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Early reversible acute kidney injury is associated with improved survival in septic shock☆,☆☆

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ABSTRACT

Introduction: The fact that acute kidney injury (AKI) is associated with worse clinical outcomes forms the basis of most AKI prognostic scoring systems. However, early reversibility of renal dysfunction in acute illness is not considered in such systems. We sought to determine whether early (≤24 hours after shock documentation) reversibility of AKI was independently associated with in-hospital mortality in septic shock.

Methods: Patient information was derived from an international database of septic shock cases from 28 different institutions in Canada, the United States and Saudi Arabia. Data from a final cohort of 5443 patients admitted with septic shock between Jan 1996 and Dec 2009 was analyzed. The following 4 definitions were used in regards to AKI status: (1) reversible AKI = AKI of any RIFLE severity prevalent at shock diagnosis or incident at 6 hours post-diagnosis that reverses by 24 hours, (2) persistent AKI = AKI prevalent at shock diagnosis and persisting during the entire 24 hours post-shock diagnosis, (3) new AKI = AKI incident between 6 and 24 hours post-shock diagnosis, and (4) improved AKI = AKI prevalent at shock diagnosis or incident at 6 hours post followed by improvement of AKI severity across at least one RIFLE category over the first 24 hours. Cox proportional hazards were used to determine the association between AKI status and in-hospital mortality.

Results: During the first 24 hours, reversible AKI occurred in 13.0%, persistent AKI in 54.9%, new AKI in 11.7%, and no AKI in 22.4%. In adjusted analyses, reversible AKI was associated with improved survival (HR, 0.64; 95% CI, 0.53-0.77) compared to no AKI (referent), persistent AKI (HR, 0.99; 95% CI, 0.88-1.11), and new AKI (HR, 1.41; 95% CI, 1.22-1.62). Improved AKI occurred in 19.1% with improvement across any RIFLE category associated with a significant decrease in mortality (HR, 0.53; 95% CI, 0.45-0.63). More rapid antimicrobial administration, lower Acute Physiology and Chronic Health Evaluation II score, lower age, and a smaller number of failed organs (excluding renal) on the day of shock as well as community-acquired infection were independently associated with reversible AKI.

Conclusion: In septic shock, reversible AKI within the first 24 hours of admission confers a survival benefit compared to no, new, or persistent AKI. Prognostic AKI classification schemes should consider integration of early AKI reversibility into the scoring system.

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1. Introduction

Acute kidney injury (AKI) is associated with adverse outcomes, universally increasing mortality, length of hospital stay and the risk of long term chronic kidney disease and kidney failure [1–10]. In septic shock, AKI is especially common with the risk of worse outcomes increasing with the severity of injury [2,4,11–16].

Current classification schemes for defining AKI, such as the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

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(RIFLE) system and the Acute Kidney Injury Network (AKIN) system define the stage and severity of AKI using criteria based on declining urine output and changes in serum creatinine compared to baseline [17–21]. AKI is then classified according to the most severe stage achieved at any time point, regardless of reversibility. Although this classification has been validated in large international AKI datasets, little is known regarding the impact of earl (≤24 hours) reversibility of AKI on outcomes [17–19]. In this retrospective analysis, we examined the effect of early reversibility of AKI on in-hospital mortality in septic shock.

2. Methods

2.1. Study population

The Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database is an international, multicenter database of patients admitted with septic shock to an intensive care unit (ICU). The CATSS database, which has been described in detail previously, uses standardized case definitions and includes repeat serum creatinine measurements during the first 24 hours of admission [13,22,23]. The database captures information on consecutive adult (>18 years old) patients admitted with septic shock from 28 medical institutions in Canada, the United States and Saudi Arabia. Patients from discrete periods between January 1996 and December 2008 were screened and included if they meet the criteria for septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference guidelines (N = 7390) [23,24]. For the current study, we excluded patients who had a history of chronic kidney disease (N = 566) or had dialysis therapy prior to ICU admission (N = 563). Patients without serum creatinine levels at each assessment time point (N = 818) were also excluded. This left 5443 patients in the study population (Fig. 1). Chronic kidney disease (CKD) was pre-defined at database creation as a stable creatinine >160 μmol/L (1.5 × normal) prior to shock occurrence. Dialysis status on admission was

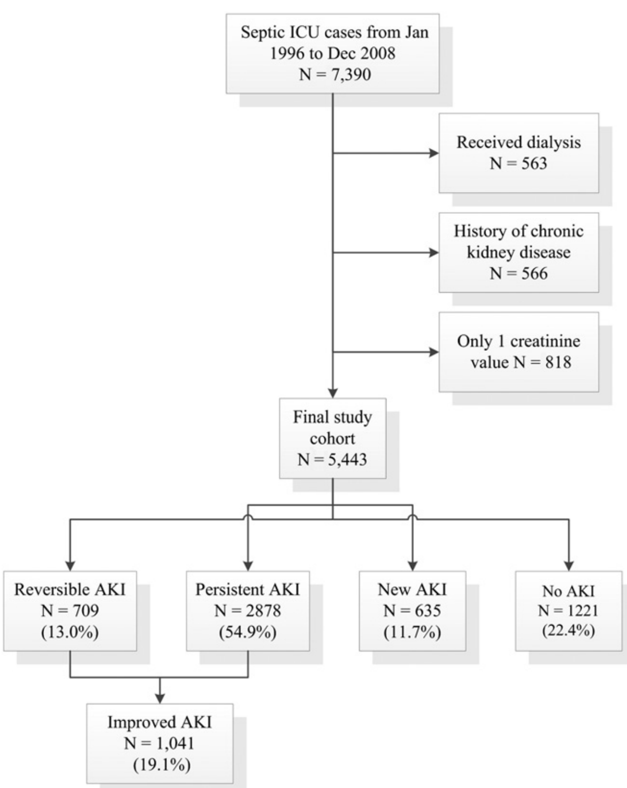

Fig. 1. Development of the study cohort.

defined as the need for renal replacement therapy (either peritoneal or hemodialysis) as an outpatient immediately prior to hospitalization. This study was approved by the Health Research Ethics Board at the University of Manitoba and all participating institutions.

2.2. Data collection

Data collection definitions and methodology have been outlined previously [22,23]. All patients required vasopressor therapy for at least 3 hours. Trained research personnel prospectively collected data on patient demographics, co-morbidities, physiological characteristics, ICU treatments and ICU and in-hospital outcomes. Serum creatinine measurements were taken at baseline (N = 7390), approximately 6 hours (range 4-8, N = 6385) and approximately 24 hours (range 20-28, N = 6971). Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated based on the most aberrant values within 24 hours of the diagnosis of septic shock [25]. Similarly, the number of organ failures was inclusive of occurrence with the first 24 hours after the diagnosis (ie, Day 1).

2.3. Definitions

AKI was defined and classified according to the RIFLE criteria. As pre-ICU creatinine values were not consistently available in our study cohort, we assumed a baseline renal function for all patients after excluding those with a history of CKD and dialysis (based on hospital, clinic and external records). Patients without a history of CKD or dialysis were assumed to have a baseline estimated glomerular filtration rate (eGFR) of 75 mL min^{-1} m^{-2}. We calculated the eGFR using the Modification of Diet in Renal Disease formula [26] for all patients using the creatinine at ICU admission and at 6 and 24 hours post ICU admission. AKI was then determined using RIFLE criteria for eGFR changes. As urine output changes were not captured in our cohort, only eGFR-based changes were used in the determination of AKI. Patients were classified as AKI if they experienced the injury upon any measure of renal function.

The following 4 definitions were used in regard to AKI status: (1) reversible AKI = AKI of any RIFLE severity prevalent at shock diagnosis or incident at 6 hours post-diagnosis that reverses by 24 hours (2) persistent AKI = AKI prevalent at shock diagnosis and persisting during the entire 24 hours post-shock diagnosis, (3) new AKI = AKI incident between 6-24 hours post-shock diagnosis and (4) improved AKI = AKI prevalent at shock diagnosis or incident at 6 hours post followed by improvement of AKI severity across at least one RIFLE category over the first 24 hours. Categories were not mutually exclusive. For example if a patient upon shock diagnosis had AKI RIFLE class failure and then at 24 hours AKI RIFLE class risk they were categorized as both persistent AKI and improved AKI.

2.4. Outcome

The primary outcome of interest was in-hospital mortality.

2.5. Statistical analysis

Continuous variables of interest were summarized as mean or medians with standard deviation or inter-quartile range as appropriate. Differences in baseline characteristics were determined by Student *t* test or 1-way analysis of variance for continuous variables and chi-square for dichotomous variables. All analyses were conducted using PASW v. 18 (www.ibm.com/SPSS_Statistics) and Stata v.11.2 (StatCorp LP).

We examined the impact of AKI status on in-hospital mortality by the Kaplan-Meier method and Cox proportional hazards model. Statistical significance was determined by the log rank method for the Kaplan-Meier. The assumptions of proportionality for the Cox

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