Predicting Acute Kidney Injury with Mean Arterial Pressure in Septic ICU Patients

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Abstract

Objective: The aim of this study was to determine the relationship between the severity and duration of hypotension and risk of AKI.

Design: Single-center retrospective cohort study.

Setting: Data were extracted from the MIMIC-III database, a database containing records of patients admitted to critical care units at Beth Israel Deaconess Medical Center between 2001 and 2012.

Patients: All available records of septic patients with creatinine and lactate measurements.

Interventions: None.

Measurements and Main Results: A total of 4,663 ICU stays were analyzed; in 2,942 of these, the patient was found to have developed AKI during the ICU stay. Increase in the minimum mean arterial pressure recorded over the course of the ICU stay was associated with decreased risk of AKI (odds ratio: 0.97, 95% CI: [0.96,0.98]). On average, patients with AKI spent a larger fraction of the ICU stay with an hourly averaged MAP between 50 - 70 mmHg than patients without AKI.

Conclusions: Increased severity of hypotension was found to be associated with increased risk of AKI, although no single threshold was that clearly differentiated patients with AKI from those without. Investigation of the fraction of the ICU stay spent with low MAP suggests that the risk of AKI is associated with the duration of hypotension, but future work is needed to clarify this relationship.

Introduction

Sepsis is a widespread critical illness, affecting over one million Americans with a mortality rate of 28% to 50% [1]. Much of the high mortality rate in septic patients is associated with the development of Acute Kidney Injury (AKI) [2,3,4]. Acute kidney injury (AKI), previously termed acute renal failure (ARF), is a syndrome describing a range of clinical conditions involving rapid loss of kidney function, largely diagnosed based on changes in serum creatinine and urine output. The RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) criteria has been widely adopted to help identify and classify the extent of damage to the kidney in patients with AKI [5,6,7]. Based on this identification strategy, AKI is common in the critically ill and associated with high mortality rates [8,9,10,11,12]. Sepsis has been identified as a leading precipitating factor to the development of AKI [9,10,11,12], and septic individuals with AKI have a higher mortality rate than AKI patients without sepsis [3,11,12,13]. Thus, understanding strategies for management of AKI in septic patients is key for decreasing AKI-related deaths.

The cause of AKI is ultimately cellular hypoxia. The cause of the cellular hypoxia is unclear and appears to be multi factorial. Factors associated with the development of AKI in the septic population include: advanced age, multiple comorbidities, delays in antimicrobial administration, failure to adequately fluid resuscitate, and hypotension [6,12,14]. Studies in experimental animals have demonstrated a relationship between hypotension and AKI, but this relationship is less well-understood in clinical ICU settings. An individual's mean arterial blood pressure (MAP) is used as an indirect indication of perfusion. The optimal blood MAP necessary to sustain adequate renal perfusion is unclear in the literature [1].

Only a handful of studies have investigated the relationship between hypotension and the development of AKI [16,17]. Liu et al. found that hypotension was a probable independent contributor to the development of AKI [16]. This conclusion was based on a single-center retrospective study that looked at only 400 participants in a general ward setting. Lehman et al. performed a single-center, retrospective study utilizing a larger database with a population of 3,613 patients [17]. This study specifically examined the ICU population and found the odds of AKI to increase by 3% per 1 mmHg decrease in the MAP below 80 mmHg. However, few studies have specifically analyzed at the relationship between hypotension and AKI in the septic population. Mayaud et al., utilizing the same database as Lehman et al., noted a higher mortality rate among ICU patient with sepsis if they had a hypotensive episodes (MAP < 65) [18].

However, the ideal threshold for distinguishing patients at elevated risk for AKI is unclear from the literature. In a review of the literature from 2000-2014 regarding the question "What is the optimal MAP in septic shock?", Leone et al. found only 12 studies; of these, only two looked specifically at the development of AKI. Six of the studies included fewer than 30 participants [15]. Their report findings were that "the literature suggests that a MAP of greater than 65 is sufficient for treatment of septic shock" and that if a history of hypertension exists MAP of 75-85 might prevent AKI. The study done by Badin et al. analyzing MAP in relation to early shock found that septic shock patients in particular would benefit from MAP greater than 65 to avoid AKI [20].

Lehman et al. directly described a relationship between hypotension and AKI for the general adult ICU population [17]. This study replicates several of the key characteristics of the

study performed by Lehman et al., but performed this analysis specifically for patients with sepsis. The objective of this study was to interrogate a large ICU database to analyze the relationship between MAP and the risk of developing AKI, specifically in patients with sepsis; a secondary aim was to determine a MAP threshold below which patients are considered at-risk for AKI. We hypothesized that the characteristics of patients' blood pressure, in particular severity and duration of hypotensive episodes, are associated with the risk of developing AKI.

Methods

This study was conducted using data from the open-access MIMIC-III database containing records from 61,532 ICU stays from 2001-2012 at Beth Israel Deaconess Medical Center [22]. Of these, only ICU stays of 3 days or longer in adult patients with sepsis as defined by the Angus criteria were studied. Patients with end-stage renal disease (ESRD) or an admission serum creatinine measurement higher than 1.5 mg/dL were further excluded from the study. Finally, any patients missing measurements for lactate or serum creatinine were excluded as well. Ultimately, 4,663 unique ICU stays were analyzed in this study. A detailed diagram of the cohort selection process is shown in Fig.1.

Patients selected for this study were labeled as either developing AKI or not based on the RIFLE criteria. In particular, patients were identified based on the 'Injury' and 'Failure' criteria. Any patient with a urine output under 0.5 mL/kg/hr over the course of a 12-hour window was labeled as having AKI, with urine output rates averaged over 4-hour blocks. For patients lacking weight data, an appropriate value was interpolated using a linear regression model based on age, square age, height, and sex. Additionally, any patient who achieved a serum creatinine over

twice their admission serum creatinine measurement was labeled as having AKI. The reference admission serum creatinine was defined to be the last serum creatinine measurement taken before admission to the ICU; if no such measurement was available, the admission serum creatinine was defined to be the first measurement taken after admission to the ICU.

In order to analyze the impact of the severity of hypotension on risk of AKI, the minimum MAP value achieved over the course of the each ICU stay was computed. Additionally, six control variables were extracted for each ICU stay: age, sex, ethnicity, the maximum lactate achieved over the first 72 hours of the ICU stay, and the percentage of the ICU stay spent on vasopressors. We developed a multivariate logistic regression model, trained on a randomly selected subset of 90% of all patients, comprised of the minimum MAP feature along with the six control variables. Then, the p-value, odds ratios, and odds ratio confidence intervals for each of these features are reported. We also report the area under the receiver-operating curve for the multivariate model's performance on the remaining 10% of patients. Additionally, we compute and report the proportion of patients developing AKI with a minimum MAP measurement within each of the following time bins: [30,40], (40, 50], (50,60], (60,70], (70,80], (80,90], (90,200].

In order to understand the impact of the duration of hypotension relative to the length of the ICU stay on risk of AKI, hourly averages of MAP measurements were computed for the first 72 hours of each ICU stay, and the percentage of time spent within each of the following MAP bins was calculated: [30,40], (40, 50], (50,60], (60,70], (70,80], (80,90], (90,200]. MAP measurements outside of physiological bounds (below 30 mmHg or above 200 mmHg) were

discarded, and MAP values were linearly interpolated for hours during which no MAP measurements were taken, which comprised 7.2% of all analyzed ICU stay hours.

All code used in this work used to perform this analysis is publicly available at https://github.com/nalinimsingh/HST.953.

Results

Of the 4,663 septic ICU stays analyzed in this study, the RIFLE criteria were used to identify AKI in 2,942 patients (63%). The patient characteristics of the AKI, no-AKI, and combined populations are shown in Table 1; the length of stay and percent of ICU stay spent on vasopressors were both higher amongst AKI patients than patients without AKI. The distribution of minimum achieved MAP values for both cohorts is shown in Fig. 2. The average minimum MAP for patients with AKI was 46.2 mmHg, while the average minimum MAP for patients without AKI was 50.9 mmHg. The results of the multivariate logistic regression performed using minimum MAP and six control covariates are shown in Table 2. The minimum MAP value achieved was related to the likelihood of a patient having AKI with an odds ratio of 0.97 per 1 mmHg increase ($p < 0.001$). The resulting logistic regression model was evaluated on the test dataset to yield an area under the receiver-operating characteristic of 0.71.

Fig. 3 shows the proportion of patients developing AKI based on the minimum MAP value recorded during the ICU stay. The proportion of patients developing AKI decreased with an increase in the minimum MAP recorded. However, there does not appear to be a clear MAP cutoff below which patients are suddenly extremely likely to develop AKI.

Fig. 4 shows the percentage of time spent within each of seven MAP bins for both the AKI and non-AKI cohorts. Patients with AKI spent, on average, a higher proportion of the ICU stay with an average hourly MAP between 50 and 70 mmHg than patients without AKI; patients without AKI spent a higher proportion of the ICU stay, on average, with an average hourly MAP between 80 and 90 mmHg. However, the confidence intervals for these measurements on both the AKI and non-AKI cohorts overlap significantly.

Discussion

The literature indicates that sepsis is a significant predisposing factor to developing AKI [9,10,11,12]. This study further supported those findings, with 63% (2942 patients) of the cohort developing AKI. Advanced age has frequently been associated with the development of AKI [10,16,23,24]; our results also indicated that it was a factor with a mean age of 67 for those who developed sepsis AKI, as opposed to a mean of 62 for non AKI. The length of stay was significantly higher for patients with AKI than for patients without AKI, a finding that was also noted by Oppert et. al [24].

The results in Fig. 2 show that the majority of patients who developed AKI had recorded minimum MAPs below 70, supporting the findings of Badin et al [20] and Leone et al. [15]. In opposition, Asfar et al. found no significant difference in the development of AKI between individuals that had MAPs 65-70 when compared to individuals with MAPs between 80-85 mmHg, indicating that a MAP greater than 70 might be optimal. However, Fig. 2 demonstrates that several individuals in this study did not develop AKI and had MAPs less than 70 mmHg;

this clearly illustrates that hypotension may be a precipitating factor to the development of AKI, but it is not the only factor.

Our study was unable to provide clarification as to what MAP threshold was associated with significantly reducing the incidence of AKI in septic patients. Our findings in Figure 3 did indicate that there was a 70% likelihood of developing AKI when the MAP was less than 50 and a 60% likelihood when the MAP was less than 60. This was consistent with Lehman et. al., who found lower MAP values associated with greater the risk of developing AKI in patients without sepsis [17].

Our investigation into the relationship between duration of hypotension and the risk of AKI was inconclusive. Figure 4 does indicate that patients with AKI spend a larger fraction of the first 72 hours in the ICU with a MAP between 50 and 70 mmHg on average, but large confidence intervals surrounding those figures suggest that further analysis is required to fully understand any association between duration of hypotension and risk of AKI.

Despite the observed association between low MAP and AKI, this retrospective cohort study is limited in that it does not identify any direct causality between hypotension and AKI. This study looked exclusively at the MAP of septic patients and its relationship to developing AKI. Given that both Asfar et al. and Cecconi suggest that individuals who have hypertension may require a higher MAP to avoid AKI, identifying individuals with a history of hypertension may have provide a clearer picture of the relationship between MAP and the development of AKI [23,25].

Conclusion

This work analyzes trends in the relationship between the severity and duration of hypotension in septic ICU patients and the risk of developing AKI. We demonstrate that severity of hypotension, as indicated by the minimum achieved MAP, is a risk factor for AKI; the odds of developing AKI decrease by 3% for every 1 mmHg increase in minimum MAP below 90 mmHg. However, no clear cutoff was observed below which there is a sharp, discontinuous increase in the risk of developing AKI. We also show that patients who develop AKI spent, on average, a higher fraction of the first 72 hours with an hourly averaged MAP value between 50 and 70 mmHg, though those measurements are characterized by large uncertainties. Future work might examine different features to characterize hypotension duration and their relation with the risk of developing AKI.

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Table 1: Characteristics of AKI, non-AKI, and combined patient populations. Categorical variables are described by the number and percentage of cases belonging to each category, while continuous variables are described by the median and interquartile range.

	AKI N = 2,942	No AKI N = 1,721	All Patients N = 4,663
Age (Years)	67 (54,78)	62 (50,75)	66 (53,77)
Sex			
Male	1502 (51%)	925 (54%)	2427 (52%)
Female	1440 (49%)	796 (46%)	2236 (48%)
Ethnicity			
White	2218 (75%)	1225 (71%)	3443 (74%)
Black/African American	194 (7%)	117 (7%)	311 (7%)
Hispanic/Latino	79 (3%)	70 (4%)	149 (3%)
Asian	44 (1%)	59 (3%)	103 (2%)
American Indian/Alaska Native	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Multi/Other	66 (2%)	51 (3%)	117 (3%)
Unknown	340 (12%)	198 (12%)	538 (12%)
LOS (Days)	9.3 (5.3,16.3)	6.2 (4.1,10.7)	8.1 (4.8,14.1)
Max Lactate (mg/dL)	2.4 (1.6,4.0)	2.2 (1.5,3.6)	2.3 (1.5,3.9)
Vasopressor Time (% of ICU stay)	4.3 (0.0,24.4)	0.0 (0.0,16.4)	2.3 (0.0,21.7)

Table 2: Results of Multivariate Logistic Regression Model.

Covariate	P-value	Odds Ratio (95% CI)
Age	<0.001	1.02 (1.01,1.02)
Gender: Female	0.966	1.00 (0.87,1.15)
Ethnicity (ref: White)		
American Indian/Alaska Native	0.714	0.59 (0.03,10.10)
Asian	<0.001	0.42 (0.27,0.64)
Black/African American	0.969	1.01 (0.77,1.32)
Hispanic/Latino	0.176	0.78 (0.55,1.12)
Multi/Other	0.337	0.82 (0.54,1.24)
Unknown	0.372	0.91 (0.74,1.12)
Length of Stay	<0.001	1.05 (1.04,1.06)
Maximum Lactate	<0.001	1.05 (1.02, 1.09)
% Time on Vasopressors	0.162	1.27 (0.91, 1.79)
Minimum MAP	<0.001	0.97 (0.96,0.98)

Figure 1: Cohort selection process.

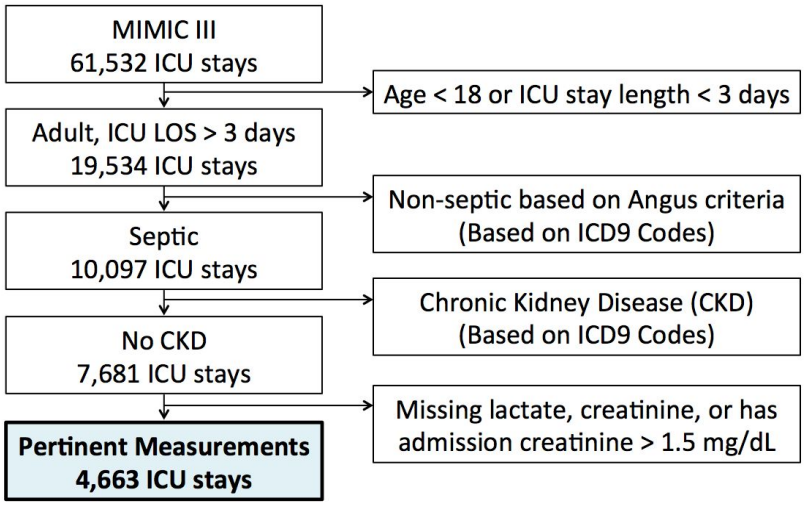

Figure 2: Histogram of minimum MAP values achieved over the ICU stay by patients in both the AKI and non-AKI cohorts.

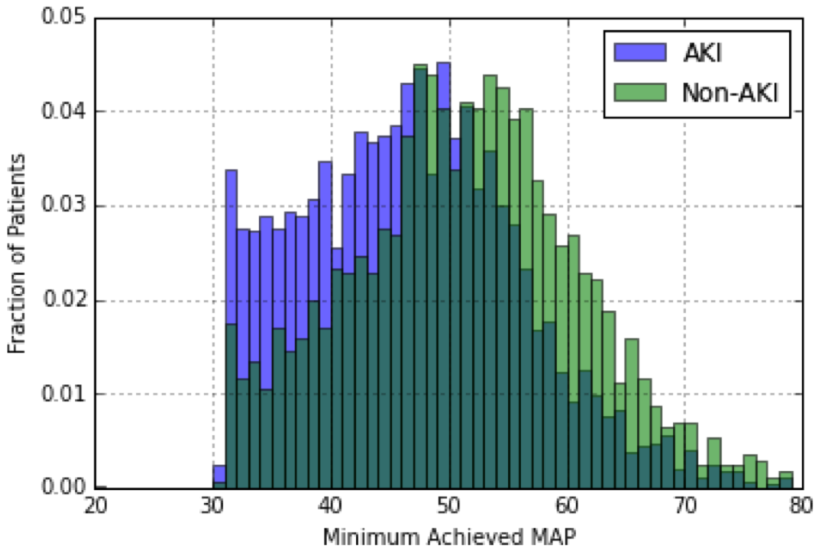

Figure 3: Proportion of patients developing AKI as a function of minimum MAP achieved over the course of the entire ICU stay.

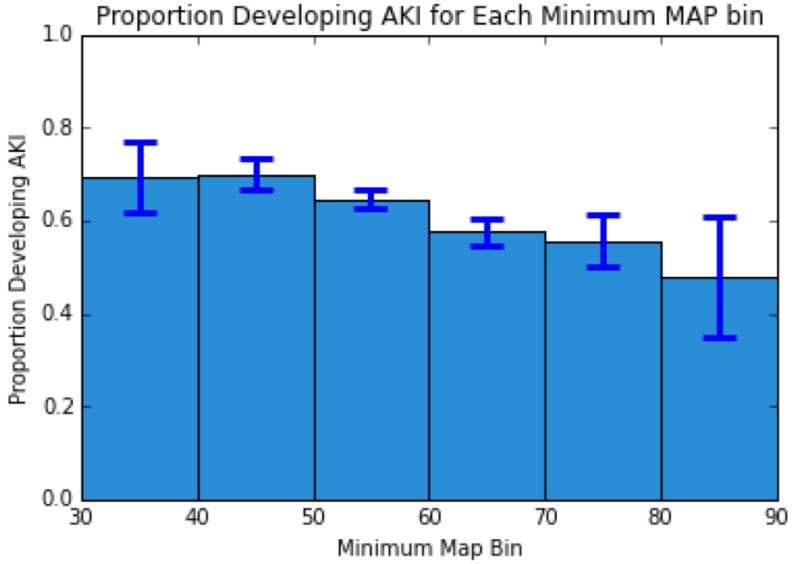

Figure 4: Proportion of the first 72 hours of the ICU stay spent within various MAP bins for both the AKI and non-AKI cohort.