ICU patients who survived 180 days after ICU admission without developing ESRD, the 181-day to 5-year ESRD risk for patients with D-AKI was 3.8% (95% CI: 3.0% to 4.8%), compared with 0.3% (95% CI: 0.3% to 0.4%) for other ICU patients. This corresponds to an unadjusted HR of 13.5 (95% CI: 10.5 to 17.5) and an adjusted HR of 6.2 (95% CI: 4.7 to 8.1) (Table 2). Again, chronic kidney disease was the most important confounder in the adjusted model.

Subgroup analyses

The association between D-AKI and ESRD was evident within all subgroups of ICU patients in the 90- to 180-day period (Table 3). Within the 181-day to 5-year follow-up period, we found that the relative impact of D-AKI on risk of ESRD was higher for patients without preexisting chronic kidney disease (adjusted HR = 11.9 (95% CI: 8.5 to 16.8)) than for patients with preexisting chronic kidney disease (adjusted HR = 2.8 (95% CI: 1.8 to 4.3)) due to a high risk of ESRD even without AKI (cumulative risk = 7.2% (95% CI: 5.9% to 8.8%)).

Table 1 Characteristics by D-AKI status among 107,937 adult ICU patients, Denmark 2005 to 2010

	D-AKI[a] *n* = 3,062	Other ICU patients[a] *n* = 104,875
Age, median (IQR), years	65 (55, 73)	62 (46, 72)
Gender		
Female	1,116 (36.4)	45,440 (43.3)
Male	1,946 (63.6)	59,435 (56.7)
Preexisting comorbidity		
Chronic kidney disease[b]	325 (10.6)	1,961 (1.9)
Diabetes	547 (17.9)	8,715 (8.3)
Hypertension	748 (24.4)	16,218 (15.5)
Congestive heart failure	307 (10.0)	5,837 (5.6)
Myocardial infarction	147 (4.8)	4,848 (4.6)
Cerebrovascular disease	244 (8.0)	7,933 (7.6)
Peripheral vascular disease	286 (9.3)	6,517 (6.2)
Malignant neoplasm	329 (10.7)	12,402 (11.8)
Primary diagnosis during current hospitalization		
Septicemia	295 (9.6)	1,373 (1.3)
Other infectious diseases	300 (9.8)	8,087 (7.7)
Endocrinology diseases	86 (2.8)	2,126 (2.0)
Cardiovascular diseases	752 (24.6)	28,154 (26.9)
Respiratory diseases	298 (9.7)	7,502 (7.2)
Gastrointestinal or liver diseases	274 (8.9)	8,123 (7.7)
Cancer	195 (6.4)	13,321 (12.7)
Trauma or poisoning	250 (8.2)	18,427 (17.6)
Other	612 (20.0)	17,762 (16.9)
Surgical status[c,d]		
No surgery	1,250 (40.8)	38,406 (36.6)
Surgery		
Acute cardiac surgery	162 (5.3)	2,510 (2.4)
Acute non-cardiac surgery	1,126 (36.8)	30,559 (29.1)
Elective cardiac surgery	248 (8.1)	14,080 (13.4)
Elective non-cardiac surgery	276 (9.0)	19,320 (18.4)
ICU treatments		
Mechanical ventilation	2,320 (75.8)	33,742 (32.1)
Inotropes/vasopressors	2,244 (73.3)	26,705 (25.5)
Length of admission, median (IQR)		
In-hospital days	47 (26 to 84)	10 (5 to 20)
In-hospital days before ICU admission	1 (0 to 4)	1 (0 to 3)
In-hospital days after ICU admission	43 (24 to 80)	8 (4 to 16)

[a]Values are expressed as numbers (percentages) unless otherwise indicated.

[b]Patients with preexisting ESRD or who were previously treated with dialysis were not included in the current study.

[c]Surgical status identified by surgery at or up to seven days before ICU admission.

[d]Acute and elective status classified according to hospital admission type.

CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit; IQR, inter-quartile range

Nonetheless, the absolute risk difference between D-AKI patients and other ICU patients was remained higher for patients with preexisting kidney disease compared to patients without this diagnosis (Table 4). The relative impact of D-AKI on risk of future ESRD was also most pronounced in the youngest age group, in females and among elective surgical patients, but similar among diabetic and non-diabetic patients (Table 4).

Discussion

Key results

This nationwide population-based cohort study extends current knowledge by examining and comparing both short-term and long-term risk of ESRD among ICU patients with and without an episode of D-AKI. Among ICU patients who survived for 90 days after ICU admission, we found the five-year absolute risk of

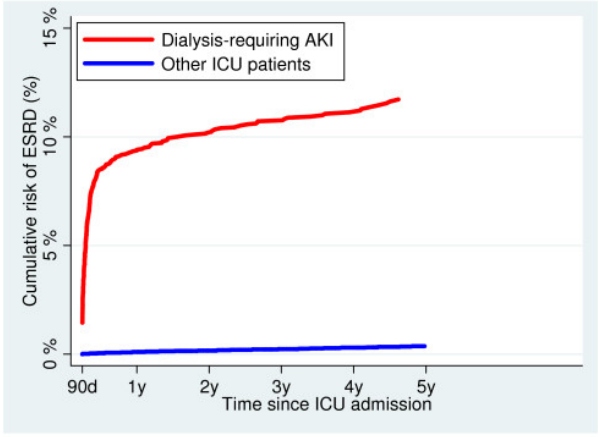

Figure 1 Cumulative five-year risk curve of ESRD by D-AKI status, Denmark, 2005 to 2010. AKI, acute kidney injury; ESRD, end-stage renal disease; ICU, intensive care unit

ESRD to be more than 10% in ICU patients with D-AKI compared with a risk of less than 0.5% for other ICU patients. Even among patients who survived more than 180 days after ICU admission without having ESRD, the subsequent ESRD risk was six-fold higher for up to five years among ICU patients with an episode of D-AKI compared to other ICU patients. The relative impact of D-AKI on ESRD risk was less pronounced for patients with chronic kidney disease, due to their high risk of ESRD even without D-AKI.

Existing studies

In line with our observations on the short-term risk of ESRD, a Swedish cohort study reported that 9.4% (104/1,102) of ICU patients with D-AKI, who were alive 90 days after commencement of acute dialysis, had started active treatment for ESRD [11]. Slightly lower estimates were reported by Bellomo *et al.* from their randomized trial that examined the optimal intensity of dialysis. They found that 5.6% (45/810) of patients with D-AKI still were dependent on dialysis 90 days after initiating acute dialysis [12]. However, in contrast, Cartin-Ceba *et al.* found that as many as 37.0% (282/784) of ICU patients who survived and were discharged from hospital needed dialysis for more than 90 days [13]. Furthermore, small studies including between 17 and 137 surviving ICU patients with D-AKI in various ICU settings have reported that between 4.2% and 28.9% are still dependent on dialysis 90 or 180 days after initiating acute dialysis [3,14-18]. This large variation may be explained primarily by differences in ICU populations with different baseline renal function.

Our estimates of long-term ESRD risk are also consistent with the Swedish study by Bell *et al.* [11]. They found that 3.4% (34/998) of ICU patients with D-AKI developed ESRD in the period from 90 days up to seven years after initiating dialysis [11]. Our results are also consistent with both a Canadian study and a US study of hospitalized patients, which found an increased risk of ESRD in patients requiring acute dialysis who initially recovered enough renal function to discontinue dialysis [8,9]. The Canadian study by Wald *et al.* reported an adjusted HR of 3.23 (95% CI: 2.70 to 3.86) for ESRD after D-AKI among hospitalized patients who did not develop ESRD in the first month after hospital discharge, compared to a matched cohort of patients without D-AKI [8]. Results were similar for a subgroup analysis of mechanically ventilated patients (n = 1,716) used as a surrogate for ICU admission. The US study by Hsu *et al.* examined patients with known chronic kidney disease (estimated glomerular filtration rate of below 45 ml/minute per 1.73m^2) with D-AKI during hospitalization who did not develop ESRD within the first month after hospital discharge. The study reported an adjusted HR of 1.47 (95% CI: 0.95 to 2.28) for ESRD [9]. However, studies including between 39 and 105 surviving ICU patients in different ICU settings have reported the proportion still dependent on dialysis to be 13.3%

Table 2 Cumulative risk and hazard ratios of ESRD for ICU patients with D-AKI compared to other ICU patients

Follow up/cohort	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
90 to 180 days					
D-AKI	3,062	260	8.5 (7.5- 9.5)	165.9 (124.6 to 221.0)	105.6 (78.1 - 142.9)
Other ICU patients	104,875	57	0.1 (0.0 - 0.1)	1 (reference)	1 (reference)
181 days to 5 years					
D-AKI	2,579	76	3.8 (3.0 - 4.8)	13.5 (10.5 - 17.5)	6.2 (4.7 - 8.1)
Other ICU patients	101,417	249	0.3 (0.3 - 0.4)	1 (reference)	1 (reference)

[a]Adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer and surgical status.

CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; HR, hazard ratio; ICU, intensive care unit; n, number

Table 3 ESRD risk and adjusted HR between 90 and 180 days after ICU admission by D-AKI status

	D-AKI			Other ICU patients _			Adjusted HR (95% CI)[a]
	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	
Age, years							
15 to 49	533	30	5.6 (3.9 - 7.8)	30,629	9	0.03 (0.01 - 0.06)	121.6 (54.2 - 272.9)
50 to 69	1,444	120	8.3 (7.0 - 9.8)	42,078	26	0.06 (0.04 - 0.09)	91.6 (58.7 -143.0)
≥70	1,085	110	10.1 (8.4 - 12.0)	32,159	22	0.07 (0.04 - 0.10)	109.0 (67.6 -175.6)
Gender							
Female	1,116	89	8.3 (6.8 - 9.9)	45,441	21	0.05 (0.03 - 0.07)	117.3 (70.8 - 194.5)
Male	1,946	171	8.4 (6.9 - 10.1)	59,435	36	0.06 (0.04 - 0.08)	98.7 (67.7 - 143.9)
Chronic kidney disease							
Yes	325	90	27.7 (22.9 - 32.6)	1,961	38	1.94 (1.40 - 2.62)	17.4 (11.8 - 25.7)
No	2,737	170	6.2 (5.3 - 7.2)	102,914	19	0.02 (0.01 - 0.03)	313.0 (193.4 - 506.4)
Diabetes							
Yes	547	62	11.3 (8.8 - 14.2)	8,715	15	0.17 (0.10 -0.28)	52.4 (29.0 - 94.8)
No	2,515	198	7.9 (6.8 - 9.0)	96,160	42	0.04 (0.03 - 0.06)	122.6 (86.5 - 173.8)
Surgical status							
No surgery	1,250	129	10.3 (8.7 - 12.1)	38,406	32	0.08 (0.06 - 0.12)	83.1 (55.2 - 125.0)
Surgery							
Acute non-cardiac surgery	1,126	83	7.3 (5.9 - 9.0)	30,559	11	0.04 (0.02 - 0.06)	145.3 (76.4 - 276.2)
Acute cardiac surgery	162	8	4.9 (2.3 - 9.0)	2,510	4	0.16 (0.06 - 0.40)	25.2 (6.7 to 94.9)
Elective non-cardiac surgery	276	28	10.1 (6.9 - 14.0)	19,320	7	0.04 (0.02 - 0.07)	218.9 (91.1 - 521.1)
Elective cardiac surgery	248	12	4.8 (2.6 - 8.0)	14,080	3	0.02 (0.00 - 0.06)	136.2 (33.1 - 561.3)

[a]Compared to ICU patents not treated with dialysis within same subgroup and adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer and surgical status.

CI, confidence interval; D-AKI, dialysis-requiring acute kidney injury; ESRD, end-stage renal disease; HR, hazard ratio; ICU, intensive care unit; n, number

(8/60), 21.8% (19/87) and 33.3% (13/39) one year after initiating acute dialysis [3,19,21], and 1.7% (1/60) three years after initiating acute dialysis [20].

We did not have data on the mechanism of the potential association between D-AKI and subsequent ESRD. We speculate that some patients may never recover normal kidney function after D-AKI, as observed among patients who developed ESRD in the 90- to 180-day period. A recent study showed that even patients who recover normal kidney function after AKI as assessed by serum creatinine measurements are at considerably increased risk of subsequent ESRD [30]. However, these patients may have residual renal function impairment, which is not detectable by elevated plasma creatinine [31].

Clinical perspectives

Our study suggests that D-AKI among ICU patients is a strong risk factor for ESRD for up to five years after ICU admission. Thus, there may be a need for systematic post-discharge follow-up of ICU patients with an episode of D-AKI, in order to avoid further kidney damage, and for development of prophylactic strategies.

Strengths and limitations

The strengths of our study include access to a well-defined population with uniform access to health care, use of high quality nationwide medical databases, and virtually complete follow-up data. This minimized selection and information biases.

Still, some limitations should be considered when interpreting our results. First, we lacked detailed nationwide data on kidney function, such as serum creatinine measurements to estimate glomerular filtration rates (eGFR). Thus, we were unable to identify and stage pre-existing chronic kidney disease by eGFR level. Neither were we able to assess the subsequent risk of kidney dysfunction less severe than ESRD. However, even if we had creatinine measurements, the availability of more measurements in patients with a D-AKI history is likely to introduce bias. Second, we lacked access to detailed data on type or intensity of dialysis performed in the ICUs. Therefore, we were unable to examine the association between type or intensity of acute dialysis and ESRD. Third, despite adjustment for potential confounders, including age group, comorbidity and surgical status, we cannot rule out unmeasured and residual confounding, for example, by severity of pre-existing chronic kidney disease.

Table 4 ESRD risk and adjusted HR between 181 days and five years after ICU by D-AKI status

	D-AKI			Other ICU patients			Adjusted HR (95% CI)[a]
	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	Total (n)	ESRD (n)	Cumulative risk % (95% CI)	
Age, y							
15 to 49	484	14	3.4 (1.9 - 5.5)	30,299	38	0.18 (0.13 - 0.24)	12.8 (6.5 - 25.4)
50 to 69	1,227	33	3.9 (2.6 - 5.4)	40,750	129	0.44 (0.37 - 0.53)	5.3 (3.6 - 8.0)
≥70	864	29	4.0 (2.7 - 5.7)	30,330	82	0.35 (0.28 - 0.43)	6.9 (4.4 - 10.9)
Gender							
Female	952	34	5.0 (3.2 - 7.5)	43,955	99	0.30 (0.24 - 0.37)	7.3 (4.8 - 11.1)
Male	1,627	42	3.3 (2.3 - 4.6)	57,462	150	0.36 (0.30 - 0.42)	5.5 (3.9 - 8.0)
Chronic kidney disease							
Yes	218	28	18.4 (12.2 - 25.6)	1,795	102	7.23 (5.94 - 8.81)	2.8 (1.8 - 4.3)
No	2,361	48	2.7 (2.0 - 3.6)	99,622	147	0.21 (0.18 - 0.25)	11.9 (8.5 - 16.8)
Diabetes							
Yes	434	29	10.3 (6.7 - 14.7)	8,232	83	1.51 (1.20 - 1.88)	6.0 (3.9 - 9.4)
No	2,145	47	2.7 (2.0 - 3.6)	93,102	166	0.23 (0.20 - 0.27)	6.7 (4.7 - 9.4)
Surgical status							
No surgery	1,033	33	4.3 (2.9 - 6.1)	36,986	100	0.35 (0.28 - 0.42)	6.0 (4.0 - 9.2)
Surgery							
Acute non-cardiac surgery	960	23	3.0 (1.9 - 4.5)	29,341	73	0.35 (0.27 - 0.44)	5.8 (3.5 - 9.5)
Acute cardiac surgery	143	1	1.0 (0.1 - 5.9)	2,478	5	0.27 (0.10 - 0.62)	3.9 (0.4 - 39.9)
Elective non-cardiac surgery	226	5	2.8 (1.0 - 6.1)	18,640	34	0.25 (0.17 - 0.36)	8.7 (3.2 - 23.3)
Elective cardiac surgery	217	14	8.2 (4.6 - 13.2)	13,972	37	0.39 (0.28 - 0.54)	10.8 (5.3 - 22.3)

[a]Compared to ICU patents not treated with dialysis within the same subgroup and adjusted for age group, gender, chronic kidney disease, diabetes, hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, cancer and surgical status.

CI, confidence interval; D-AKI, dialysis requiring acute kidney injury; ESRD, end-stage renal disease; HR, hazard ratio; ICU, intensive care unit; n, number

Conclusions

We found that more than one out of 10 ICU patients who survived 90 days after ICU admission with D-AKI developed ESRD during the five years of follow-up, compared with less than one out of 200 in other ICU patients. Thus, an episode of D-AKI among ICU patients is an important risk factor for subsequent ESRD up to five years after ICU admission. While the increased risk compared with other ICU patients was evident within all subgroups of ICU patients, it was highest within subgroups with low baseline risk of ESRD, such as young patients and patients without chronic kidney disease.

Key messages

- One out of 10 ICU patients surviving the first 90 days of D-AKI developed ESRD during the five years of follow-up.
- D-AKI is an important risk factor for ESRD, even among patients who initially recovered sufficient kidney function to discontinue dialysis.
- The relative risk of ESRD was highest within subgroups with low baseline risk of ESRD, such as young patients and patients without chronic kidney disease.

Additional material

Additional File 1: Relevant codes used in the current study

Abbreviations

D-AKI: dialysis-requiring acute kidney injury; CI: confidence interval; CRS: Danish Civil Registration System; DNRP: Danish National Registry of Patients; eGFR: estimated glomerular filtration rates; ESRD: end-stage renal disease; HR: hazard ratio; ICU: intensive care unit; ICD-10: International Classification of Diseases: 10th revision; IQR: inter-quartile range; NRDT: Danish National Registry on Regular Dialysis and Transplantation

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HG, CFC and HTS conceived the study idea. HG, CFC, MBJ, BJ and HTS designed the study. MBJ and HTS collected the data. HG and MBJ performed the statistical analyses. HG and CFC reviewed the literature. HG wrote the first draft. HG, CFC, MBJ, ET, BJ and HTS interpreted the findings. All authors critically reviewed and edited the manuscript and approved the final version.

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Additional file 1

Relevant codes used in the current study

Description	Codes
ICU admission[a]	
Intensive observation	NABE
Intensive therapy	NABB
Treatments[a]	
Acute dialysis	BJFD0
Mechanical ventilation	BGDA0
Treatment with inotropes or vasopressors	BFHC92, BFHC93, BFHC95
Primary diagnosis during current hospitalization[b]	
Septicemia	A02.1, A22.7, A26.7, A28.2B, A32.7, A39.2, A40-A41, A.42.7, A54.8G, B37.7, J95.0A, O08.0S, O08.0T, O08.0U, O08.0V,O08.0Y, O85.9, R57.2, T80.2D, T80.2E, T80.2F, T81.4D, T88.0A
Other infectious diseases	A00–B99 (except: A02.1, A22.7, A26.7, A28.2B, A32.7, A39.2, A40-A41, A.42.7, A54.8G, B37.7), G00–G07, I00–I02, I30.1, I32.0, I33, I38, I40.0, J00–J06, J36, J39.0, J10–J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00–L03, L05–L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70–N77
Cancer	C00–D89
Endocrinological diseases	E00–E90
Cardiovascular diseases	I00–I99 without I00–I02, I30.1, I32.0, I33, I38, I40.0
Respiratory diseases	J00–J99 without J00–J06, J10–J22, J36, J39.0, J85.1, J86, J95.0A
Gastrointestinal or liver diseases	K00–K99 without K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0.
Trauma or poisoning	S00–S99, T00–T97 without T80.2D, T80.2E, T80.2F, T81.4D, T88.0A
Others	All codes not included in other categories
Preexisting morbidity[b]	
Chronic kidney disease	N00–N08, N11, N14–N16, N18–N19, N26–N27, N28.0, N39.1, E10.2, E11.2, E14.2, I12.0, I13.1, I13.2, I15.0, I15.1
Diabetes mellitus	E10–E11
Hypertension	I10–I15
Congestive heart failure	I50.x, I11.0, I13.0, I13.2
Myocardial infarction	I21, I22, I23
Peripheral vascular disease	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	I60–I69, G4, G46
Malignant neoplasm	C00–C96

[a] Danish treatment codes in the Danish National Registry of Patients
[b] International Classification of Diseases, 10th revision codes in the Danish National Registry of Patients

Study III

Three-year Risk of Cardiovascular Disease among Intensive Care Patients with Acute Kidney Injury: A Population-Based Cohort Study

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ABSTRACT

Context Acute kidney injury (AKI) is common among intensive care unit (ICU) patients, but follow-up data on subsequent risk of cardiovascular disease remain sparse.

Objectives To examine the impact of AKI on 3-year risk of first-time heart failure, myocardial infarction (MI), and stroke among ICU patients surviving to hospital discharge, and to determine whether this risk is modified by renal recovery before hospital discharge.

Design, Setting, and Participants We used population-based medical registries to identify all adult patients admitted to an ICU in Northern Denmark during 2005-2010, without previous or concurrent diagnosis of heart failure, MI, or stroke and who survived to hospital discharge. AKI was defined according to the serum creatinine criteria in the Kidney Disease Improving Global Outcomes classification.

Main Outcome Measures Three-year cumulative risk of hospitalization with first-time heart failure, MI, or stroke for patients with and without AKI and hazard ratios (HRs), using a Cox model adjusted for potential confounders.

Results Among 21 556 ICU patients surviving to hospital discharge, 4792 (22.2%) had an AKI episode. Three-year cumulative risk of heart failure was 2.2% in patients without AKI, 5.0% for AKI stage 1, and 5.0% for stages 2-3. The corresponding adjusted HRs were 1.34 (95% confidence interval (CI), 1.08-1.69) for patients with AKI stage 1 and 1.46 (95% CI, 1.15-1.87) for AKI stages 2-3, compared to patients without AKI. Patients without AKI, AKI stage 1, and AKI stages 2-3 had 3-year cumulative MI risks of 1.0%, 1.8% and 2.3%, respectively. The adjusted

HR for MI was 1.05 (95% CI, 0.72-1.52) for patients with AKI stage 1 and 1.49 (95% CI, 1.04-2.15) for patients with AKI stages 2-3. We found no association between AKI and stroke. Increased risk of heart failure and MI persisted in patients with renal recovery before discharge, although less pronounced than in patients without renal recovery.

Conclusion ICU patients surviving any stage of AKI are at increased 3-year risk of heart failure, but not stroke. Only AKI stages 2-3 are associated with increased MI risk.

INTRODUCTION

Acute kidney injury (AKI), which occurs in approximately one out of three intensive care unit (ICU) patients,[1,2] is associated with increased risk of both chronic kidney disease and death.[1-5]

AKI also may have long-term adverse cardiovascular effects.[6] The potentially increased risk of cardiovascular disease (CVD) following AKI might be mediated through chronic renal impairment, a well-known CVD risk factor.[7] In addition, animal studies have shown that AKI causes a systematic inflammatory response and activation of the renin-angiotensin system, subsequently promoting apoptosis and interstitial/perivascular fibrosis in the myocardium, and ultimately cardiac dysfunction.[8,9]

These findings are supported by a few cohort studies in humans, which reported that patients with AKI as a complication to myocardial infarction (MI), coronary intervention, or heart failure have an increased risk of subsequent heart failure and MI.[10-14] AKI during hospitalization also increases the risk of subsequent heart failure in patients infected with human immunodeficiency virus (HIV).[15] However, it is not known whether AKI has similar implications for incident heart failure and MI among ICU patients, among whom AKI is common. [1,2] Although it has been suggested that AKI may increase stroke risk,[16] the potential association between AKI and long-term stroke risk has received little attention.[10]

We therefore conducted a population-based cohort study to examine (1) the impact of AKI on 3-year risk of first-time heart failure, MI, and stroke among ICU patients surviving to hospital discharge, and (2) whether recovery of renal function before hospital discharge modifies subsequent risk of these cardiovascular diseases.

METHODS

Setting

We conducted this cohort study using population-based medical databases in Northern Denmark with approximately 1.15 million inhabitants.

The Danish health care system provides tax-funded health care to all Danish residents. The study region has 12 ICUs, 8 at university hospitals (1 cardiothoracic, 1 mixed cardiothoracic and multidisciplinary, 1 mixed neurosurgery and multidisciplinary, 1 neurosurgical, and 4 multidisciplinary) and 4 at regional hospitals (all multidisciplinary). The unique civil registration number assigned to all Danish residents allowed us to link Danish medical and administrative databases.[17]

Intensive Care Patients

We used the Danish National Registry of Patients (DNRP) covering all Danish hospitals to identify all adult residents of Northern Denmark (aged 15 years or older) who had a first-time ICU admission from 1 January 2005 to 31 December 2010 and who survived to hospital discharge. We required one year of residency in the study region to ensure availability of previous test results from the regional laboratory database. The study period was chosen based on availability of data. The DNRP includes data on all non-psychiatric hospitalizations in Denmark since 1977. Since 1995 the DNRP also has included data from outpatient clinic visits, emergency room visits, and psychiatric units. The DNRP records patients' civil registration number, treating hospital and department, dates of admission and discharge, type of admission (emergency vs. planned), surgical and other major procedures performed, ICU admissions and treatments, and one primary and up to 19 secondary discharge diagnoses assigned by the discharging physician. According to Danish guidelines, the primary diagnosis is

the main reason for the hospital admission. Since 1994, discharge diagnoses have been coded using the *International Classification of Diseases*, *10th revision* (ICD-10).[18] We used the primary ICD-10 diagnosis for the current hospitalization to categorize patients into one of the following 8 major disease groups: infectious disease, endocrine disease, cardiovascular disease, respiratory disease, gastrointestinal or liver disease, cancer, trauma or poisoning, and other. In addition, we categorized patients into five groups according to surgical status: no surgery, acute cardiac surgery, acute non-cardiac surgery, elective cardiac surgery, and elective non-cardiac surgery.[3]

Acute Kidney Injury

We used the population-based laboratory database that covers the study region to identify occurrences of AKI. The laboratory database contains test results from all inpatient stays, outpatient clinic visits, and visits to general practitioners.[19] We classified AKI according to the serum creatinine criteria in the Kidney Disease Improving Global Outcome (KDIGO) AKI classification (eTable 1).[20] We searched the laboratory database for the highest plasma creatinine (equivalent to serum creatinine[21]) value from ICU admission until hospital discharge to determine the highest level of AKI. All other ICU patients were classified as being "without AKI". We defined the baseline creatinine level as the most recent creatinine measurement from an outpatient clinic or general practitioner visit in the period from one year to seven days before the current hospitalization.[22] Plasma creatinine assessments later than seven days before the current hospitalization were not considered, because acute renal impairment may precede the admission. For patients without chronic kidney disease (CKD) who lacked a baseline creatinine measurement, we estimated baseline creatinine using the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation based on age, race, and gender, as recommended by the Second International Consensus Conference of the Acute

Dialysis Quality Initiative (ADQI) Group.[23] Patients previously treated with chronic dialysis or hemofiltration, those with a previous kidney transplant, and those lacking information on plasma-creatinine levels following ICU admission were excluded from the study.

Heart failure, Myocardial Infarction, and Stroke

Study outcomes were any hospital admission with a diagnosis of heart failure, MI, or stroke (ischemic and hemorrhagic cerebral stroke) registered in the DNRP subsequent to the current hospital admission up to 3-year after hospital discharge. In order to exclude prevalent cases, we omitted all patients with any previous diagnosis of heart failure, MI, or stroke up to 10 years prior to or during the admission.

Renal Recovery at Hospital Discharge

Patients were considered to have achieved renal recovery at hospital discharge if they did not receive any type of dialysis or hemofiltration treatment up to seven days before hospital discharge and their last plasma-creatinine measurement before discharge was less than 50% above their baseline level, *i.e.*, they no longer fulfilled the criteria for AKI.[24]

Covariates

We obtained data on covariates potentially associated with both AKI and the study outcomes from the DNRP,[18] the laboratory database,[19] and the Aarhus University Prescription Database covering all community pharmacies in the study region[25] (Table 1). Detailed descriptions of the identification of covariates, together with codes used to retrieve data from the DNRP, the laboratory database, and the Aarhus University Prescription Database are provided in eMethods and eTable 2.

Statistical Analyses

For each outcome, we followed patients from date of hospital discharge for up to three years or until first-time hospital admission with a study outcome, death, or the end of follow-up on 31 December 2011, whichever came first.

We used the cumulative incidence method to compute the cumulative risk of admission with heart failure, MI, or stroke for patients with AKI stage 1, AKI stages 2-3, and those without AKI, taking death into account as a competing risk.[26] Using hazard ratios (HRs) computed with Cox regression models, we compared the risk of each outcome for patients with AKI stage 1 and AKI stages 2-3 with that of patients without AKI.[27] In multivariate analyses we adjusted for the following potential confounders: age, gender, other heart disease, other cerebrovascular disease, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status at ICU admission, and preadmission use of any drug listed in Table 1. To examine the influence of renal recovery on subsequent cardiovascular disease risk, we stratified the analysis by renal recovery status at hospital discharge. All estimates were reported with 95% confidence intervals (CI).

The assumption of proportional hazards for all Cox regression models was assessed graphically using log(-log(survival probability))-plots and found valid. Analyses were performed using the statistical software package Stata, version 11.1 (StataCorp LP. College Station; TX, USA).

All data were obtained from Danish registries, which are generally available to researchers without ethics approval or informed consent. The study was approved by the Danish Data Protection Agency (record number 2009-41-3987).

RESULTS

Characteristics of the Study Population

The study population comprised 21 556 ICU patients who survived to hospital discharge, after excluding those with a previous kidney transplant or chronic dialysis treatment (n = 314), those with a previous or concurrent diagnosis of heart failure, MI, or stroke (n = 6702), and those lacking a plasma-creatinine measurement upon or after ICU admission (n = 1846). Compared to patients with a plasma-creatinine measurement, patients lacking this measurement were younger, had less comorbidity, and had a markedly shorter hospital stay (eTable 3). Median duration of follow-up was 2.7 years for all three study outcomes.

We found that 4792 (22.2%) of the 21 556 ICU patients had an episode of AKI; 2666 (12.4%) with AKI stage 1 and 2126 (9.9%) with AKI stages 2-3. Patients with AKI were older, more often male, and had a higher degree of comorbidity than other ICU patients. AKI patients also were more frequently users of cardiovascular drugs and non-steroidal anti-inflammatory drugs (NSAIDs) (Table 1). The primary diagnosis during the current hospitalization was most frequently trauma and poisoning for patients without AKI (25.0%), cardiovascular disease for patients with AKI stage 1 (32.7%), and infectious disease for patients with AKI stages 2-3 (20.4%). Patients with AKI were more frequently treated with mechanical ventilation and inotropes/vasopressors and had longer hospital stays (Table 1).

Risk of Heart Failure

During the 3 years following hospital discharge, 2.2% of patients without AKI, 5.0% of patients with AKI stage 1, and 5.0% of patients with AKI stages 2-3 were hospitalized with first-time heart failure (Figure 1 and Table 2). Compared to patients without AKI, the adjusted HR was

1.35 (95% CI, 1.08-1.69) for patients with AKI stage 1 and 1.46 (95% CI, 1.15-1.87) for patients with AKI stages 2-3 (Table 2).

Risk of Myocardial Infarction

The 3-year cumulative risk of MI was 1.0% for patients without AKI, 1.8% for patients with AKI stage 1 and 2.3% for patients with AKI stages 2-3 (Figure 1 and Table 2). The adjusted HR was 1.05 (95% CI, 0.72-1.52) for patients with AKI stage 1 and 1.49 (95% CI, 1.04-2.15) for patients with AKI stages 2-3 (Table 2).

Risk of Stroke

Stroke risk within the first 3 years after hospital discharge was 0.9% for patients without AKI, 1.7% for patients with AKI stage 1, and 1.4% for patients with AKI stages 2-3 (Figure 1 and Table 2). The adjusted HRs were 1.09 (95% CI, 0.74-1.60) for patients with AKI stage 1 and 1.08 (95% CI, 0.70-1.65) for patients with AKI stages 2-3 (Table 2).

Renal Recovery

Of the 4792 ICU patients with AKI who survived to hospital discharge, 3888 (81.1%) recovered renal function by the time of discharge. The increased risk of heart failure following any stage of AKI and of MI following AKI stages 2-3 persisted in patients who recovered their renal function, although their risk was lower than among patients without renal recovery (Table 3).

DISCUSSION

In this population-based study of more than 21 000 ICU survivors, patients with AKI stages 2-3 were at 50% increased risk of heart failure and MI in the 3-year follow-up period. Even AKI stage 1 was associated with increased risk of heart failure. The increased risk persisted in patients who recovered their renal function by the time of hospital discharge, but was less pronounced than the risk among patients without recovery of renal function. No associations were found between AKI and stroke or between AKI stage 1 and MI.

Other Studies

Our study is the first to examine the impact of AKI on first-time hospitalization for heart failure, MI, and stroke following an ICU stay. Previous studies primarily examined the impact on subsequent cardiovascular disease of AKI secondary to heart failure, MI or coronary intervention,[10-12,14] and none focused on first-time cardiovascular events. [10-12,14]

Five earlier studies examined the impact of AKI on heart failure. [10-13,15] Similar to our findings among ICU patients with AKI, they reported that AKI, as a complication of coronary angiography,[10] MI,[11] coronary arterial bypass grafting (CABG) surgery,[12] heart failure[13] and HIV[15] increased the risk of hospitalization for subsequent heart failure. In a Canadian cohort of 14 782 patients who underwent coronary angiography, procedures complicated by AKI were associated with increased risk of subsequent hospital admission for heart failure after median follow-up of 20 months. The adjusted HRs ranged from 1.48 (95% CI, 1.16-1.91) for patients with AKI stage 1 to 2.17 (95% CI, 1.49-3.15) for patients with AKI stages 2-3.[10] Similarly, a single-center Israeli study of 1957 patients admitted for ST-elevation MI found that during median follow-up of 36 months AKI was associated with subsequent risk of heart failure among patients who survived until hospital discharge. This study also found that the

association persisted in patients who recovered renal function before hospital discharge, which our findings confirmed.[11] A large Swedish study of 24 018 patients who underwent CABG surgery found that among 30-day survivors the adjusted HR of heart failure during mean follow-up of 4.1 years was 1.69 (95% CI, 1.48-1.94), 2.33 (95% CI, 1.69-3.22) and 1.87 (95% CI, 0.84-4.20) for AKI stages 1, 2 and 3, respectively. The association between AKI and subsequent increased risk of heart failure was also evident in a cohort of US veterans with HIV who survived the first three months after hospital discharge. Choi *et al.* reported an adjusted HR of subsequent heart failure of 1.17 (95% CI, 1.34-2.35) in patients with stage 1 AKI, 2.11 (95% CI, 1.07-2.35) in patients with AKI stages 2-3 not requiring dialysis, and 4.20 (95% CI, 2.24-7.88) in patients with AKI stages 2-3 requiring dialysis, during mean follow-up of 5.7 years.[15] In addition, a Chinese single-center study of 1,005 patients found that patients hospitalized for heart failure complicated by AKI were readmitted more frequently for heart failure during the following year.[13]

A few studies have examined risk of MI after AKI in different study populations.[10,11,14] Like our ICU study, they found that AKI was associated with later MI. However, these relatively small studies were hampered by imprecise risk estimates.[10,11] The study by James *et al.* found that the adjusted HRs of MI complicated by AKI stage 1 and AKI stages 2-3 were 1.47 (95% CI, 1.12-1.91) and 1.19 (95% CI, 0.70-2.02), respectively, compared with non-AKI patients. The Israeli study by Goldberg *et al*. found that the adjusted HR of recurrent MI after initial MI complicated by AKI was 1.6 (95% CI, 0.9-1.8) for patients with mild AKI who did not regain renal function by hospital discharge, 1.4 (95% CI, 0.7-3.0) for patients with moderate/severe AKI who did regain renal function, and 1.4 (95% CI, 0.7-2.8) for those with moderate/severe AKI who did not recover renal function. However, they found no increased risk of MI among patients with mild AKI who regained renal function (adjusted HR = 0.6 (95% CI, 0.2-1.8). In their single-center study, Lindsay *et al.* found that AKI (serum creatinine > 50% over baseline) after

percutaneous intervention was associated with a twofold increased risk of MI among hospital survivors (adjusted OR = 2.0; 95% CI, 1.3-3.2).

To our knowledge only one study has examined the association between AKI and long-term (beyond 90 days) risk of stroke.[10] In line with our results, the study by James *et al*. did not find marked evidence for an association between AKI and subsequent hospitalization for a cerebrovascular event among patients who survived to hospital discharge.[10]

Strengths and Limitations

The main strengths of this study are its population-based design in the setting of a uniform tax-supported health care system providing equal access to health care. As well, patient follow-up was virtually complete, and data on ICU admissions were highly valid. This reduced potential selection bias.

Several limitations should be considered when interpreting our results. First, like most other studies of AKI, we lacked data on urine output and thus could not include the urine output criteria specified in the KDIGO classification. However, urine output is affected by diuretics, which are commonly used in ICUs. Second, our outcome assessment relies on correct coding. Previous studies have found that the positive predictive values of discharge diagnoses recorded for heart failure, MI, and stroke are 81%,[28] 92%,[29] and 84%[30], respectively. However, any misclassification is expected to be non-differential, biasing the study towards a null result. Third, we had few outcomes for MI and stroke, resulting in imprecise estimates. Fourth, patients with coexisting heart failure may have been undiagnosed due to this disease's asymptomatic nature in its early phases. The association between AKI and apparent subsequent heart failure therefore could be partly due to reverse causation. Finally, although we controlled for potential confounders using highly valid data on known comorbidities and

drug use, our results may have been affected by unmeasured or residual confounding, such as undiagnosed cardiac dysfunction and severity of various comorbidities.

CONCLUSION

ICU patients who survive an AKI stages 2-3 episode are at increased risk of heart failure and MI up to 3 years after hospital discharge. The increased risk of heart failure is evident even among patient with AKI stage 1. These outcomes were less pronounced but persisted among patients who recovered renal function by hospital discharge. This suggests a need for systematic follow-up of patients discharged after an AKI episode, especially those who do not regain their renal function before discharge.

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Study concept and design: Gammelager, Christiansen, and Sørensen

Acquisition of data: Johansen and Sørensen

Analysis and interpretation of data: Gammelager, Christiansen, Johansen, Tønnesen, Jespersen, and Sørensen

Drafting the manuscript: Gammelager

Critical revision of the manuscript for important intellectual content: Gammelager, Christiansen, Johansen, Tønnesen, Jespersen, and Sørensen

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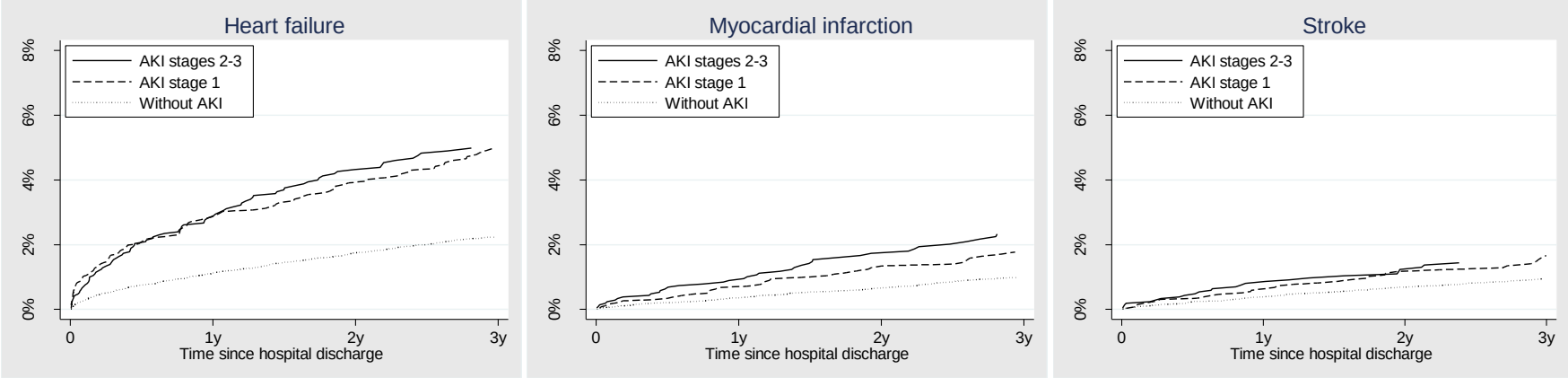
Online-Only material: eMethods and 3 eTables.

Figure 1. Three-year Cumulative Incidence of Heart Failure, Myocardial Infarction, and Stroke by AKI Stage.



Abbreviations: AKI; acute kidney injury; y, year

Table 1. Patient Characteristics by AKI Status among ICU Patients Surviving to Hospital Discharge, Northern Denmark, 2005-2010.[a]

	Without AKI n = 16 764	**AKI stage 1** n = 2666	**AKI stages 2-3** n = 2126
Age			
Age, median (IQR)	57 (39-69)	68 (58-77)	67 (56-75)
Gender			
Female	7788 (46.5)	1031 (38.7)	944 (44.4)
Male	8976 (53.5)	1635 (61.3)	1182 (55.6)
Comorbidity			
Ischemic heart disease except MI[b]	1863 (11.1)	513 (19.2)	244 (11.5)
Cerebrovascular disease except stroke[c]	537 (3.2)	124 (4.7)	86 (4.0)
Diabetes	1490 (8.9)	460 (17.3)	433 (20.4)
Chronic kidney disease	1063 (6.3)	502 (18.8)	338 (15.9)
Hypertension	2216 (13.2)	664 (24.9)	511 (24.0)
Peripheral vascular disease	721 (4.3)	266 (10.0)	202 (9.5)
Cancer	2282 (13.6)	522 (19.6)	375 (17.6)
No surgery	6455 (38.5)	662 (24.8)	793 (37.3)
Surgery			
Acute cardiac surgery	195 (1.2)	88 (3.3)	59 (2.8)
Acute non-cardiac surgery	5558 (33.2)	834 (31.3)	764 (35.9)
Elective cardiac surgery	1701 (10.1)	528 (19.8)	169 (7.9)
Elective non-cardiac surgery	2855 (17.0)	554 (20.8)	341 (16.0)
Preadmission drug use			
ACE inhibitors/AT2 antagonists	2677 (16.0)	763 (28.6)	698 (32.8)
Beta blockers	2318 (13.8)	667 (25.0)	487 (22.9)
Calcium channel antagonists	1587 (9.5)	483 (18.1)	401 (18.9)
Acetylsalicylic acid	5286 (31.5)	1362 (51.1)	1005 (47.3)
Diuretics	1348 (8.0)	357 (13.4)	272 (12.8)
Nitrates	756 (4.5)	236 (8.9)	83 (3.9)
Statins	2533 (15.1)	671 (25.2)	441 (20.7)
NSAIDs	2486 (14.8)	430 (16.1)	436 (20.5)
Primary diagnosis during current hospitalization			
Infectious diseases	1673 (10.0)	276 (10.4)	434 (20.4)
Endocrine diseases	302 (1.8)	69 (2.6)	99 (4.7)
Cardiovascular diseases	2910 (17.4)	873 (32.7)	390 (18.3)
Respiratory diseases	741 (4.4)	118 (4.4)	108 (5.1)
Gastrointestinal or liver diseases	1564 (9.3)	287 (10.8)	303 (14.3)
Cancer or other neoplasm	2463 (14.7)	471 (17.7)	304 (14.3)
Trauma or poisoning	4198 (25.0)	282 (10.6)	190 (8.9)
Other	2913 (17.4)	290 (10.9)	298 (14.0)
Laboratory information			
Measured baseline creatinine	10 213 (60.9)	2143 (80.4)	1610 (75.7)
Maximum creatinine during admission[d], µmol/L, mean (IQR)	74 (62-88)	123 (101-149)	254 (180-397)
ICU treatments			
Mechanical ventilation	4362 (26.0)	1297 (48.6)	1126 (53.0)
Inotropes/vasopressors	3083 (18.4)	1158 (43.4)	1155 (52.9)
Length of admission			
In-hospital days,[e] median (IQR)	8 (3-15)	15 (10-28)	23 (12-45)

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; AT2, angiotensin 2; CI, confidence interval; ICU, intensive care unit; IQR, inter-quartile range; NSAIDS, non-steroidal anti-inflammatory drugs

[a] Values are expressed as number (percentage) unless otherwise indicated.

[b] Patients with a previous diagnosis of myocardial infarction were not included in the study.

[c] Patients with a previous diagnosis of stroke were not included in the study.

[d] From ICU admission until hospital discharge.

[e] From hospital admission to hospital discharge. If date of discharge from one department and/or hospital and admission to another department and/or hospital was ≤ 1 calendar day, this was considered as one hospital admission.

Table 2. Three-year Risk of Cardiovascular Disease According to AKI Stage, Northern Denmark, 2005-2010.

	Without AKI		AKI Stage 1				AKI Stages 2-3			
	Events, n	Cumulative risk % (95% CI)	Events, n	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Events, n	Cumulative risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Heart failure	320	2.2 (2.0-2.5)	114	5.0 (4.2-6.0)	2.43 (1.96-3.01)	1.35 (1.08-1.69)	91	5.0 (4.0-6.1)	2.53 (2.01-3.01)	1.46 (1.15-1.87)
MI	135	1.0 (0.8-1.2)	38	1.8 (1.3-2.4)	1.93 (1.35-2.76)	1.05 (0.72-1.52)	40	2.3 (1.7-3.1)	2.68 (1.88-3.82)	1.49 (1.04-2.15)
Stroke	131	0.9 (0.8-1.1)	35	1.7 (1.2-2.4)	1.83 (1.26-2.65)	1.09 (0.74-1.60)	26	1.4 (1.0-2.1)	1.79 (1.17-2.72)	1.08 (0.70-1.65)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MI, myocardial infarction; n, number.

[a] Adjusted for age, gender, other ischemic heart diseases, other cerebrovascular diseases, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status, and preadmission use of drugs listed in Table 1.

Table 3. Risk of Cardiovascular Disease According To Renal Recovery Status Among AKI Patients at Hospital Discharge.

	Recovery (= 3888)		Non Recovery (n = 904)	
	Events n	Adjusted HR[b] (95% CI)	Events n	Adjusted HR[b] (95% CI)
AKI stage 1				
Heart failure	98	1.29 (1.02-1.63)	15	1.80 (1.07-3.04)
Myocardial infarction	35	1.06 (0.72-1.55)	3	0.81 (0.26-2.57)
Stroke	32	1.12 (0.75-1.67)	3	0.99 (0.31-3.13)
AKI stages 2-3				
Heart failure	62	1.49 (1.13-1.96)	30	1.55 (1.06-2.27)
Myocardial infarction	23	1.27 (0.81-2.00)	17	2.02 (1.20-3.40)
Stroke	19	1.17 (0.78-1.90)	7	0.91 (0.42-1.97)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; n, number.

[a] Compared to ICU patients without AKI

[b] Adjusted for age , gender, other ischemic heart diseases, other cerebrovascular diseases, hypertension, peripheral vascular disease, diabetes, chronic kidney disease, cancer, surgical status, and preadmission use of drugs listed in Table 1.

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Online-Only Material

eMETHODS

Covariates

We obtained data from the Danish National Registry of Patients (DNRP) on diagnoses of other ischemic heart diseases, other cerebrovascular diseases, hypertension, peripheral vascular disease, cancer, and diabetes up to 10 years before the current hospitalization. Because many patients with diabetes are treated outside hospitals, we also defined patients as having diabetes if they had a hemoglobin A1c level at or above 6.5%[1] in the laboratory database up to one year before the current admission or had any prescription for an antidiabetic drug (insulin or oral anti-diabetic agent) in the Aarhus University Prescription Database up to five years before the current admission. Diabetes patients who were identified solely by a prescription of metformin and who had coexisting polycystic ovary syndrome were classified as not having diabetes. The Aarhus University Prescription Database contains information on all filled drug prescriptions in the study region. Variables included in this database are patients' civil registration number, type of drug according to the Anatomic Therapeutic Chemical Classification System (ATC), dosage, and prescription date.[2] Information on chronic kidney disease was obtained from the laboratory database, defined as estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73 m^2 using the four-variable Modification of Diet in Renal Disease (MDRD) equation (stage 3 or higher chronic kidney disease (CKD) according to National Kidney Foundation guidelines).[3] We used the most recent plasma creatinine measurement from an outpatient clinic or general practitioner visit within one year to seven days before the current hospitalization to compute the eGFR.[4] Patients lacking a plasma creatinine measurement were considered as not having CKD. We also retrieved information on preadmission drug use, defined as a prescription filled from 90 days before the current hospitalization until hospital admission.[5] Information was obtained for all drugs listed in Table 1.

All relevant codes used to retrieve data from the DNRP, the laboratory database, and the Aarhus University Prescription Database are provided in eTable 2.

eTable 1. KDIGO Serum Creatinine Classification of Acute Kidney Injury

Stage	Serum creatinine criteria
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase within 48 hours[a]
2	2.0-2.9 times baseline
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥353.6 µmol/l) OR Initiation of renal replacement therapy

Abbreviation: KDIGO, Kidney Disease Improving Global Outcomes

[a] We defined 48 hours as 2 calendar days.

eTable 2. Codes Used to Retrieve Data From the Danish National Registry of Patients, Laboratory database, and the Aarhus University Prescription Database

Description	Codes
Diseases (ICD-10)	
Myocardial infarction	I21
Stroke	I61,I63, I64
Heart failure	I50, I11.0, I13.0, I13.2
Ischemic heart disease (except MI)	I20-I25 (except I21)
Cerebrovascular disease (except stroke)	I60-I69 (except I63-I64)
Diabetes	E10E14, O24 (except O24.4), G63.2, H36.0, N08.3
Peripheral vascular disease	I70, I71, I72, I73, I74, I77
Hypertension	I10-I15
Cancer	C00-C96
Primary diagnosis during current hospitalization (ICD-10)	
Infectious diseases	A00-B99, G00-G07, I00-I02, I30.1, I32.0, I33, I38, I40.0, J00-J06, J36, J39.0, J10-J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00-L03, L05-L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70-N77
Cancer	C00-D89
Endocrine diseases	E00-E90
Cardiovascular diseases	I00-I99 without I00-I02, I30.1, I32.0, I33, I38, I40.0
Respiratory diseases	J00-J99 without J00-J06, J10-J22, , J36, J39.0, J85.1, J86
Gastrointestinal or liver diseases	K00-K99 without K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0.
Trauma or poisoning	S00-S99, T00-T97
Other	All codes not included in other categories
Treatments (Procedure codes)	
Intensive therapy	NABE, NABB
Acute dialysis	BJFD0
Mechanical ventilation	BGDA0
Treatment with inotropes or vasopressors	BFHC92, BFHC93, BFHC95
Laboratory data (NPU- and local laboratory codes	
Plasma Creatinine	NPU18016, NPU01807, NPU04998. ASS00356, ASS00354, ASS00355
Hemoglobin A1c	NPU03835, NPU02307, NPU27300, DNK35249, AAB00092, AAB00091, AAA00740, AAB00061
Drugs (ATC-codes)	
Diuretics	C03
Beta blockers	C07
Calcium channel antagonists	C08
ACE inhibitors/AT2 antagonist	C09A, C09BA, C09BB, C09CA, C09DA, C09DB
Acetylsalicylic acid	B01AC06;
Nitrates	C01DA
Statins	C10AA
NSAIDS	M01A
Surgical procedures (NCSP codes)	
Cardiac surgery	KF
Non-cardiac surgery	All codes include in other categories

Abbreviations: ACE, angiotensin converting enzyme; ATC, Anatomical Therapeutic Chemical; AT2, angiotensin 2; ICD-10, International Classification of Diseases, 10th revision; NCSP, Nordic Medico-Statistical Classification of Surgical Procedures; NPU, Nomenclature, Properties and Units in Laboratory Medicine; NSAIDS, non-steroidal anti-inflammatory drugs

eTable 3. Characteristics of Patients Missing Plasma creatinine Measurements and of Patients Without and With AKI Among ICU Patients Surviving to Hospital Discharge[a]

	Missing P-creatinine n = 1846	**Without AKI** n = 16 764	**AKI stage 1** n = 2666	**AKI stages 2-3** n = 2126
Age				
Age, median (IQR)	39 (28–56)	57 (39–69)	68 (58–77)	67 (56–75)
Gender				
Female	1041 (56.4)	7788 (46.5)	1031 (38.7)	944 (44.4)
Male	805 (43.6)	8976 (53.5)	1635 (61.3)	1182 (55.6)
Comorbidity				
Ischemic heart disease[b]	61 (3.3)	1863 (11.1)	513 (19.2)	244 (11.5)
Cerebrovascular disease[c]	26 (1.4)	537 (3.2)	124 (4.7)	86 (4.0)
Diabetes	74 (4.0)	1490 (8.9)	460 (17.3)	433 (20.4)
Chronic kidney disease	69 (3.7)	1063 (6.3)	502 (18.8)	338 (15.9)
Hypertension	131 (7.1)	2216 (13.2)	664 (24.9)	511 (24.0)
Peripheral vascular disease	26 (1.4)	721 (4.3)	266 (10.0)	202 (9.5)
Cancer	110 (6.0)	2282 (13.6)	522 (19.6)	375 (17.6)
Surgical Status				
No surgery	589 (31.9)	6455 (38.5)	662 (24.8)	793 (37.3)
Surgery				
Acute cardiac surgery	3 (0.2)	195 (1.2)	88 (3.3)	59 (2.8)
Acute non-cardiac surgery	867 (47.0)	5558 (33.2)	834 (31.3)	764 (35.9)
Elective cardiac surgery	6 (0.3)	1701 (10.1)	528 (19.8)	169 (7.9)
Elective non-cardiac surgery	381 (20.6)	2855 (17.0)	554 (20.8)	341 (16.0)
Preadmission drug use				
ACE inhibitors/AT2 antagonists	154 (8.4)	2677 (16.0)	763 (28.6)	698 (32.8)
Beta blockers	165 (8.9)	2318 (13.8)	667 (25.0)	487 (22.9)
Calcium channel antagonists	78 (4.2)	1587 (9.5)	483 (18.1)	401 (18.9)
Acetylsalicylic acid	281 (15.2)	5286 (31.5)	1362 (51.1)	1005 (47.3)
Diuretics	83 (4.5)	1348 (8.0)	357 (13.4)	272 (12.8)
Nitrates	17 (0.9)	756 (4.5)	236 (8.9)	83 (3.9)
Statins	99 (5.4)	2533 (15.1)	671 (25.2)	441 (20.7)
NSAIDs	252 (13.6)	2486 (14.8)	430 (16.1)	436 (20.5)
Primary diagnosis during current hospitalization				
Infectious diseases	257 (13.9)	1673 (10.0)	276 (10.4)	434 (20.4)
Endocrine diseases	50 (2.7)	302 (1.8)	69 (2.6)	99 (4.7)
Cardiovascular diseases	140 (7.6)	2910 (17.4)	873 (32.7)	390 (18.3)
Respiratory diseases	53 (2.9)	741 (4.4)	118 (4.4)	108 (5.1)
Gastrointestinal or liver diseases	133 (7.2)	1564 (9.3)	287 (10.8)	303 (14.3)
Cancer or other neoplasm	98 (5.3)	2463 (14.7)	471 (17.7)	304 (14.3)
Trauma or poisoning	371 (20.1)	4198 (25.0)	282 (10.6)	190 (8.9)
Other	744 (40.3)	2913 (17.4)	290 (10.9)	298 (14.0)
Laboratory information				
Measured baseline creatinine	782 (42.4)	10 213 (60.9)	2143 (80.4)	1610 (75.7)
Maximum creatinine during admission[d], µmol/L, mean (IQR)	NA	74 (62–88)	123 (101–149)	254 (180–397)
ICU treatments				
Mechanical ventilation	52 (2.8)	4362 (26.0)	1297 (48.6)	1126 (53.0)
Inotropes/vasopressors	21(1.1)	3083 (18.4)	1158 (43.4)	1155 (52.9)
Length of admission				
In-hospital days,[e] median (IQR)	2 (1–4)	8 (3–15)	15 (10–28)	23 (12–45)

Abbreviations: ACE, angiotensin converting enzyme; AKI, acute kidney injury; AT2, angiotensin 2; CI, confidence interval; ICU, intensive care unit; IQR, inter-quartile range; NA, not available; NSAIDS, non-steroidal anti-inflammatory drugs; S-creatinine, serum-creatinine

[a] Values are expressed as number (percentage) unless otherwise indicated.

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