

Research Article

Impact of central venous pressure measurement on the prognosis of patients with septic shock: A retrospective analysis of the MIMIC- IV database

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Highlights

- The measurement of central venous pressure in patients diagnosed with septic shock does not yield prognostic improvements.
- Central venous pressure measurement in patients with septic shock is associated with prolonged ICU stay.
- Central venous pressure measurement is not advised for patients diagnosed with septic shock.

Abstract

Objective: To assess the impact of measuring central venous pressure (CVP) on the prognosis of patients with septic shock. **Methods:** Septic shock patients with and without CVP measurements were identified in the Medical Information Mart for Intensive Care IV database. The primary outcome was 28-day mortality, and a multivariate logistic regression model was used to analyze the association between CVP measurement and 28-day mortality in patients with septic shock. The results were validated using logistic regression after propensity score matching. Secondary outcomes were in-hospital mortality, 1-year mortality, incidence of acute kidney injury within the first 7 days in the intensive care unit (ICU), and length of stay in the ICU. After propensity score matching, logistic regression analysis was conducted to analyze the correlation between CVP measurements and secondary outcomes in patients with septic shock. **Results:** A total of 2966 patients were included, including 1219 patients whose CVP was measured within 24h after admission to the ICU. CVP measurement was found to be not correlated with 28-day mortality (odds ratio=0.978, 95% Confidence Interval 0.798-1.200, P=0.835). Analyzing the cohort after propensity score matching, CVP measurement was found to be associated with prolonged ICU stay (4.9 vs. 3.2 days; P<0.001). No statistical differences were found in the primary outcome and other secondary outcomes between those with CVP measurement and those not. **Conclusion:** CVP measurement is associated with prolonged ICU stay in patients with septic shock but not associated with mortality and incidence of acute kidney injury within 7 days.

Keywords: Septic shock, central venous pressure, 28-day mortality, length of intensive care unit stay

Introduction

Septic shock is a distinct subset within the spectrum of sepsis, a pathological condition characterized by a potentially fatal dysregulated immune response to infection, resulting in impaired organ function [1]. Septic shock is diagnosed if patients exhibit confirmed or suspected infection, and a Sequential Organ Failure Assessment score of ≥ 2 , which necessitate the administration of vasopressor medications to sustain a mean arterial pressure of 65 mmHg,

accompanied by a blood lactate level exceeding 2 mmol/L [2]. Various factors, such as trauma, fungal infection, and bacterial infection, can inflict harm upon the vascular endothelial cells of patients, resulting in interstitial fluid leakage, compromised microvascular blood flow, and insufficient tissue and organ perfusion, ultimately precipitating septic shock [3]. Septic shock is closely linked to a substantial incidence of complications, with a mortality rate exceeding 40% among affected individuals. This condition poses a severe threat to human life and impos-

es a significant economic burden on both patients and society [4, 5]. Despite the significant advancements in pharmacologic therapy witnessed in recent years, septic shock continues to pose a substantial challenge for healthcare systems globally.

The implementation of the “sepsis bundle” has been a fundamental approach in managing septic shock since the initial release of the Surviving Sepsis Campaign (SSC) in 2004. In the 2018 guideline update, the 3-hour and 6-hour management bundles were consolidated into a 1-hour management bundle, emphasizing the urgency of initiating resuscitation and treatment upon sepsis diagnosis [6]. The assessment of fluid status in septic shock patients and subsequent implementation of personalized fluid therapy are crucial determinants of patient survival and prognosis. Central venous pressure (CVP) represents the pressure at the juncture of upper and lower veins as they enter the right atrium, and its value is influenced by a multitude of factors including right ventricular preload, afterload, contractility, compliance, venous tone, and volume status, among others [7].

In the 2012 SSC publication, CVP was recognized as an initial objective in resuscitation, and existing literature has indicated that elevated CVP levels are linked to both acute kidney injury (AKI) and mortality [8-11]. However, the 2021 SSC release asserted that CVP is an inadequate indicator of a patient’s fluid status [12]. Consequently, there is ongoing debate regarding the early monitoring of CVP in fluid management for septic shock patients. This study aimed to assess the effects of early monitoring of CVP on the survival and prognosis of patients diagnosed with septic shock. This was achieved by analyzing the clinical characteristics of patients with septic shock in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database.

Materials and Methods

Study design

This study utilized the freely accessible clinical database known as the MIMIC-IV [13]. The MIMIC-IV (v2.0) database encompasses clinical data from the year 2008 to 2019, comprising information of over 40,000 patients admitted to the intensive care unit (ICU). To ensure patient privacy protection, the database automatically removes patient identifiers in accordance with the Health Insurance Portability and Accountability Act security regulations. Conse-

quently, this study does not involve any ethical concerns, and no ethics review is required. The researcher obtained access to the database and was responsible for data extraction (certification number 50199917).

Selection of participants

Patients diagnosed with septic shock were included in the study. The determination of septic shock was based on sepsis 3.0 criteria as well as International Classification of Diseases-9 (ICD-9) and ICD-10 codes in the MIMIC-IV database. Patients who were admitted to the ICU for less than 24 hours or had their initial CVP measurement taken after 24 hours of ICU admission were excluded from the analysis. Furthermore, patients with multiple admissions to the ICU were only considered for analysis based on their first admission. Patients who underwent their initial CVP measurement within 24 hours of ICU admission were categorized into a CVP group, while those who did not were classified into a no CVP group.

Variable extraction

Variables were obtained from the MIMIC-IV-2.0 database, and those with missing indicators $\geq 30\%$ were excluded. The remaining variables were imputed for missing values using multiple imputation. The variables included demographic characteristics, vital signs, and laboratory indices measured within the initial 24 hours of ICU admission. In cases where a variable was recorded multiple times during this period, the value corresponding to the highest severity of disease was utilized. The primary outcome was 28-day mortality, while secondary outcomes included in-hospital mortality, 1-year mortality, the incidence of AKI within 7 days after ICU admission, and length of ICU stay. Data extraction for this study was conducted using STATA and Structured Query Language in Postgre STATA and Structured Query Language (v15.0).

Statistical analysis

Variables that adhered to a normal distribution were presented as mean (standard deviation), and intergroup comparisons were conducted using the t-test. Variables that did not adhere to a normal distribution were presented as median (interquartile range), and intergroup comparisons were conducted using the Wilcoxon rank-sum test. Categorical variables were presented as percentages, and intergroup comparisons were conducted using the chi-square test. Baseline variables that showed a correlation with prognosis through univariate analysis

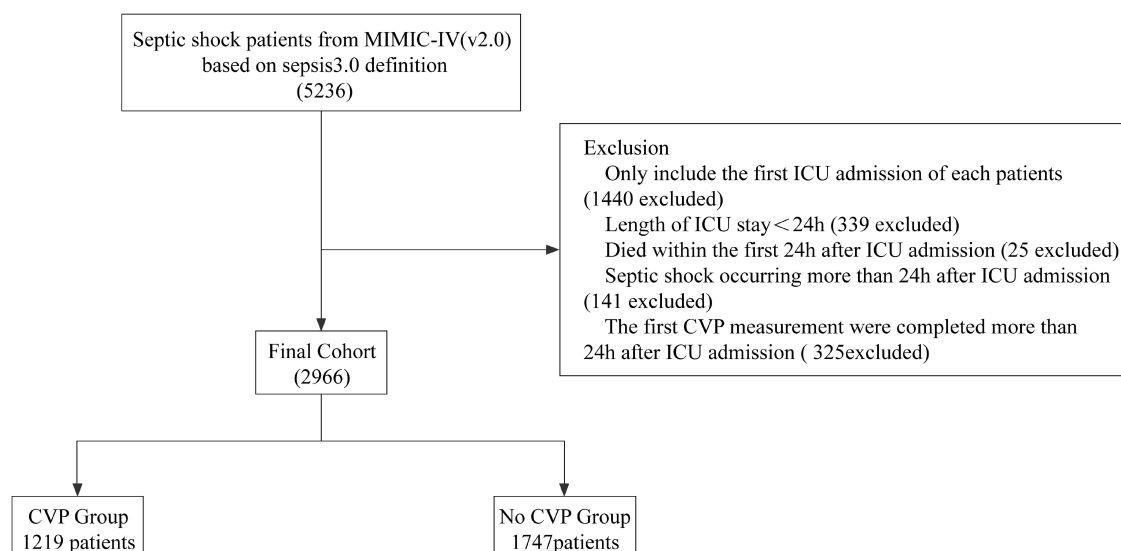


Figure 1. The flow chart of this study. MMIC-IV, Medical Information Mart for Intensive Care IV; ICU, intensive care unit; CVP, central venous pressure.

($P < 0.10$) were included as covariates in the multivariate logistic regression model. These variables included age, body weight, sequential organ failure assessment score, Glasgow coma scale score, Charlson Comorbidity Index score, use of vasoactive medications, congestive heart failure, chronic lung disease, mild liver disease, diabetes mellitus, nephropathy, heart rate, mean blood pressure, body temperature, S partial pressure of oxygen, urea nitrogen, creatinine, lactate, partial pressure of oxygen, partial pressure of carbon dioxide, urine output, and incidence of acute kidney injury. The relationship between CVP measurement and the 28-day mortality of patients was then analyzed. Propensity score matching was employed to equalize the distribution of baseline indicators across groups, with a caliper value of 0.4 utilized to match CVP/no CVP in a 1:1 ratio. Subsequently, logistic regression analysis was conducted on the matched datasets using the R software. A statistical significance level of $P < 0.05$ was adopted to determine the observed differences between the two groups.

Results

Baseline characteristics

A total of 5236 patients diagnosed with septic shock were identified in this study. Among these patients, 1440 patients were admitted to the ICU on multiple occasions, 339 patients had an ICU stay of less than 24 hours, 25 patients died within 24 hours of ICU admission, 141 patients were diagnosed with septic shock more than 24 hours after ICU admission, and 325 patients received their initial CVP mea-

surement after 24 hours of ICU admission. After applying the final inclusion criteria, 1219 included patients (41.10%) received their initial CVP measurement within 24 hours of admission (CVP group), while 1747 patients (58.90%) did not undergo CVP monitoring (no CVP group). The selection flowchart can be seen in **Figure 1**. The baseline characteristics of the patients in the CVP and no CVP groups are presented in **Table 1**. The CVP group exhibited significantly higher Sequential Organ Failure Assessment score (10 (IQR 7 - 13) vs. 8 (IQR 8 - 9)), simplified acute physiology score (SAPS II) (48 (IQR 37-59) vs. 44 (IQR 36-55)), and lactate level (2.8 mmol/L (IQR 1.7-5.0 mmol/L) vs. 2.6 mmol/L (IQR, 1.7-4.3 mmol/L)) compared to the no CVP group. There were no significant differences in baseline characteristics between the two groups following propensity score matching (PSM) (**Table 2**).

Primary outcome

Multivariate logistic regression analysis was conducted on the original cohort to assess the odds ratio (OR) of 28-day mortality in patients with septic shock based on CVP measurement. The analysis revealed an OR of 0.837 (95% CI 0.690-1.016), indicating no statistical difference between the CVP and no CVP groups. After PSM, the 28-day mortality rate was 33.9% in the CVP group and 33.4% in the no CVP group. The logistic regression analysis yielded an OR of 0.978 (95% CI 0.798-1.200), suggesting no significant difference between the two groups (**Figure 2**).

Secondary outcomes

Table 1. Baseline characteristics of the original cohort

Covariates	Original cohort No CVP	CVP	P values
Age	69 (58-80)	69 (56-80)	0.163
Male (%)	941/1747 (53.9)	688/1219 (56.4)	0.165
Weight (kg)	77.0 (63.6-94.4)	80.0 (37.5-96.8)	0.001
Severity of illness			
SOFA score	8 (6-12)	10 (7-13)	<0.001
SAPSII score	44 (36-55)	48 (37-59)	<0.001
GCS score	13 (9-15)	12 (7-14)	<0.001
CCI score	6 (5-9)	3(4-8)	<0.001
Interventions, n (%)			
RRT use	176/1747 (10.1)	105/1219 (8.6)	0.181
MV use	1251/1747 (71.6)	924/1219 (75.8)	0.011
Vasopressor use	1266/1747 (72.5)	1116/1219 (91.6)	<0.001
Comorbidities			
Myocardial infarction	307/1747 (17.6)	234/1219 (19.2)	0.260
Congestive heart failure	512/1747 (29.3)	428/1219 (35.1)	0.001
Chronic lung disease	456/1747 (26.1)	364/1219 (29.9)	0.024
Diabetes mellitus	588/1747 (33.7)	377/1219 (30.9)	0.118
Kidney disease	448/1747 (25.6)	285/1219 (23.4)	0.160
Malignant cancer	415/1747 (23.8)	196/1219 (16.1)	<0.001
Severe liver disease	394/1747 (22.6)	301/1219 (24.7)	0.176
Vital signs			
Heart rate (bpm)	111 (97-125)	114 (98-129)	0.001
MAP (mmHg)	54 (48-60)	53 (45-58)	<0.001
Respiratory rate (bpm)	30 (26-34)	30 (26-34)	0.406
Temperature (°C)	37.4 (37.0-38.11)	37.6 (37.1-38.3)	0.001
Laboratory tests			
SpO ₂	92 (89-94)	92 (89-94)	0.514
WBC (× 10 ⁹ /L)	16.3 (11.0-23.2)	17.2 (11.6-24.3)	0.019
Hemoglobin (× 10 ¹² /L)	9.3 (7.8-10.7)	9.7 (8.5-11.1)	<0.001
Platelet (× 10 ⁹ /L)	147 (93-213)	157 (100-229)	0.010
Bicarbonate (mmol/L)	19 (15-22)	18 (15-21)	0.001
Bun (mg/dL)	32 (20-53)	35 (22-54)	0.003
Creatinine (mg/dL)	1.5 (1.0-2.5)	1.7 (1.2-2.8)	<0.001
Lactate (mmol/L)	2.6 (1.7-4.3)	2.8 (1.7-5.0)	0.015
PH	7.30 (7.22-7.37)	7.26 (7.18-7.34)	<0.001
pO ₂	43 (34-66)	49 (38-76)	<0.001
pCO ₂	44 (38-53)	45 (38-54)	0.024
Urine volume (ml/24h)	1250 (640-2050)	1180 (594-2135)	0.617
AKI, n (%)	1037/1747 (59.4)	820/1219 (67.3)	<0.001

Note: CVP, central venous pressure; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; GCS, glasgow coma scale; CCI, Charlson Comorbidity Index; RRT, renal replacement therapy; MV, mechanical ventilation; MAP, mean arterial pressure; WBC, white blood cell; Bun, blood urea nitrogen; pO₂, partial pressure of oxygen; pCO₂, partial pressure of carbon dioxide; AKI, acute kidney injury.

Table 2. Baseline characteristics of the matched cohort

Covariates	Matched cohort No CVP	CVP	P values
Age	68 (57-80)	69 (57-81)	0.261
Male (%)	439/823 (53.3)	432/823 (52.5)	0.730
Weight (kg)	78.5 (64-97)	79 (67-97)	0.331
Severity of illness			
SOFA score	10 (7-13)	10 (7-13)	0.273
SAPSII score	46 (36-56)	47 (36-58)	0.317
GCS score	13 (8-14)	13 (8-14)	0.715
CCI score	6 (4-8)	6 (4-8)	0.825
Interventions, n (%)			
RRT use	76/823 (9.2)	73/823 (8.9)	0.797
MV use	618/823 (75.1)	618/823 (75.1)	1.000
Vasopressor use	731/823 (88.8)	735/823 (89.3)	0.752
Comorbidities			
Myocardial infarction	152/823 (18.5)	155/823 (18.8)	0.849
Congestive heart failure	264/823 (32.1)	280/823 (34.0)	0.402
Chronic lung disease	235/823 (28.6)	234/823 (28.4)	0.956
Diabetes mellitus	253/823 (30.7)	261/823 (31.7)	0.671
Kidney disease	184/823 (22.4)	200/823 (24.3)	0.351
Malignant cancer	160/823 (19.4)	136/823 (16.5)	0.124
Severe liver disease	191/823 (23.2)	188/823 (22.8)	0.861
Vital signs			
Heart rate (bpm)	113 (97-127)	112 (98-127)	0.735
MAP (mmHg)	53 (47-59)	53 (46-58)	0.080
Respiratory rate (bpm)	29 (26-34)	30 (26-34)	0.946
Temperature (°C)	37.4 (37.1-38.2)	37.4 (37.0-38.3)	0.852
Laboratory tests			
SpO ₂	92 (88-94)	92 (89-94)	0.762
WBC (× 10 ⁹ /L)	17.5 (11.8-24.4)	17.0 (11.6-23.7)	0.228
Hemoglobin (× 10 ¹² /L)	9.5 (8.1-11.0)	9.6 (8.3-11.0)	0.202
Platelet (× 10 ⁹ /L)	153 (95-218)	154 (99-223)	0.715
Bicarbonate (mmol/L)	18 (15-21)	18 (15-21)	0.322
Bun (mg/dL)	33 (21-56)	34 (23-54)	0.309
Creatinine (mg/dL)	1.7 (1.1-2.7)	1.7 (1.2-2.7)	0.140
Lactate (mmol/L)	2.5 (1.7-4.3)	2.7 (1.7-4.8)	0.194
PH	7.28 (7.20-7.35)	7.27 (7.19-7.34)	0.122
pO ₂	44 (36-61)	44 (36-61)	1.000
pCO ₂	45 (38-54)	46 (38-54)	0.960
Urine volume (ml/24h)	1200 (595-2120)	1190 (580-2135)	0.888
AKI, n (%)	530/823 (64.4)	534/823 (64.9)	0.837

Note: CVP, central venous pressure; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; GCS, glasgow coma scale; CCI, Charlson Comorbidity Index; RRT, renal replacement therapy; MV, mechanical ventilation; MAP, mean arterial pressure; WBC, white blood cell; Bun, blood urea nitrogen; pO₂, partial pressure of oxygen; pCO₂, partial pressure of carbon dioxide; AKI, acute kidney injury.

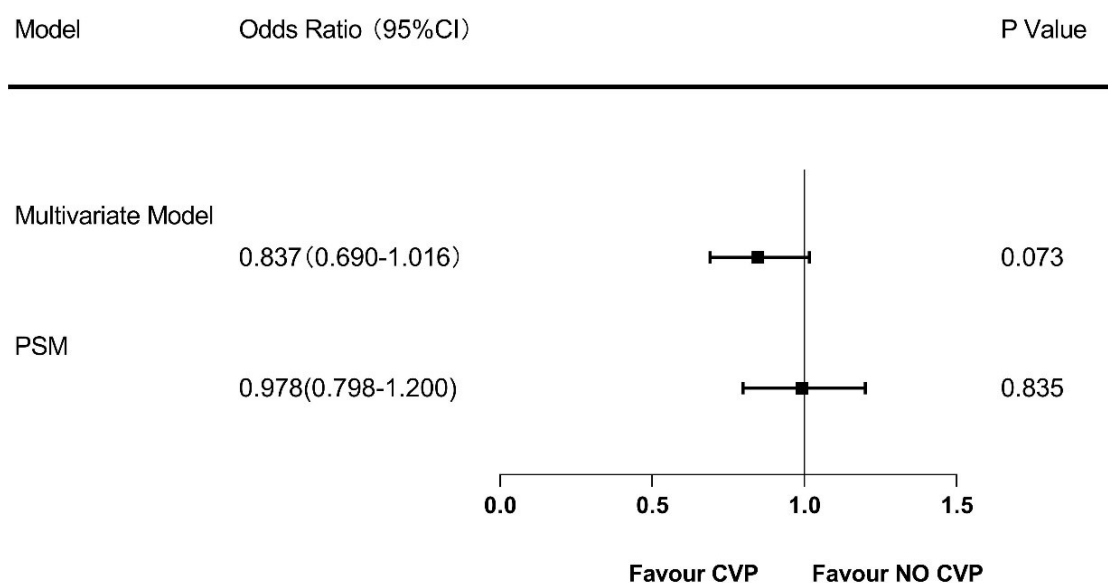


Figure 2. Association between CVP measurement and 28-day mortality. The odds ratios and 95% confidence intervals, represented by error bars, were computed in both cohorts based on the method of covariate adjustment. PSM, propensity score matching; CVP, central venous pressure.

After PSM, CVP measurement was also not associated with the in-hospital mortality (OR 0.994(95% CI 0.807-1.225), $P=0.958$), ICU mortality (OR 1.125(95% CI 0.893-1.416), $P=0.318$), 1-year mortality (OR 0.925(95% CI 0.763-1.122), $P=0.430$) and incidence of AKI within 7 days after ICU admission (OR 1.242 (95% CI 0.977-1.579), $P=0.077$). However, it is worth noting that the CVP group displayed a significantly prolonged ICU stay when compared to the no CVP group (4.4(2.7-9.2) vs. 3.6(2.1-7.5), $p<0.001$) (Figure 3, Table 3).

Discussion

The mortality rate associated with septic shock continues to be high, and prompt identification and resuscitation are crucial in mitigating patient mortality. Nevertheless, there has been a contentious debate on the necessity of CVP monitoring for patients with septic shock. In this investigation, employing PSM, we conducted an analysis which revealed that CVP monitoring significantly prolonged the ICU stay among septic shock patients. However, it did not exhibit any impact on 28-day mortality, ICU mortality, in-hospital mortality, 1-year mortality, or the incidence of AKI within 7 days after ICU admission.

Septic shock arises from diverse etiological factors that induce microvascular dilatation, extensive blood stasis within the microvessels, and subsequent plasma protein extravasation, leading to a reduction in plasma osmolality. This condition is further aggravated by plasma

extravasation, ultimately resulting in inadequate effective circulating blood volume for the affected patients [14, 15]. In the management of septic shock, expeditious and efficacious fluid therapy assumes utmost importance and is closely linked to patient prognosis [16]. Inadequate fluid therapy can lead to inadequate maintenance of circulating blood volume, thereby exacerbating the patients' condition. Conversely, excessive fluid therapy poses a potential hazard of fluid accumulation or overload, which can induce vasodilation, damage cardiomyocytes, worsen glycocalyx injury, and prolong mechanical ventilation due to the formation of pulmonary edema [17, 18]. Conducting a meticulous evaluation of intravascular volume status and organ perfusion in order to guide fluid therapy is crucial to prevent both excessive and inadequate resuscitation. CVP serves as a frequently employed clinical monitor because it is easily accessible in clinical settings. Elevated CVP often signifies a heightened likelihood of organ impairment, thereby indicating the potential occurrence of peripheral edema [19, 20]. The extent of CVP elevation was found to demonstrate a correlation with mortality rates among septic patients [21].

However, it should be noted that CVP is a static measure that is influenced by numerous confounding variables, thus limiting its ability to fully and accurately depict a patient's volume status and responsiveness. As Hiroshi et al. elucidated, veins possess thinner walls compared to arteries, rendering them more compliant [22]. Consequently, CVP exhibits

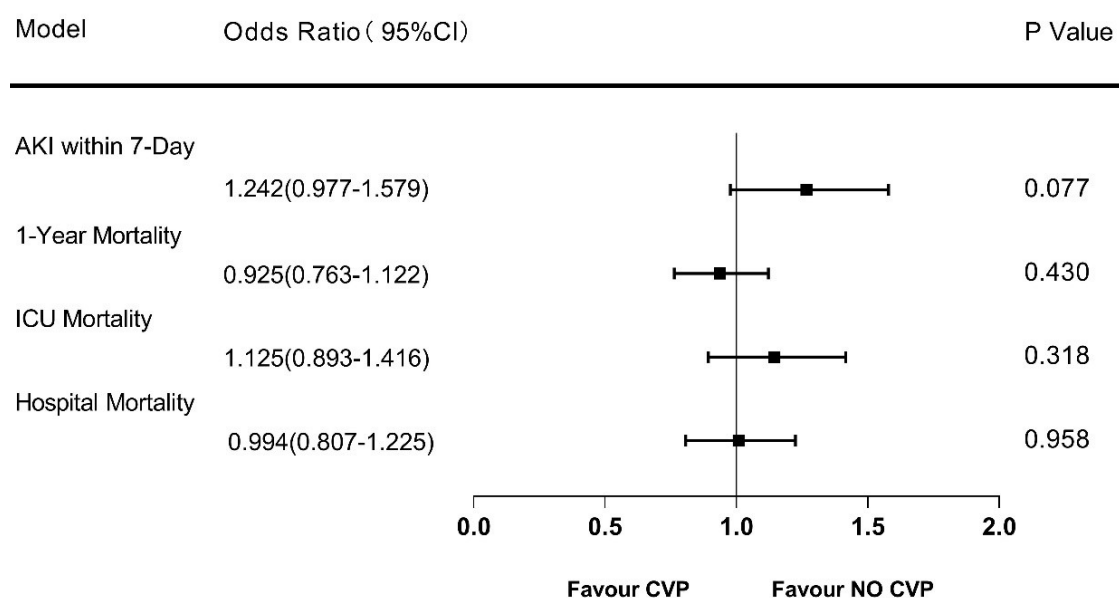


Figure 3. Association between CVP measurement and secondary outcomes. The logistic regression was utilized to calculate the odds ratios and 95% confidence intervals (error bars) in both cohorts. AKI, acute kidney injury; ICU, intensive care unit; CVP, central venous pressure.

Table 3. Clinical outcomes in PSM cohort

Outcomes	NO CVP	CVP	P value
Primary outcome			
28-day mortality	279/823 (33.9)	275/823 (33.4)	0.835
Secondary outcomes			
Hospital mortality	256/823 (31.1)	255/823 (31.0)	0.958
ICU mortality	179/823 (21.7)	196/823 (23.8)	0.318
1-year mortality	426/823 (51.8)	410/823 (49.8)	0.430
Incidence of AKI within 7 days, n (%)	640/823 (77.8)	669/823 (81.3)	0.077
Length of ICU stay	3.6 (2.1-7.5)	4.4 (2.7-9.2)	<0.001

Note: PSM, propensity score matching; CVP, central venous pressure; ICU, intensive care unit; AKI, acute kidney injury.

minimal fluctuations in response to alterations in blood volume [22]. The SSC 2021 guideline proposes the implementation of a dynamic monitoring approach to assess pertinent indicators in patients. This approach includes conducting the passive leg-raising test for cardiac output-related measurements, evaluating fluid challenge against output per beat, systolic blood pressure, pulse pressure, and observing the response of cardiac output per beat to alterations in intrathoracic pressure or positive end-expiratory pressure [12, 23, 24]. In clinical practice, CVP is typically measured through a central venous cannula, which carries the potential for complications such as infection and thrombosis, as well as the risk of unreliable CVP values due to different skill levels [25, 26]. When there is a lack of other dynamic indices to assess fluid status, it is important to consider the relationship between CVP and cardiac output. Only when there is a small change in CVP and an increase in cardiac output can it be

inferred that the patient is responsive to fluid. CVP should not be considered as the primary target for fluid administration, but rather as a safety indicator. When CVP values are higher, discontinuing fluid infusion is often beneficial as it indicates the risk of capillary fluid leakage and organ edema. However, there is no precise range for CVP values, and setting the CVP value too high can expose patients to the risk of fluid accumulation.

The most recent guidelines have discontinued the endorsement of CVP-guided fluid resuscitation for patients with septic shock. Our research findings revealed that the implementation of CVP monitoring not only failed to enhance the prognosis of septic shock patients, but also contributed to the extended length of ICU stays, which amplifies the economic burden on patients. Nevertheless, certain studies have validated that CVP measurement substantially diminishes mortality rates among septic shock

patients, contradicting our outcomes. There are several reasons for the observed disparities in this study compared to the study conducted by Chen et al. [27]. Firstly, Chen et al. utilized the MIMIC-III database encompassing patient data from 2001-2012, whereas this study employed the MIMIC-IV database containing patient information from 2008-2019 [27]. Additionally, the definition of septic shock has undergone multiple revisions over the past two decades, resulting in variations in the diagnosis criteria of septic shock. This study encompassed patients who met both the septic shock ICD codes and sepsis 3.0 criteria, resulting in variations in patient inclusion between the two studies.

This study is still subject to several limitations. Firstly, the utilization of a retrospective study design to examine the impact of early CVP monitoring on the survival of patients with septic shock inherently introduces limitations associated with the nature of retrospective studies and the selection bias of the target population. However, it is worth noting that patients with septic shock were identified according to the sepsis 3.0 criteria. Secondly, our study only included patients who underwent CVP monitoring within the first 24 hours of admission to the ICU, thereby excluding those who received CVP monitoring beyond this time frame. Lastly, the inclusion of patients solely from the MIMIC-IV database introduces potential bias, necessitating the need for multicenter validation, such as a prospective study or a retrospective analysis of electronic medical record systems from multiple centers.

Conclusion

In conclusion, the utilization of CVP measurement in patients diagnosed with septic shock does not result in improved prognosis. Moreover, CVP monitoring in these patients is correlated with prolonged ICU stay. Consequently, it is not recommended to administer CVP measurement for patients diagnosed with septic shock.

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