Central Venous Pressure and Acute Kidney Injury in Critically Ill Patients with Multiple Comorbidities: A Large Retrospective Cohort Study

Runlu Sun
Sun Yat-sen Memorial Hospital
Qi Guo
Sun Yat-sen Memorial Hospital
Junjie Wang
Sun Yat-sen Memorial Hospital
Yaoyao Zou
Sun Yat-sen Memorial Hospital
Zhiteng Chen
Sun Yat-sen Memorial Hospital
Jingfeng Wang
Sun Yat-sen Memorial Hospital
Yuling Zhang (zhyul@mail.sysu.edu.cn)
Sun Yat-sen Memorial Hospital

Research Article

Keywords: central venous pressure, acute kidney injury, KDIGO stage, critically ill patients

Posted Date: April 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-445291/v1

Version of Record: A version of this preprint was published at BMC Nephrology on February 28th, 2022.
See the published version at https://doi.org/10.1186/s12882-022-02715-9.

Central Venous Pressure and Acute Kidney Injury in Critically Ill Patients with Multiple Comorbidities: A Large Retrospective Cohort Study

Runlu Sun, MD, PhD[1,2,#]; Qi Guo, MD[1,2,#]; Junjie Wang, MS[1,2]; Yaoyao Zou, MD, PhD[3]; Zhiteng Chen, MD, PhD[1,2]; Jingfeng Wang, MD, PhD[1,2*]; Yuling Zhang, MD, PhD[1,2*]

[1]Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

[2]Guangdong Province Key Laboratory of Arrhythmia and Electrophysiology, Guangzhou, China.

[3]Department of Rheumatology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

[#] Runlu Sun and Qi Guo contributed equally to this article.

*Correspondence: Yuling Zhang, Cardiac Care Unit, Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No. 107, the West Yanjiang Road, Yuexiu District Guangzhou, China, 510120, Email: zhyul@mail.sysu.edu.cn. Fax number: +8602081332360, Telephone number: +8613751825652. Jingfeng Wang, Cardiac Care Unit, Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No. 107, the West Yanjiang Road, Yuexiu District Guangzhou, China, 510120, Email: wjingf@mail.sysu.edu.cn. Fax number: +8602081332360, Telephone number: +8618928916398.

Keywords: central venous pressure, acute kidney injury, KDIGO stage, critically ill patients

Abstract

Background: Given the traditional acceptance of higher central venous pressure (CVP) levels, clinicians ignore the incidence of acute kidney injury (AKI). The objective of this study is to assess whether elevated CVP is associated with increased AKI in critically ill patients with multiple comorbidities.

Methods: This was a retrospective observational cohort study using data collected from Medical Information Mart for Intensive Care (MIMIC-III) open-source clinical database (version 1.4). Critically ill adult patients with CVP and serum creatine measurement records were included. Linear and multivariable logistic regression were performed to determine the association between elevated CVP and AKI.

Results: A total of 11135 patients were enrolled in our study. Critically ill patients in higher quartiles of mean CVP presented greater KDIGO AKI severity stages in 2 and 7 days. Linear regression showed CVP quartile was positively correlated with the incidence of AKI within 2 (R^2=0.989, P=0.005) and 7 days (R^2=0.990, P=0.004). Furthermore, patients in the highest quartile of mean CVP had a higher risk of AKI in 7 days compared with those in the lowest quartile of mean CVP, with an OR of 2.21 (95% CI: 1.85-2.65) after adjusting for demographics, treatments and comorbidities. The adjusted odds of AKI were 1.07 (95% CI: 1.06-1.09) per 1 mmHg increase in mean CVP.

Conclusions: Elevated CVP is associated with an increased risk of AKI in critically ill patients with multiple comorbidities. The optimal CVP should be personalized and kept at a low level to avoid AKI in critical care settings.

Keywords: central venous pressure, acute kidney injury, KDIGO stage, critically ill patients

Introduction

AKI is a common complication in critically ill patients and has high morbidity and mortality [1]. Systemic and renal perfusion noticeably determines the development of AKI. However, optimal hemodynamic indicators of the risk of AKI have not been identified [2]. Although elevated fluid volume improves renal perfusion, aggressive fluid loading may lead to elevated CVP. Given the traditional acceptance of higher CVP levels [3, 4], clinicians ignore elevated CVP, and the incidence of AKI is potentially interlaced.

CVP, a local hemodynamic parameter, reflects intravascular volume and is determined by the interaction between venous return and cardiac function [5].Therefore, CVP is usually used for bedside assessment of volume status and responsiveness in critically ill patients [6]. Nonetheless, the validity of CVP in critical care settings has recently been challenged [7]. Based on the rationale provided by the Starling curves and Guyton theory on cardiac function [8], elevated CVP may impede venous return to the heart and disturb microcirculatory blood flow, harming organ function, which contributes to a poor prognosis. However, in critically ill patients with multiple comorbidities including sepsis, heart failure, arrhythmias, hypertension, diabetes or others, the association between elevated CVP and AKI remains unclear.

Until recently, studies have shown inconsistent conclusions about the association

of CVP and AKI in critically ill patients [9-11]. Herein, we sought to characterize the association of elevated CAP and AKI in critical care settings by using the large, public, deidentified clinical database MIMIC-III [12]. Specifically, we hypothesized that elevated CVP is associated with an increased incidence of AKI in critically ill patients with multiple comorbidities.

Methods

Study design

The study is a large-scale, single-center, retrospective cohort study. The overall research workflow is depicted in Fig. 1, including patient selection, data extraction, statistical analysis and conclusion. A brief description is as follows. We selected the ill critically patients from the database based on the inclusion and exclusion criteria. CVP and creatine records were then extracted from the patients selected. Next, the linear and logistical regression analysis was used to determine the association CVP and AKI. Finally, we draw a conclusion that elevated CVP is associated with an increased risk of AKI in critically ill patients with multiple comorbidities.

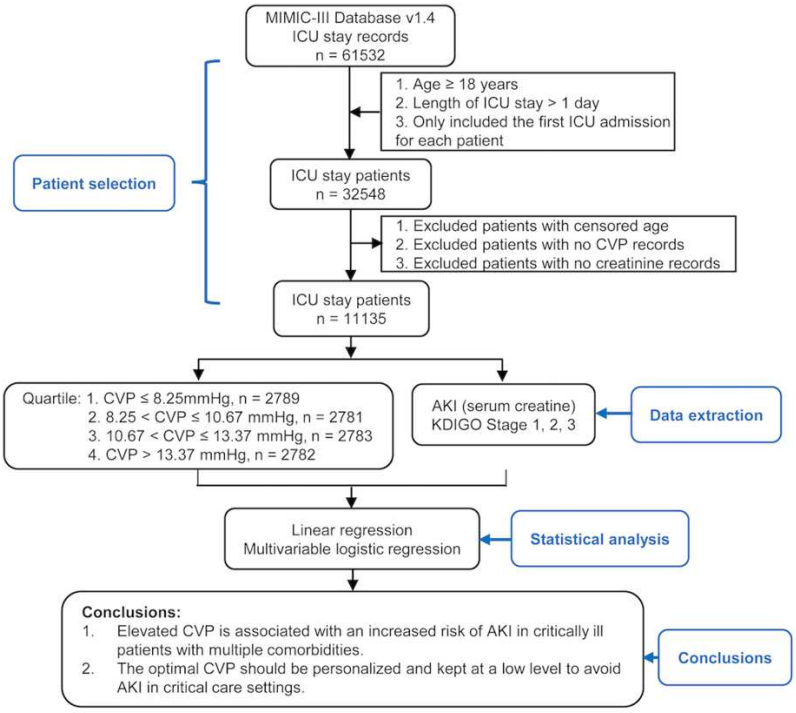

Fig. 1. Workflow and major findings of this study. ICU, intensive care unit; CVP, central venous pressure; AKI, acute kidney injury.

Data Source

We conducted a large-scale, single-center, retrospective cohort study using data collected from the MIMIC-III open source clinical database (version 1.4), which was developed and maintained by the Massachusetts Institute of Technology, Philips Healthcare, and Beth Israel Deaconess Medical Center [12]. One author (Qi Guo) obtained access to the database and was responsible for data extraction (certification number: 25233333). Information derived from the 61532 electronic medical records of critically ill patients admitted to intensive care units (ICUs) between 2001 and 2012 was included in this free, accessible database. The database was approved for research use by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and studies using the database are granted

a waiver of informed consent.

Patients

All patients in the database were screened according to the following inclusion criteria for this study: (1) adults (≥18 years of age at ICU admission) with complete medical records including available CVP and serum creatine measurement records; (2) ICU stay ≥24 h; and (3) continuous CVP monitoring for ≥24 h. For patients with multiple ICU stays, only the data for the first stay were considered.

Day 1 ICU measurement records were extracted. Other variables included age, sex, weight, blood pressure and admission illness scores (the Simplified Acute Physiology Score (SAPS) [13] and the Sequential Organ Failure Assessment (SOFA) score) [14]. Moreover, data on the use of vasopressors, sedatives, mechanical ventilation, and diuretics, and comorbidities, including sepsis, chronic heart failure (CHF), arrhythmias, hypertension, diabetes, renal failure and cancer, were extracted from the database. The comorbidities were determined from the International Classification of Disease, 9^{th} Edition, Clinical Modification (ICD-9-CM) codes.

Exposure

The primary exposure was the mean CVP during the first 24 h after ICU admission. We divided the mean CVP into four levels according to interquartile range as follows: Quartile 1, CVP ≤ 8.25 mmHg; Quartile 2, 8.25 < CVP ≤ 10.67 mmHg; Quartile 3, 10.67 < CVP ≤ 13.37 mmHg; and Quartile 4, CVP > 13.37 mmHg.

Outcomes

The primary outcome was the odds of 2-day and 7-day AKI after ICU admission. We defined AKI by serum creatine based on the KDIGO criteria[15] and categorized AKI as Stage 1 if there was a 1.5-<2x increase from baseline, a 0.3 mg/dL increase within 48 h or a urine output < 0.5 ml/kg/h for 6-12 h. Stage 2 was when there was a 2- <3x increase from baseline or a urine output < 0.5 ml/kg/h for ≥12 h, and Stage 3 was when there was a ≥ 3x increase from baseline or an increase ≥ 4.0 mg/dL or urine output < 0.3 ml/kg/h for ≥24 h. The first serum creatine measured on ICU day 1 was the "baseline".

Statistical analysis

Normally distributed continuous variables are presented as the mean ± standard deviation, while nonnormally distributed data are presented as the median (IQR, interquartile range). Categorical variables are presented as numbers (percentages). Baseline characteristics were stratified by quartiles of mean CVP during the first 24 h after ICU admission. Baseline data were compared using the analysis of variance test or rank-sum test, as appropriate, for categorical variables, and the chi-square test was used for categorical variables. We performed linear and logistic regression to compute odds ratios (ORs) for the association of mean CVP with the odds of AKI. Adjusted variables included age, male sex, weight, cardiac surgery recovery unit (CSRU), ventilation use, vasopressor use, sedative use, diuretic use, SAPS score, SOFA score, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, cancer, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

All statistical analyses were performed by using SPSS 23.0 SPSS software (V.23.0,

IBM, New York, USA) and R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Any $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among the 61532 ICU admissions in the MIMIC-III v1.4 database, 11135 patients were enrolled in our study based on the inclusion and exclusion criteria in the Methods section, as illustrated in Fig. 1. The number of patients in each quartile of the first 24 h mean CVP was approximately 2780. The mean (±SD) CVP in each quartile was 6.4±1.4 mmHg, 9.5±0.7 mmHg, 12.0±0.8 mmHg, and 16.6±3.7 mmHg in the lowest to highest quartiles, respectively. Interestingly, patients in the highest quartile of mean CVP presented the greatest weight and highest SAPS and SOFA scores. Furthermore, patients with the highest quartile of mean CVP were likely to be treated with vasopressors and diuretics and more likely to have comorbidities of sepsis, CHF, arrhythmia, hypertension and renal failure (Table 1).

Table 1. Characteristics of the enrolled subjects by CVP quartiles

	CVP				
Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
n	2789	2781	2783	2782	
CVP, mmHg	6.4±1.4	9.5±0.7	12.0±0.8	16.6±3.7	<0.001
Age, years	64.8±15.2	65.5±14.1	65.9±13.6	64.1±14.4	<0.001
Male	1709 (61.3)	1781 (64.0)	1703 (61.2)	1650 (59.3)	0.004
Weight, kg	76.3±22.1	81.7±18.6	85.2±21.0	90.4±15.1	<0.001
SBP, mmHg	116.4±14.2	113.9±12.5	112.7±12.2	110.8±12.8	<0.001

DBP, mmHg	57.7±8.8	57.7±7.8	57.1±7.7	58.2±8.5	0.016
SAPS	20.0 (17.0-22.0)	20.0 (17.0-23.0)	20.0 (18.0-23.0)	21.0 (18.0-25.0)	<0.001
SOFA	4.0 (3.0-6.0)	5.0 (3.0-7.0)	5.0 (4.0-8.0)	7.0 (5.0-10.0)	<0.001
CSRU	1308 (46.9)	1644 (59.1)	1625 (58.4)	1296 (46.6)	<0.001
Treatment					
Vasopressors	1544 (55.4)	1897 (58.2)	2023 (72.7)	2103 (75.6)	<0.001
Sedatives	1976 (70.8)	2225 (80.0)	2310 (83.0)	2264 (81.4)	<0.001
Ventilation	2104 (75.4)	2342 (84.2)	2438 (87.6)	2411 (86.7)	<0.001
Diuretics	199 (7.1)	297 (10.7)	356 (12.8)	414 (14.9)	<0.001
Comorbidities					
Sepsis	770 (27.6)	729 (26.2)	812 (29.2)	1258 (45.2)	<0.001
CHF	275 (9.9)	243 (8.7)	287 (10.3)	417 (15.0)	<0.001
Arrhythmias	287 (10.3)	248 (8.9)	287 (10.3)	423 (15.2)	<0.001
Hypertension	167 (6.0)	200 (7.2)	209 (7.5)	286 (10.3)	<0.001
Diabetes	680 (24.4)	823 (29.6)	885 (31.8)	864 (31.1)	<0.001
Renal failure	214 (7.7)	245 (8.8)	256 (9.2)	378 (13.6)	<0.001
Cancer	140 (5.0)	82 (2.9)	71 (2.6)	76 (2.7)	<0.001

Normally distributed continuous variables are presented as the mean ± standard deviation, while nonnormally distributed data are presented as the median (IQR, interquartile range). Differences in continuous variables were tested using analysis of variance or the rank-sum test as appropriate. Categorical variables were presented as numbers (percentages) and tested by the chi-square test. Quartile 1, CVP ≤ 8.25 mmHg; Quartile 2, 8.25 < CVP ≤ 10.67 mmHg; Quartile 3, 10.67 < CVP ≤ 13.37 mmHg; Quartile 4, CVP > 13.37 mmHg. CVP, central venous pressure; CSRU, cardiac surgery recovery unit; SAPS, simplified acute physiology score; SOFA, Sequential Organ Failure Assessment; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure. $P < 0.05$ was considered significant.

Elevated central venous pressure and acute kidney injury outcome in 2 days and 7 days

During the first 2 days and 7 days, 8544 and 9289 patients had AKI, respectively. The incidence of AKI in 2 days was higher among patients with higher CVP, ranging from 64.6% in patients with a mean CVP ≤ 8.25 mmHg (Quartile 1) to 87.2% in patients with a mean CVP > 13.37 mmHg (Quartile 4). A similar trend was detected between the incidence of AKI in 7 days and the mean CVP (Table 2). Moreover, patients in the higher quartiles of mean CVP presented greater KDIGO AKI severity stages in 2 days and 7 days (Table 2 and Fig. 2). Additionally, linear regression showed that CVP quartile was positively correlated with the incidence of AKI in 2 days (R^2=0.989, P=0.005) and 7 days (R^2=0.990, P=0.004) (Fig. 2).

Table 2. Incidence of AKI within 2 or 7 days according to CVP on ICU day 1

	CVP				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
AKI in 2 days					
AKI (n, %)	1802 (64.6)	2067 (74.3)	2248 (80.8)	2427 (87.2)	<0.001
Stage 1 (n, %)	620 (22.2)	692 (24.9)	597 (21.5)	509 (18.3)	<0.001
Stage 2 (n, %)	917 (32.9)	1110 (39.9)	1244 (44.7)	1159 (41.7)	<0.001
Stage 3 (n, %)	265 (9.5)	265 (9.5)	407 (14.6)	759 (27.3)	<0.001
AKI in 7 days					
AKI (n, %)	2050 (73.5)	2257 (81.2)	2422 (87.0)	2560 (92.0)	<0.001
Stage 1 (n, %)	666 (23.9)	715 (25.7)	595 (21.4)	441 (15.9)	<0.001
Stage 2 (n, %)	1030 (36.9)	1176 (42.3)	1309 (47.0)	1209 (43.5)	<0.001
Stage 3 (n, %)	354 (12.7)	366 (13.2)	518 (18.6)	910 (32.7)	<0.001

Categorical variables are presented as numbers (percentages) and tested by the chi-square test. KDIGO stage represents the severity of AKI according to the baseline measurement and the increase in serum creatinine or urine output. KDIGO Stage 1 is defined as a low severity of AKI, Stage 2 is defined as medium severity AKI, and Stage

3 is defined as high severity AKI. Quartile 1, CVP ≤ 8.25 mmHg; Quartile 2, 8.25 < CVP ≤ 10.67 mmHg; Quartile 3, 10.67 < CVP ≤ 13.37 mmHg; Quartile 4, CVP > 13.37 mmHg. Quartile 1, CVP ≤ 8.25 mmHg; Quartile 2, 8.25 < CVP ≤ 10.67 mmHg; Quartile 3, 10.67 < CVP ≤ 13.37 mmHg; Quartile 4, CVP > 13.37 mmHg. CVP, central venous pressure; AKI, acute kidney injury. $P < 0.05$ was considered significant.

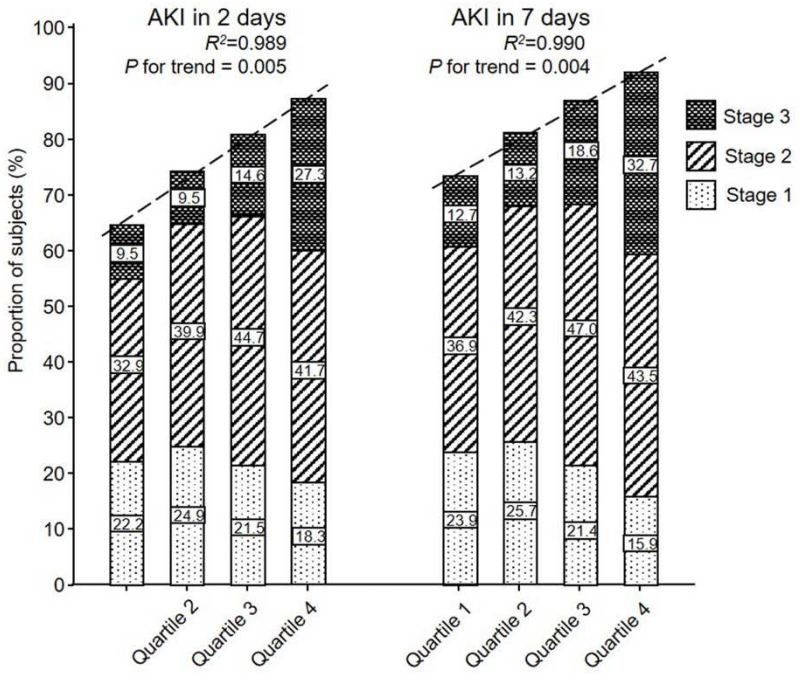

Fig. 2. Proportion of AKI patients in different CVP quartiles and correlation between quartile CVP and AKI. Proportion of patients with different AKI severity stages were shown in each group with different CVP quartiles. Linear regression was used to evaluate the association between AKI and CVP. AKI, acute kidney injury; CVP, central venous pressure. $P < 0.05$ as significance.

We further performed a logistic regression analysis to determine the association between quartiles of mean CVP and AKI outcomes in 7 days. For the crude model, patients in higher quartiles of mean CVP had a greater incidence of AKI in 7 days than those in the lowest quartile of mean CVP, ranging from OR =1.55 (95% CI: 1.37-1.76) to OR=4.16 (95% CI: 3.54-4.88). After adjusting for age, male sex, weight, CSRU,

ventilation status, vasopressor use, sedative use, diuretic use, SAPS, SOFA score, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, cancer, SBP, and DBP, the mean CVP quartile remained a significant predictor of AKI in 7 days, as shown in Fig. 3. Furthermore, the odds of AKI were 1.15 (95% CI: 1.13-1.17) times higher per 1 mmHg increase in mean CVP. After adjusting for demographics, treatments and comorbidities, the odds of AKI was 1.07 (95% CI: 1.06-1.09).

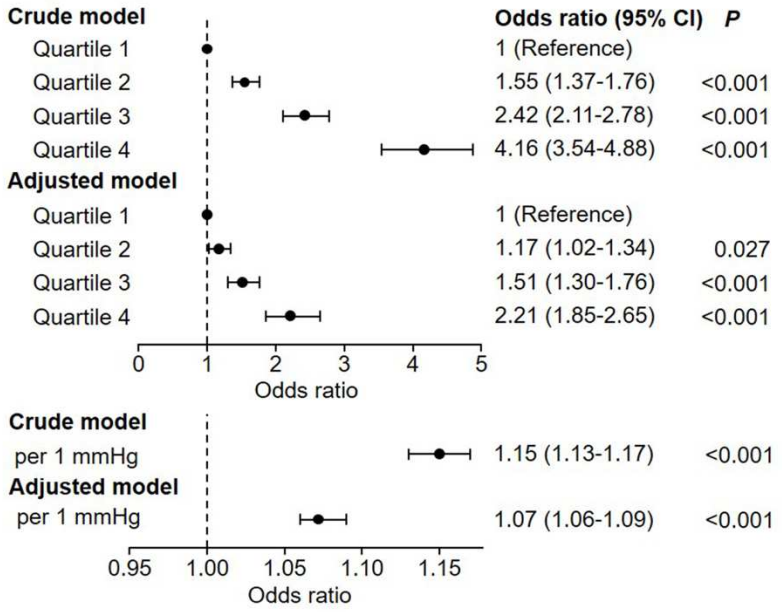

Fig. 3. Odds ratios for AKI within 7 days associated with quartile CVP in critically ill patients. Odds ratios (95% CI) were showed to evaluate the association between CVP and AKI by both crude and adjusted logistic regression model. For categorical variable, odds ratios (95% CI) were calculated compared with the lowest quartile. For continuous variable, odds ratios (95% CI) corresponded to per 1 mmHg increase of CVP. Adjusted variables included age, male, weight, CSRU, ventilation, vasopressor, sedative, diuretic, SAPS, SOFA, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, Cancer. CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval. $P < 0.05$ as

219 significance.

220 **Subgroup analysis by demographics, treatments and comorbidities**

221 Next, we determined the association between mean CVP and AKI in subgroups of
222 patients with an older age, low SBP and a history of cardiac surgery, patients treated
223 with vasopressors, diuretics and ventilation, and patients with CHF and sepsis as
224 comorbidities. Our data showed that CVP in all 11135 subjects was positively
225 correlated with AKI (Fig.4a). Additionally, 6079 elderly patients (age ≥ 65 years) had
226 higher odds of AKI when the mean CVP was more than 11 mmHg than when the mean
227 CVP=5 mmHg (Fig.4b). Moreover, 5008 subjects with SBP ≤ 110 mmHg and higher
228 mean CVPs had higher odds of AKI (Fig. 4c). Additionally, a higher mean CVP
229 (approximately CVP > 10 mmHg for diuretics and CVP> 8 mmHg for vasopressors)
230 suggested a higher incidence of AKI in patients treated with diuretics, vasopressors or
231 ventilation (Fig. 4d & 4e & 4f). However, in subjects with CHF, mean CVP was not
232 correlated with AKI (Fig. 4h). Nevertheless, an elevated mean CVP was positively
233 correlated with the incidence of AKI in patients with sepsis (approximately CVP > 12
234 mmHg) and a history of cardiac surgery (Fig. 4g & 4i).

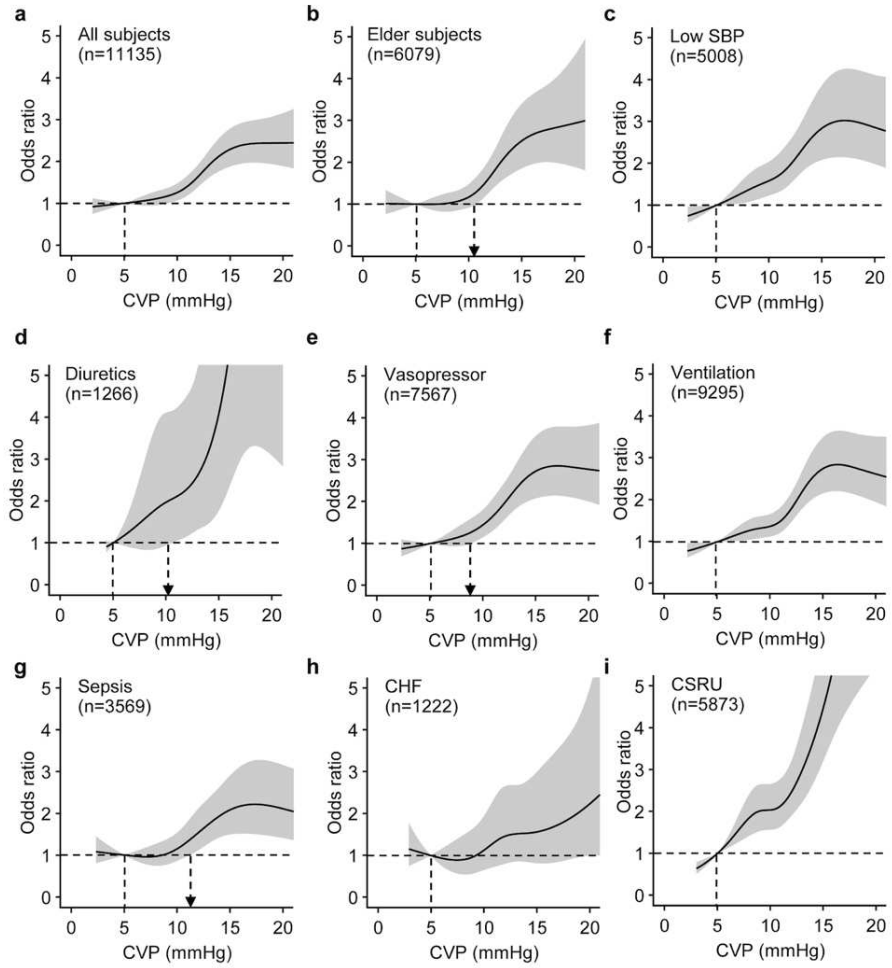

Fig. 4. Odds ratios and 95% CI for AKI within 7 days associated with CVP in subgroups. Odds ratios (solid line) and 95% CI (gray area) for AKI associated with CVP in **(a) Overall subjects. (b) Subgroup with age > 65 years. (c) Subgroup with SBP < 110 mmHg. (d) Subgroup with use of diuretics. (e) Subgroup with use of vasopressors. (f) Subgroup with use of ventilation. (g) Subgroup with sepsis. (H) Subgroup with CHF. (i) Subgroup in CSRU.** Results were calculated by adjusted restricted cubic spline model with a reference of CVP on 5 mmHg (dotted line). Adjusted variables included age, male, weight, CSRU, ventilation, vasopressor, sedative, diuretic, SAPS, SOFA, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, Cancer, SBP, and DBP. CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

Discussion

To our knowledge, this study is the first study to evaluate the association between elevated CVP and AKI in critically ill patients with multiple comorbidities from a large-scale, public, deidentified clinical database (MIMIC-III). The three principal findings are summarized as follows: (1) Elevated mean CVP is associated with an increased risk of AKI in critically ill patients; (2) A 1 mmHg elevation in CVP increases the odds of AKI in critically adult patients; (3) In critically ill patients with an older age, low SBP, a history of treatment with diuretics, vasopressors and ventilation, or comorbidities of sepsis and cardiac surgery, the mean CVP level remained a significant predictor of AKI.

Clinicians use CVP as a measure of venous congestion in critically ill patients. Indeed, CVP has been censured as an unusable measurement of venous congestion because of other variables that can alter its value, including the relative height of the intravenous catheter to that of the barometer, artificial ventilation patterns, and changes in cardiac performance [16]. Despite the valid criticism, CVP is a potentially admirable measure of venous congestion when we recognize its fluctuations due to the above variables [17].

The association between CVP and AKI has been determined previously,[18] and higher CVP is associated with poorer kidney function [9, 11, 19]. However, these findings were restricted to patients receiving diuretics, undergoing cardiac surgery and experiencing heart failure. Therefore, the association between elevated CVP and AKI remains unclear in overall critically ill patients after adjustment for demographics, treatments and comorbidities. A healthy individual has a low CVP (0-2 mmHg) [20].

Legrand et al. found a linear relationship between CVP and the incidence of AKI [21], and a meta-analysis demonstrated that a 1 mmHg increase in CVP increases the odds of AKI in critically adult patients [10], which is in line with our study. In particular, in subgroups of patients with older age, low SBP and cardiac surgery, those undergoing treatment with vasopressors, diuretics and ventilation, and those with sepsis as a comorbidity, we found that elevated CVP was still correlated with the odds of AKI. However, in subjects with CHF, the trend was not found, possibly because of the limited sample size (n=1222).

A more thorough understanding enables reevaluation of CVP as an indicator of cardiac preload and renal afterload [22, 23]. CVP is determined by the interaction between cardiac function and venous return. Based on Guyton's theory, cardiac output equals venous return, and venous reflux is dependent on the mean circulatory filling pressure (MCFP) and CVP gradient [24]. In contrast to the common, misleading understanding that CVP should be increased to increase cardiac output, excessive fluid administration, leading to the increase in CVP, does not increase cardiac output when the venous return curve intersects this area of the cardiac function curve [16]. Specifically, extra fluid only increases CVP and tissue edema but does not significantly increase end-diastolic volume or stroke volume. When CVP was increased or MCFP was decreased, venous reflux was decreased; in contrast, venous reflux was increased when CVP was decreased or MCFP was increased [25, 26]. Therefore, lower CVP is necessary to ensure venous reflux and cardiac output when MCFP is in the flat part of the Starling curve. According to this theory, a high CVP is transmitted backwards,

increasing renal venous pressure, reducing renal perfusion pressure and increasing renal venous congestion, further leading to AKI [18, 27].

Our study was based on data extracted from electronic medical records in MIMIC-III v1.4 [12], a large, open clinical database, allowing precise research on the effects of an elevated CVP load. This study is the first to characterize the association between elevated CVP and AKI in a large population of patients with multiple comorbidities managed in critical settings. Furthermore, the use of database technologies and statistics played a critical role in achieving the meaningful conclusion of the present study. Additionally, this study has several limitations. To begin with, this study is imperfect owing to its retrospective nature and the source of the data used. Hence, no valid causal relationship can be established. Next, preadmission serum creatine determinations were unavailable, and some patients may have already developed AKI on admission. Thus, the odds of AKI may have been underestimated during the ICU stay. Finally, although some predictors of disease severity were included in our study and adjusted analysis confirmed the association between elevated CVP and the incidence of AKI, the results may be affected by other confounding factors associated with AKI. Additional prospective studies should be conducted to evaluate these parameters and the potential cause of elevated CVP load.

Conclusions

In conclusion, this study found that elevated mean CVP is associated with an increased risk of AKI in critically ill patients with multiple comorbidities.

Individualizing CVP measurements and keeping CVP low should be encouraged to avoid unnecessary renal damage.

Declarations

Ethics approval and consent to participate

The database was approved for research use by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and studies using the database are granted a waiver of informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

Competing interests

The authors declared that they have no competing interests.

Funding

Runlu Sun received funding from the National Natural Science Foundation of China

(Grant number: 81700397). Qi Guo received funding from Guangdong Basic and Applied Basic Research Foundation (Grant number: 2020A1515110313), and Yat-sen Start-up Foundation of Yat-sen Start-up Foundation (YXQH202014). Yuling Zhang received funding from the National Natural Science Foundation of China (Grant number: 81970388) and the Natural Science Foundation of Guangdong Province (Grant number: 2019A1515011682), and. Jingfeng Wang received funding from National Natural Science Foundation of China (Grant number: 82070237, 81870170), Bioland Laboratory (Guangzhou Regenerative Medicine and Health Guangdong Laboratory) (Grant number: 2019GZR110406004), and the Guangzhou Science and Technology Plan Projects (Grant number: 201803040010). Yaoyao Zou received funding from National Natural Science Foundation of China (Grant number: 81801605), Guangdong Natural Science Foundation (Grant number: 2018A030313690), Guangdong Medical Scientific Research Foundation (Grant number: A2018062).

Authors' contributions

R.L.S. and Q.G. had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis; Concept and design: Y.L.Z. and J.F.W.; Analysis or interpretation of data: Q.G., J.J.W., Y.Y.Z. and Z.T.C.; Drafting of the manuscript: R.L.S. and Q.G. Statistical analysis: All authors.

Acknowledgements

We would like to thank the participants, developers and investigators associated with the Medical Information Mart for Intensive Care (MIMIC)-III database.

Authors' information

[1]Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [2]Guangdong Province Key Laboratory of Arrhythmia and Electrophysiology, Guangzhou, China; [3]Department of Rheumatology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

References

1. Kellum JA: **Why are patients still getting and dying from acute kidney injury?** *Curr Opin Crit Care* 2016, **22**(6):513-519.
2. Matejovic M, Ince C, Chawla LS, Blantz R, Molitoris BA, Rosner MH, Okusa MD, Kellum JA, Ronco C, Group AXW: **Renal Hemodynamics in AKI: In Search of New Treatment Targets**. *J Am Soc Nephrol* 2016, **27**(1):49-58.
3. Gambardella I, Gaudino M, Ronco C, Lau C, Ivascu N, Girardi LN: **Congestive kidney failure in cardiac surgery: the relationship between central venous pressure and acute kidney injury**. *Interact Cardiov Th* 2016, **23**(5):800-805.
4. Fiaccadori E: **[Fluid overload in acute kidney injury: an underestimated toxin?]**. *G Ital Nefrol* 2011, **28**(1):11.
5. Marik PE, Baram M, Vahid B: **Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares**. *Chest* 2008, **134**(1):172-178.
6. Marik PE, Cavallazzi R: **Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense**. *Crit Care Med* 2013, **41**(7):1774-1781.
7. Ho KM: **Pitfalls in haemodynamic monitoring in the postoperative and critical care setting**. *Anaesth Intens Care* 2016, **44**(1):14-19.
8. Magder S: **Bench-to-bedside review: An approach to hemodynamic monitoring - Guyton at the bedside**. *Crit Care* 2012, **16**(5).
9. Chen KP, Cavender S, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ, Danziger J: **Peripheral Edema, Central Venous Pressure, and Risk of AKI**

in Critical Illness. *Clin J Am Soc Nephrol* 2016, **11**(4):602-608.

10. Chen CY, Zhou Y, Wang P, Qi EY, Gu WJ: **Elevated central venous pressure is associated with increased mortality and acute kidney injury in critically ill patients: a meta-analysis**. *Crit Care* 2020, **24**(1).

11. McCoy IE, Montez-Rath ME, Chertow GM, Chang TI: **Central venous pressure and the risk of diuretic-associated acute kidney injury in patients after cardiac surgery**. *Am Heart J* 2020, **221**:67-73.

12. Johnson AEW, Pollard TJ, Shen L, Lehman LWH, Feng ML, Ghassemi M, Moody B, Szolovits P, Celi LA, Mark RG: **MIMIC-III, a freely accessible critical care database**. *Sci Data* 2016, **3**.

13. Le Gall JR, Loirat P, Alperovitch A, Glaser P, Granthil C, Mathieu D, Mercier P, Thomas R, Villers D: **A simplified acute physiology score for ICU patients**. *Crit Care Med* 1984, **12**(11):975-977.

14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine**. *Intensive Care Med* 1996, **22**(7):707-710.

15. Khwaja A: **KDIGO clinical practice guidelines for acute kidney injury**. *Nephron Clin Pract* 2012, **120**(4):c179-184.

16. Gelman S: **Venous function and central venous pressure - A physiologic story**. *Anesthesiology* 2008, **108**(4):735-748.

17. Magder S: **How to use central venous pressure measurements**. *Current Opinion in Critical Care* 2005, **11**(3):264-270.

18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW: **Importance of venous congestion for worsening of renal function in advanced decompensated heart failure**. *J Am Coll Cardiol* 2009, **53**(7):589-596.

19. Williams JB, Peterson ED, Wojdyla D, Harskamp R, Southerland KW, Ferguson TB, Smith PK, Milano CA, Lopes RD: **Central venous pressure after coronary artery bypass surgery: does it predict postoperative mortality or renal failure?** *J Crit Care* 2014, **29**(6):1006-1010.

20. Pinsky MR, Payen D: **Functional hemodynamic monitoring**. *Crit Care* 2005, **9**(6):566-572.

21. Legrand M, Dupuis C, Simon C, Gayat E, Mateo J, Lukaszewicz AC, Payen D: **Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study**. *Crit Care* 2013, **17**(6).

22. Magder S: **Understanding central venous pressure: not a preload index?** *Curr Opin Crit Care* 2015, **21**(5):369-375.

23. Honore PM, Jacobs R, Hendrickx I, Bagshaw SM, Joannes-Boyau O, Boer W, De Waele E, Van Gorp V, Spapen HD: **Prevention and treatment of sepsis-induced acute kidney injury: an update**. *Ann Intensive Care* 2015, **5**(1):51.

24. Magder S: **Bench-to-bedside review: An approach to hemodynamic**

monitoring--Guyton at the bedside. *Crit Care* 2012, **16**(5):236.

25. Beard DA, Feigl EO: **Understanding Guyton's venous return curves**. *Am J Physiol-Heart C* 2011, **301**(3):H629-H633.

26. Brengelmann GL: **A critical analysis of the view that right atrial pressure determines venous return**. *J Appl Physiol* 2003, **94**(3):849-859.

27. Prowle JR, Bellomo R: **Fluid administration and the kidney**. *Curr Opin Crit Care* 2010, **16**(4):332-336.

Figures

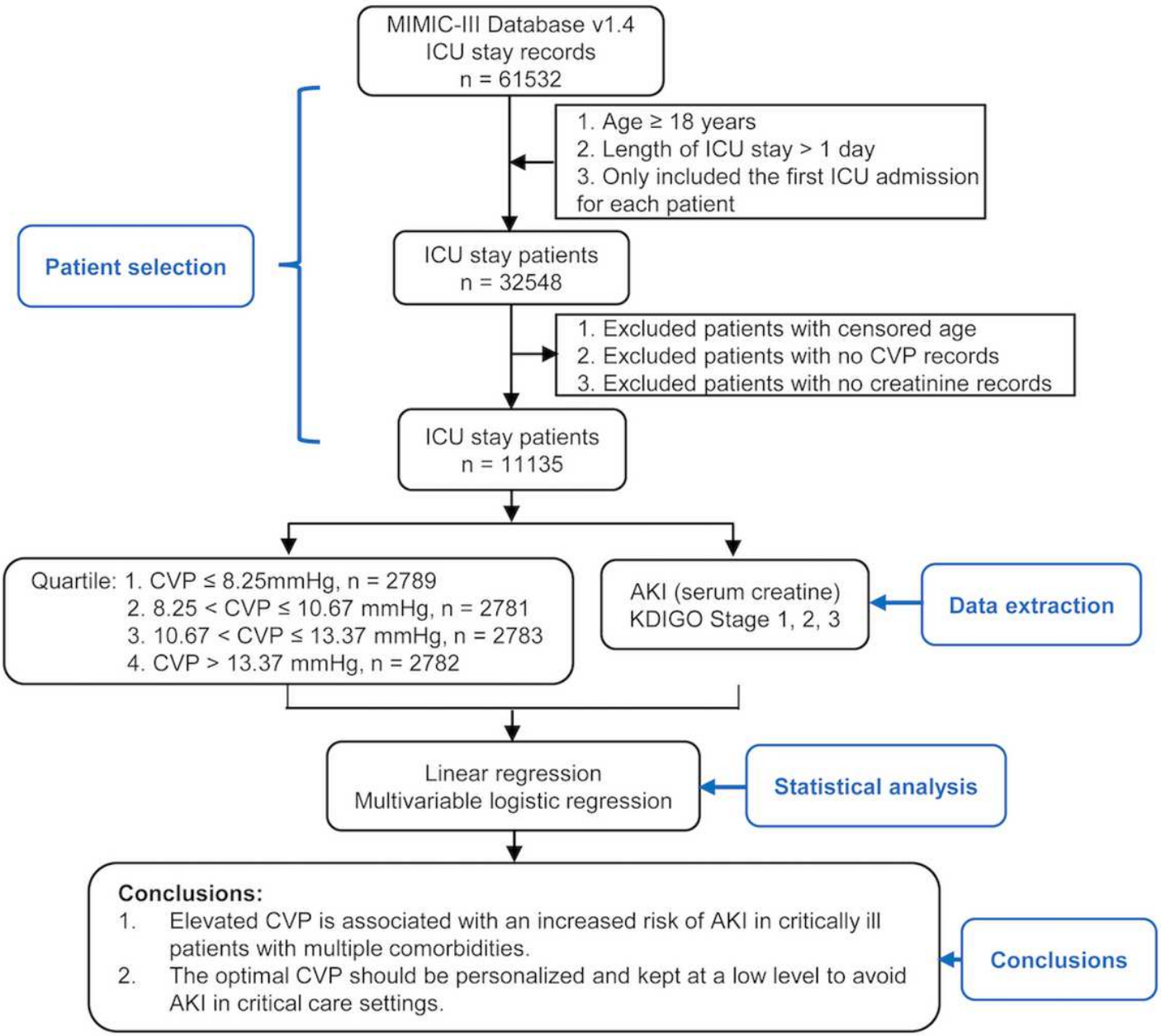

Figure 1

Workflow and major findings of this study. ICU, intensive care unit; CVP, central venous pressure; AKI, acute kidney injury.

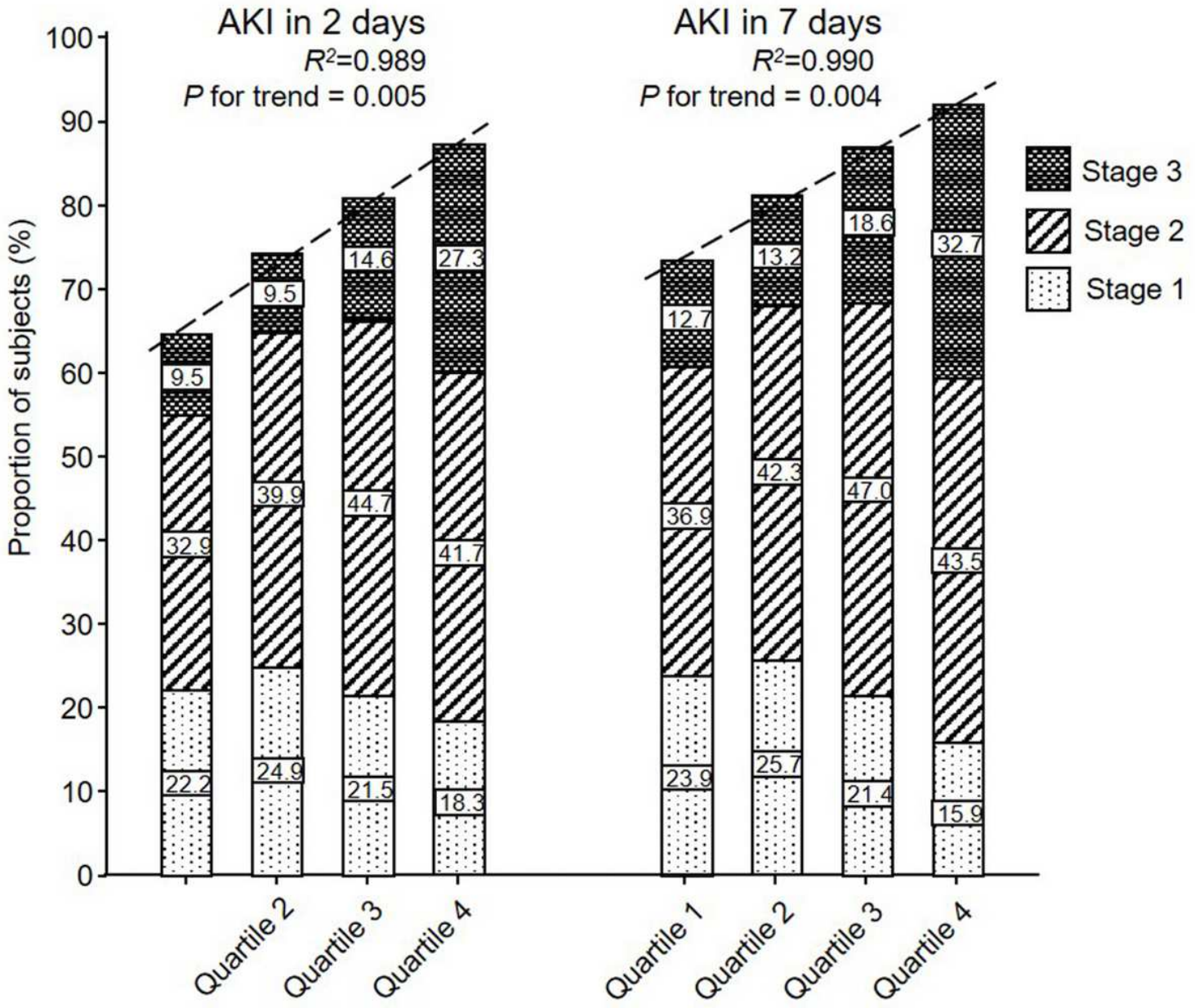

Figure 2

Proportion of AKI patients in different CVP quartiles and correlation between quartile CVP and AKI. Proportion of patients with different AKI severity stages were shown in each group with different CVP quartiles. Linear regression was used to evaluate the association between AKI and CVP. AKI, acute kidney injury; CVP, central venous pressure. $P < 0.05$ as significance.

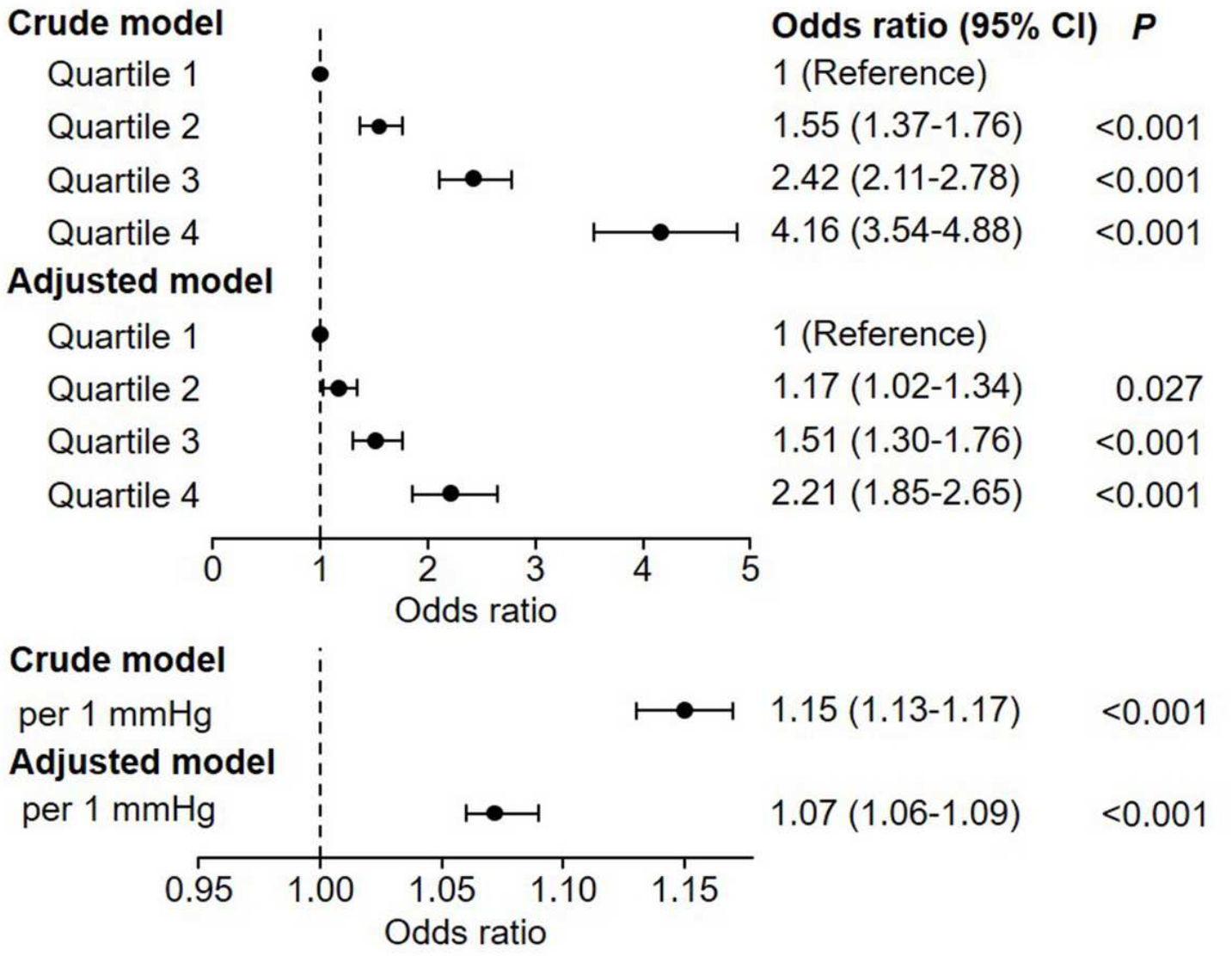

Figure 3

Odds ratios for AKI within 7 days associated with quartile CVP in critically ill patients. Odds ratios (95% CI) were showed to evaluate the association between CVP and AKI by both crude and adjusted logistic regression model. For categorical variable, odds ratios (95% CI) were calculated compared with the lowest quartile. For continuous variable, odds ratios (95% CI) corresponded to per 1 mmHg increase of CVP. Adjusted variables included age, male, weight, CSRU, ventilation, vasopressor, sedative, diuretic, SAPS, SOFA, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, Cancer. CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval. $P < 0.05$ as significance.

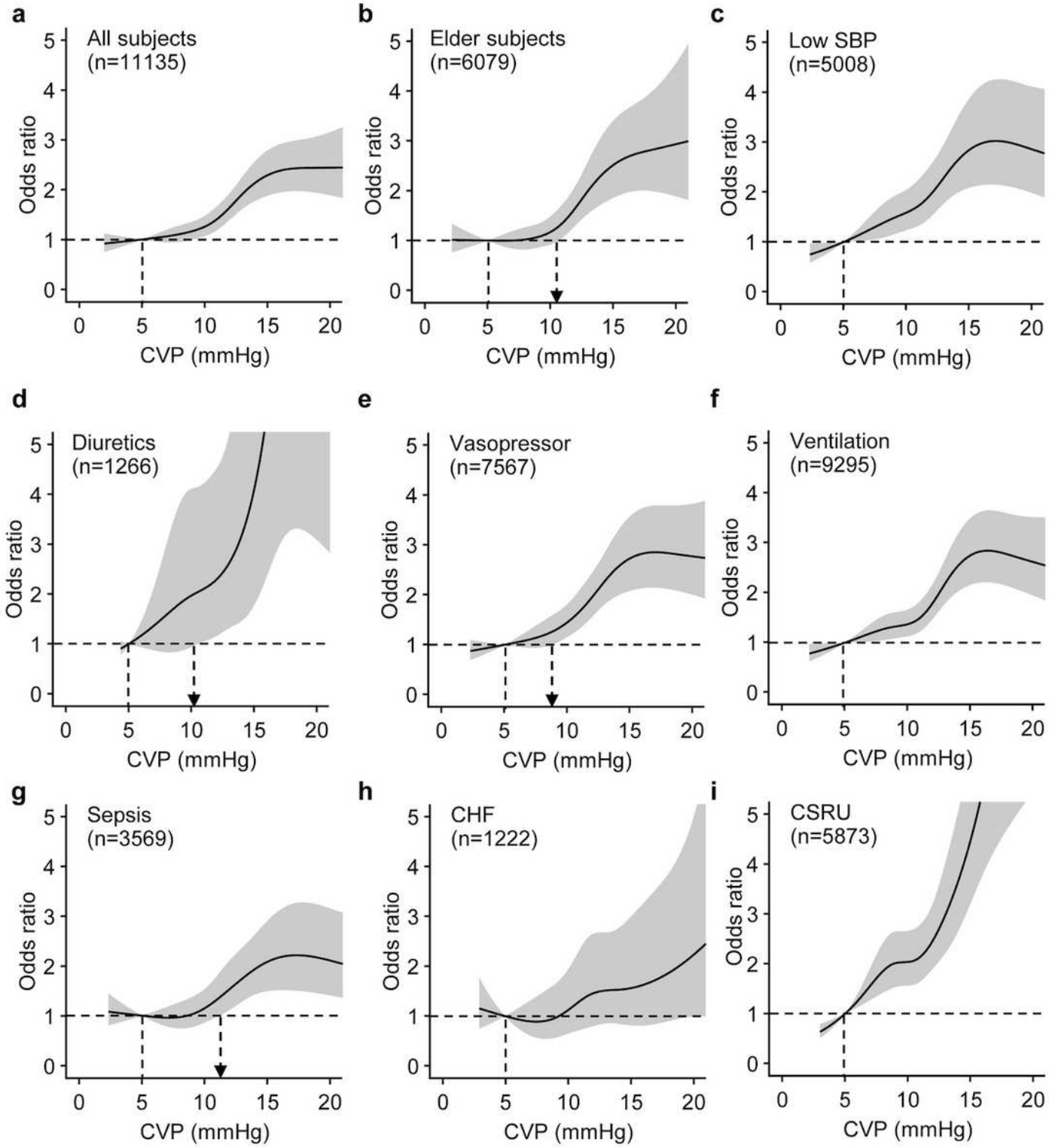

Figure 4

Odds ratios and 95% CI for AKI within 7 days associated with CVP in subgroups. Odds ratios (solid line) and 95% CI (gray area) for AKI associated with CVP in (a) Overall subjects. (b) Subgroup with age > 65 years. (c) Subgroup with SBP < 110 mmHg. (d) Subgroup with use of diuretics. (e) Subgroup with use of vasopressors. (f) Subgroup with use of ventilation. (g) Subgroup with sepsis. (H) Subgroup with CHF. (i) Subgroup in CSRU. Results were calculated by adjusted restricted cubic spline model with a reference of

CVP on 5 mmHg (dotted line). Adjusted variables included age, male, weight, CSRU, ventilation, vasopressor, sedative, diuretic, SAPS, SOFA, sepsis, CHF, arrhythmias, hypertension, diabetes, renal failure, Cancer, SBP, and DBP. CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.