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Risk of de novo infection following acute kidney injury: A retrospective cohort study

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ABSTRACT

Purpose: Recent studies suggest that acute kidney injury (AKI) can affect distant organ function and increase non-renal complications. We determined whether AKI is associated with an increased risk of incident infections.
Material and methods: We conducted a one-year single-center retrospective cohort study, excluding patients readmitted to the ICU or for <24 h, on chronic dialysis, and kidney transplant recipients. The primary outcome was the development of incident infections analyzed by multivariate time-dependent Cox models.
Results: Of the 1001 included patients, infections were more frequent in those with AKI (62% vs. 37% without AKI; $p < .001$). To characterize predictors of incident infections, we excluded patients with an infection until ICU admission ($n = 244$). Patients with AKI presented infections more often than without AKI (44% vs. 20%; $p < .001$). AKI, chronic obstructive pulmonary disease, and mechanical ventilation (MV) were associated with incident infections (HR 1.62, 95%CI:1.15–2.30, HR 1.51, 95%CI 1.04–2.18 and HR 2.14, 95%CI:1.48–3.09, respectively) while age, MV, higher fluid balance, and AKI were independent predictors of mortality.
Conclusions: AKI was associated with incident in-hospital infections. However, newly occurring infections were not associated with an increased risk of mortality. Further studies are needed to understand how AKI affects distant organ function and associated clinical outcomes.

1. Introduction

Acute kidney injury (AKI) occurs in up to 25% of critically ill patients [1] and is independently associated with significant morbidity and mortality [1-4]. The mechanisms underlying increased morbidity and mortality in patients with AKI remain uncertain [5, 6]. Septic AKI, or sepsis leading to AKI, is a well-known independent predictor of mortality and morbidity in critically ill patients [7-15]. However, the pathophysiology of non-septic AKI differs from the pathophysiology of septic AKI [16, 17]. Consequently, clinical characteristics and outcomes associated with infections occurring after AKI may differ from those associated with septic AKI. Impaired monocyte production, as well as slow neutrophil rolling and transmigration have been observed within hours in AKI models [18-20]. These findings could promote the development of infections following AKI [18]. However, there is limited data on the epidemiology of infections occurring after AKI [21-24]. To our knowledge, only one study has assessed whether AKI could be an independent risk factor for the development of incident infections [24].

As suggested by an international group of experts [25, 26], the timing, etiology and prognosis of infectious complications occurring in AKI patients need to be better described to facilitate future research in the field and improve AKI outcomes. In addition, whether AKI is an independent risk factor for infection or simply a surrogate marker of increased severity of illness is still to be determined.

Our objectives were to characterize the epidemiology and prognosis associated with infectious events according to AKI status and to determine whether AKI is independently associated with an increased risk of infectious complications. We hypothesized that AKI is an independent risk factor for the development of subsequent infections.

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2. Material and methods

2.1. Study design and population

We performed a retrospective cohort study of critically ill patients admitted to a tertiary care academic center between January 1st and December 31st, 2012. We included randomly selected critically ill patients aged ≥18 using computer-generated random numbers, and excluded kidney transplant recipients, patients on dialysis, readmitted to the ICU or admitted for <24 h. We determined the timing of AKI, and the timing of infections in relation to the diagnosis of AKI. In patients with infection preceding AKI, we also characterized the incidence and timing of distinct new episodes of infections. We presented our results in two cohorts. First, a *descriptive cohort* with all included patients who do not meet any exclusion criterion to characterize the epidemiology and prognosis associated with infectious events according to AKI status. This cohort allows assessing the generalizability of our results. We then presented a *comparative cohort* with all patients from the first cohort except those who had an infection before or at ICU admission to characterize the predictors of incident infections. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies [27]. The ethics' committee of our institution approved the study. Written consent was waived given the retrospective observational nature of the study. The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

2.2. Data collection

We collected demographic characteristics and past medical history, data on laboratory and microbiological results, severity of illness and processes of care including surgical status, cumulative fluid balance, administration of antimicrobial agents, vasopressors, and colloids, use of central catheters, mechanical ventilation (MV) and dialysis. The primary outcome was the development of incident infections after ICU admission, which was independently adjudicated by two investigators by chart review. Infection status and site were determined according to standardized definitions from the International Sepsis Forum Consensus Conference [28]. Other outcomes included mortality at hospital discharge, and requirement for dialysis.

AKI was defined by the serum creatinine (SCr) Kidney Disease Improving Global Outcomes (KDIGO) criteria [29]. Chronic kidney disease (CKD) status was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2. Sequential Organ Failure Assessment (SOFA) and non-renal SOFA scores were assessed at ICU admission [30]. Cumulative fluid balance was the sum of daily fluid balances during the first week of ICU admission.

2.3. Statistical analyses and sample size calculation

We analyzed continuous variables using *t*-test or Mann-Whitney when comparing 2 groups and ANOVA or Kruskall-Wallis when comparing >2 groups, where appropriate. We compared categorical variables using χ^2-test or Fisher exact test, where appropriate. We used Kaplan-Meier curves and log-rank test to compare the length of time after ICU admission until occurrence of first incident infection in patients with and without AKI. For this analysis, we included patients free of infection before or at ICU admission. In the same population, we determined predictors of incident infections after ICU admission with a time-dependent Cox regression model. Patients were considered free of AKI until they met AKI criteria. Once a patient was diagnosed with AKI, the patient remained in the AKI category regardless of renal recovery, as a previous study found the risk of infection to pertain for months after the initial AKI event [24]. Variables with a *p*-value ≤.20 by univariate analysis were included in the multivariate Cox regression model which was adjusted for age and gender. The assumption of proportionality was met and interaction terms were verified. We also determined predictors of mortality at hospital discharge with a multivariate Cox regression model. Statistical tests were two sided and *p*-values <.05 were considered statistically significant. Statistical analyses were performed using SPSS, version 22.0 (IBM, Armonk, NY) and SAS 9.3 (SAS Institute, Cary, NC).

Based on a previous study, the incidence of AKI and infections at our center were 25% and 45% respectively [31]. A sample size of 1000 patients would achieve a study power of 80% at a type I error of 0.05 to detect a hazard ratio of 1.3 for the development of infections.

3. Results

Among 2464 patients admitted over a year, 1073 (43.5%) were randomly selected for the study population. From these, 72 patients were excluded (Fig. 1). The remaining 1001 patients were included in the descriptive analysis. For the comparative analysis, we excluded patients with an infection before or at ICU admission ($n = 244$) to determine predictors of incident infections ($n = 757$).

3.1. Overall population – descriptive cohort ($n = 1001$)

Patient characteristics, types of infections and outcomes are presented according to AKI and infection status (Table 1). Among our population (n = 1001), 25.7% ($n = 257$) developed AKI, and 43.7% ($n = 437$) had infections at or following ICU admission. AKI occurred at a median time of 1 day (IQR 0–3) after ICU admission, and 54% were stage 1, 18%, stage 2, and 28%, stage 3. Among the 111 patients infected before AKI, 23 (20.7%) had one or more new infections after AKI, at a median time of 11 (IQR 6–18) days after AKI. For the 48 patients who had their first infection after AKI, the infection occurred 3 (IQR 1–6) days after AKI. Most infections were from respiratory, abdominal or urinary tract origin. The proportion of catheter-related infection was low (0.5%). Eight percent of patients were colonized with a multiresistant bacteria. There were no significant differences in the type of infections between patients without AKI, with infections before or after AKI.

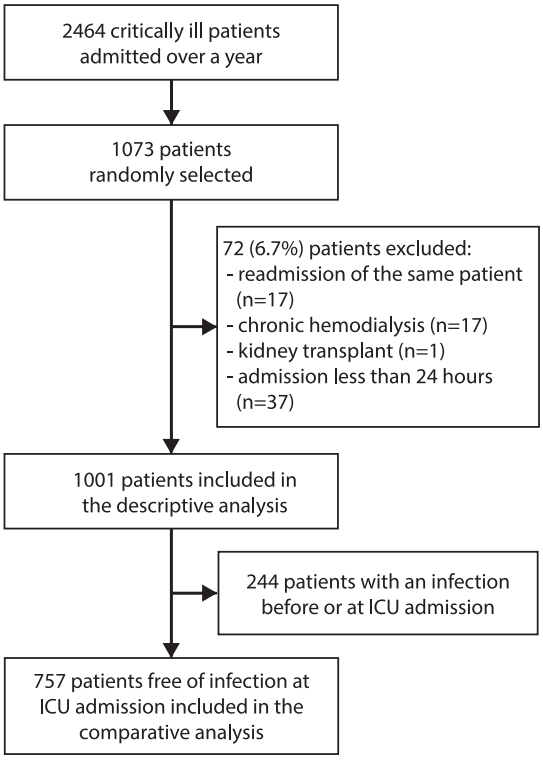

Fig. 1. Study population.