

# Measurement of central venous pressure is associated with better outcomes in septic patients: a retrospective observational study

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*central venous pressure, sepsis, lactate, 28-day mortality*

## Abstract

**Purpose:** With the proper insights, measurement of central venous pressure (CVP) can be a useful clinical aid. However, the formal utility of CVP measurement on mortality in septic patients has never been proved.

**Methods:** The Medical Information Mart for Intensive Care III (MIMIC-III) was applied to identify septic patients who had and did not have CVP measured. The primary outcome was 28-day mortality. The statistical approaches including multivariate regression, propensity score matching (PSM) and an inverse probability of treatment weighing (IPTW) and causal mediation analysis (CMA) were utilized to elucidate the relationship between CVP measurement and 28-day mortality.

**Results:** A total of 10275 patients were included in our study, of which 4516 patients (44%) had CVP measured within 24 h after ICU admission. A significant beneficial effect of CVP measurement in terms of 28-day mortality was observed (OR 0.60 (95% CI 0.51–0.70;  $p < 0.001$ )). Patients in CVP group received more fluid on day 1, had a shorter duration of mechanical ventilation and vasopressor use, and the reduction of serum lactate was higher than that in the no CVP group. The mediation effect of serum lactate reduction was significant for the whole cohort ( $p = 0.04$  for average causal mediation effect (ACME)) and patients in the CVP group with an initial CVP level below 8mmHg ( $p = 0.04$  for ACME).

**Conclusion:** CVP measurement is associated with a lower risk-adjusted 28-day mortality among patients with sepsis, which is proportionally mediated through serum lactate reduction.

## Introduction

Sepsis is one of the major problems in the intensive care unit (ICU) settings that accounts for about 30–50% of short term mortality [1, 2]. Hemodynamic monitoring plays a critical role in the management of sepsis. Previous guidelines have recommended the central venous pressure (CVP) to guide fluid therapy during the resuscitation phase of sepsis [3]. While studies regarding CVP as an indicator of volume status or fluid responsiveness were disappointing [4–6]. However, CVP remains to be widely used in clinical practice despite that the latest guidelines hadn't recommended CVP to guided fluid administration in sepsis any more [7, 8].

CVP gives an indication of the interaction between heart and venous return [9]. Hence, the change of CVP and cardiac output (CO) should be combined to titrate fluid administration in septic patients [10, 11], minimal changes in CVP with increases in CO could indicate fluid responsiveness. Besides, since the CVP is the backpressure to extrathoracic organs, CVP can be used as a safety variable during the fluid challenge [12]. According to 137 septic patients, Legrand et al. [13] found that the increased CVP value during the first 24 hours of admission was associated with the risk of developing new or persistent acute kidney injury (AKI). What's more, the waveform of CVP gives more about inspiratory effort, compliance of chest wall and right ventricular, and the likelihood of cardiac tamponade etc., which could provide important information for clinicians [14]. With the proper insights, measurement of CVP can be a useful clinical aid. However, the formal utility of CVP measurement on mortality in septic patients has never been proved.

The mediation effects of CVP measurement on mortality are equally important. Therapeutic interventions triggered by CVP measurement aimed at providing adequate oxygen availability and revising tissue hypoperfusion [15]. Elevated lactate levels in sepsis is a predictor of poor clinical outcome as a biomarker of tissue hypoperfusion, and reduction of lactate level seems to be associated with reduced mortality in critically ill patients [16]. The Causal mediation analysis (CMA) [17] was used to investigate the mediation effects of lactate reduction on CVP measurement in terms of mortality.

In present study, we aimed at elucidating the effect of CVP measurement on 28-day mortality in septic patients. We hypothesized that CVP measurement was associated with a lower 28-day mortality, and proportionally mediated through the reduction of lactate.

## Methods

### **Study Design**

We conducted a retrospective cohort study based on a large US-based critical database named Medical Information Mart for Intensive Care III (MIMIC-III) [18]. The MIMIC-III (v1.4) contains comprehensive and high-quality data of well-defined and characterized ICU patients admitted to ICUs at the Beth Israel Deaconess Medical Center between 2001 and 2012. One author (HC) obtained the

access of database and was responsible for the data extraction (certification number 27252652). Our study was complied with the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement [19].

### **Selection of participants**

Patients in the MIMIC-III fulfilled the definition of sepsis were eligible for inclusion. The diagnoses of sepsis were consistent with the third sepsis definition [20], briefly, patients with documented or suspected infection and an acute change in total SOFA score  $\geq 2$  points. Infection was identified from the ICD-9 code in the MIMIC-III. We excluded patients who were younger than 18 years or stayed less than 24 h in the ICU. Additionally, we only analyzed the first ICU stay for patients who were admitted to the ICU more than once. Included patients in whom initial CVP measurements were completed within 24 h after ICU admission were divided into CVP group, and the rest of patients making up the no CVP group.

### **Variable extraction**

The primary exposure was whether the patients had measurements of CVP, time to initial CVP measurement and the initial level of CVP were collected. Baseline characteristics within the first 24 h after ICU admission were collected using structured query language (SQL): age, gender, weight, ICU type, severity at admission measured by Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II), and Elixhauser comorbidity score. Use of mechanical ventilation, use of renal replacement therapy (RRT), and administration of vasopressors. Vital signs including mean arterial pressure (MAP), heart rate, temperature ( $^{\circ}\text{C}$ ) and respiratory rate. Laboratory variables of white blood cell (WBC) count, hemoglobin, platelet count, lactate, pH, partial pressure of oxygen ( $\text{PO}_2$ ) and partial pressure of carbon dioxide ( $\text{PCO}_2$ ) were measured during the first 24 h of ICU stay. If a variable was recorded more than once in the first 24 h, we used the value related to the greatest severity of illness. The incidence of acute kidney injury (AKI) was also extracted, the definition of AKI was according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Comorbidities including congestive heart failure (CHF), atrial fibrillation (AFIB), chronic renal disease, liver disease, chronic obstructive pulmonary disease (COPD), stroke, and malignant tumor were also

collected for analysis based on the recorded ICD-9 codes in MIMIC-III.

## **Outcomes**

The primary outcome in present study was 28-day mortality. Secondary outcomes included in-hospital and 1-year mortality; the incidence of AKI within 7 days after ICU admission; volume (L) of intravenous fluid (IVF) during the first, second and third day in the ICU; the number of ventilator-free and vasopressor-free days within 28 days after ICU admission; and reduction in serum lactate (calculated as the difference between the maximum lactate level on day 1 and day 3).

## **Statistical analysis**

Values were presented as mean (standard deviation) or median [interquartile range (IQR)] for continuous variables as appropriate, and categorical variables as total number and percentage.

Comparisons between groups were made using  $\chi^2$  test or Fisher's exact test for categorical variables and student's t test, or Mann-Whitney U test for continuous variables as appropriate.

Multivariate regression was selected to characterize the relationship between CVP measurement and the primary outcome. Baseline variables that were considered clinically relevant or that showed a univariate relationship with the outcome ( $p < 0.10$ ) were entered into a multivariate logistic regression model as covariates, including age, gender, weight, admission period, severity scores, use of mechanical ventilation, use of RRT, use of vasopressors, comorbidities, AKI, vital signs and initial lactate level. To avoid bias induced by missing data, the analysis of the primary outcome was duplicated after multiple imputation.

Propensity score matching (PSM) and propensity score based inverse probability of treatment weighing (IPTW) were also used for adjusting the covariates to ensure the robustness of our findings [21, 22]. A multivariate logistic regression model was used to estimate the patient's propensity scores for CVP measurement. A 1:1 nearest neighbor matching was applied with a caliper width of 0.05 in present study. An IPTW model was created using the estimated propensity scores as weights. The standardized mean differences (SMDs) were calculated to evaluate the effectiveness of the PSM and IPTW. A logistic regression was then performed on the matched cohort and weighted cohort, separately.

CMA is a method for separating the total effect of a treatment into direct and indirect effects. The indirect effect on the outcome is mediated via a mediator. The analysis reports consist of the average causal mediation effect (ACME), average direct effect (ADE), and total effect. To explore whether the effect of CVP measurement on the primary outcome is proportionally mediated by the reduction of serum lactate, we used CMA to characterize the causality relationship in our retrospective study. All statistical analyses were performed using the RStudio (version 1.2.5019), and  $p < 0.05$  was considered statistically significant.

## Results

### **Baseline characteristics**

After reviewing 18592 septic patients, a total of 10275 patients were included in our study. The flow diagram of study patients is presented in Additional file 1 (Figure S1). Of the study cohort, 4516 patients (44%) had CVP measured within 24 h after ICU admission, with a median value of 11mmHg (IQR, 8-15 mmHg), the time to initial CVP measurement was 3 h (IQR, 1.6-7.8 h) (Additional file 1: Figure S2). The baseline characteristics of the CVP and no CVP groups are summarized in Table 1. Patients in the CVP group had significantly higher SOFA score (6 (4-9) vs. 4 (3-6)) and lactate level (1.9 (1.3-3.1) vs. 1.5 (1.1-2.1)) on admission. Within the first 24 h after ICU entry, the CVP group were more likely to use mechanical ventilation (74.5% vs. 34.2%) and vasopressors (31.1% vs. 4.3%).

### **Primary outcome**

The multivariate logistic regression analyses showed a significant beneficial effect of CVP measurement in terms of the 28-day mortality (Fig. 1), and the adjusted odds ratio (OR) was 0.60 (95% CI 0.51–0.70;  $p < 0.001$ ). The results were reserved after multiple imputation for missing values (Additional file 1: Table S1 and S2). After PSM and IPTW, the imbalance of covariates between the CVP and no CVP groups were significantly minimized (Additional file 1: Figure S3), and the association remained robust (Fig. 1). We also constructed a subgroup analysis to investigate patients with positive blood culture and drew the same conclusion (Additional file 1: Table S3).

### **Secondary outcomes with propensity score matched cohorts**

CVP measurement was also associated with lower risk-adjusted in-hospital mortality and 1-year

mortality, but not with AKI within 7-day after ICU admission (Fig. 2). Numerous therapeutic interventions that might account for the beneficial effects of CVP measurement were also investigated. Compared with the no CVP group, volume of IVF in the CVP group was significantly higher on day 1 (2.4 vs. 1.9 L;  $p < 0.001$ ), but no difference on day 2 and day 3. Patients in the CVP group had a shorter duration of mechanical ventilation and vasopressor use. With respect to lactate, we observed that the reduction of serum lactate between day 1 and day 3 was higher in the CVP group (1.48 vs. 1.13 mmol/L;  $p = 0.029$ ). Table 2 shows the detailed results.

After CMA, Fig. 3 showed that the reduction of serum lactate mediated 11% (95%CI 0.7%-66%;  $p = 0.04$ ) of the beneficial effect of CVP measurement ( $p = 0.04$  for ACME) in terms of 28-day mortality in septic patients.

### **Sensitivity analyses**

Considering that the initial CVP level might influence the interventions triggered by CVP measurement, we first conducted a sensitivity study to include patients with an initial CVP level below 8mmHg as the CVP group and contrasted them against the no CVP group. The beneficial effect of CVP measurement (Additional file 1: Table S4) and mediation effect of serum lactate reduction ( $p = 0.04$  for ACME) were similar with the main analysis. In addition, patients in the CVP group received more IVF on day 1 and day 2 (Additional file 1: Table S5).

We then enrolled patients with an initial CVP level above 15mmHg as the CVP group and reproduced analyses. Although CVP measurement remained associated with lower risk of 28-day mortality (Additional file 1: Table S6), but the differences in the reduction of lactate (1.53 vs. 1.64 mmol/L;  $p = 0.543$ ) and the mediation effect of serum lactate reduction ( $p = 0.08$  for ACME) were insignificant (Additional file 1: Table S7).

### **Discussion**

Our study demonstrated that CVP measurement was associated with a significant lower risk adjusted 28-day mortality for the first time, as well as hospital and 1-year mortality, whilst no association was detected on AKI within 7-day. What's more, the mediation effect of serum lactate reduction on CVP measurement in terms of 28-day mortality was noticeable.

Despite studies undertaken so far provide conflicting evidence concerning the impact of CVP on septic patients [6, 23, 24], CVP has been widely used for more than 60 years to guide fluid therapy [25]. Understanding how CVP measurement influence the clinician's decision has improved over recent years. We abandoned to target a specific CVP value due to the heterogeneity of patients; we combined the trends of CVP and CO to titrate fluid administration rather than CVP alone; we realized to maintain CVP as low as possible after initial hemodynamic stabilization; we also extracted more valid information from CVP waves to aid clinicians [26]. However, the implications of CVP measurement for septic patient outcomes have never been questioned.

In our study, SOFA score, SAPS II score, lactate level and incidence of AKI were significantly higher in the CVP group than in the no CVP group, patients in the CVP group received more mechanical ventilation and vasopressors, and the MAP was lower in the CVP group compared the no CVP group. In spite of this, we found a noteworthy lower mortality among patients in CVP group after adjustment for confounding, and the relationship was robust regardless of the initial CVP level. Consistent with the previous limited results, in a nationwide 1-day, prospective, point prevalence study, Machado et al. [1] declared that the limited of resources to treat sepsis (including reduced availability of CVP measurements) was associate with increased mortality. In conclusion, our results accentuated an essential role of CVP measurement for septic patients, and CVP measurement should not be abandoned at any time.

It's difficult to explore whether the therapeutic interventions were triggered by CVP measurement, and which interventions might account for the beneficial effect of CVP measurement in our retrospective observational study. CMA was applied to cover this shortage, we hypothesized that CVP measurement related triggers including fluid therapy could normalize lactate in septic patients with elevated lactate levels and further improved outcomes. In present study, volume of IVF on day 1 and the reduction of serum lactate between day 1 and day 3 was higher in CVP group than in no CVP group. We used CVP measurement as the treatment, the reduction of serum lactate between day 1 and day 3 as a mediator variable, and found that the effect of CVP measurement on 28-day mortality is proportionally mediated by the reduction of serum lactate.

CVP measurement related triggers may be influenced by the initial CVP level. Eskesen et al. found a clear gradient of CVP level in fluid responsiveness going from 75% at 0–5 mmHg, 55% at 6–10 mmHg, 15% from 10 to 14 mmHg, with no patient responding above 13 mmHg based on 1148 individual data sets [24]. We conducted sensitivity analyses to further understand the impact of initial CVP level on the association and mediation effect described above. For patients in the CVP group with an initial CVP level below 8 mmHg, volume of IVF within 48 after ICU admission and serum lactate reduction were higher than in the no CVP group, and the mediation effect of serum lactate reduction was significantly. While the differences in serum lactate reduction and mediation effect were insignificant for patients in the CVP group with an initial CVP level above 15 mmHg. In line with these findings, a consensus statement recommended immediate fluid resuscitation in shock states associated with very low levels of preload parameters which included CVP [27]; and an “extreme” high CVP level should not be used to predict or guide fluid resuscitation but may be used as a safety endpoint to avoid extrathoracic organ injury [26, 28, 29]. However, additional studies will be needed to determine which interventions or protective factors mediated the beneficial effect of CVP measurement in patients, especially for patients with an “extreme” high CVP level.

Our results simply reflect the truths manifest of CVP measurement in a real-world clinical practice, and confirmed the benefit of CVP measurement in septic patients despite the initial CVP level. Clinicians should not abandon the measurement of CVP but consider how to utilize the CVP in a right way.

Several limitations to the present study should be considered. First, the definition of sepsis was based on the infection and organ failure, but the diagnoses of infection were undefined [30]. Hence, we tried to include septic patients with positive blood culture results in the subgroup analysis. Second, since the MIMIC-III data ranging from 2001 till 2015, the versions of the bundles might have changed during the period, and the results may not be adapted to current practice, hence, our results were adjusted for the admission period, in MIMIC-III, we couldn't get the exact year of patients' admission, we then divided patients into two groups in terms of admission year (before 2008 and 2008–2012) and enrolled in the model. Third, there are multiple unmeasured confounders in our study which was

based on electronic healthcare records (EHR) that could mar our findings, such as different decision by clinicians after CVP measurement, and the interventions before CVP measurement, and other hemodynamic monitoring including transthoracic echocardiography, pulmonary arterial catheters in each group were also unclear. Finally, the causal relationship between CVP measurements and 28-day mortality was not explored clearly, the reduction of lactate could have nothing to do with CVP measurement [31], and CVP measurement related trigger were complex in clinical practice. These effects need to be explored in future studies.

## Conclusion

In conclusion, CVP measurement is associated with a lower risk-adjusted 28-day mortality in septic patients. The reduction of serum lactate may have mediated this effect, especially for patients with low CVP level. For patients with high CVP level, the mediation effect may be related to the reduced risk of extrathoracic organ injury.

## Declarations

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### **Ethic approval and consent to participate**

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

## Authors' contributions

Hui Chen, Zhu Zhu and Chenyan Zhao contributed equally to this work. Jun Jin and Yao Wei conceptualized the research aims, planned the analyses, and guided the literature review. Hui Chen extracted the data from the MIMIC-III database. Chenyan Zhao, Zhu Zhu participated in processing data and doing the statistical analysis. Hui Chen wrote the first draft of the paper and other authors provided comments and approved the final manuscript.

## Availability of data and material

The datasets presented in the current study are available in the MIMIC III database (<https://physionet.org/works/MIMICIIIClinicalDatabase/files/>).

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## Tables

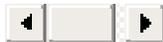
Table 1 **Comparisons of baseline characteristics between the original cohort and matched cohort**

| Covariates                             | Original cohort     |                     |       |                  |
|--|---------------------|---------------------|-------|------------------|
|  | CVP                 | No CVP              | SMD   | CVP              |
| N                                      | 4516                | 5759                |       | 2174             |
| Age                                    | 69 (56-79)          | 71 (56-82)          | 0.079 | 69 (56-80)       |
| Male (%)                               | 2473/4516<br>(54.8) | 2931/5759<br>(50.9) | 0.078 | 1131/2174 (52)   |
| Weight (kg)                            | 79.5 (66.8-95)      | 75 (62.6-90.2)      | 0.168 | 78 (65-94)       |
| Service unit, n (%)                    |                     |                     | 0.675 |                  |
| MICU                                   | 1811/4516<br>(40.1) | 3251/5759<br>(56.5) |       | 1113/2174 (51.2) |
| SICU/TSICU                             | 1213/4516<br>(26.9) | 1451/5759<br>(25.2) |       | 637/2174 (29.3)  |
| CCU/CSRU                               | 1492/4516<br>(33.0) | 1057/5759<br>(18.3) |       | 424/2174 (19.5)  |
| Admission period, n (%)                |                     |                     | 0.273 |                  |
| Before 2008                            | 2854/4516<br>(63.2) | 2868/5759<br>(49.8) |       | 1307/2174 (60.1) |
| 2008-2012                              | 1662/4516<br>(36.8) | 2891/5759<br>(50.2) |       | 867/2174 (39.9)  |
| Severity of illness                    |                     |                     |       |                  |
| SOFA score                             | 6 (4-9)             | 4 (3-6)             | 0.795 | 5 (4-7)          |
| SAPS II score                          | 43 (34-54)          | 37 (30-46)          | 0.465 | 41 (32-49)       |
| Elixhauser comorbidity score           | 7 (3-12)            | 7 (2-12)            | 0.025 | 7 (3-13)         |
| Interventions, n (%)                   |                     |                     |       |                  |
| MV use (1 <sup>st</sup> 24 h)          | 3366/4516<br>(74.5) | 1971/5759<br>(34.2) | 0.885 | 1189/2174 (54.7) |
| Vasopressor use (1 <sup>st</sup> 24 h) | 1406/4516<br>(31.1) | 246/5759 (4.3)      | 0.752 | 259/2174 (11.9)  |
| RRT use (1 <sup>st</sup> 24 h)         | 238/4516 (5.3)      | 280/5759 (4.9)      | 0.019 | 116/2174 (5.3)   |
| Comorbidities, n (%)                   |                     |                     |       |                  |
| CHF                                    | 996/4516 (22.1)     | 1296/5759<br>(22.5) | 0.011 | 535/2174 (24.6)  |
| AFIB                                   | 990/4516 (21.9)     | 1428/5759<br>(24.8) | 0.068 | 535/2174 (24.6)  |
| Chronic renal disease                  | 608/4526 (13.5)     | 1129/5759<br>(19.6) | 0.166 | 334/2174 (15.4)  |
| Liver disease                          | 405/4526 (9.0)      | 440/5759 (7.6)      | 0.048 | 183/2174 (8.4)   |
| COPD                                   | 908/4526 (20.1)     | 1272/5759<br>(22.1) | 0.049 | 477/2174 (21.9)  |
| Stroke                                 | 151/4526 (3.3)      | 231/5759 (4.0)      | 0.035 | 90/2174 (4.1)    |
| Malignancy                             | 152/4526 (3.4)      | 201/5759 (3.5)      | 0.007 | 73/2174 (7.4)    |
| Vital signs                            |                     |                     |       |                  |
| MAP (mmHg)                             | 54 (48-60)          | 58 (51-65)          | 0.358 | 55 (49-62)       |
| Heart rate (bpm)                       | 108 (94-124)        | 104 (90-119)        | 0.229 | 107 (92-122)     |
| Temperature (°C)                       | 37.7 (37.2-38.3)    | 37.4 (37-38)        | 0.260 | 37.6 (37-38.2)   |
| Respiratory rate (bpm)                 | 28 (24-33)          | 27 (24-32)          | 0.102 | 28 (24-33)       |
| Laboratory tests                       |                     |                     |       |                  |
| WBC (*10 <sup>9</sup> /L)              | 15.2 (10.8-20.8)    | 12.2 (8.7-16.9)     | 0.253 | 14.5 (10.2-19.7) |
| Hemoglobin (*10 <sup>12</sup> /L)      | 9.2 (8-10.5)        | 10.2 (8.9-11.6)     | 0.486 | 9.7 (8.5-11)     |
| Platelet (*10 <sup>9</sup> /L)         | 158 (105-231)       | 197 (133-270)       | 0.277 | 186 (126-257)    |
| Bicarbonate (mmol/L)                   | 21 (18-23)          | 23 (19-26)          | 0.435 | 21 (18-24)       |
| Bun (mg/dl)                            | 26 (17-43)          | 26 (17-42)          | 0.023 | 27 (17-44)       |
| Creatinine (mg/dl)                     | 1.3 (0.9-2.1)       | 1.2 (0.8-1.9)       | 0.009 | 1.2 (0.9-2.0)    |
| Lactate level (mmol/L)                 | 1.9 (1.3-3.1)       | 1.5 (1.1-2.1)       | 0.419 | 1.6 (1.2-2.4)    |
| pH                                     | 7.36 (7.32-7.40)    | 7.40 (7.36-7.44)    | 0.535 | 7.38 (7.33-7.42) |
| pO <sub>2</sub> (mmHg)                 | 131 (98-178)        | 109 (84-146)        | 0.345 | 117 (90-156)     |
| pCO <sub>2</sub> (mmHg)                | 39 (35-43)          | 39 (35-44)          | 0.132 | 39 (35-44)       |
| AKI, n (%)                             | 3488/4526<br>(77.2) | 3502/5759<br>(60.8) | 0.361 | 1507/2174 (69.3) |

MICU: medical intensive care; SICU: surgical intensive care unit; TSICU: trauma surgical intensive care unit; CCU: coronary care unit; CSRU: cardiac surgery unit; SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score II; MV: Mechanical ventilation; RRT: renal replacement

therapy; CHF: congestive heart failure; AFIB: atrial fibrillation; COPD: chronic obstructive pulmonary disease; MAP: mean arterial pressure; WBC: white blood cell; PO<sub>2</sub>: partial pressure of oxygen; PCO<sub>2</sub>:partial pressure of carbon dioxide; AKI: acute kidney injury.

**Table 2 Clinical outcomes analysis with propensity score matched cohorts**

| Outcomes                        | CVP              | NO CVP               | Effect size   |
|---------------------------------|------------------|----------------------|---|
| <b>Primary outcome</b>          |                  |                      |   |
| 28-Day mortality                | 396/2174 (18.2)  | 500/2174 (23)        | 0.118   |
|                                 |                  |                      |  |
| <b>Secondary outcomes</b>       |                  |                      |   |
| In-hospital mortality           | 366/2174 (16.8)  | 415/2174 (19.1)      | 0.059   |
|                                 |                  |                      |  |
| 1-Year mortality                | 789/2174 (36.3)  | 920/2174 (42.3)      | 0.124   |
| AKI within 7-day, n (%)         | 1722/2174 (79.2) | 1692/2174 (77.8)     | 0.029   |
| Volume of IVF on day 1(ml)      | 2380 (1037-4245) | 1897.5 (890-3070)    | 0.327   |
| Volume of IVF on day 2(ml)      | 997 (289.2-2150) | 1000 (268.25-1953.6) | 0.142   |
| Volume of IVF on day 3(ml)      | 605 (240-1500)   | 625 (230-1580.5)     | 0.051   |
| Vasopressor-free day in 28 days | 26.6 (25-27.4)   | 26.2 (22.9-27.2)     | 0.472   |
| Ventilation-free day in 28 days | 25.8 (22.3-27.1) | 23.3 (17.3-26.2)     | 0.291   |
| Delta-lactate                   | 1.48 (2.35)      | 1.13 (2.32)          | 0.148   |

IVF: intravenous fluid; AKI: acute kidney injury.

## Additional File

**Additional file 1: Table S1:** Percentage of missing data in the variables of interest. **Table S2:**

Association between CVP measurements and 28-day mortality with different models. **Table S3:**

Analysis for patients with positive blood culture. **Table S4:** Sensitivity analysis for patients with an

initial CVP level below 8mmHg in CVP group. **Table S5:** Clinical outcomes after sensitivity analysis

(CVP < 8 mmHg). **Table S6:** Sensitivity analysis for patients with an initial CVP level above 15mmHg

in CVP group. **Table S7:** Clinical outcomes after sensitivity analysis (CVP >15 mmHg). **Figure S1:**

Study flow diagram in present study. **Figure S2:** Distribution of time to initial CVP measurements.

**Figure S3:** Standardized mean difference (SMD) of variables before and after propensity score

matching and weighting (DOCX 1.7M).

## Figures

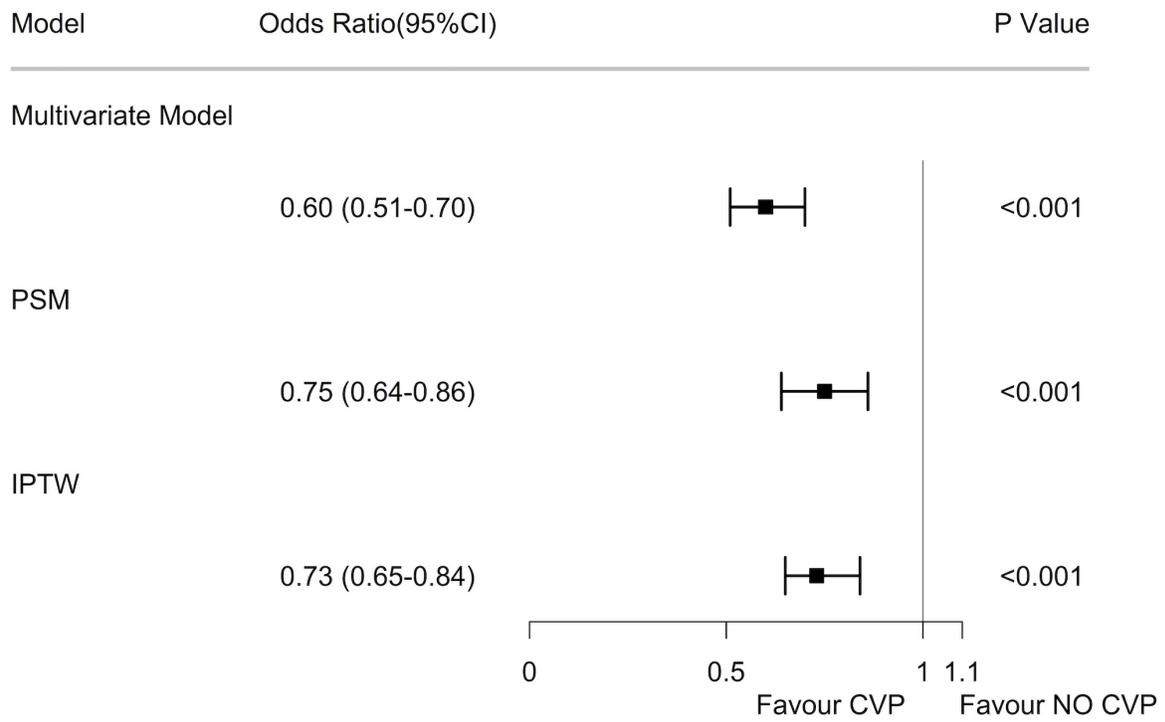


Figure 1

Association between CVP measurement and 28-day mortality. The odds ratios and 95% confidence intervals (error bars) in both cohorts were calculated dependent on method of covariate adjustment. PSM: Propensity score matching, IPTW: inverse probability of treatment weight.

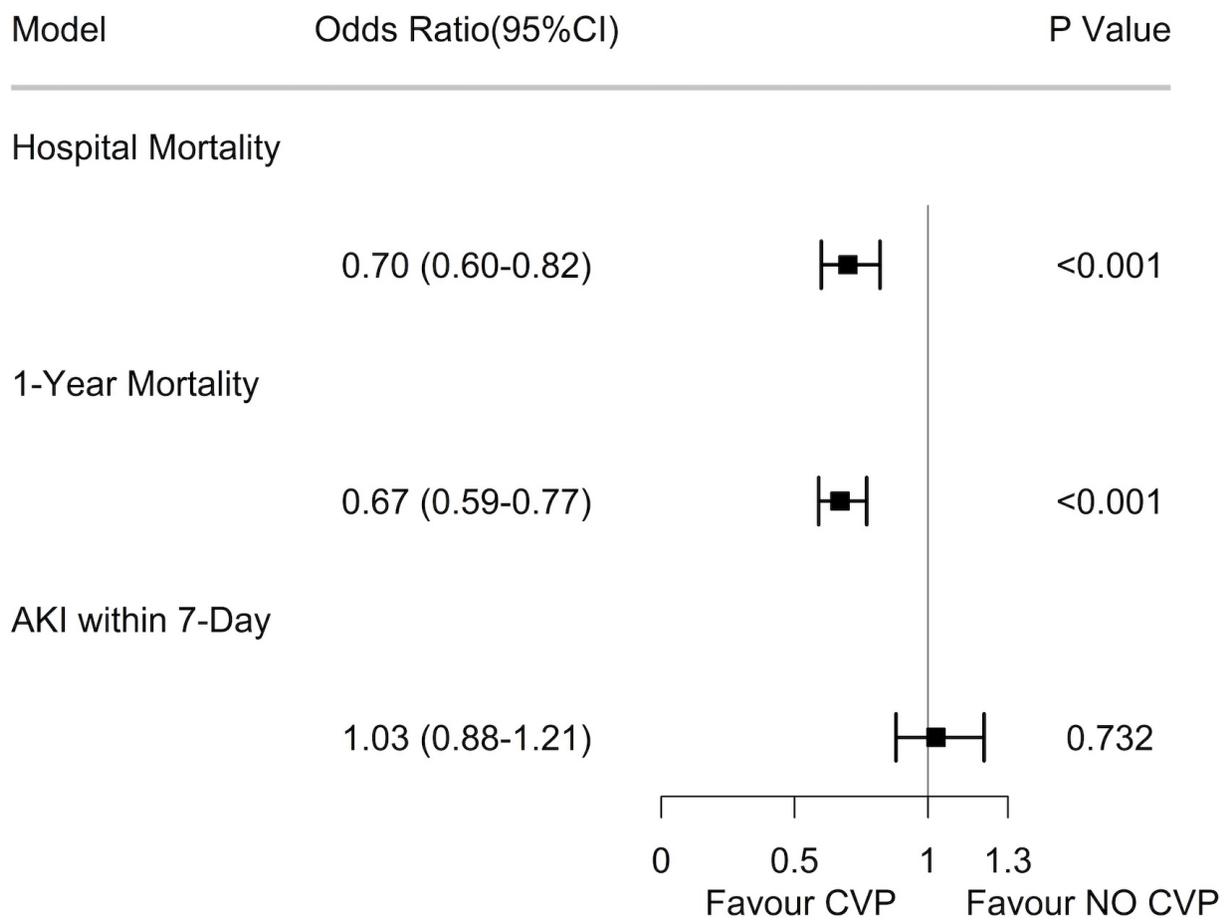


Figure 2

Association between CVP measurement and secondary outcomes. The odds ratios and 95% confidence intervals (error bars) in both cohorts were calculated from the multivariable logistic regression. AKI: acute kidney injury.

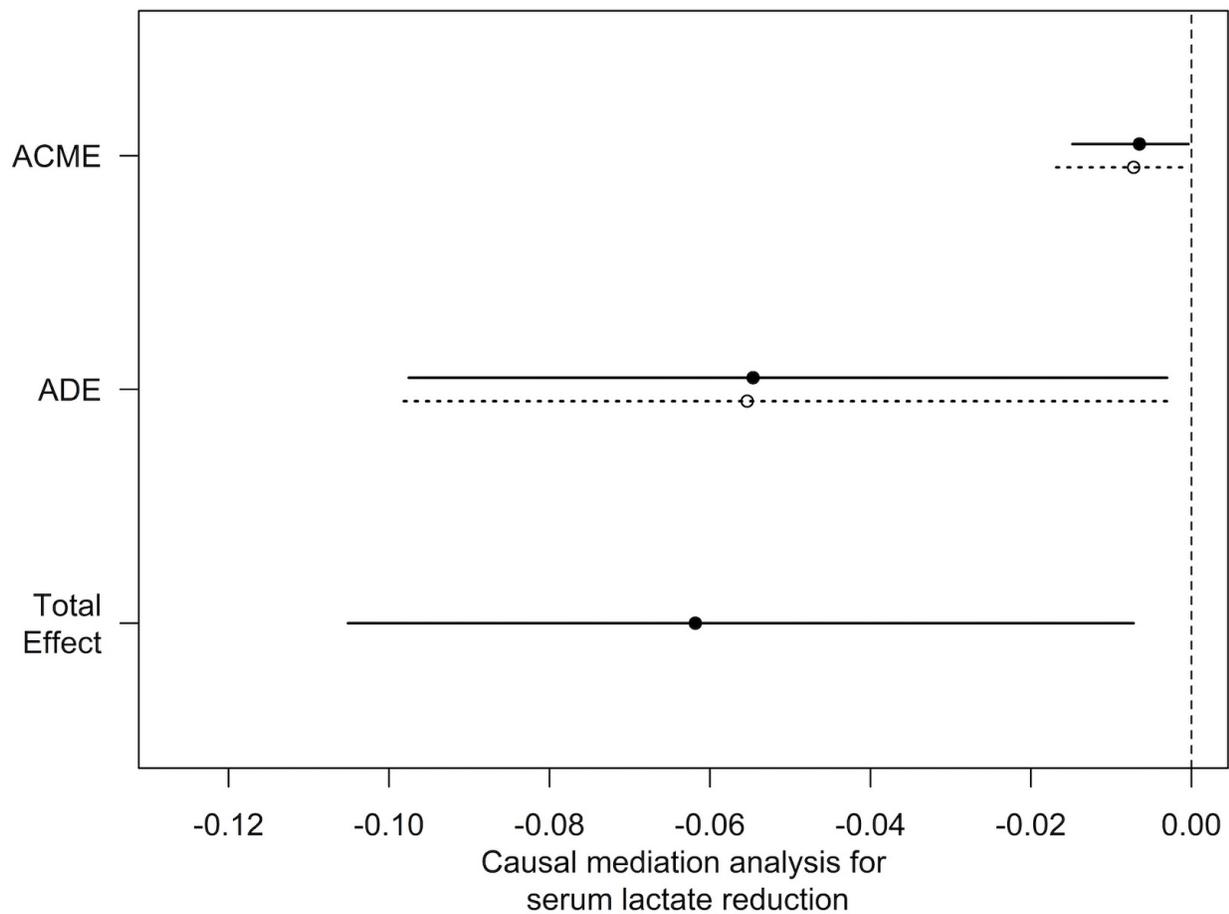


Figure 3

Causal mediation analysis for serum lactate reduction. The solid line represents the CVP group, and the dashed line represents the no CVP group.

### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Supplementary.docx