Variability of CVP and Fluid Overload are Associated with Sepsis-associated Acute Kidney Injury: a case-control study

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Research article

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Abstract

Background: The relationship between central venous pressure (CVP) and sepsis-associated acute kidney injury is not extensively explored. The study aimed to investigate the association of CVP and new-onset SAKI.

Methods: Septic patients with new-onset AKI (SAKI) were identified from the Medical Information Mart for Intensive Care (MIMIC)-III database. Propensity score (PS) was used to account for the baseline differences between SAKI and non-SAKIs. In order to estimate association between CVP variability and AKI, we applied the generalized estimating equation (GEE) to adjust for potential confounding such as cumulative fluid balance and in-ICU medication usage.

Results: A total of 916 septic patients with new-onset AKI were enrolled in the study, including 458 in the SAKI group and 458 in non-SAKI group. After PS matching, baseline factors such as SOFA, SAOSII, APSIII and LODS score, as well as baseline diseases including hypertension, diabetes, liver and renal disease were balanced between SAKIs and non-SAKIs. SAKI groups showed higher CVP variation (SAKI vs. non-SAKI: 0.83 vs. 0.68, $p=0.03$) and accumulative fluid balance (SAKI vs. non-SAKI: Day 1: 3449.8 vs. 2930.3; Day 2: 4801.1 vs. 3916.6; Day 3: 6018.5 vs. 5005.8, $p=0.007$). GEE was further used to estimate the association between CVP variation and SAKI. The model showed that, increased CVP variation (OR=1.14, 95%CI 1.01-1.28, $p=0.03$), higher fluid accumulation (OR=1.02 95%CI 1.00-1.05, $p=0.04$) were associated with increased risk of SAKI.

Conclusions: We found that variability of CVP and higher fluid accumulation were associated with higher risk of new-onset SAKI in septic patients in this study. The results need to be verified in further prospective trials.

Background

Severe sepsis is a major concern in critically ill patients and is often complicated by acute kidney injury (AKI) [1, 2]. Patients with sepsis-associated AKI (SAKI) is associated with significant morbidity and mortality[3]. A sub-study of FINNAKI study showed that, 53.2% of sepsis patients had AKI, the 90-day mortality rate was 38.1% for severe sepsis patients with AKI and 24.7% for those without AKI[4].

In clinical practice, maintaining the optimal blood pressure is believed to prevent AKI. Mean arterial pressure (MAP) is considered the driving pressure of tissue perfusion and the Surviving Sepsis Campaign guideline recommends an initial target MAP of 65 mm Hg in patients with septic shock[5]. However, there is little evidence that MAP adequately reflects kidney perfusion[6]. Furthermore, when the downstream pressure of organ perfusion (e.g. CVP) is very high, the sole MAP can be insufficient to reflect the organ perfusion pressure[7, 8]. An observational study reported that higher CVP was associated with the risk of developing new or persistent AKI in septic shock patient[9]. It is believed that to avoid the elevation of CVP

may prevent SAKI[10]. However, to date, there is limited evidence about the association between CVP and AKI in sepsis patients.

The present case control study was designed to investigate the relation between CVP and new-onset of AKI in sepsis patients using the data from MIMIC-III database.

Method

Study design

In order to reveal the association between CVP and new-onset AKI in sepsis patients, we conducted a case control study by retrieving electronic health record (EHR) from Medical Information Mart for Intensive Care III(MIMIC-III) database. Sepsis patients who had new-onset AKI within the first 48h or 7d after their ICU admission were categorized as the SAKI group, with the remaining patients making up the non-SAKI group.

We discovered significant differences of the baseline demographic and clinical characters between SAKI patients and non-SAKI patients in our preliminary dataset, thus 1:1 propensity score matching (PSM) was applied to balance out these baseline difference that may confound the CVP-SAKI relation (Figure 1).

Data source

Data used for this study was retrieved from the MIMIC-III (Medical Information Mart for Intensive Care III) Clinical Database, which is a large, freely-available database comprising deidentified health-related data associated with over forty thousand patients who admitted to critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012[11]. The current version of the MIMIC-III Clinical Database is 1.4 version which contains data from 53,423 distinct hospital admissions for adult patients admitted to ICUs during the study period, the data covers 38,597 distinct adult patients and 49,785 hospital admissions, the median age of adult patients is 65.8 years, 55.9% patients are male, and in-hospital mortality is 11.5%. All data are extracted from the MIMIC-III database using custom PostgreSQL which is a powerful, open source, object-relational database system and can be downloaded from internet freely. Since the Institutional Review Board of the Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts Institute of Technology have approved the use of the MIMIC-III database by any investigator who fulfills data user requirements, IRB approval from our institution and Informed consent were exempted.

This study was reported according to The Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement[12].

Patient inclusion and exclusion

Inclusion criteria was patients: (1) adult patient with sepsis(aged 18 years or above); (2)admitted to MICU or SICU; and (3) with the data of CVP measured in 24h,and the data of new-onset AKI recorded within the first 48h or 7d. In this study, the diagnosis of sepsis was in accordance with Angus criteria[13] to retrospectively identify patients using billing codes. To identify cases with severe sepsis, we selected all cases from MIMIC-III database with ICD-9-CM codes for both a bacterial or fungal infections process and a diagnosis of acute organ dysfunction. The code of Angus criteria for searching the database and other related concepts could be captured at the MIMIC Code Repository[14] which is available online and is open[15].

Patients aged over 89 were excluded because date of birth for patients aged over 89 were shifted to obscure their true age for the reason of deidentification in MIMIC-III database[11].

Demographical and laboratory variables

The following baseline variables were extracted from the MIMICIII database for the at the time of ICU admission: age at the time of hospital admission, gender, sequential organ failure assessment(SOFA), Simplified Acute Physiology Score II (SAPSII), The Logistic Organ Dysfunction system (LODS), Acute Physiology Score III(APS III), use of vasopressors and renal replacement therapy (RRT).

Information regarding the baseline comorbidities were also extracted. We collected at the baseline the history of congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disease, peripheral vascular disease, hypertension, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, solid tumor, metastatic cancer, coagulopathy, deficiency anemias. All comorbidities were identified according to the method defined by Elixhauser which's coding algorithms was developed by Quan et. al[16].(A detailed coding of the Elixhauser comorbidities used for querying MIMIC-III database is also available online)

Variables that represent early admission hemodynamic stability, such as CVP, MAP, DAP were collected within the first 24 hours after the ICU admission as the lowest, mean, highest values. If a variable was measured more than once in the first 24h, the value associated with the greatest severity of illness was used. For example, the lowest value of mean BP reported in the first 24 h were used in the study. Daily fluid balance (input-output) of the first 3 days were also included for analysis. Usage of nephrotoxic antibiotics such as vancomycin, aminoglycosides which was a confounding factor of AKI was also analyzed.

Laboratory variables during the first 24 hours of admissions were collected for analysis, including white blood cell count, hematocrit, platelet count, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, lactate, creatinine, pH, anion gap, bilirubin, albumin and creatinine kinase. For patients with multiple measurements, the lowest value of hematocrit, platelet count, bicarbonate, pH, albumin, and highest value of WBC, potassium, chloride, sodium, potassium, BUN, lactate, creatinine, anion gap, bilirubin, and creatinine kinase.

Definition of other clinical variables

CVP-variation: we used coefficient of variation to describe the variability of CVP which calculated as the standard deviation of the CVP divided by the mean of the CVP. Accumulative fluid balance was defined as total net fluid balance after ICU admission.

Primary outcome

The primary outcome was new-onset AKI (SAKI) within the first 48 hour or 7 days after their ICU admission. New-onset AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria where AKI was defined as any of the following – Increase in creatinine by 0.3 mg/dl within 48 hours; or Increase in creatinine to 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days; or urine volume 0.5 ml/kg/h for 6 hours[17]. In this study, baseline creatinine was defined as first measurement in 6 hours before or 24 hours after ICU admit. For urine output, the highest UO in 0-48 hours was used, and for creatinine, creatinine value from days 0-2 or 0-7 is used.

Statistical analysis

Continuous variables were compared using independent t-test. Categorical variables were compared using chi-squared, if the expected value in the cell was less than 5, Fisher's exact test will be used.

Repeated measures such as the fluid accumulation between the SAKI and non-SAKI for the first 3 days were compared using Two-way repeated measure ANOVA. In consider that the fluid accumulation was measured repeatedly and may confound the effect of CVP on SAKI risk, we chose to use generalized estimate equation (GEE) to evaluate the potential factors and their effect on the SAKI risk. All statistical analysis was completed by using SPSS 24.0

Results

After screening 38,605 MIMIC-III adult admissions, we identified sepsis in 17,420 admissions according to the Angus criteria[13]. We only include patient age between 18 and 90 years who admitted to MICU or SICU. Those without data of CVP and AKI were excluded. In our preliminary cohort of 3,672 patient, 3,207 were in SAKI group (87.3%) and 465 non-SAKI group (12.7%). We checked the baseline demographic and clinical characteristics in our preliminary cohort and observed significant differences between SAKI and non-SAKI. The 1:1 propensity score matching (PSM) was applied to give 458 SAKI case and 458 non-SAKI controls (Fig.1). After matching, the baseline characteristics including admission age, SAPSII, LODS, APS III and disease history were balanced between cases and controls (Table 1). Clinical characteristics after admissions were then compared between cases and controls (Table 2), we were able to find that CVP variation and accumulative fluid balance showed statistical differences between SAKI cases and controls.

SAKI cases had higher accumulative fluid balance, the mean fluid accumulation of SAKI groups increased from 3449 ml in the first 24 hours of their admission to 6018 ml in following the 72 hours, the non-AKI controls fluid balance, increase from an average of 2930 ml to 5005 ml ($p=0.007$)(Fig.2). We also found that CVP variation is large in the SAKI group than the non-AKI group. We performed a generalized equation model to see the relation between CVP variation, accumulative fluid balance, mean blood pressure, medication usage, diseases history and SAKI. After backward selection, higher CVP-variation and accumulative fluid balance were associated with SAKI (Table 3).

Table 1 Baseline characteristics between SAKI and non-SAKI before and after PSM matching

Variable	Before PSM			After PSM		
	No-SAKI	SAKI	p value	No-SAKI	SAKI	p value
Total Number	465	3270	-	458	458	-
Admission age	64.6 (63.21-66.04)	64.1(63.55-64.59)	0.47	64.6 (63.15-66.01)	64.7(63.30-66.03)	0.93
Male, No. (%)	221(47.5%)	1781(55.5%)	0.01	219(47.8%)	245(53.5%)	0.09
Table 1 continued						
APSI	53.0 (50.69-55.39)	63.6(62.77-64.37)	<0.0001	53.4 (51.09-55.81)	54.1(52.22-56.13)	0.64
LODS	5.2(4.95-5.55)	6.6(6.51-6.73)	<0.0001	5.3 (4.99-5.61)	5.4(5.11-5.65)	0.68
SAPSI	42.9(41.39-44.46)	47.8(47.28-48.33)	<0.0001	42.9 (41.42-44.4)	43.5(42.14-44.78)	0.65
Liver disease, No. (%)	65(14.8%)	826(25.8%)	<0.0001	69(15.1%)	73(15.9%)	0.72
Congestive heart failure, No. (%)	143(30.8%)	1162 (36.2%)	0.021	143(31.2%)	139(30.3%)	0.77
Renal failure, No. (%)	37(8.0%)	715(22.3%)	<0.0001	37(8.1%)	44(9.6%)	0.42
Pulmonary circulation dysfunction, No. (%)	30(6.5%)	273(8.5%)	0.13	30(6.6%)	23(5.0%)	0.32
Diabetes	18(3.9%)	281(8.8%)	<0.0001	18(3.9%)	31(6.8%)	0.06
with complication, No. (%)						
Fluid electrolyte unbalance, No. (%)	189(40.6%)	1716(53.5%)	<0.0001	188(41%)	174(38%)	0.34

Table 2 Comparison of the characteristics between SAKI and non-AKI after ICU admission

Clinical Characteristics	SAKI	Non-AKI	p-value
	Mean(95%CI)	Mean(95%CI)	
Mean SBP	110.81 (109.47-112.16)	110.68 (109.18-112.19)	0.90
Mean DBP	57.29 (56.49-58.10)	57.93 (57.04-58.84)	0.30
Mean MAP	74.13 (73.11-74.97)	74.04 (73.16-75.19)	0.89
Mean CVP	15.86(13.80-17.91)	15.99 (13.89-18.18)	0.93
DPP(DBP-CVP)	41.43 (39.21-43.66)	41.94 (39.49-44.39)	0.76
MPP(MAP-CVP)	58.17 (55.84-60.51)	58.14 (55.63-60.73)	0.98
Accumulative fluid balance in the 1 st day	3439.79 (3093.02-3808.56)	2930.28 (2623.49-3237.08)	0.007
Accumulative fluid balance in the 2 nd day	4801.05 (4277.39-5324.71)	3916.56 (3521.47-4311.66)	
Accumulative fluid balance in the 3 rd day	6018.57 (5395.69-6641.45)	5005.81 (4561.03-5450.58)	
CVP Variability,	0.82 (0.71-0.94)	0.67 (0.60-0.75)	0.03

Fig.2 comparison of the Accumulative Fluid Balance between non-AKI and SAKI Group

Table 3 Generalize estimate equation model for SAKI

Clinical Characteristics	OR (95%CI)	p-value
CVP variability*	1.14(1.01-1.28)	0.03
Fluid Accumulation*	1.02(1-1.05)	0.04

CVP variability defined as the coefficient of variance of CVP

Discussion

Key results

This retrospective study showed that no association between CVP during the 24h following ICU admission and new-onset AKI among septic ICU patients, this was not correspondence with previous study[9]. However, we found that variability of CVP, is statistically associated with new-onset AKI in septic patients.

Meanwhile, we found that higher accumulation of fluid within first 72 hours, were independent risk factors for SAKI, The findings are similar to those in a previous studies which found fluid overload was a risk factor of AKI[18]. This indicate that when expanding body volume, doctors should consider the accumulation speed to stabilize CVP level, especially when patient had baseline creatinine elevation, liver dysfunction.

Interpretation

According to Surviving Sepsis Campaign, Sepsis has been defined as life-threatening organ dysfunction resulting from infection[19].AKI is a common complication of septic shock and is associated with high mortality[20, 21]. SAKI is characterized by a distinct pathophysiology, Renal hypoperfusion is considered one of the leading causes of AKI in sepsis. Therefore, it was thought that MAP was a therapeutic target for prevention of SAKI[22]. A retrospective study showed that a MAP of more than 75 mmHg may be required to maintain kidney function in septic patient [23]. However, there is little evidence that MAP can represent renal hypoperfusion, no association between MAP and AKI in septic patients was observed in some respective studies[8, 9, 24] . In our study, we still found that no association between MAP and new-onset AKI in sepsis. Therefore, using MAP as a sole therapeutic goal for prevention of SAKI is not adequate.

On the other hand, increasing MAP by aggressive fluid loading may harm the kidney via enhancing venous congestion and blocking venous outflow. Based on rationale provided by the Guyton model on cardiac function, venous return is determined by the gradient between the mean circulatory filling pressure (MCFP) and CVP[25]. An increase in the CVP or a fall in the MCFP will impede venous return, cardiac output. In addition, a high CVP is transmitted backwards increasing venous pressure. This can reduce renal blood flow and decrease the pressure gradient for ultrafiltration. The finding of elevated CVP can lead to renal dysfunction was first demonstrated in experimental animal studies, and was also found in patients with cardiac disease[8].A CVP > 8 mmHg has been demonstrated to decrease microcirculatory flow, as well as renal blood flow[26]. In additional, Legrand found that higher CVP levels was associated with an increased incidence and morbidity of AKI in septic shock[9, 27].In our study, the association between CVP and new-onset AKI among septic patients is very weak before PSM, but after PSM the association is not

significant, this is a little different with previous studies[8, 9]. One reason for the different findings is the sample size of our study is bigger. Another reason is that PSM was used to balance the baseline of severity of disease of two group in our study, but the previous studies did not. However, we found that variability of CVP and higher accumulation of fluid within first 72 hours are also associated with new-onset AKI in septic patients, this finding is still consistent with the mechanism of renal venous return, and fluid restriction in septic patients is a considerable option from the perspective of kidney protection.

Limitations

First, our analysis has all limitations of a retrospective, observational, single center study. To overcome this limitation. We conducted a matched case-control study mainly because of two major concerns. First, majority of the baseline clinical characteristics showed differences between AKI and non-AKI in our preliminary exploration, which indicate the AKI groups and non-AKI groups may not be viewed as originated from the same source population, thus potential selection bias may be introduced. Second, there was much more AKI patients than non-AKI, a matched design may add some power to model construction. We chose APSIII score to create the stratum for matching because APSIII is a comprehensive score that used in the clinical setting to evaluate overall health by scoring multi-organ function. Comparable APSIII score indicate similar multi-organ function. Matching on APSIII will automatically balance out other unmeasured clinical confounding. Finally, these selected clinical variables were used to test the model prediction performances in an independent testing sample, the AUC of 0.742 indicate that our model is stable and had good performance in AKI prediction. However, our results must be confirmed in a larger, multicenter cohort.

Second, the data from MIMIC III database we used was collected without specific a priori research questions developed prior to our study, there were missing data and outliers, some statistics method was used to collect the abnormal values. And the study was reported adhered to the RECORD statement in order to improve the quality of reporting.

Third, the value of CVP is affected by IAP, right heart function and mechanical ventilation. The retrospective nature of this study also prevented us from obtaining information on heart function, intraabdominal pressure, or intrathoracic pressure. Therefore, we were not able to investigate the etiology of elevated CVP.

Finally, the results of the association between CVP and AKI obtained from this noninterventional study does not prove a causal relationship. Whether stabilizing CVP may reduce the risk of new-onset AKI in sepsis patient needs to be evaluated in future studies.

Conclusions

In this study, we observed association between variability of CVP and development of AKI in septic patients. This may indicate that we should control the speed of fluid infusion and stable CVP to prevent AKI when resuscitate sepsis patients. We also found that higher accumulation of fluid within first 72 hours were independent risk factors for SAKI, which implies that fluid overload is harmful to the renal function. These findings must be confirmed in further prospective study.

Declarations

Abbreviations

AKI: Acute kidney injury; CVP: Central venous pressure; DAP: Diastolic arterial blood pressure; MAP: Mean arterial blood pressure; SAKI: sepsis-associated AKI; SAPSII: Simplified Acute Physiology Score II; LODS: The Logistic Organ Dysfunction system

Ethics approval and consent to participate

the Institutional Review Board of the Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts Institute of Technology have approved the use of the MIMMIIICII database by any investigator who fulfills data user requirements, IRB approval from our institution and Informed consent were exempted.

Consent for publication

Not applicable

Availability of data and material

MIMIC-III Clinical Database is freely available online.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Minqiang Huang conceived and designed the study, contributed to the analysis and interpretation of data as well as drafting the manuscript, and gave final approval of the version to be published. Lei Kuang contributed to the acquisition, analysis and interpretation of data and gave final approval of the version to be published. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart of included in the study. CVP, central venous pressure; AKI, acute kidney injury. SAKI, sepsis-associated AKI.

Figure 2

comparison of the Accumulative Fluid Balance between non-AKI and SAKI Group

Supplementary Files

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