CRITICAL CARE

COMMENTARY

AKI patients have worse long-term outcomes, especially in the immediate post-ICU period

Eric AJ Hoste*[1,2] and Wouter De Corte[3]

See related research by Gammelager *et al.*, http://ccforum.com/content/16/4/R124

Abstract

Acute kidney injury (AKI) is associated with worse outcome in the acute phase of acute illness but also in the chronic phase. In a large Danish study in this issue of *Critical Care*, 1-year mortality was higher in patients with AKI than in patients without AKI. Mortality was most important during the first 50 days after admission to the intensive care unit (ICU), whereas after 2 months the survival curves of patients with AKI and those of patients without AKI were similar. The reasons for this observation are not clear, but protracted critical illness and fragility after acute critical illness probably play important roles. Because we see more and more of these patients, they should be the focus of ICU research. Consequently, ICU and post-ICU care for these patients requires focus and a more integrated approach to the specific problems of these survivors of acute critical illness.

Acute kidney injury (AKI) occurs in one third to two thirds of patients in the intensive care unit (ICU) [1-7]. The majority of clinical studies in ICU patients have found that AKI was associated with increased in-hospital mortality [8,9]. This effect persists after correction for other confounders in multivariate analyses. We can only speculate why even small increases of serum creatinine lead to worse outcomes. Plausible causes for this are volume overload, inflammation of and adverse effects on other organs (so-called 'organ cross-talk'), and inadequate drug dosing [10].

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The adverse effects of an episode of AKI may also persist for longer follow-up times. In their center in Florida, Hobson and Bihorac and their colleagues [11,12] found that, in specific ICU cohorts such as those who are recovering from major surgery or cardiac surgery, AKI leads to worse outcomes over a period of years. In a large cohort of hospitalized veterans, mortality in patients who had 90-day survival was higher in patients with AKI, and there was a stepwise increase for increasing AKI severity class [13]. In this issue of *Critical Care*, Gammelager and colleagues [14] nicely demonstrated similar findings in a large cohort of general ICU patients recruited in a large region in Denmark. The authors identified more than 30,000 patients during a 6-year study period. More than 15% had AKI at ICU admission. Among patients surviving for 30 days, 1-year mortality rates were 20.5% for the AKI-Risk group, 23.8% for the AKI-Injury group, and 23.2% for the AKI-Failure group in comparison with 10.7% for the patients without AKI. The strengths of the study are the relatively large sample size, the multicenter setting, and the complete follow-up data. The increased risk for long-term worse outcome persisted in different subgroups, making it even more plausible that the increased mortality observed is not caused by a confounder but indeed is associated with the study variable AKI itself.

How can we explain this increased long-term mortality after an episode of AKI? The data presented in the article by Gammelager and colleagues do not provide an answer for this. We can only speculate on the possible link between an episode of AKI and long-term mortality. One of the most claimed reasons for long-term worse outcomes after AKI is incomplete renal recovery [12,15], which covers a spectrum from patients whose glomerular filtration rate is discrete lower than their kidney function was beforehand to patients who remain dependent on dialysis. Incomplete renal recovery is most likely in patients who had the most severe stage of AKI (that is, AKI treated by renal replacement therapy), and the effects on mortality will be most pronounced in patients who remain dependent on dialysis. Unfortunately, the

authors could not provide data on renal recovery, such as a serum creatinine or estimated glomerular filtration rate at the time of hospital discharge or, for example, 3- or 6-month follow-up time. However, we question whether incomplete renal recovery did play an important role in their findings. In the study, a total of 987 patients with AKI were treated with renal replacement therapy. When ICU mortality of these patients is comparable to that of patients in other Western countries, approximately 50%, or 493, of the former will have died. Of the survivors, 10% to 25% (or 50 to 123) will remain dialysis-dependent. Here, as many as 642 patients died after day 30. So non-dialysis-dependent incomplete renal recovery would account for 80% of the additional deaths. Although every nephrologist will confirm that decreased kidney function has an impact on long-term outcomes, the implications are measurable only when observed over a period of several years. In other words, incomplete renal recovery may explain only in part the impressive mortality between day 30 and 1 year as observed in this study.

Careful analysis of the cumulative mortality curves reveals that there was a biphasic pattern: a steep increase in mortality from ICU admission until day 50 and a relatively flat curve afterwards. Importantly, the second half of the curve for patients with AKI is very similar to that for patients without AKI. As 25% of patients with AKI were still hospitalized after day 30, it is very likely that the steep curve still represents in-hospital mortality. In other words, patients who survived the immediate 1-month period after AKI died in the second month after AKI diagnosis – a period still linked to the original disease that lay at the origin of AKI.

This is an observation that makes sense. Modern-day intensivists are challenged by the care for patients who survived a first episode of critical illness and stay in the unit and hospital for several weeks. Why patients with AKI do still worse in this period is not clear and should be evaluated in future studies. Apart from this, several lessons can be learned from these observations. First, in modern-day ICU care, we should aim for endpoints that are more relevant, such as 60- or 90-day survival instead of the classic 30-day survival. Second, we are challenged by care for initial ICU survivors, who remain fragile and in moderate organ dysfunction for longer periods of time. The challenges that we face for these patients are not fully understood. In the ICU, we probably need to develop new therapies that are in contrast to the immediate 'point and shoot' approach of the old-style intensivists. When these patients are discharged to a step-down ward, they should be cared for by a team that is specialized in their care. As a consequence, we need to look beyond simple ICU mortality. There is a growing consensus that other issues of long-term outcome, such as quality of life, are worth studying [16].

In conclusion, we should increase our knowledge of these initial ICU survivors, try to elucidate why patients who had an episode of AKI do particularly worse, and develop integrated care with a focus on immediate, but also long-term, outcomes.

Abbreviations
AKI, acute kidney injury; ICU, intensive care unit.

Competing interests
The authors declare that they have no competing interests.

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Published: 27 August 2012

References

1. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: **RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis.** *Crit Care* 2006, **10:**R73.
2. Ostermann M, Chang RW: **Acute kidney injury in the intensive care unit according to RIFLE.** *Crit Care Med* 2007, **35:**1837-1843.
3. Ostermann M, Chang R: **Correlation between the AKI classification and outcome.** *Crit Care* 2008, **12:**R144.
4. Bagshaw SM, George C, Dinu I, Bellomo R: **A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients.** *Nephrol Dial Transplant* 2008, **23:**1203-1210.
5. Bagshaw SM, George C, Bellomo R: **A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients.** *Nephrol Dial Transplant* 2008, **23:**1569-1574.
6. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG: **Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database.** *Intensive Care Med* 2009, **35:**1692-1702.
7. Mandelbaum T, Scott DJ, Lee J, Mark RG, Malhotra A, Waikar SS, Howell MD, Talmor D: **Outcome of critically ill patients with acute kidney injury using the Acute Kidney Injury Network criteria.** *Crit Care Med* 2011, **39:**2659-2664.
8. Hoste EAJ, Schurgers M: **Epidemiology of AKI: How big is the problem?** *Crit Care Med* 2008, **36:**S1-4.
9. Ricci Z, Cruz D, Ronco C: **The RIFLE criteria and mortality in acute kidney injury: a systematic review.** *Kidney Int* 2008, **73:**538-546.
10. Hoste EA, De Corte W: **Clinical consequences of acute kidney injury.** *Contrib Nephrol* 2011, **174:**56-64.
11. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, Layon AJ, Segal MS: **Long-term risk of mortality and acute kidney injury during hospitalization after major surgery.** *Ann Surg* 2009, **249:**851-858.
12. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A: **Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery.** *Circulation* 2009, **119:**2444-2453.
13. Lafrance JP, Miller DR: **Acute kidney injury associates with increased long-term mortality.** *J Am Soc Nephrol* 2010, **21:**345-352.
14. 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.** *Crit Care* 2012, **16:**R124.
15. Schiffl H, Fischer R: **Five-year outcomes of severe acute kidney injury requiring renal replacement therapy.** *Nephrol Dial Transplant* 2008, **23:**2235-2241.
16. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM: **Quality of life after intensive care: a systematic review of the literature.** *Crit Care Med* 2010, **38:**2386-2400.

doi:10.1186/cc11470
Cite this article as: Hoste EAJ, De Corte W: **AKI patients have worse long-term outcomes, especially in the immediate post-ICU period.** *Critical Care* 2012, **16:**148.

Critical Care

CRITICAL CARE

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

Critical Care 2012, **16**:R124 doi:10.1186/cc11420

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ISSN 1364-8535

Article type Research

Submission date 22 May 2012

Acceptance date 11 July 2012

Publication date 12 July 2012

Article URL http://ccforum.com/content/16/4/R124

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: 2.38-2.85) and 2.41 (95% CI: 2.21-2.64), compared to patients without AKI. Among patients surviving 30 days (n = 25,539), 31-365 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: 1.17-1.51), 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 31-365 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 a 1.4- to 3.2- fold increase in 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 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 (1) to examine the prevalence of AKI at ICU admission, (2) to examine its impact on mortality during one year of follow-up, and (3) to 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 (*e.g*. liver transplantation and lung transplantation), are provided in the study region, which has 12 ICUs: eight ICUs at university hospitals and four ICUs 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 report information on all hospital contacts electronically 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 admissions: 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 plasma creatinine (equivalent to serum creatinine [17]) 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 [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%-100% increase in creatinine from the baseline level, “AKI-Injury” as a 100%-200% increase, and “AKI-Failure” 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 at day of, day before and day after ICU 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

Charlson Comorbidity Index (CCI) scores. [20] Patients were categorized as having low (score = 0), medium (score 1-2) 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 60ml/min per 1.73m^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 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, 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: 0-30 days, 31-365 days, and 0-365 days following ICU admission. We computed hazard ratios (HRs) within 0-30 day and 31-365 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 by plot of log(-log(survival probability)) plots and 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). Total time of follow up were 23,850 person years (median duration 365 days [interquartile range: 258 ; 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 (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/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 (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 ; 17]), another 3,099 (10.1%) patients developed AKI.

Mortality

The one-year mortality was 48.7% (95% CI: 46.5-50.9%) for the "AKI-Risk" group, 57.4% (95% CI: 54.8-60.1%) for the "AKI-Injury" group and 54.7% (95% CI: 52.1-57.2%) for the "AKI-Failure" group, compared with 22.1% (95% CI: 21.6-22.7) for the patients without AKI (Figure 1).

0-30 day overall mortality

Thirty-day mortality was 35.5% (95% CI: 33.4-37.6%) for the "AKI-Risk" group, 44.2% (95% CI: 41.5-46.9%) for the "AKI-Injury" group, and 41.0% (95% CI: 38.5-43.5%) for the "AKI-Failure" group, compared with 12.8% (95% CI: 12.4-13.2%) 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 2).

31-365 day overall mortality

Among patients surviving 30 days (n = 25,539), mortality between 31 days and 365 days was 20.5% (95% CI: 18.4-22.8%) for the "AKI-Risk" group, 23.8% (95% CI: 20.9-

27.0%) for the “AKI-Injury” group, and 23.2% (95% CI: 20.6-26.1%) for the “AKI-Failure” group compared with 10.7% (95% CI: 10.3-11.1%) 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 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 15-40 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) (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 (adjusted HR: 3.76 [95% CI: 1.62-8.77], 3.43 [2.65-4.45], and 3.27 [95% CI: 2.48-4.31], respectively), and among patients with low CCI scores (adjusted HR: 2.55 [95% CI: 2.31-2.81]), due to 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]) or 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 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: 1.80-2.12) 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), 1.66 (95 % CI 1.43-1.92) 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 31-365 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% - 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 [4-7]. 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. previous studies and among previous studies may be explained by 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 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 30-365 day mortality among both acute and elective surgical ICU patients are 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. They reported the following 10-year adjusted hazard ratios 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", compared to patients without AKI [9]. 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 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 septic ICU patients who survived to hospital discharge found a relative risk of two-year mortality of 3.2 (95% CI: 1.6-6.5) 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 31-365 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 (*i.e*, those measured only with an arterial blood gas analyzer in the ICUs) 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, *i.e*., 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 31-365-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.

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.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

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.

Acknowledgment

The study was made possible through financial support from the Danish Medical Research Council (journal number 271-05-0511), the Clinical Epidemiology Research

Foundation, and the Snedkermester Sophus Jacobsen and Hustru Astrid Jacobsens Foundation. The sponsors had no influence on the study design, the collection, analysis, the interpretation of data, the writing of the article, or the decision to submit it for publication.

Reference

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: **Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.** *Crit Care* 2004, **8:** R204-R212.

2. Srisawat N, Hoste EE, Kellum JA: **Modern classification of acute kidney injury.** *Blood Purif* 2010, **29:** 300-307.

3. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: **RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis.** *Crit Care* 2006, **10:** R73.

4. Bagshaw SM, George C, Dinu I, Bellomo R: **A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients.** *Nephrol Dial Transplant* 2008, **23:** 1203-1210.

5. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG: **Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database.** *Intensive Care Med* 2009, **35:** 1692-1702.

6. Ostermann M, Chang RW: **Acute kidney injury in the intensive care unit according to RIFLE.** *Crit Care Med* 2007, **35:** 1837-1843.

7. Clec'h C, Gonzalez F, Lautrette A, Nguile-Makao M, Garrouste-Org, Jamali S, Golgran-Toledano D, Descorps-Declere A, Chemouni F, Hamidfar-Roy R, Azoulay E, Timsit JF: **Multiple-center evaluation of mortality associated with acute kidney injury in critically ill patients: a competing risks analysis.** *Crit Care* 2011, **15:** R128.

8. Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM: **The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability.** *Am J Kidney Dis* 2005, **46:** 1038-1048.

9. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, Layon AJ, Segal MS: **Long-term risk of mortality and acute kidney injury during hospitalization after major surgery.** *Ann Surg* 2009, **249:** 851-858.

10. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A: **Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery.** *Circulation* 2009, **119:** 2444-2453.

11. Lopes JA, Fernandes P, Jorge S, Resina C, Santos C, Pereira A, Neves J, Antunes F, Gomes da CA, Costa A: **Long-term risk of mortality after acute kidney injury in patients with sepsis: a contemporary analysis.** *BMC Nephrol* 2010, **11:** 9.

12. Frank L: **Epidemiology. When an entire country is a cohort.** *Science* 2000, **287:** 2398-2399.

13. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tonnesen E, Sorensen HT: **The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study.** *Acta Anaesthesiol Scand* 2011, **55:** 962-970.

14. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH: **The Danish National Hospital Register. A valuable source of data for modern health sciences.** *Dan Med Bull* 1999, **46:** 263-268.

15. Le Gall JR, Lemeshow S, Saulnier F: **A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study.** *JAMA* 1993, **270:** 2957-2963.

16. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW: **Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark.** *Clin Epidemiol* 2011, **3:** 133-138.

17. Miles RR, Roberts RF, Putnam AR, Roberts WL: **Comparison of serum and heparinized plasma samples for measurement of chemistry analytes.** *Clin Chem* 2004, **50:** 1704-1706.

18. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL: **Serial evaluation of the SOFA score to predict outcome in critically ill patients.** *JAMA* 2001, **286:** 1754-1758.

19. Go AS, Parikh CR, Ikizler TA, Coca S, Siew ED, Chinchilli VM, HSU CY, Garg AX, Zappitelli M, Liu KD, Reeves WB, Ghahramani N, Devarajan P, Faulkner GB, Tan TC, Kimmel PL, Eggers P, Stokes JB: **The assessment, serial evaluation, and**

subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. *BMC Nephrol* 2010, **11:** 22.

20. Needham DM, Scales DC, Laupacis A, Pronovost PJ: **A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research.** *J Crit Care* 2005, **20:** 12-19.

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40:** 373-383.

22. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT: **The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients.** *BMC Med Res Methodol* 2011, **11:** 83.

23. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G: **National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.** *Ann Intern Med* 2003, **139:** 137-147.

24. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB: **The Danish Civil Registration System. A cohort of eight million persons.** *Dan Med Bull* 2006, **53:** 441-449.

25. Rothman KJ: **Measuring Interactions.** In *Epidemiology: an introduction*. New York: Oxford University Press Inc.; 2002.

26. Royston P: **Multiple imputation of missinfg values.** *The Stata Journal* 2004, 227-241.

27. Royston P: **Multiple imputation of missing values: Update of ice.** *The Stata Journal* 2005, 527-536.

28. Royston P: **Multiple imputation of missing values: update.** *The Stata Journal* 2005, 188-201.

29. White IR, Royston P: **Imputing missing covariate values for the Cox model.** *Stat Med* 2009, **28:** 1982-1998.

30. Bagshaw SM, Uchino S, Cruz D, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: **A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury.** *Nephrol Dial Transplant* 2009, **24:** 2739-2744.

31. Guerin C, Girard R, Selli JM, Perdrix JP, Ayzac L: **Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhone-Alpes Area Study Group on Acute Renal Failure.** *Am J Respir Crit Care Med* 2000, **161:** 872-879.

32. Watson RS, Angus D.C: **Assessing outcomes in critical care.** *J Intensice Care Med* 2002, **17:** 103-111.

33. Rothman K, Greenland S, Lass T: **Cohort Studies.** In *Mordern Epidemiology*. 3 edition Lippincott Williams & Wilkins, Philadelphia, PA; 2008:106-107.

34. Suissa S: **Immortal time bias in pharmaco-epidemiology.** *Am J Epidemiol* 2008, **167:** 492-499.

35. Schisterman EF, Cole SR, Platt RW: **Overadjustment bias and unnecessary adjustment in epidemiologic studies.** *Epidemiology* 2009, **20:** 488-495.

Figure 1. Cumulative 0-365 day risk of death by AKI level, Northern Denmark, 2005-2010.

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: 1-2)	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				
Measured baseline creatinine, n (%)	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)

[a] Charlson Comorbidity Index score after exclusion of kidney diseases.

[b] eGFR < 60 ml/min per 1.73m^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, inter quartile range.

Table 2. Cumulative 30-day and 31-365 day mortality and corresponding hazard ratios (HRs) 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(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)
31-365 day					
Without AKI	2,421	22,642	10.7% (10.3-11.1)	1(ref.)	1(ref.)
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.

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

	N	Without AKI		With AKI	
		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 (ref.)	39.6 (38.2-41.0)	2.27 (2.14-2.40)
Age group					
≥15<40	4,670	2.5 (2.1-3.0)	1 (ref.)	16.8 (12.8-21.9)	4.87 (3.33-7.13)
≥40<60	7,397	7.6 (7.0-8.3)	1 (ref.)	29.2 (26.4-32.2)	3.18 (2.72-3.70)
≥60<80	14,184	14.1 (13.5-14.8)	1 (ref.)	39.1 (37.2-41.1)	2.28 (2.11-2.47)
≥80	4,511	31.4 (29.9-33.0)	1 (ref.)	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 (ref.)	35.0 (32.9-37.2)	2.55 (2.31-2.81)
Medium (score: 1-2)	10,544	15.7 (15.0-16.5)	1 (ref.)	41.4 (39.2-43.6)	2.17 (1.99-2.38)
High (score ≥3)	4,492	21.1 (19.8-22.5)	1 (ref.)	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 (ref.)	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 (ref.)	42.0 (40.8-44.3)	2.40 (2.20-2.63)
Acute cardiac	1,096	15.8 (13.6-18.3)	1 (ref.)	44.3 (37.3-52.0)	3.27 (2.48-4.31)
Elective non-cardiac	4,334	5.4 (4.8-6.2)	1 (ref.)	20.5 (16.9-24.8)	3.43 (2.65-4.45)
Elective cardiac	3,425	1.9 (1.5-2.4)	1 (ref.)	7.4 (3.4-15.8)	3.76 (1.62-8.77)
Primary diagnosis during current hospitalization					
Septicemia	646	38.8 (32.9-45.4)	1 (ref.)	52.2 (47.5-57.1)	1.53 (1.19-1.96)
Other infectious diseases	2,959	15.0 (13.6-16.5)	1 (ref.)	36.5 (32.9-40.4)	1.97 (1.66-2.33)
Endocrinology diseases	558	7.2 (5.0-10.5)	1 (ref.)	17.1 (12.5-23.1)	1.89 (1.11-3.19)
Cardiovascular diseases	8,220	13.8 (13.0-14.6)	1 (ref.)	44.3 (41.0-47.7)	2.14 (1.89-2.41)
Respiratory diseases	1,750	27.8 (25.5-30.2)	1 (ref.)	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 (ref.)	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 (ref.)	34.5 (30.2-39.1)	2.59 (2.12-3.16)
Trauma or poisoning	5,035	7.6 (6.9-8.4)	1 (ref.)	32.6 (28.1-37.6)	2.41 (1.95-2.99)

Other	4,497	8.8 (8.0-9.8)	1 (ref.)	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 (ref.)	44.3 (41.3-47.3)	1.80 (1.60-2.02)
No	26,415	11.2 (10.7-11.6)	1 (ref.)	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 (ref.)	46.2 (44.2-48.2)	1.60 (1.48-1.72)
Inotropes/vasopressors	10,382	19.3 (18.4-20.2)	1 (ref.)	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 1.73m^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.

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

	N	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(ref.)	22.2 (20.7-23.7)	1.49 (1.36-1.63)
Age group					
≥15<40	4,516	1.7 (1.4-2.1)	1(ref.)	5.1 (2.8-8.9)	1.52 (0.79-2.94)
≥40<60	6,627	7.5 (6.9-8.2)	1(ref.)	15.4 (12.9-18.3)	1.58 (1.27-1.97)
≥60<80	11,561	13.8 (13.2-14.5)	1(ref.)	23.8 (21.7-26.0)	1.41 (1.25-1.59)
≥80	2,835	21.8 (20.2-23.6)	1(ref.)	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(ref.)	15.3 (13.4-17.4)	1.88 (1.59-2.22)
Medium (score: 1-2)	8,403	14.5 (13.7-15.4)	1(ref.)	25.8 (23.3-28.5)	1.60 (1.40-1.83)
High (score ≥3)	3,302	24.6 (23.0-26.2)	1(ref.)	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(ref.)	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(ref.)	23.97 (21.5-26.5)	1.46 (1.27-1.68)
Acute cardiac	873	5.6 (4.2-7.4)	1 (ref.)	21.4 (14.5-30.9)	4.44 (2.63-7.51)
Elective non-cardiac	4,039	14.3 (13.2-15.4)	1(ref.)	19.1 (15.2-23.9)	1.28 (0.98-1.67)
Elective cardiac	3.355	3.8 (3.2-4.5)	1 (ref.)	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 (ref.)	17.7 (13.0-23.7)	0.81 (0.49-1.32)
Infectious diseases	2,380	10.0 (8.8-11.4)	1(ref.)	19.8 (16.2-24.0)	1.28 (1.02-1.61)
Endocrinology diseases	498	10.2 (7.4-14.0)	1(ref.)	12.1 (8.0-18.2)	0.85 (0.48-1.50)
Cardiovascular diseases	6,829	6.2 (5.7-6.9)	1(ref.)	20.9 (17.5-24.8)	2.21 (1.76-2.78)
Respiratory diseases	1,202	22.0 (19.6-24.7)	1(ref.)	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(ref.)	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(ref.)	32.0 (26.9-37.7)	1.17 (0.93-1.46)
Trauma or poisoning	4,560	5.3 (4.6-6.0)	1(ref.)	20.7 (16.2-26.2)	1.85 (1.36-2.53)
Other	3,894	8.1 (7.3-9.1)	1(ref.)	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(ref.)	28.7 (25.2-32.5)	1.43 (1.19-1.71)
No	22,455	9.6 (9.2-10.0)	1(ref.)	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(ref.)	24.6 (22.3-27.0)	1.49 (1.30-1.70)
Inotropes/vasopressors	7,691	12.3 (11.5-13.2)	1(ref.)	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] eGFR < 60 ml/min per 1.73m^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.

Additional files

Additional file 1. Relevant codes used in the current study. Danish treatment codes defining ICU admission; Nomenclature, Properties and Units in Laboratory Medicine (NPU) codes and local Danish laboratory codes used to identify creatinine measurements in the laboratory database; ICD-10 codes defining primary diagnosis during current hospitalization; ICD-10 disease categories included in non-renal Charlson Comorbidity Index score; Danish treatment codes for intensive care unit treatments; ICD-10 codes and Danish treatment codes for chronic renal replacement therapy and kidney transplantation.

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

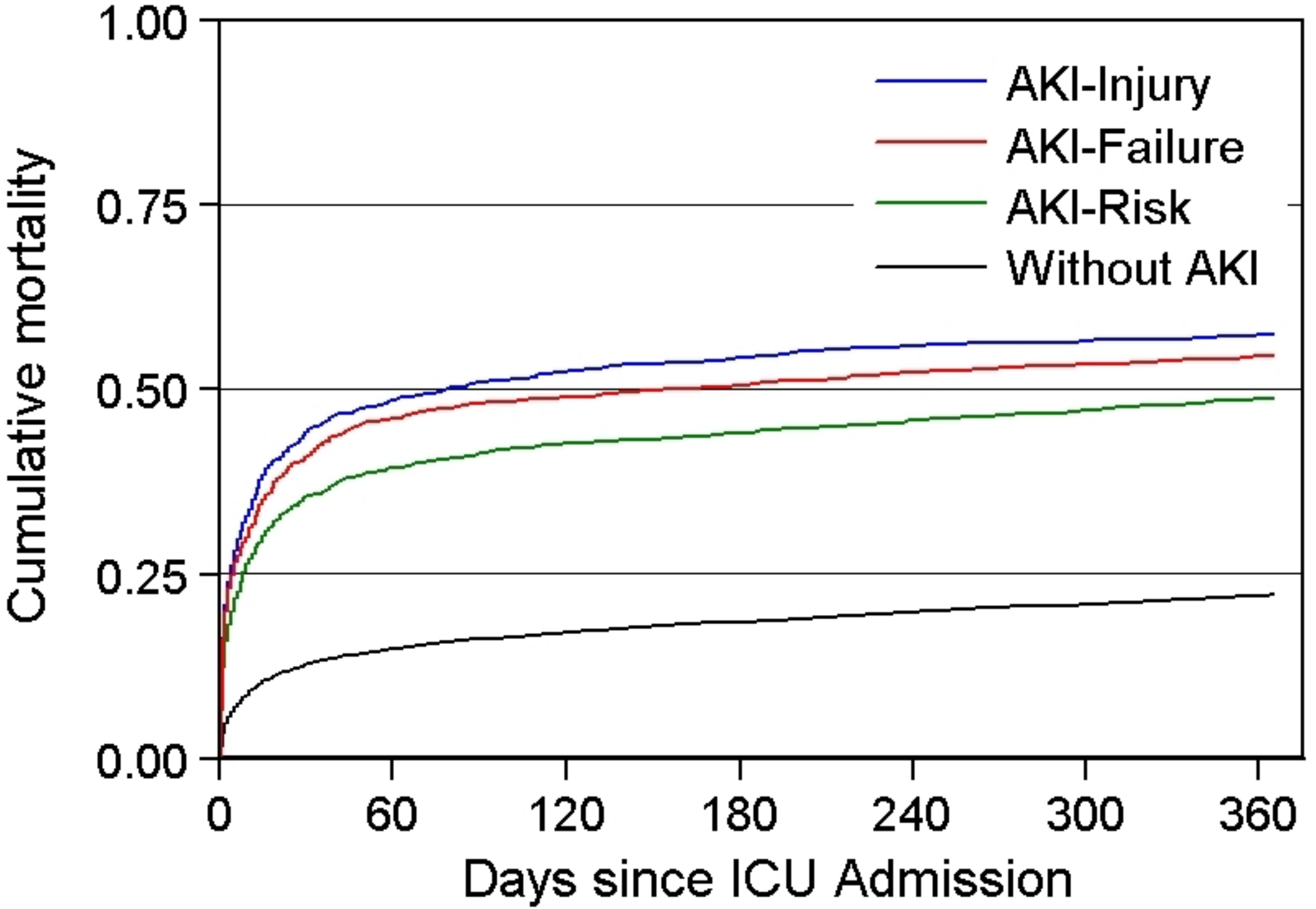
1.00
0.75
0.50
0.25
0.00
Cumulative mortality
AKI-Injury
AKI-Failure
AKI-Risk
Without AKI
0
60
120
180
240
300
360
Days since ICU Admission

Figure 1

Additional files provided with this submission:

Additional file 1: Addtional file 1.pdf, 271K
http://ccforum.com/imedia/5895415277634480/supp1.pdf
Additional file 2: Additional file 2.pdf, 269K
http://ccforum.com/imedia/2109175145763448/supp2.pdf