Exploring the Optimal Range of Central Venous Pressure in Sepsis and Septic Shock Patients: A Retrospective Study in 208 Hospitals

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Research

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Abstract

Background: The appropriate range of central venous pressure (CVP) in sepsis patients remains controversial. The aim of this study was to investigate the optimal CVP range in sepsis and septic shock patients admitted to intensive care unit.

Methods: We performed a retrospective study with adult sepsis patients with CVP records based on the eICU Collaborative Research Database. Cases were divided into three groups according to mean CVP level during ICU stay: low (< 8 mmHg), normal (8–12 mmHg), and high (> 12 mmHg). Baseline characteristics and clinical outcomes of three groups were compared. Multivariable logistic regression was used to assess the relationship between different CVP levels (by equal interval of 4 mmHg) and in-hospital death risk.

Results: 5302 sepsis patients were included in this study. Lactate level, serum creatinine, proportion of mechanical ventilation and dialysis were significantly higher in high CVP group compared to normal CVP group (2.6 [1.6,3.4] vs 2.2 [1.4,2.9] mmol/L; 1.5 [1,2.4] vs 1.2 [0.8,2] mg/dL; 52.2% vs 48.2%; 14.6% vs 9.7%; $p < 0.05$, respectively). In addition, high CVP group tended to have higher ICU mortality (24.8% vs 15.9%, $p < 0.05$) and hospital mortality (32.2% vs 22.4%, $p < 0.05$). The logistic regression analyses revealed that, in sepsis patients, CVP range of 12-16 mmHg, 16-20 mmHg and > 20 mmHg was related to increased in-hospital death risk compared to 8-12 mmHg level (OR: 1.349, 2.287, 3.210, respectively; 95% CI: 1.161–1.568, 1.897–2.757, 2.403–4.290, respectively); there were no significant differences between 0-4 mmHg, 4-8 mmHg and 8-12 mmHg levels regarding in-hospital death risk. Whereas in septic shock patients, CVP level of 0-4 mmHg, 12-16 mmHg, 16-20 mmHg and > 20 mmHg all contributed to increased in-hospital death risk (OR: 1.914, 1.652, 3.305, 3.554, respectively; 95% CI: 1.165–3.146, 1.299–2.101, 2.444–4.47, 2.233–5.654, respectively).

Conclusions: High CVP level (> 12 mmHg) was related to worse clinical outcomes in both sepsis and septic shock patients; while very low CVP level (< 4 mmHg) in septic shock patients was also harmful. More strict fluid administration was essential in septic shock population.

Background

Central venous pressure (CVP) is frequently measured to monitor the circulatory status of critically ill patients. As a widely used hemodynamic index, achieving a CVP > 8 mmHg is considered standard policy during fluid resuscitation (Early Goal Directed Therapy, EGDT)[1, 2]. CVP is influenced by venous return and cardiac function[3, 4]. High CVP will impede venous return to the heart in turn, which may disturb microcirculatory perfusion[5], damage organ function and increase mortality: A single center retrospective study showed that critically ill patients with a peak CVP > 12 mmHg were associated with prolonged ICU stay and worse organ function[6]. A meta-analysis also revealed that elevated CVP is associated with an increased risk of mortality and acute kidney injury in critically ill adult patients (mainly sepsis)[7]. Meanwhile, several studies also demonstrate that low CVP level may improve clinical outcomes. In septic

shock patients, a single center study found that patients whose CVP dropped to less than 8 mmHg during 7 days had survival advantage[8]. Another multicenter retrospective research enrolling 778 septic shock patients also revealed that patients with CVP < 8 mmHg had lowest mortality rate at 12 hours after ICU admissions[9]. The phenomenon elevated CVP was linked to poor clinical outcomes had caught the attention of clinical staff, nevertheless the appropriate CVP ranges in critically ill patients are still up in the air and it seemed that the association between CVP and clinical outcomes differed in subgroups.

What is the optimal CVP range in sepsis patients? Would it be different in septic shock population? In this study, we aimed to assess the association between mean CVP level and clinical outcomes in sepsis and septic shock patients, utilizing the real-world data obtained from the multi-center database for critical care research (the eICU Collaborative Research Database).

Methods

Database

We employed the eICU Collaborative Research Database for this study. The eICU database is a freely available multi-center database for critical care research with high granularity data monitored by eICU Programs for over 200,000 admissions to ICUs from 208 hospitals across the United States. After completing the Collaborative Institutional Training Initiative training course “Data or Specimens Only Research”, we have obtained approval to access the database. The up-to-date version 2.0 of eICU database was used[10].

Study Population And Data Extraction

All patients in the database were screened. The following inclusion criteria were applied: (1) age above 18 years; (2) meet the diagnosis of “sepsis”; (3) at least one CVP record during ICU stay.

Data on the following aspects were extracted: age, gender, Acute Physiology and Chronic Health Evaluation IV (Apache IV), ethnicity, admission ICU type, sepsis classification, comorbidities (hypertension, diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), heart failure, cancer, and septic shock), interventions (ventilation, dialysis, vasopressor, and antibiotics), vital laboratory test (white blood cell count, hemoglobin, platelets, glucose, lactate, blood urea nitrogen (BUN), serum creatinine (Scr), alanine aminotransferase (ALT), and aspartate transaminase (AST)), ICU length of stay (LOS), hospital LOS, ICU mortality, and hospital mortality. The database had obscured the true ages of patients over 89 years old. The median age of those patients was 91.5 years, and we used this value as a surrogate age for those patients. According to our clinical experience, a CVP value above 25 mmHg was considered as an invalid measurement and was excluded in the procedure of data extraction. Data extraction was accomplished using structure query language (SQL) by PostgreSQL tools (v12.1; PostgreSQL Global Development Group).

Exposure And Outcomes

The primary exposure in our research was the mean CVP level during ICU stay. We set the normal CVP range at 8–12 mmHg according to the description of Surviving Sepsis Campaign 2016[11]. The primary outcomes were the hospital mortality. The secondary outcomes included in-ICU mortality, ICU LOS, hospital LOS, demands for mechanical ventilation/dialysis/vasopressors and laboratory results related to organ dysfunction.

Statistical analysis

Numeration variables were expressed as absolute values and percentages; the Pearson chi-square test was used for comparisons between groups. Continuous variables are expressed as mean ± SD (standard deviation) for normally distributed data or median [interquartile range (IQR)] for non-normally distributed data. Continuous variables were compared using t test or one-way analysis of variance for normally distributed quantitative data, and Wilcoxon rank-sum test or Mann–Whitney U test for non-normally distributed quantitative data to determine differences between groups.

Kaplan–Meier survival curves of 30-day survival probability were generated with the log-rank test to determine whether survival probability differs in different mean CVP group.

Univariate analysis was carried out between survivors and non-survivors to screen variables associated with hospital mortality by Pearson chi-square test. The variables with $P < 0.2$ in the univariate analysis were included in the logistic regression model as covariates to determine the factors that impact the hospital mortality.

SPSS (version 22.0; IBM, Armonk, NY) and R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) were used for statistical analyses. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Population and baseline characteristics

As shown in Fig. 1, we extracted 5307 admissions diagnosed as “sepsis” with CVP record during ICU stay, of whom there were 5 patients aged less than 18 years. At last we included 5302 admissions for 5057 unique patients in our study population.

We stratified patients into three groups according to mean CVP level during ICU stay: low CVP group: CVP $\leq$ 8 mmHg; normal CVP group: 8 mmHg < CVP $\leq$ 12 mmHg; high CVP group: CVP > 12 mmHg. Results of the baseline characteristics of 5307 septic patients are summarized in Table 1. Compared to patients in normal CVP group, patients in high CVP group tended to be younger, owning larger proportion of CKD, COPD and heart failure and required greater demands for ventilation and dialysis. Compare to patients in

low CVP group, patients in high CVP group were associated with higher APACHE IV score, larger proportion of CKD/COPD/heart failure/septic shock and greater demands for ventilation/dialysis/vasopressor. Patients in normal CVP group were associated with younger year and greater demands for ventilation/dialysis compared to patients in low CVP group.

Table 1
Baseline characteristics of sepsis patients stratified by mean CVP level during ICU stay.

Variables	Low CVP ≤ 8 mmHg	Normal CVP (8 ~ 12] mmHg	High CVP > 12 mmHg	P
No. of patients	1423	1894	1985	
Age	70 (58, 80)[a]	67 (56, 77)[b]	65 (56, 76)[c]	< 0.001
Gender (male), n (%)	771 (54.2)[a]	920 (48.6)[b]	978 (49.3)[b]	0.003
Apache IV	72 (57, 90)[a]	75 (57, 95)[a,b]	76 (60, 96)[b]	< 0.001
ICU type, n (%)				0.013
Cardiac ICU	72 (5.1)[a]	143 (7.6)[b]	135 (6.8)[a,b]	
CCU-CTICU	85 (6)[a]	108 (5.7)[a]	132 (6.6)[a]	
CSICU	23 (1.6)[a]	24 (1.3)[a]	39 (2)[a]	
CTICU	11 (0.8)[a]	20 (1.1)[a]	10 (0.5)[a]	
Med-Surg ICU	952 (66.9)	1255 (66.3)	1316 (66.3)	
MICU	213 (15)[a]	240 (12.7)[a]	256 (12.9)[a]	
Neuro ICU	26 (1.8)[a]	21 (1.1)[a]	24 (1.2)[a]	
SICU	41 (2.9)[a]	83 (4.4)[a]	73 (3.7)[a]	
Sepsis, n (%)				< 0.001
Cutaneous/soft tissue	73 (5.1)[a]	121 (6.4)[a]	191 (9.6)[b]	
Gastrointestinal	217 (15.2)[a]	319 (16.8)[a]	295 (14.9)[a]	
Gynecologic	5 (0.4)[a]	6 (0.3)[a]	5 (0.3)[a]	
Pulmonary	545 (38.3)[a]	725 (38.3)[a]	782 (39.4)[a]	
Renal/UTI	345 (24.2)[a]	427 (22.5)[a,b]	386 (19.4)[b]	
Other/unknown	238 (16.7)[a]	296 (15.6)[a]	326 (16.4)[a]	
Comorbidities, n (%)				
Hypertension	104 (7.3)[a]	116 (6.1)[a]	147 (7.4)[a]	0.232
Diabetes	190 (13.4)[a,b]	240 (12.7)[b]	322 (16.2)[a]	0.004

Variables	Low CVP ≤ 8 mmHg	Normal CVP (8 ~ 12] mmHg	High CVP > 12 mmHg	P
CKD	140 (9.8)[a]	194 (10.2)[a]	285 (14.4)[b]	< 0.001
COPD	113 (7.9)[a]	137 (7.2)[a]	206 (10.4)[b]	0.001
Heart failure	95 (6.7)[a]	138 (7.3)[a]	224 (11.3)[b]	< 0.001
Cancer	76 (5.3)[a]	91 (4.8)[a]	105 (5.3)[a]	0.724
Septic shock	469 (33)[a]	687 (36.3)[a,b]	758 (38.2)[b]	0.007
Intervention				
Ventilation, n (%)	535 (37.6)[a]	912 (48.2)[b]	1037 (52.2)[c]	< 0.001
Dialysis, n (%)	92 (6.5)[a]	184 (9.7)[b]	290 (14.6)[c]	< 0.001
Vasopressor, n (%)	671 (47.2)[a]	955 (50.4)[a,b]	1058 (53.3)[b]	0.002
Antibiotics, n (%)	777 (54.6)[a]	1023 (54)[a]	1070 (53.9)[a]	0.914

Clinical Outcomes And Kaplan–meier Survival Analysis

We showed the main clinical outcomes of the study population in Table 2. Higher mean CVP level was associated with higher level of Scr, ALT and AST. Lactate and BUN level in high CVP group were higher than low CVP group and normal CVP group; there were no statistical significance regarding lactate and BUN level between low CVP group and normal CVP group. Patients in low CVP group owned shortest ICU LOS (3 (1.8, 5.8) days vs 3.7 (2, 7.5) days vs 3.6 (1.8, 7) days, p < 0.001); patients in high CVP group owned shortest Hospital LOS (8.5 (5, 14.3) days vs 8.6 (5, 15) days vs 8 (4.2, 14.1) days, p = 0.002). Higher level of CVP group was associated with higher ICU mortality (12.1% vs 15.9% vs 24.8%, P < 0.001). Patients in high CVP group owned highest hospital mortality (32.2%); there were no significant difference between low CVP group and normal CVP group regarding hospital mortality (20.4% vs 22.4%, P > 0.05).

Table 2
Clinical outcomes of sepsis patients stratified by mean CVP level during ICU stay.

Variables	Low CVP ≤ 8 mmHg	Normal CVP (8 ~ 12] mmHg	High CVP > 12 mmHg	P
Wbc, (10^9/L)	12 (8.8, 16.1)[a]	12.5 (9.3, 16.4)[a,b]	13 (9.3, 17.1)[b]	0.001
Hemoglobin, (g/dL)	9.8 (8.8, 11)[a]	9.8 (8.8, 11.1)[a]	9.8 (8.8, 11.2)[a]	0.586
Platelets, (K/uL)	192.7 (135.6, 260.6)[a]	188 (126.1, 252.9)[a]	173.7 (114.2, 238.2)[b]	< 0.001
Glucose, (mg/dL)	127.2 (107.3, 153.1)[a]	130.3 (110.6, 157.9)[b]	133.4 (112.5, 161.9)[b]	< 0.001
Lactate, (mmol/L)	2.2 (1.4, 2.7)[a]	2.2 (1.4, 2.9)[a]	2.6 (1.6, 3.4)[b]	< 0.001
BUN, (mg/dL)	25.5 (16, 41.5)[a]	27.6 (17.2, 42.3)[a]	31.8 (20.7, 46.5)[b]	< 0.001
Scr, (mg/dL)	1.1 (0.8, 1.8)[a]	1.2 (0.8, 2)[b]	1.5 (1, 2.4)[c]	< 0.001
ALT, (U/L)	28 (17, 57.5)[a]	32 (19, 74.5)[b]	39.2 (22, 81.6)[c]	< 0.001
AST, (U/L)	33 (20, 70.2)[a]	40.4 (23, 99)[b]	51 (27.9, 122.5)[c]	< 0.001
ICU LOS, (day)	3 (1.8, 5.8)[a]	3.7 (2, 7.5)[b]	3.6 (1.8, 7)[b]	< 0.001
Hospital LOS, (day)	8.5 (5, 14.3)[a]	8.6 (5, 15)[a]	8 (4.2, 14.1)[b]	0.002
ICU mortality, n (%)	172 (12.1)[a]	301 (15.9)[b]	493 (24.8)[c]	< 0.001
Hospital mortality, n (%)	290 (20.4)[a]	425 (22.4)[a]	640 (32.2)[b]	< 0.001

Abbreviations: CVP: central venous pressure, ICU intensive care unit, WBC: white blood cell count, BUN: blood urea nitrogen, Scr: serum creatinine, ALT: alanine aminotransferase, AST: aspartate transaminase, LOS: length of stay.

a b c: There is statistical difference in target variable between groups with the different superscript letters at the 0.05 level.

Kaplan–Meier survival curves of 30-day survival probability are shown in Fig. 2. Notable survival advantage in low CVP group and normal CVP group existed compared with high CVP group ($p < 0.001$, respectively). While there was no significant difference between low CVP group and normal CVP group ($P = 0.238$).

Hospital mortality in sepsis patients grouped by equal interval of 4 mmHg

Considering that there were no statistical differences between low CVP group and normal CVP group in hospital mortality and Kaplan–Meier survival curves of 30-day survival probability. We divided CVP level into more detailed groups by equal interval of 4 mmHg: 0–4 mmHg, 4–8 mmHg, 8–12 mmHg (normal CVP range), 12–16 mmHg, 16–20 mmHg and > 20 mmHg. As Fig. 3 showed, 4–8 mmHg group owned the lowest hospital mortality (19.7%), though no statistical difference existed between 0–4 mmHg group and 8–12 mmHg group (24.5% vs 22.4%, $P < 0.05$), and between 4–8 mmHg group and 8–12 mmHg group (19.7% vs 22.4%, $P < 0.05$). Mortalities of the other 3 groups all exceeded 8–12 mmHg group with statistical differences (27.4% vs 22.4%, 39% vs 22.4%, 45.2% vs 22.4%; $P < 0.05$, respectively).

Logistic Regression Analyses Of Hospital Mortality In Sepsis Patients

After comparing the variables between hospital survivors and non-survivors in the univariate analysis (see Supplemental Table 1), we chose age, gender, APACHE IV score, sepsis classification, Comorbidities (hypertension, diabetes, CKD, heart failure, cancer and septic shock), interventions (ventilation, dialysis, vasopressor and antibiotics) and groups of mean CVP level into the logistic regression model. In order to study the association between hospital mortality and mean CVP level, we used CVP groups by equal interval of 4 mmHg.

Our multivariate regression model revealed relations between CVP and hospital mortality (see Fig. 4): in case CVP level of 8–12 mmHg as reference (normal CVP range), when mean CVP level exceeds 12 mmHg, the odds ratio of hospital mortality increased with it: in-hospital death risk in 12–16 mmHg level was 0.349-times higher than the 8–12 mmHg level (OR 1.349, 95% CI 1.161–1.568, $P = 0.001$); in-hospital death risk in 16–20 mmHg level was 1.287-times higher than 8–12 mmHg level (OR 2.287, 95% CI 1.897–2.757, $P < 0.001$); in-hospital death risk in > 20 mmHg level was 2.21-times higher than 8–12 mmHg level (OR 3.210, 95% CI 2.403–4.290, $P < 0.001$). While there were no significant differences between 0–4 mmHg, 4–8 mmHg and 8–12 mmHg levels regarding in-hospital death risk ($P = 0.143$, $P = 0.353$, respectively). Generally, elder age or higher Apache IV score were related to increased death risk (OR 1.022, 95% CI 1.018–1.026; OR 1.021, 95% CI 1.018–1.023; $P < 0.001$, respectively). Mechanical ventilation, dialysis, use of vasopressor and comorbidity of cancer were correlated with increased death risk (OR 1.636, 95% CI 1.434–1.868, $P < 0.001$; OR 1.263, 95% CI 1.056–1.511, $P = 0.032$; OR 1.369, 95% CI 1.205–1.555, $P < 0.001$). Use of antibiotics were correlated with decreased death risk (OR 0.715, 95% CI 0.636–0.805, $P < 0.001$).

Clinical outcomes and logistic regression analyses of hospital mortality in sepsis patients with/without septic shock

In order to explore the association between different mean CVP level with clinical outcomes in sepsis patients with/without septic shock. We divided 5302 patients into septic shock population (n = 1914) and

non-septic-shock population (n = 3388) according to whether these patients underwent septic shock during hospitalization.

Supplemental Table 2 showed the clinical outcomes in septic shock patients. Similar to sepsis population, higher CVP level was associated with higher level of Lactate, BUN, Scr, ALT, AST. Patients in high CVP group owned highest ICU and hospital mortality (30.7% and 39.3%, respectively); there were no significant difference between low CVP group and normal CVP group regarding ICU and hospital mortality (17.5% vs 17% for ICU mortality; 26% vs 23.3% for hospital mortality; P > 0.05, respectively). Clinical outcomes in non-septic-shock patients (see Supplemental Table 3) also revealed the association between higher CVP level and higher level of Lactate, BUN, Scr, ALT, AST in non-septic-shock patients. ICU and hospital mortality increased with the mean CVP level gradually (9.4% vs 15.2% vs 21.2% for ICU mortality; 17.6% vs 22% vs 27.9% for hospital mortality; P < 0.05, respectively).

Table 3 showed the association between adjusted odds ratio of different mean CVP level and hospital mortality: in septic shock population, there was no significant difference in odds ratio between 4–8 mmHg and 8–12 mmHg levels (P = 0.284). While CVP in range of 0–4 mmHg, 12–16 mmHg, 16–20 mmHg and > 20 mmHg was associated with increased in-hospital death risk compared to 8–12 mmHg level (OR 1.914, 95% CI 1.165–3.146, P = 0.032; OR 1.652, 95% CI 1.299–2.101, P < 0.001; OR 3.305, 95% CI 2.444–4.470, P < 0.001; OR 3.554, 95% CI 2.233–5.654, P < 0.001). In non-septic-shock patients, there were no significant differences in death risk between 4–8 mmHg and 8–12 mmHg (P = 0.803), 0–4 mmHg and 8–12 mmHg (P = 0.063), and 12–16 mmHg and 8–12 mmHg (P = 0.131). CVP range of 16–20 mmHg and > 20 mmHg was associated with increased death risk compared to 8–12 mmHg level (OR 1.826, 95% CI 1.433–2.328; OR 3.023, 95% CI 2.082–4.390; P < 0.001, respectively).

Table 3 Association between different CVP level and hospital mortality in sepsis patients with/without septic shock.

a. Septic shock patients

CVP level	Death, n (%)	Unadjusted odds ratio	Adjusted odds ratio
0–4 mmHg	22 (30.1%)	1.421 (0.91–2.217) P = 0.194	1.914(1.165–3.146) P = 0.032
4–8 mmHg	100 (25.3%)	1.113 (0.874–1.416) P = 0.466	1.189(0.912–1.551) P = 0.284
8–12 mmHg	160 (23.3%)	1.000 (reference)	1.000 (reference)
12–16 mmHg	158 (33.1%)	1.626 (1.307–2.023) P < 0.001	1.652(1.299–2.101) P < 0.001
16–20 mmHg	104 (49.3%)	3.201 (2.442–4.197) P < 0.001	3.305(2.444–4.47) P < 0.001
> 20 mmHg	36 (52.2%)	3.593 (2.353–5.487) P < 0.001	3.554(2.233–5.654) P < 0.001

1. b. Non septic shock patients

CVP level	Death, n (%)	Unadjusted odds ratio	Adjusted odds ratio
0–4 mmHg	30 (21.6%)	0.978 (0.684–1.399) P = 0.92	1.061 (0.719–1.566) P = 0.803
4–8 mmHg	138 (16.9%)	0.725 (0.598–0.878) P = 0.006	0.793(0.645–0.973) P = 0.063
8–12 mmHg	265 (22%)	1.000 (reference)	1.000 (reference)
12–16 mmHg	185 (23.9%)	1.118 (0.934–1.339) P = 0.306	1.196(0.984–1.454) P = 0.131
16–20 mmHg	113 (32.7%)	1.724 (1.383–2.149) P < 0.001	1.826(1.433–2.328) P < 0.001
> 20 mmHg	44 (40.7%)	2.444 (1.736–3.440) P < 0.001	3.023(2.082–4.39) P < 0.001

Discussion

In this retrospective analysis based on the real-world data extracted from the multi-center database eICU, we focused on the association between mean CVP level during ICU stay with the clinical outcomes in sepsis population. We found that in sepsis patients, high mean CVP level (> 12 mmHg) was related to higher ICU and hospital mortality, higher level of Scr, ALT, AST, lactate and BNU level and greater demands for mechanical ventilation and dialysis, compared with normal CVP range (8–12 mmHg). In-hospital death risk increased with mean CVP level when CVP > 12 mmHg in sepsis population; however, in septic-shock population, both CVP < 4 mmHg and CVP > 12 mmHg were related with increased risk of in-hospital death compared with normal CVP range. Thus, our study recommended a mean CVP level not exceeding 12 mmHg in the management of sepsis patients. While a relative narrow CVP range (4–12 mmHg) was recommended in septic shock patients.

CVP is frequently used by clinicians to help determinate the status of circulating blood volume and cardiac function. Is there a safe range of CVP for sepsis and septic shock patients? The Surviving Sepsis Campaign 2012 has recommended achieving a CVP of 8 mmHg in the first 6 h of resuscitation of sepsis-induced tissue hypoperfusion[2]. Lately in 2014 and 2015, three independent, multicenter, government-funded, randomized controlled trials all concluded that no survival benefit of EGDT was found compared to usual resuscitation in severe sepsis and septic shock[12–14]. With increasing evidences demonstrating the ineffectiveness of achieving a CVP of 8 mmHg in the management of sepsis, the Surviving Sepsis Campaign 2016 no longer took this approach into recommendation[11]. In 2015, a retrospective study by Wang XT et al indicated that septic shock patients whose CVP dropped to less than 8 mmHg during 7 days after ICU admission had a higher survival rate[8]. The same study group lately demonstrate in 488 critically ill patients that exposure to higher levels of central venous pressure was associated with a poorer prognosis and worse organ function in 2017[6]. Similar articles describing the worse prognosis accompanied with high CVP level in different subgroups of critically ill population sprang up in recent years. Along with former studies, our research revealed a higher ICU and hospital mortality as well as worse organ function in sepsis patients whose CVP level > 12 mmHg, indicating that keeping a relatively low CVP level may be the correct choice in management of sepsis patients. Though CVP performed badly in reflecting blood volume or predicting fluid responsiveness[3, 4, 15], the

association between elevated CVP with worse clinical outcomes might act as a warning that clinical staff should be cautious to give massive fluid bolus to critically ill patients.

Our study also demonstrated increased in-hospital mortality risk in septic shock patients whose CVP < 4 mmHg compared with those with normal mean CVP level. At first, we divided sepsis patients into three groups by low/normal/high CVP group as former research did in the step of grouping study population. We found no statistical difference in hospital mortality and Kaplan–Meier survival curves of 30-day survival rate between low CVP group and normal CVP group; but hospital mortality in Fig. 3 showed a U-like tendency when we grouped patients into six groups by equal interval of 4 mmHg, with 4–8 mmHg group owning lowest mortality. In the step of logistic regression analysis, therefore, we divided CVP into six levels as above and set 8–12 mmHg level as reference. In our logistic regression model of septic shock patients, we found that both very low (< 4 mmHg) or high (> 12 mmHg) CVP level were related to increased in-hospital death risk. Former researches exploring the survival advantage of different CVP level tended to divide patients into three groups (low/normal/high). The association of very low CVP level and poor prognosis may be covered up by this kind of grouping method. For example, the study by Dr. Boyd concluded that at 12 hours after ICU admission, patients whose CVP < 8 mmHg had a survival advantage over those with 8–12 mmHg in septic shock patients[9]. It might convey the message that clinical staff should control the CVP level of septic shock patients as low as possible. Maintaining hemodynamic stability should be the first priority in the initial resuscitation phase of septic shock. In patients with high CVP level, fluid perfusion may compromise organ function. If CVP level is very low, an initial moderate fluid bolus is less likely to cause harm[16]. We recommended strict fluid administration in septic shock population to maintain the proper range of CVP at 4–12 mmHg based on our findings.

Our findings were partly consistent to the study based on another critical care database (MIMIC-Ⅲ) generally, which included 9090 critically ill patients[17]. They found that higher mean CVP level within 3 days after ICU admission was associated with increased 28-day mortality, prolonged duration of vasopressor treatment and mechanical ventilation, and worse organ dysfunction. Nevertheless, there were some differences between the two studies based on real-world database: first, MIMIC database is a single-center for 46,476 unique critical care patients admitted to ICUs at the Beth Israel Deaconess Medical Centre in the US from 2001 to 2012[18]; while the eICU Collaborative Research Database is a multi-center database with high granularity data for 139,367 unique patients to ICUs between 2014 and 2015 monitored by eICU Programs across the United States[10]. In our opinion, the eICU database had better generalizability owing to the nature of multi-center database. Second, Liu's study focused on the critically ill patients, while we were interested in the specific sepsis and septic shock population. Third, Liu's study demonstrated increased hazard ratio 28-day mortality in groups of higher CVP by quartiles; while our study showed increased odds ratio in-hospital mortality with higher CVP level by equal interval of 4 mmHg, and a relatively low level of CVP in septic shock population was also related to increased in-hospital death risk. There were differences in study population and statistic methods between the two big-data researches, while both studies conveyed the similar warning that clinical staff should pay attention to high CVP level and its negative impacts on critically ill patients.

There are some limitations in our study: first, due to the nature of retrospective analysis, no causal relationships could be established from our study. We could conclude that there was association between elevated CVP and wore clinical outcomes. But how to explain this phenomenon needs further research and discussion. Second, the research data came from the public database eICU. We only included patients with CVP records during ICU stay, which caused selective bias virtually. Meanwhile, the CVP value in eICU database consisted of manual records by nurses and automatic records by monitor instruments. We removed measurements of CVP above 25 mmHg and claimed them to ineffective measurements by our clinical experience. This might make contribution to bias, too. To be honest, it's hard to avoid these biases in the process of data extraction and process because of the property of Big Data research.

Conclusions

In this retrospective multi-center sepsis cohort based on public database, we observed that high CVP level (> 12 mmHg) was related to worse clinical outcomes in both septic and septic shock patients; while different from septic patients, very low CVP range (< 4 mmHg) in septic shock patients was also related to greater risk of death. More strict fluid administration was essential in septic shock patients.

Abbreviations

CVP
central venous pressure, ICU intensive care unit, Apache IV:Acute Physiology and Chronic Health Evaluation IV, CCU-CTICU:Coronary Care Unit/Cardiothoracic intensive care unit, CSICU:Cardiac Surgery intensive care unit, CTICU:Cardiothoracic intensive care unit, Med-Surg ICU:Medical-Surgical intensive care unit, MICU:Medical intensive care unit, Neuro ICU:Neurological intensive care unit, SICU:Surgical intensive care unit, UTI:urinary tract infection, CKD:Chronic kidney disease, COPD:chronic obstructive pulmonary disease.
a b c
There is statistical difference in target variable between groups with the different superscript letters at the 0.05 level.

Declarations

Ethics approval and consent to participate

Raw data in this research came from the eICU Collaborative Research Database, which was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA Certification no. 1031219-2). We gained access to the database after completion of the National Institute of Health web-based training course named "Protecting Human Research Participants" (Certification Number: 2093226).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author in response to reasonable requests.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XS and ZT participated in the study design, data extraction, statistical analysis, manuscript writing and revision. SL, JX and FH participated in data extraction and statistical analysis. XH, LT, LC, YZ, JY, XL and XG helped study design and manuscript revision. KL and CC were the guarantors of the content of the manuscript, and took full responsibility for the content of the manuscript, including data and analysis. XS and ZT contributed equally to the article and should be regarded as co-first authors. All authors read and approved the final manuscript.

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Figures

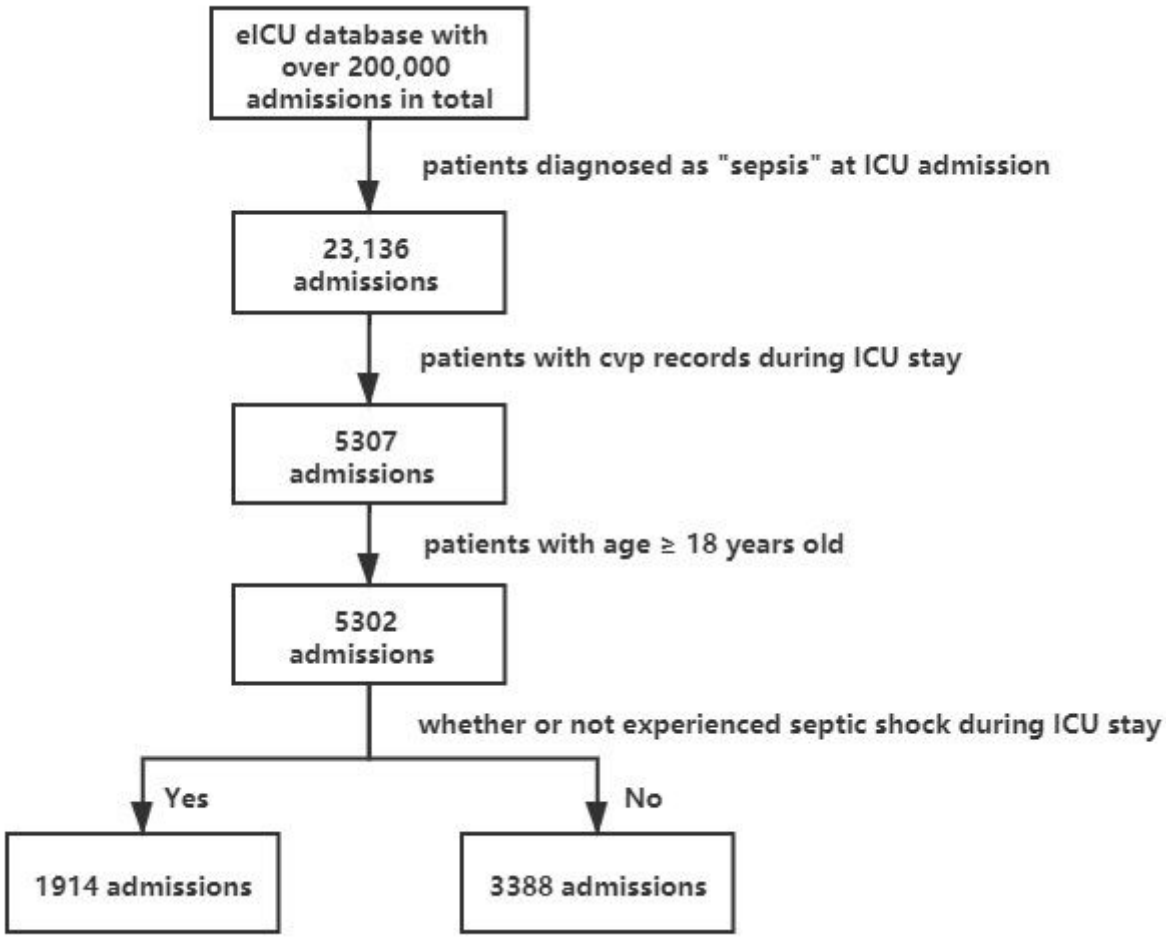

Figure 1

Flowchart of patient selection in the database.

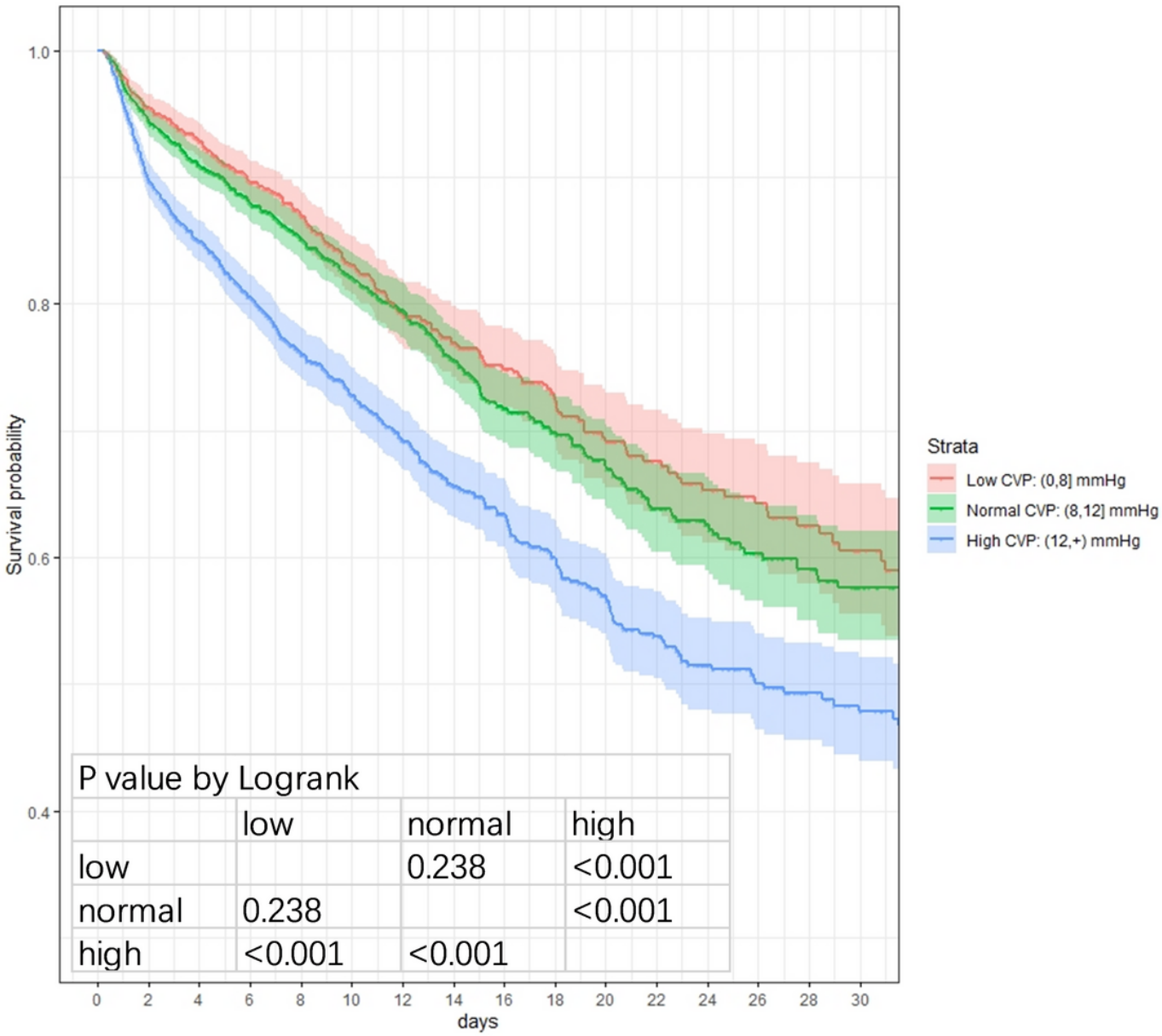

Figure 2

Kaplan-Meier Curve of 30-day survival probability of different CVP group during ICU stay. Corresponding colorful area represent the 95% confidence interval of each CVP group. (CVP: central venous pressure)

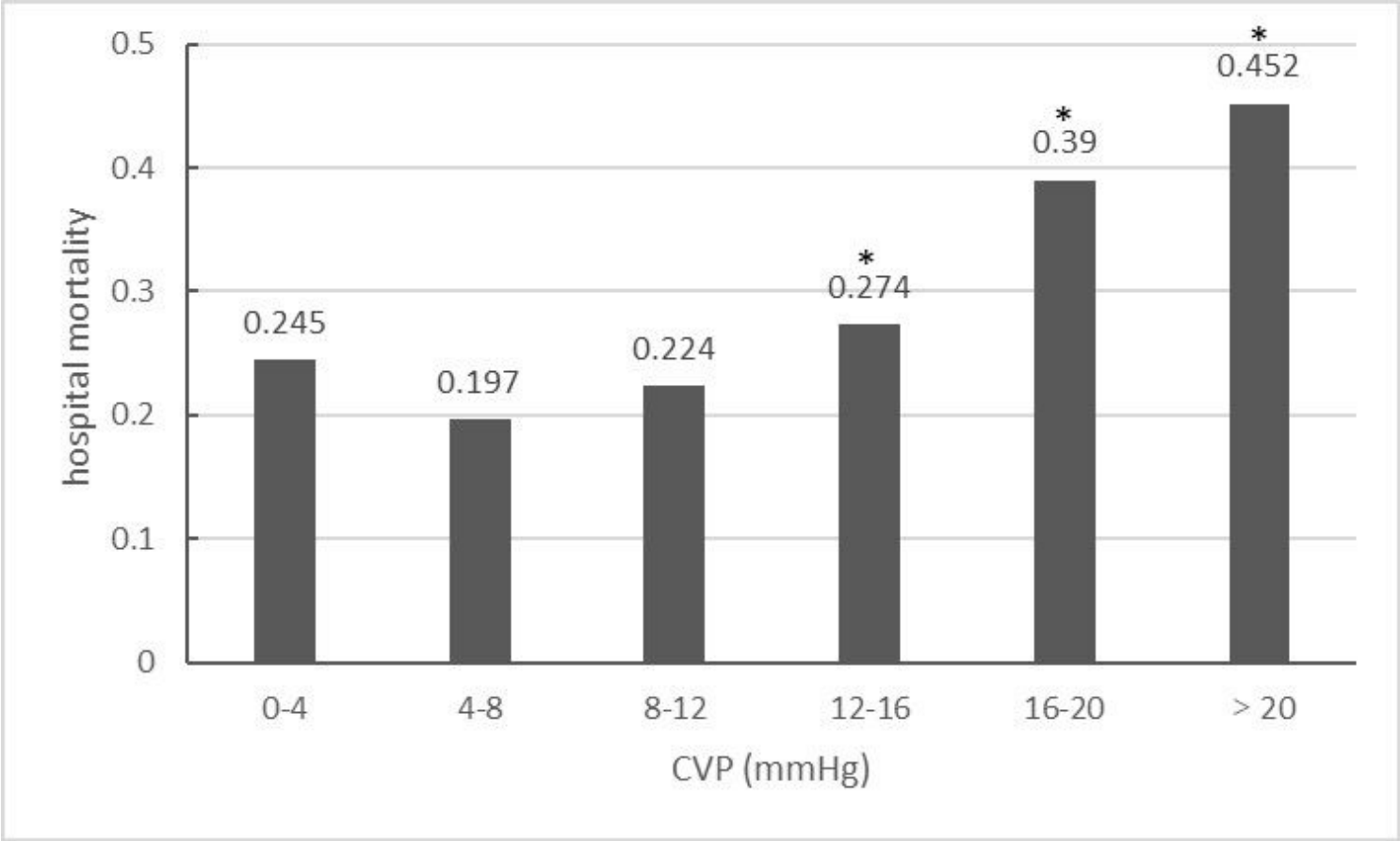

Figure 3

Hospital mortality in sepsis patients grouped by equal interval of 4 mmHg. * means that there is statistically difference between corresponding group and (8, 12] mmHg group. (CVP: central venous pressure)

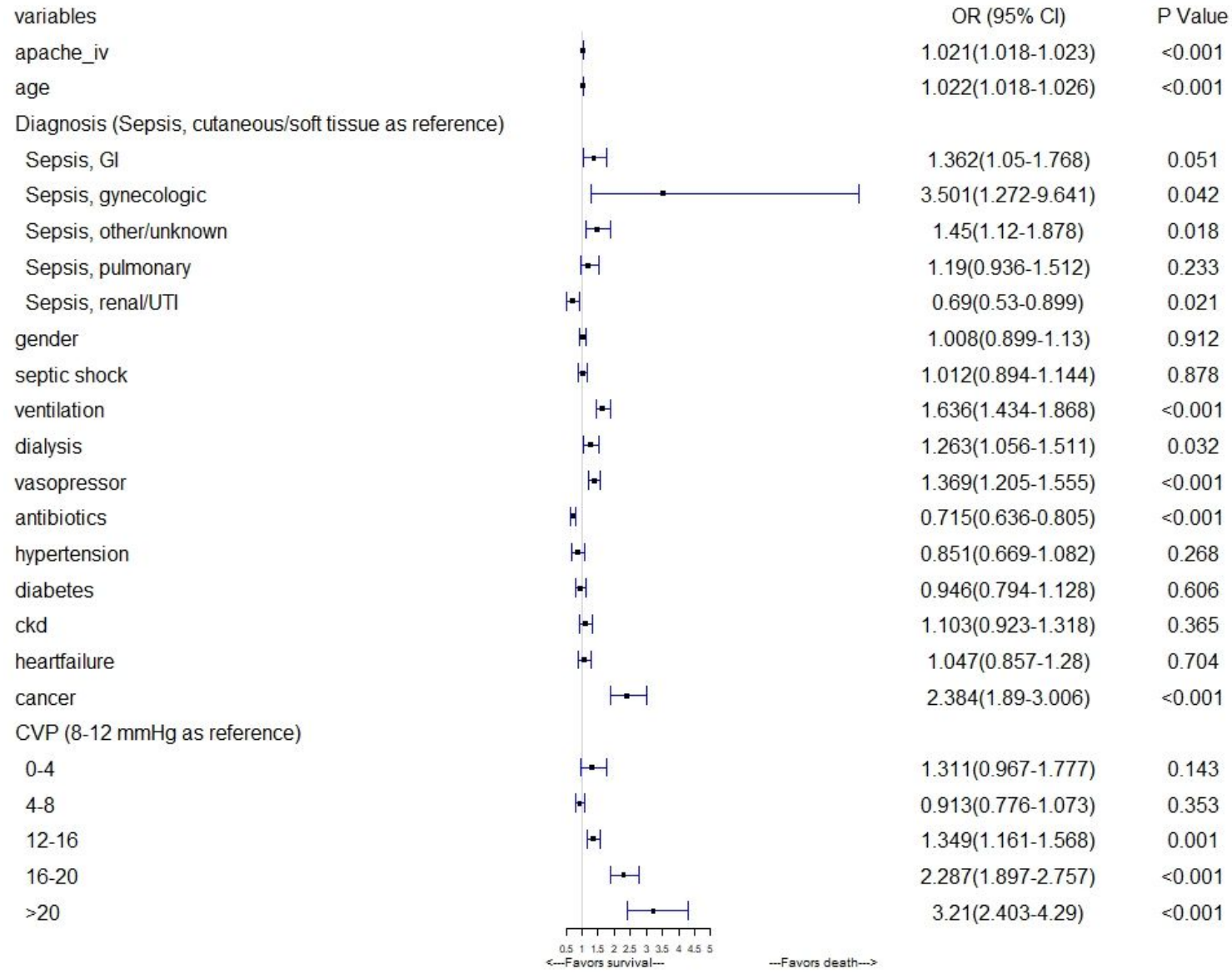

Figure 4

The multivariate logistics regression model for hospital mortality of sepsis patients. Each horizontal line represents the 95% CI range, and the small black spots in the middle of the crosses represent the OR value. (Apache IV: Acute Physiology and Chronic Health Evaluation IV, UTI: urinary tract infection, CKD: Chronic kidney disease, CVP: central venous pressure)

Supplementary Files

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- SupplementaryMaterial.docx