

ARTICLE

An evaluation on the association of vancomycin trough concentration with mortality in critically ill patients: A multicenter retrospective study

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Abstract

To determine the impact of initial vancomycin trough concentration (VTC) on mortality in adult patients in the intensive care unit (ICU) undergoing vancomycin therapy. During their first ICU stay, patients with initial VTC records after vancomycin treatment were recruited from the eICU Collaborative Research Database to this multicenter retrospective cohort study, and classified into four groups according to VTC: less than 10, 10–15, 15–20, and greater than 20 mg/L. Multivariable logistic regression and sensitivity analyses were performed to explore the association of VTC, as a continuous and categorical variable, with mortality. This study enrolled 7220 patients from 335 different ICUs at 208 hospitals. Multivariable logistic regression models indicated that VTC was positively correlated with ICU (odds ratio [OR], 1.028, 95% confidence interval [CI], 1.019–1.037) and hospital (OR 1.028, 95% CI, 1.020–1.036) mortalities. Moreover, compared with VTC less than 10 mg/L, VTCs of 10–15, 15–20, and greater than 20 mg/L were associated with a higher risk of ICU mortality (OR, 1.330, 95% CI, 1.070–1.653; OR, 1.596, 95% CI, 1.265–2.015; and OR, 1.875, 95% CI, 1.491–2.357, respectively), and VTCs of 15–20 and greater than 20 mg/L were also correlated with increased hospital mortality (OR, 1.482, 95% CI, 1.225–1.793; and OR, 1.831, 95% CI, 1.517–2.210, respectively). Similar results persisted in patients with different Acute Physiology and Chronic Health Evaluation IV scores, creatinine clearance levels, ages, and body mass indexes. Our findings indicated a potential relationship of initial VTC with ICU and hospital mortalities in patients in the ICU. However, due to the retrospective nature of this study, future prospective studies or randomized controlled trials are needed to validate those results.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

Although monitoring vancomycin trough concentration as a feasible pharmacokinetic method was recommended for personalized vancomycin dosing by the Infectious Diseases Society of America in 2009, it remains controversial regarding the

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association of trough concentration with treatment outcomes in patients with gram-positive bacterial infection.

WHAT QUESTION DID THIS STUDY ADDRESS?

A large-scale multicenter cohort was performed to identify the association between initial trough concentration and prognosis in 7220 patients in the intensive care unit (ICU), aiming to evaluate the clinical value of trough concentration for ensuring vancomycin efficacy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our study demonstrated that trough concentration was positively related with ICU and hospital mortalities. Trough concentration greater than or equal to 10 mg/L was associated with increased ICU mortality. Moreover, hospital mortality failed to decrease at trough concentration 10–15 mg/L, even raised at trough concentration greater than 15 mg/L, compared with trough concentration less than 10 mg/L. The present study revealed that increased initial vancomycin trough concentration might not guarantee treatment success for critically ill patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

We found that high initial VTC might be associated with incremental ICU and hospital mortalities. However, due to the retrospective nature of this study, those findings are worth further investigation with prospective studies or randomized controlled trials.

INTRODUCTION

Gram-positive cocci are common pathogens involved in both community- and hospital-acquired infections.¹ Nevertheless, antibiotic resistance in gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA), has been continuously increasing worldwide in recent years, which has led to increased mortality, lengths of hospital stay, and hospital costs.^{2–4} Early empirical vancomycin therapy is generally used against suspected MRSA infections in both adult and pediatric patients.^{1,5} Serum vancomycin trough concentration (VTC) is a commonly monitored index to improve clinical efficacy.⁶ The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Society of Infectious Diseases Pharmacists, and the Japanese Society of Chemotherapy and Therapeutic Drug Monitoring have recommended that the VTC should be maintained at 10–20 mg/L to avoid development of resistance, and 15–20 mg/L for complicated infections, such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.^{6,7} The Chinese Pharmacological Society recommended 10–15 mg/L as the target VTC for adult patients, and 10–20 mg/L for adult patients with serious MRSA infections.⁸ Some studies have suggested that VTC should be greater than 15 mg/L to reduce the risk of persistent *S. aureus* bacteremia and vancomycin treatment failure.^{9–11} However, other studies have shown that different levels of VTC were

not significantly correlated with clinical outcomes.^{12–16} As a result, the latest consensus suggests that vancomycin area under the concentration-time curve (AUC) values obtained by Bayesian software are the most accurate and optimal approach for managing vancomycin dosing and that the trough-only monitoring target of 15–20 mg/L is no longer recommended in patients with serious MRSA infections.¹⁷ However, it remains uncertain whether monitoring VTC should be used among patients with noninvasive MRSA or other infections.¹⁷ To evaluate the correlation between initial VTC and mortality in patients in the intensive care unit (ICU) quantitatively, we performed a retrospective, multicenter, observational cohort study, which extracted VTC measurements and clinical data from 208 US hospitals from the eICU Collaborative Research Database (eICU-CRD, version 2.0).

METHODS

Study design and data source

This multicenter observational cohort data were extracted from eICU-CRD, which is a public de-identified ICU database maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology, and covers 200,859 patient unit encounters for 139,367 unique patients at 208 US hospitals between 2014 and

2015.^{18,19} The eICU-CRD includes data on vital signs, laboratory measurements, severity of illness measures, care plan information, admission diagnoses, and treatments. The database is released under the Health Insurance Portability and Accountability Act safe harbor provision. As all protected patient health-related information in the eICU has been de-identified, the requirement for individual patient consent was waived. All researchers of this study received the necessary training and obtained approval to access the database.

Patient selection

Adult patients (≥ 18 years) with a single hospital admission who received vancomycin therapy and VTC monitoring during the first ICU stay were included in this study. The exclusion criteria were: (1) patients with ICU length of stay less than or equal to 24 h, (2) patients without records of ICU discharge status, and (3) patients with missing or unqualified covariates for the multivariable adjustment.

Outcomes

The primary outcomes of this study were ICU and hospital mortalities. Mortality data used were from the first ICU stay only. ICU mortality was defined as the occurrence of death before first ICU discharge for any reason. Hospital mortality, including ICU mortality, referred to death in patients before single hospital discharge.

Data extraction

The primary variable was initial VTC during the first ICU admission, which was generally obtained prior to the fourth or fifth dose of vancomycin.¹ According to the consensus review of the Infectious Diseases Society of America,^{6,17} we divided patients into four categories according to VTC: less than 10, 10–15, 15–20, and greater than 20 mg/L. The following covariates of each patient were also extracted: (1) demographics (age, sex, ethnicity, weight, and height); (2) initial APACHE IV score and serum creatinine (Scr) within 24 h of ICU admission; (3) admission diagnoses during the first 24 h of the ICU stay according to International Classification of Diseases-9th revision codes (sepsis, burns, pancreatitis, gastrointestinal bleed, diabetes, heart failure, chronic obstructive pulmonary disease [COPD], hepatic failure, tumor, pneumonia, and renal failure); (4) related treatments performed between ICU admission and initial VTC record (ventilation, dialysis, and vasopressor administration); (5) duration, initial dose, total dose, and average daily dose of vancomycin; and

(6) survival outcome. Renal creatinine clearance (Ccr) was calculated according to the Cockcroft-Gault equation.²⁰

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and compared using the Kruskal-Wallis H test. Categorical variables are presented as frequency (percentage) and compared using χ^2 or Fisher's exact tests. We explored the relationship of initial VTC, as a continuous and categorical variable, with ICU and hospital mortalities using univariable and multivariable logistic regression models and documented the odds ratios (ORs) and 95% confidence intervals (CIs). The multivariable model was adjusted for covariates, including age (category), sex, ethnicity, body mass index (BMI), APACHE IV score, Ccr, the use of ventilation, dialysis, and vasopressor, and diagnoses, following collinearity was tested using the variance inflation factor (VIF) method, where a VIF greater than or equal to five indicates the presence of multicollinearity. Restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles were used to flexibly model and visualize the relationship between initial VTC and mortality. Meanwhile, sensitivity analyses were conducted to determine whether the association between initial VTC and mortality persisted when the severity of illness (<65 or ≥ 65), Ccr (<70 , 70–130 or >130 ml/min), age (<65 or ≥ 65 years), or BMI (<30 or ≥ 30 kg/m²) changed.⁸ In addition, another analysis was performed in the subpopulation with records of vancomycin dose and duration. All statistical tests were two-sided and a *p* value less than 0.05 was considered statistically significant. Data were extracted using SAS version 9.4 (SAS Institute, Cary, NC). Data analyses were performed using SPSS 23.0 (IBM Corp., Armonk, NY) and Stata 14.0 (Stata Corp., College Station, TX).

RESULTS

Individual selection and baseline characteristics

A total of 9550 adult patients with a single hospital admission and VTC level measurements at the first ICU admission were extracted from the eICU-CRD. We excluded 1715 patients with a length of ICU stay less than or equal to 24 h, one patient without a record of ICU discharge status, and 614 patients with missing or unqualified covariates for the multivariable adjustment. Finally, 7220 patients were included in this study (Figure 1). There were 3412 (47.3%) patients with age greater than or equal to 65 years, 4081 (56.5%) male patients, and 5600 (77.6%) White patients. The median (IQR) VTC at admission was 13.10 (9.10–18.40) mg/L. The

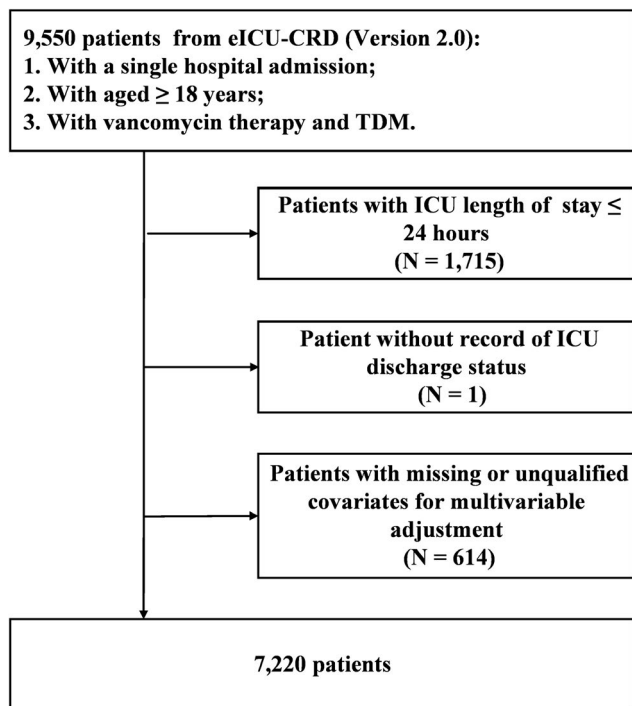


FIGURE 1 Flow chart of participant selection. Cohort selection and exclusion criteria, a total of 7220 patients are included in the analysis. eICU-CRD, eICU Collaborative Research Database; TDM, therapeutic drug monitoring; ICU, intensive care unit

patients were divided into the following 4 groups: less than 10 mg/L ($n = 2176$, 30.1%), 10–15 mg/L ($n = 2203$, 30.5%), 15–20 mg/L ($n = 1426$, 19.8%), and greater than 20 mg/L ($n = 1415$, 19.6%) according to initial VTC. Table 1 shows the demographic characteristics in the four groups. Age, BMI, VTC, APACHE IV score, Scr, Ccr, the use of ventilation, dialysis, and vasopressor, and diagnoses (COPD, heart failure, and renal failure) were different among the four groups ($p < 0.05$). Additionally, increased VTC was associated with an incremental increase in ICU (7.6%, 11.2%, 13.7%, and 16.1%, respectively; $p < 0.001$) and hospital mortalities (13.5%, 17.6%, 21.2%, and 24.7%, respectively; $p < 0.001$; Table 1).

Association of VTC with mortality

Univariable logistic regression results revealed that VTC, as a continuous variable, was positively correlated with ICU (OR, 1.034, 95% CI, 1.026–1.042) and hospital (OR, 1.031, 95% CI, 1.024–1.038) mortalities. This association was still remarkable (OR, 1.028, 95% CI, 1.019–1.037; and OR, 1.028, 95% CI, 1.020–1.036, respectively) after adjusting for a series of covariates (Table 2). When VTC was categorized into 4 groups, patients with VTC 10–15, 15–20, and greater than 20 mg/L had higher ICU (OR, 1.522, 95% CI, 1.238–1.871; OR, 1.918, 95% CI, 1.541–2.387; and OR, 2.326,

95% CI, 1.881–2.876, respectively) and hospital (OR, 1.374, 95% CI, 1.165–1.620; OR, 1.734, 95% CI, 1.453–2.069; and OR, 2.112, 95% CI, 1.778–2.510, respectively) mortalities compared with patients with VTC less than 10 mg/L in the univariable logistic regression analyses. After multivariable adjustment, patients with VTC 10–15, 15–20, and greater than 20 mg/L were associated with an increased risk of ICU mortality (OR, 1.330, 95% CI, 1.070–1.653; OR, 1.596, 95% CI, 1.265–2.015; and OR, 1.875, 95% CI, 1.491–2.357, respectively) and patients with VTC 15–20 and greater than 20 mg/L were also correlated with a high risk of hospital mortality (OR, 1.482, 95% CI, 1.225–1.793; and OR, 1.831, 95% CI, 1.517–2.210, respectively). However, hospital mortality in the VTC 10–15 mg/L group did not differ significantly from that of the VTC less than 10 mg/L group (OR, 1.187, 95% CI, 0.995–1.415; Table 2). Restricted cubic splines revealed that the risks of ICU (A) and hospital (B) mortalities increased with an increase in VTC (Figure 2).

Sensitivity analyses for association of VTC with mortality

The possible interaction effects of initial VTC and different variables (APACHE IV score < 65 [$n = 3574$] and APACHE IV score ≥ 65 [$n = 3646$], Ccr < 70 ml/min [$n = 3551$], Ccr 70–130 ml/min [$n = 2562$], and Ccr > 130 ml/min [$n = 1107$], age < 65 years [$n = 3808$] and age ≥ 65 years [$n = 3412$], BMI < 30 kg/m² [$n = 4433$], and BMI ≥ 30 kg/m² [$n = 2787$]) on mortality were evaluated. An interaction effect was observed between initial VTC and different age groups (ICU mortality, $p_{\text{interaction}} = 0.022$; hospital mortality, $p_{\text{interaction}} = 0.047$). There were no statistically significant differences across different APACHE IV scores (ICU mortality, $p_{\text{interaction}} = 0.644$; hospital mortality, $p_{\text{interaction}} = 0.897$), Ccr levels (ICU mortality, $p_{\text{interaction}} = 0.412$; hospital mortality, $p_{\text{interaction}} = 0.583$), and BMIs (ICU mortality, $p_{\text{interaction}} = 0.122$; hospital mortality, $p_{\text{interaction}} = 0.679$).

To validate our findings, we still analyzed the association between initial VTC and mortality in all those subgroups. The VTC, as a continuous variable, was associated with increased ICU and hospital mortalities in all different subgroups (Figure 3). When VTC was treated as a categorical variable, similar results were observed across the different subgroups (Figure 4). Groups with VTCs of 10–15 and 15–20 mg/L had a higher risk of ICU mortality than those with VTC less than 10 mg/L in the APACHE IV score greater than or equal to 65 (OR, 1.336, 95% CI, 1.033–1.726; and OR, 1.698, 95% CI, 1.294–2.227, respectively), Ccr less than 70 ml/min (OR, 1.536, 95% CI, 1.152–2.048; and OR, 1.667, 95% CI, 1.225–2.269, respectively), age greater than or equal to 65 years (OR, 1.560, 95% CI, 1.174–2.075; and OR, 1.776, 95% CI, 1.300–2.427, respectively), and BMI less than 30 kg/m² (OR,

TABLE 1 Demographic characteristics of the study cohort according to VTC categories

Characteristic	Entire population (N = 7220)	Initial VTC				p Value
		<10 mg/L (N = 2176)	10–15 mg/L (N = 2203)	15–20 mg/L (N = 1426)	>20 mg/L (N = 1415)	
Age n (%)						<0.001
<65 years	3808 (52.7)	1190 (54.7)	1050 (47.7)	745 (52.2)	823 (58.2)	
≥65 years	3412 (47.3)	986 (45.3)	1153 (52.3)	681 (47.8)	592 (41.8)	
Sex n (%)						0.370
Female	3139 (43.5)	972 (44.7)	938 (42.6)	603 (42.3)	626 (44.2)	
Male	4081 (56.5)	1204 (55.3)	1265 (57.4)	823 (57.7)	789 (55.8)	
Ethnicity n (%)						0.444
White	5600 (77.6)	1663 (76.4)	1724 (78.3)	1105 (77.5)	1108 (78.3)	
Others	1620 (22.4)	513 (23.6)	479 (21.7)	321 (22.5)	307 (21.7)	
BMI kg/m ² median (IQR)	27.59 (23.44–33.60)	26.42 (22.44–31.34)	27.52 (23.47–33.48)	28.52 (24.11–34.18)	29.50 (24.67–36.56)	<0.001
VTC mg/L, median (IQR)	13.10 (9.10,18.40)	7.50 (5.90,8.80)	12.30 (11.10,13.70)	17.30 (16.10,18.60)	25.00 (22.20,30.10)	<0.001
APACHE IV score median (IQR)	65 (49,84)	60 (45,78)	66 (50,85)	67 (50,86)	68 (52,88)	<0.001
Scr, mg/dl median (IQR)	1.01 (0.73–1.54)	0.86 (0.65–1.24)	1.02 (0.76–1.53)	1.11 (0.78–1.75)	1.20 (0.88–1.81)	<0.001
Ccr, ml/min median (IQR)	70.93 (43.59–107.46)	82.83 (50.61–116.89)	68.81 (42.87–104.31)	66.25 (37.68–100.51)	65.40 (41.10–99.31)	<0.001
Vasopressor n (%)	2048 (28.4)	547 (25.1)	625 (28.4)	422 (29.6)	454 (32.1)	<0.001
Ventilation n (%)	4113 (57.0)	1178 (54.1)	1279 (58.1)	804 (56.4)	852 (60.2)	0.002
Dialysis n (%)	170 (2.4)	31 (1.4)	40 (1.8)	51 (3.6)	48 (3.4)	<0.001
Diagnoses n (%)						
Tumor	610 (8.4)	173 (8.0)	186 (8.4)	130 (9.1)	121 (8.6)	0.673
Hepatic failure	50 (0.7)	12 (0.6)	10 (0.5)	17 (1.2)	11 (0.8)	0.051
COPD	609 (8.4)	149 (6.8)	220 (10.0)	119 (8.3)	121 (8.6)	0.003
Heart failure	604 (8.4)	119 (5.5)	211 (9.6)	131 (9.2)	143 (10.1)	<0.001
Diabetes	918 (12.7)	253 (11.6)	287 (13.0)	175 (12.3)	203 (14.3)	0.104
Gastrointestinal bleed	533 (7.4)	182 (8.4)	140 (6.4)	103 (7.2)	108 (7.6)	0.084
Pancreatitis	80 (1.1)	28 (1.3)	24 (1.1)	10 (0.7)	18 (1.3)	0.370
Burns	11 (0.2)	2 (0.1)	5 (0.2)	2 (0.1)	2 (0.1)	0.721
Pneumonia	1851 (25.6)	584 (26.8)	581 (26.4)	357 (25.0)	329 (23.3)	0.080
Sepsis	2512 (34.8)	723 (33.2)	796 (36.1)	513 (36.0)	480 (33.9)	0.142
Renal failure	1093 (15.1)	267 (12.3)	347 (15.8)	253 (17.7)	226 (16.0)	<0.001
ICU mortality n (%)	835 (11.6)	166 (7.6)	246 (11.2)	195 (13.7)	228 (16.1)	<0.001
Hospital mortality n (%)	1334 (18.5)	293 (13.5)	388 (17.6)	303 (21.2)	350 (24.7)	<0.001

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Ccr, creatinine clearance; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; Scr, serum creatinine; VTC, vancomycin trough concentration.

1.550, 95% CI, 1.193–2.014; and OR, 1.627, 95% CI, 1.214–2.179, respectively) subgroups. There was also an increased hospital mortality among patients with VTC 15–20 mg/L in the presence of APACHE IV score less than 65 (OR, 1.558, 95% CI, 1.120–2.166), APACHE IV score greater than or equal to 65 (OR, 1.516, 95% CI, 1.206–1.906), Ccr less than 70 ml/min (OR, 1.628, 95% CI, 1.272–2.085), age less than

65 years (OR, 1.424, 95% CI, 1.057–1.917), age greater than or equal to 65 years (OR, 1.521, 95% CI, 1.185–1.953), and BMI less than 30 kg/m² (OR, 1.563, 95% CI, 1.236–1.975). In all subgroups, compared with patients with VTC less than 10 mg/L, those with VTC greater than 20 mg/L had significantly higher ICU and hospital mortalities, except for the Ccr greater than 130 ml/min subgroup.

TABLE 2 Logistic regression analysis for the association of VTC with mortality

Variable	ICU mortality		Hospital mortality	
	OR (95% CI)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value
Univariable Model				
Continuous variable	1.034 (1.026–1.042)	<0.001	1.031 (1.024–1.038)	<0.001
Categorical variable				
<10 mg/L	1		1	
10–15 mg/L	1.522 (1.238–1.871)	<0.001	1.374 (1.165–1.620)	<0.001
15–20 mg/L	1.918 (1.541–2.387)	<0.001	1.734 (1.453–2.069)	<0.001
>20 mg/L	2.326 (1.881–2.876)	<0.001	2.112 (1.778–2.510)	<0.001
Multivariable model				
Continuous variable	1.028 (1.019–1.037)	<0.001	1.028 (1.020–1.036)	<0.001
Categorical variable				
<10 mg/L	1		1	
10–15 mg/L	1.330 (1.070–1.653)	0.010	1.187 (0.995–1.415)	0.056
15–20 mg/L	1.596 (1.265–2.015)	<0.001	1.482 (1.225–1.793)	<0.001
>20 mg/L	1.875 (1.491–2.357)	<0.001	1.831 (1.517–2.210)	<0.001

Note: Multivariable model: adjusted for age (category), sex, ethnicity, BMI, APACHE IV score, Ccr, the use of ventilation, dialysis, and vasopressor, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure).

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; VTC, vancomycin trough concentration.

To exclude the impact of vancomycin administration on the prognosis of patients, 3035 patients with the records of the duration of vancomycin exposure, initial vancomycin dose (adjusted for weight), total vancomycin dose over the observation period, and average daily dosage were abstracted. Univariable logistic analyses indicated that only the duration of vancomycin exposure was associated with ICU ($p = 0.014$) and hospital ($p = 0.005$) mortalities. Then collinearity analysis found a mean VIF of 1.19 for all the variables included in the multivariable logistic regression models, which demonstrated that the relationship between VTC and mortality remained robust (Supplementary Table S1).

DISCUSSION

In this research, we performed a large-scale multicenter retrospective cohort study of adults with VTC measurements after receiving vancomycin to explore the association between mortality and initial VTC quantitatively in patients in the ICU. Multivariable analyses indicated that VTC was positively related with ICU and hospital mortalities. VTC greater than or equal to 10 mg/L was associated with increased ICU mortality. Moreover, hospital mortality failed to decrease at VTC 10–15 mg/L, even raised at VTC greater than 15 mg/L, compared with VTC less than 10 mg/L. Therefore, the present study revealed that increased initial VTC might not guarantee treatment success for critically ill patients.

Because monitoring VTC as a feasible pharmacokinetic method was recommended for personalized vancomycin dosing by the Infectious Diseases Society of America in 2009, several studies have found controversial results regarding the association of VTC with clinical outcomes in patients with gram-positive bacterial infections. An observational, multicenter study, which included 35 adult patients with MRSA-associated septic shock reported that the percentage of patients with VTC greater than or equal to 15 mg/L was 2.5-fold higher in the survivor group than in the nonsurvivor group.¹⁰ Additionally, in a single-center retrospective analysis of 320 patients with documented MRSA bacteremia, Kullar et al.⁹ observed that VTC 15–20 mg/L was associated with a lower rate of vancomycin treatment failure. However, some retrospective studies focusing on patients with MRSA bacteremia showed that there was no association between VTC level and treatment response.^{12,14–16} Another two prospective studies in Chinese patients with gram-positive bacterial infections suggested that no significant correlations were identified between VTC and clinical or microbiological efficiency.^{13,21} Several clinical and simulation studies have even found that patients can achieve strong benefit when vancomycin therapy was guided by AUC/minimum inhibitory concentration rather than VTC.^{22,23}

Because the sample size of these aforementioned studies was relatively small and most of them focused on definitive MRSA infection, a large-scale multicenter cohort was performed to identify the association of initial VTC with prognosis in 7220 patients in the ICU, aiming to evaluate

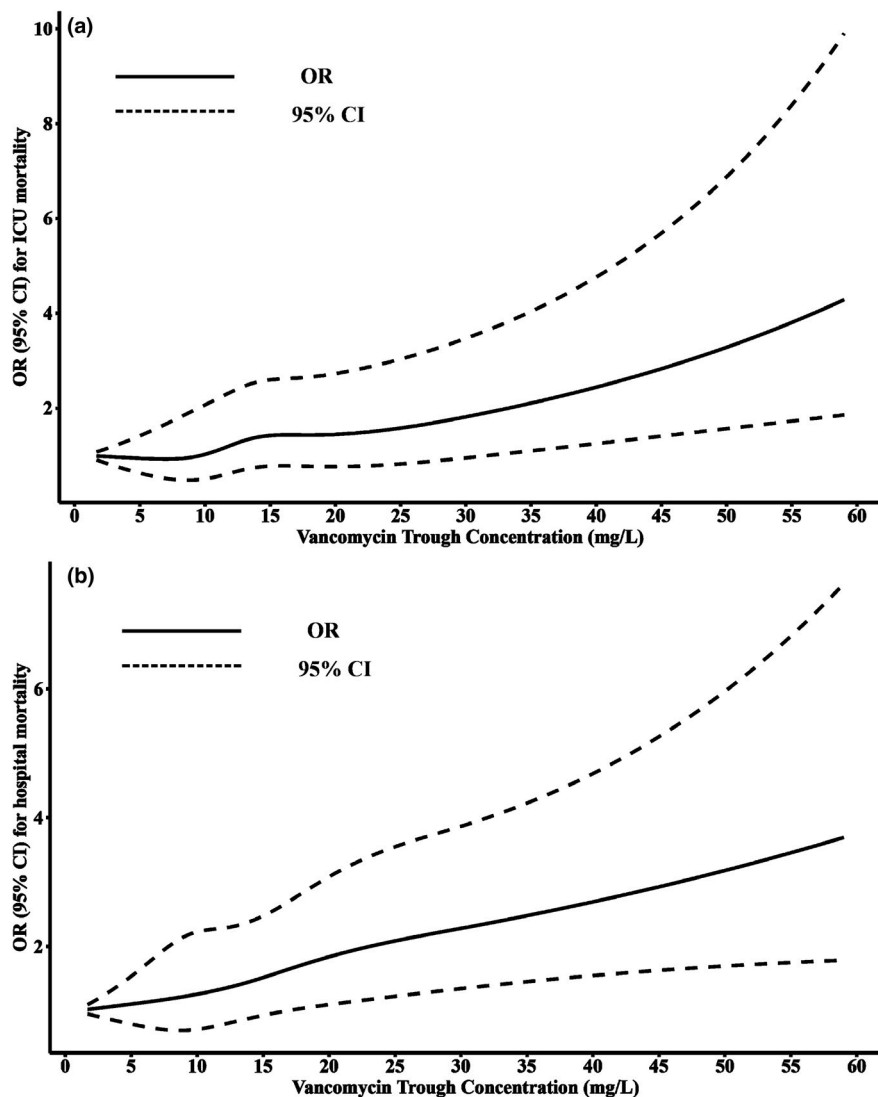


FIGURE 2 Association of VTC with ICU (a) and hospital (b) mortalities. Restricted cubic splines reveal that the risks of ICU (a) and hospital (b) mortalities increased with an increase in VTC. All models were adjusted for age (category), sex, ethnicity, BMI, APACHE IV score, Ccr, the use of ventilation, dialysis, and vasopressor, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure). APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; VTC, vancomycin trough concentration

the clinical value of initial VTC for ensuring vancomycin efficacy. When VTC was as a continuous variable, multivariable logistic regression results revealed that ICU and hospital mortality rates increased by 2.8% and 2.8%, respectively, per 1 mg/L increase in VTC. When VTC was categorical into 4 groups, our results showed that VTC 10–15, 15–20, and greater than 20 mg/L were associated with a higher risk of mortality in ICU patients compared with VTC less than 10 mg/L. This finding not only reiterates the recommendations of the latest consensus, which no longer suggests a target of VTC 15–20 mg/L based on existing efficacy data on patients with serious MRSA infections,¹⁷ but also indicates that a VTC of 10–15 mg/L should not be maintained to ensure vancomycin efficacy for critically ill patients. In short, we concluded that there is no benefit of larger doses of vancomycin to achieve the suggested VTC, and proposed that monitoring of VTC might not improve clinical outcomes for critically ill patients. A prospective randomized trial comparing the relationship between VTC and clinical response is needed in the future.

The APACHE IV score is useful to assess the severity of illness and predict outcomes among critically ill patients.²⁴ In order to diminish the influence of disease severity on the relationship between VTC and mortality, patients were divided into two subgroups based on the median of the first APACHE IV score (<65 or ≥65). The process of vancomycin elimination from the body occurs primarily via the renal route, which means the degree of kidney function has a significant effect on the VTC level.²⁵ A prospective observational study in the ICU found a significant negative correlation between Ccr and serum VTC.²⁶ Meanwhile, age and weight were also significantly associated with vancomycin clearance.^{27,28} In the sensitivity analyses, we further investigated whether the effect of initial VTC on mortality varied in patients with different Ccr levels, ages, and BMIs. The analyses found that no interactions were observed between those variables (except for the ages) and initial VTC for mortality, and the associations of VTC with mortality were similar in different subgroups. Although suggested VTC was not an independent risk factor for ICU or hospital mortalities in subgroups with APACHE

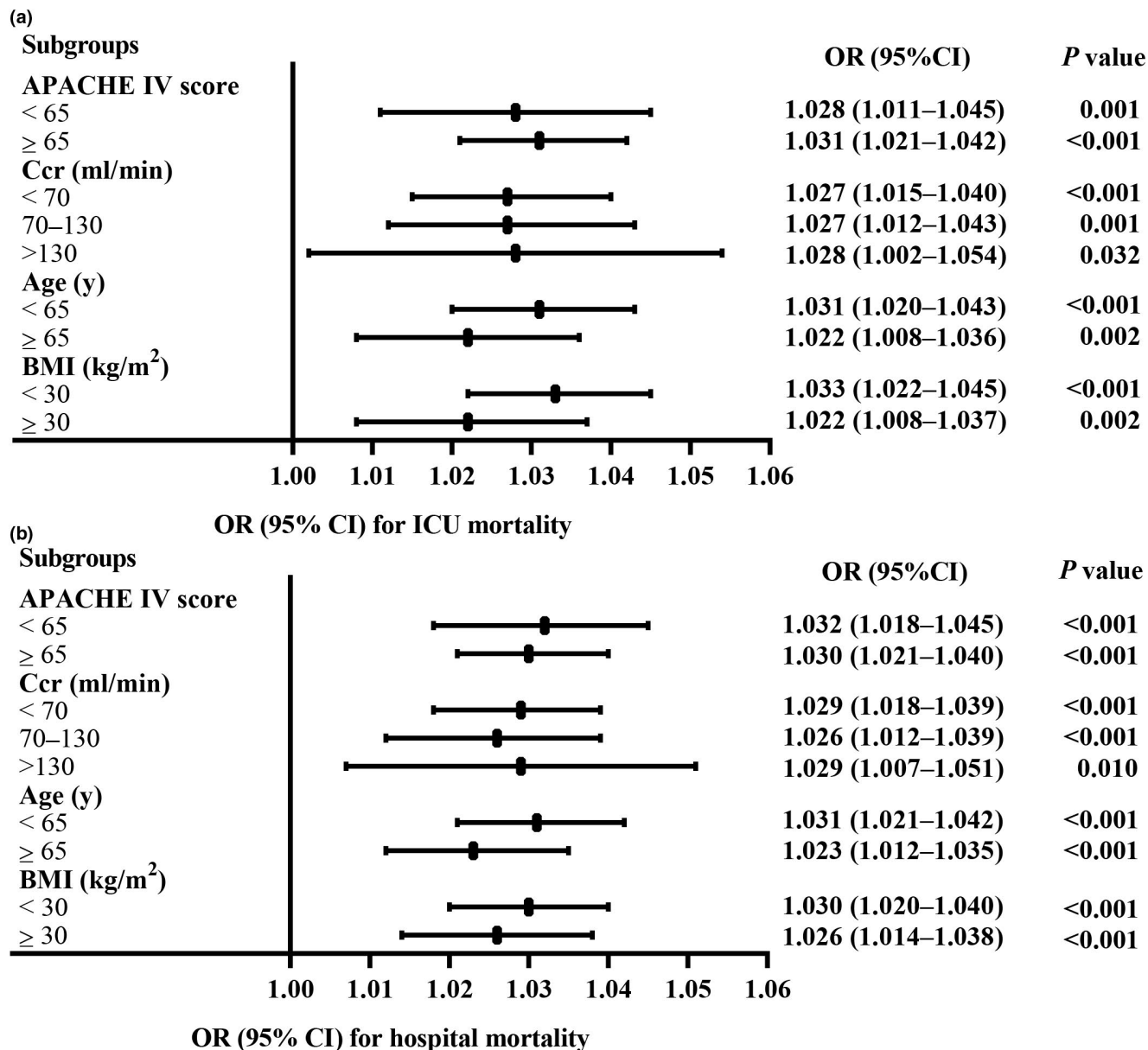


FIGURE 3 Sensitivity analyses for the association of VTC, as a continuous variable, with ICU (a) and hospital (b) mortalities. All multivariable models were adjusted for age (category, except for the age subgroup), sex, ethnicity, BMI (except for the BMI subgroup), APACHE IV score (except for the APACHE IV score subgroup), Ccr (except for the Ccr subgroup), the use of ventilation, dialysis, and vasopressor, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure). APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; VTC, vancomycin trough concentration

IV score less than 65, Ccr 70–130 ml/min, Ccr greater than 130 ml/min, age less than 65 years, or BMI greater than or equal to 30 kg/m², it was not associated with improved prognosis either. Therefore, higher initial VTC might not ensure vancomycin efficacy regardless of the severity of illness, the degree of renal function, age, or BMI.

Our study indicated that VTC might fail to work as a suitable indicator for ensuring vancomycin efficacy, which is consistent with the recent consensus.¹⁷ The failure of VTC may be due to the following reasons. First, although VTC has

been used as a potential surrogate for AUC in clinical practice,⁶ several studies have reported a nonlinear relationship between VTC and AUC_{0–24} because of high interindividual variability.^{27–29} VTC was obtained at a single timepoint at the end of the dosing interval. Nevertheless, vancomycin AUC was a reflection of the cumulative quantity of drug exposure over time. Thus, VTC may not be able to represent the concentration-time profile, much less ensure the efficacy of vancomycin.^{6,30} Second, vancomycin has been associated with several adverse events, including pruritus, flushing,

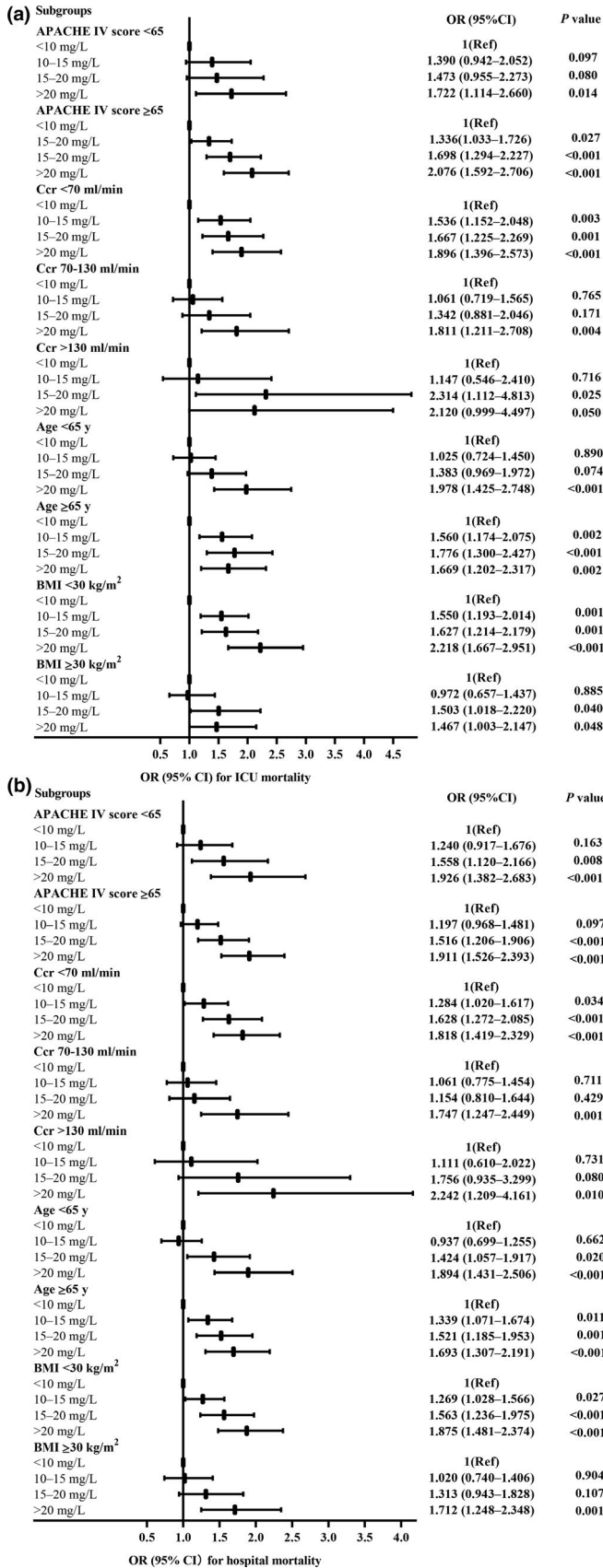


FIGURE 4 Sensitivity analyses for the association of VTC, as a categorical variable, with ICU (a) and hospital (b) mortalities. All multivariable models were adjusted for age (category, except for the age subgroup), sex, ethnicity, BMI (except for the BMI subgroup), APACHE IV score (except for the APACHE IV score subgroup), Ccr (except for the Ccr subgroup), the use of ventilation, dialysis, and vasopressor, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure). APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Ccr, creatinine clearance; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; VTC, vancomycin trough concentration

of mortality.³¹ A prospective multicenter clinical study observed that increased VTC might increase the risk of vancomycin nephrotoxicity and the applicable cutoff of VTC was 13 mg/L in Chinese patients with gram-positive bacterial infections.¹³ Another retrospective trial found that VTC greater than or equal to 15 mg/L was an independent risk factor for nephrotoxicity in elderly critically ill patients.³² These results are similar to those of our study, in which VTC greater than or equal to 10 mg/L was significantly associated with ICU mortality or VTC greater than 15 mg/L with hospital mortality. Therefore, the optimal indicator for ensuring vancomycin effectiveness in patients in the ICU warrants further investigation in future studies.

This study had some potential limitations. First, this was a retrospective nonexperimental study, and thus the risk of unmeasured confounders and introduction of bias were unavoidable. Nonetheless, to the best of our knowledge, this is the first multicenter study on VTC with a large sample of patients in the ICU, which can claim better reliability and generalizability of the findings. Second, no clinical and microbiological outcomes after vancomycin treatment are documented in the eICU-CRD. Whereas, mortality is a more precisely measured outcome than clinical response, and high mortality was observed in critically ill patients with gram-positive bacterial infections, especially MRSA infection.³³ Thus, we believe that mortality largely represents clinical outcomes in terms of verification of the prognostic value of VTC. Third, some information on microbial culture/sensitivity results and time of death were not available due to the retrospective design. Although only less than half of the patients had records on vancomycin dose and duration, we still performed a sensitivity analysis and found the association was persisted. Fourth, we can provide only the association between initial VTC and mortality rather than causality. In the future, a well-designed prospective study or randomized controlled trial with more detailed therapy information should be conducted to evaluate causality between VTC and mortality.

In conclusion, our study found that high initial VTC was associated with incremental ICU and hospital mortalities

rash, and/or nephrotoxicity. Of those, nephrotoxicity is the most serious common side effect, and it is linked to longer hospital stays, higher medical costs, and even a higher risk

in patients in the ICU. However, considering that the observed relationship is also possibly confounded by baseline covariates (such as renal dysfunction) or other unmeasured confounders in this retrospective study, cautions should be exercised on interpreting the results. In addition, high-quality randomized controlled trials remain needed to further investigate the pharmacokinetic monitoring of VTC.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.W., J.R., Y.H., J.L., Y.G., R.L., X.J., J.Z., and X.W. wrote the manuscript. G.W., J.R., and Y.H. designed the research. G.W., J.R., Y.H., J.L., Y.G., R.L., X.J., J.Z., and X.W. performed the research. G.W., J.R., Y.H., and X.J. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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