Relationship Between Mean Vancomycin Trough Concentration and Mortality in Critically Ill Patients: A Multicenter Retrospective Study

Yanli Hou
Xi'an Jiaotong University Second Affiliated Hospital
Jiajia Ren
Xi'an Jiaotong University Second Affiliated Hospital
Jiamei Li
Xi'an Jiaotong University Second Affiliated Hospital
Xuting Jin
Xi'an Jiaotong University Second Affiliated Hospital
Ya Gao
Xi'an Jiaotong University Second Affiliated Hospital
Ruohan Li
Xi'an Jiaotong University Second Affiliated Hospital
Jingjing Zhang
Xi'an Jiaotong University Second Affiliated Hospital
Xiaochuang Wang
Xi'an Jiaotong University Second Affiliated Hospital
Xinyu Li
Xi'an Jiaotong University Second Affiliated Hospital
Gang Wang (gang_wang@xjtu.edu.cn)
Xi'an Jiaotong University Second Affiliated Hospital https://orcid.org/0000-0002-5905-7760

Research

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Abstract

Background: It remains unclear whether the mean vancomycin trough concentration (VTC) derived from the entire course of therapy is of potential benefit for critically ill patients. This study was conducted to explore the association between mean serum VTC and mortality in intensive care units (ICUs).

Methods: 3,364 adult patients with two or more VTC records after receiving vancomycin therapy in the eICU Collaborative Research Database were included in this multicenter retrospective cohort study. Mean VTC was estimated using all measured VTCs and investigated as a continuous and categorical variable. Patients were categorized into four groups according to mean VTC: <10, 10–15, 15–20, and >20 mg/L. Multivariable logistic regression and subgroup analyses were performed to investigate the relationship of mean VTC with mortality.

Results: After adjusting for a series of covariates, logistic regression analyses indicated that mean VTC, as a continuous variable, was positively correlated with ICU (odds ratio, 1.042, 95% confidence interval, [1.017–1.068]) and hospital (1.025 [1.004–1.046]) mortalities. As a categorical variable, mean VTC at 10–15 mg/L failed to reduce ICU mortality (1.512 [0.849–2.694]). Moreover, mean VTCs of 15–20 and >20 mg/L were significantly associated with higher ICU mortality (1.946 [1.106–3.424]; 2.314 [1.296–4.132]) than mean VTC <10 mg/L. Mean VTCs of 10–15, 15–20, and >20 mg/L were not associated with increased hospital mortality (1.154 [0.766–1.739]; 1.342 [0.896–2.011]; 1.496 [0.981–2.281]). Similar results were observed in different Acute Physiology and Chronic Health Evaluation IV score or creatinine clearance subgroups.

Conclusions: Increasing mean VTC showed no benefit regarding ICU and hospital mortalities in critically ill patients. Our results suggested that continuous VTC monitoring might not guarantee vancomycin efficacy for ICU patients.

Background

Vancomycin, a bactericide that acts by obstructing the synthesis of the bacterial cell wall, was isolated from streptomycin approximately half a century ago and exhibits time-dependent bactericidal activity with a long post-antibiotic effect [1–4]. Therapeutic drug monitoring (TDM) is an adjuvant and practical method used for vancomycin dosing adjustment in intensive care units (ICUs) because of its narrow therapeutic window [5]. Based on infection models and clinical pharmacokinetic/pharmacodynamic (PK/PD) studies, the area under the concentration-time curve over 24 h/minimum inhibitory concentration ($AUC_{0-24\,h}$/MIC) has been established as the most predictive index to reflect the clinical and microbiological efficacies of vancomycin [6, 7]. Bacterial clearance, along with improvements in clinical signs and symptoms, has been suggested to be associated with $AUC_{0-24h}/MIC \geq 400$ [8, 9]. However, it is difficult to precisely determine multiple serum/tissue vancomycin concentrations during the same dosing interval to calculate the AUC in clinical practice [10].

Serum vancomycin trough concentration (VTC) monitoring before the fourth dose has been suggested as the most practical method for TDM of vancomycin, as a VTC 15–20 mg/L may achieve an $AUC_{0-24h}/MIC \geq 400$ if the MIC is ≤ 1 mg/L [10]. However, plenty of studies have demonstrated that VTC did not have a considerable effect on treatment outcomes [7, 8, 11, 12]. Nevertheless, to our knowledge, those most retrospective and prospective studies only focused on the initial VTC after vancomycin therapy. It remains unclear whether the mean VTC, estimated using all measured VTCs during the entire course of therapy, is beneficial for critically ill patients. Therefore, this multicenter observational study with a large sample was further performed to investigate the association of mean VTC with mortality in critically ill patients.

Patients And Methods

Study Design and Data Source

This multicenter observational study was performed using the eICU Collaborative Research Database (eICU-CRD, version 2.0), which is a public de-identified ICU database comprising 200,859 patient unit encounters for 139,367 unique patients admitted between 2014 and 2015. The eICU database is available from https://physionet.org/content/eicu-crd/. Patients were admitted to 1 of 335 units at 208 hospitals located throughout the United States [13]. The eICU-CRD includes data on vital signs, laboratory measurements, medications, Acute Physiology and Chronic Health Evaluation (APACHE) components, care plan information, admission diagnoses, time-stamped diagnoses, and treatments. All researchers of this study received the necessary training and obtained permission to access the database.

Patient Selection

All patient information was obtained from the eICU-CRD. Adult patients (≥18 years) receiving vancomycin therapy with a single hospital admission and two or more TDM records on the first ICU stay were included. The exclusion criteria were as follows: (1) patients with an ICU length of stay ≤24 h, (2) patients without records of their ICU discharge status, (3) patients with missing or unqualified covariates for multivariable adjustment, and (4) patients with an outlier value of VTC. The outlier value of VTC was defined when the maximum VTC was greater than 1.5-times the interquartile range (IQR) above Q_3 or when the minimum VTC was less than 1.5-times the IQR under Q_1 (IQR was calculated using the formula: $Q_3 - Q_1$).

Outcomes and Covariates

The outcomes of this study were ICU and hospital mortalities. The variables, mean VTC or serum creatinine (Scr), were calculated by dividing the sum of all collected VTC or Scr by the frequency of monitoring. Mean creatinine clearance (CCl) was determined by the Cockcroft-Gault equation: ([140 - age in years] × weight in kg / [72 × mean Scr concentration in mg/dl]) × 0.85 if female [14]. Related treatments (such as dialysis, ventilation, hypotensor, and hyperensort administration) were included, as these may reflect illness severity and/or affect VTC throughout ICU stay. Variables such as demographic data (e.g., age, sex, and ethnicity), initial body mass index (BMI), APACHE IV score, and comorbidities that could influence mortality (e.g., sepsis, burns, pancreatitis, gastrointestinal bleed, diabetes, heart failure, chronic obstructive pulmonary disease [COPD], hepatic failure, tumor, pneumonia, and renal failure) were also assessed during the first 24 h of ICU admission.

Statistical Analysis

Based on the recommended VTC in a series of guidelines [10, 15, 16], we divided the mean VTC into four categories: <10, 10–15, 15–20, and >20 mg/L. Continuous variables were presented as the medians (IQRs) and compared using the Kruskal-Wallis H test. Categorical variables were presented as frequencies (percentages) and compared using χ^2 or Fisher's exact tests. A Chord diagram showed the connection between the initial VTC and mean VTC for each patient. Logistic regression models were used to investigate the association of the mean VTC, as a continuous and categorical variable, with ICU and hospital mortalities. To flexibly model and visualize the relationship between mean VTC and mortality, we also used restricted cubic splines with four knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles. Interaction and subgroup analyses were conducted to determine whether the clinical outcomes persisted when the severity of the clinical status changed or CCl fluctuated. All tests were two-sided, and a *P* value <0.05 was considered statistically significant. Data were extracted using the SAS version 9.4 software (SAS Institute, Cary, NC, USA) and all

statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA) and Stata 14.0 (Stata Corp., College Station, TX, USA).

Results

Individual Selection and Clinical Characteristics

4,256 adult patients with a single hospital stay and at least two VTC records at the first ICU admission were extracted from the eICU-CRD. The following were excluded: 628 patients with a length of ICU stay ≤ 24 h, 1 patient without a record of ICU discharge status, 68 patients with missing or unqualified covariates for multivariable adjustment, and 72 patients with a discrete VTC. Finally, 3,364 patients were included in this study (Fig. 1). The patients were divided into the following four groups according to the mean VTC during ICU stay: <10 mg/L (n = 346, 10.3%), 10–15 mg/L (n = 1.090, 32.4%), 15–20 mg/L (n = 1,161 34.5%), and > 20 mg/L (n = 767, 22.8%). Age, BMI, mean VTC, APACHE IV score, Scr, CCl, and use of hypotensor, hyperensort and dialysis were significantly different among the four groups (P < 0.05). Additionally, there was a significant difference in the prevalence of COPD, heart failure, and renal failure (P< 0.05). Groups with a higher mean VTC had higher ICU (4.6%, 7.7%, 11.9%, and 14.7%, respectively; P< 0.001) and hospital (10.7%, 14.0%, 18.9%, and 21.4%, respectively; P< 0.001) mortalities (Table 1). The Chord diagram presented the connection between the mean VTC and initial VTC for each patient (Fig. 2). Among all patients, there were 1,514 (45%) patients with the mean VTC same as the initial VTC. 230 (19.48%) of patients with initial VTC < 10 mg/L had a mean VTC 15–20 mg/L, Among patients with initial VTC 10–15 mg/L, 439 (44.3%) patients reached a mean VTC within 15–20 mg/L and 172 (27.4%) of patients with initial VTC > 20 mg/L had a mean VTC 15–20 mg/L.

Table 1
Baseline Characteristics of the Study Cohort According to Mean VTC Categories

Characteristics	Entire population	mean VTC				*P* value
		<10 mg/L	10–15 mg/L	15–20 mg/L	>20 mg/L	
	(N = 3,364)	(N = 346)	(N = 1,090)	(N = 1,161)	(N = 767)	
Age n (%)						< 0.001
≤ 60 y	1,559 (46.3)	196 (56.6)	523 (49.0)	494 (42.5)	346 (45.1)	
> 60 y	1,805 (53.7)	150 (43.4)	567 (52.0)	667 (57.5)	421 (54.9)	
Sex n (%)						0.122
Male	1,961 (58.3)	182 (52.6)	652 (59.8)	675 (58.1)	452 (58.5)	
Female	1,403 (41.7)	164 (47.6)	438 (40.2)	486 (41.9)	315 (41.1)	
Ethnicity n (%)						0.354
Caucasian	2,557 (76.0)	256 (74.0)	838 (76.9)	894 (77.0)	569 (74.2)	
Others/Unkown	897 (24.0)	90 (26.0)	252 (23.1)	267 (23.0)	198 (25.8)	
BMI (kg/m^2) median (IQR)	27.45 (23.23,33.34	26.05 (22.19,31.64)	26.81 (22.99,32.64)	27.69 (23.47,33.32)	28.96 (24.18,35.24)	< 0.001
VTC (mg/L) median (IQR)	15.94 (12.6,19.67	8.45 (7.25,9.33)	12.80 (11.51,13.95)	17.17 (16.05,18.45)	22.53 (21.00,24.85)	< 0.001
APACHE IV score median (IQR)	64 (48,82)	58 (41,76)	62 (47,80)	64 (48,84)	68 (52,87)	< 0.001
Hypotensor n (%)	1,651 (49.1)	156 (43.9)	518 (47.5)	574 (49.4)	407 (53.1)	0.022
Hyperensort n (%)	1,235 (36.7)	116 (33.5)	362 (33.2)	458 (39.4)	299 (39.0)	0.005
Ventilation n (%)	2,201 (65.4)	221 (63.9)	688 (63.1)	791 (68.1)	501 (65.3)	0.082
Scr (mg/dl) median (IQR)	0.89 (0.66,1.34)	0.68 (0.52,0.89)	0.78 (0.61,1.11)	0.95 (0.70,1.37)	1.17 (0.82,1.88)	< 0.001
CCl (ml/min) median (IQR)	90.52 (55.78,135.21)	121.98 (79.51,71.60)	102.44 (63.45,147.20)	86.37 (53.33,124.68)	69.40 (42.12,111.20)	< 0.001
Dialysis n (%)	215 (6.4)	5 (1.4)	46 (4.2)	79 (6.8)	85 (11.1)	< 0.001
Diagnoses n (%)						

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

Characteristics	Entire population	mean VTC				*P* value
		<10 mg/L	10–15 mg/L	15–20 mg/L	>20 mg/L	
	(N = 3,364)	(N = 346)	(N = 1,090)	(N = 1,161)	(N = 767)	
Tumor	284 (8.4)	25 (7.2)	91 (8.3)	98 (8.4)	70 (9.1)	0.768
Hepatic failure	24 (0.7)	0 (0)	7 (0.6)	11 (0.9)	6 (0.8)	0.313
COPD	285 (8.5)	18 (5.2)	100 (9.2)	118 (10.2)	49 (6.4)	0.003
Heart failure	290 (8.6)	13 (3.8)	80 (7.3)	117 (10.1)	80 (10.4)	< 0.001
Diabetes	394 (11.7)	36 (10.4)	130 (11.9)	141 (12.1)	87 (11.3)	0.818
Gastrointestinal bleed	266 (7.9)	34 (9.8)	81 (7.4)	94 (8.1)	57 (7.4)	0.496
Pancreatitis	53 (1.6)	4 (1.2)	18 (1.7)	17 (1.5)	14 (1.8)	0.841
Burns	8 (0.2)	2 (0.6)	3 (0.3)	3 (0.3)	0 (0)	0.216
Pneumonia	884 (26.3)	79 (22.8)	292 (26.8)	319 (27.5)	194 (25.3)	0.319
Sepsis	1,151 (34.2)	105 (30.3)	363 (33.3)	419 (36.1)	264 (34.4)	0.210
Renal failure	479 (14.2)	105 (30.3)	146 (13.4)	178 (15.3)	123 (16.0)	0.013
ICU mortality n (%)	351 (10.4)	16 (4.6)	84 (7.7)	138 (11.9)	113 (14.7)	< 0.001
Hospital mortality n (%)	573 (17.0)	37 (10.7)	153 (14.0)	219 (18.9)	164 (21.4)	< 0.001

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

Association of Mean VTC with Mortality

The univariable logistic regression model revealed that the mean VTC, as a continuous variable, was positively correlated with ICU (odds ratio, 1.073, 95% confidence interval, [1.050–1.096]) and hospital (1.052 [1.033–1.070]) mortalities. This association was still robust (1.042 [1.017–1.068]; 1.025 [1.004–1.046], respectively) after adjusting for age, sex, ethnicity, BMI, APACHE IV score, CCl, the use of ventilation, dialysis, hypotensor and hyperensort, and diagnoses at ICU admission (Table 2). When mean VTC was considered as a categorical variable, patients with mean VTCs of 15–20 and > 20 mg/L were associated with higher ICU (2.782 [1.634–4.738]; 3.564 [2.077–6.115]) and hospital (1.942 [1.339–2.815]; 2.271 [1.550–3.329]) mortalities, and those with mean VTC of 10–15 mg/L showed no significant difference in ICU ($P = 0.052$) and hospital ($P = 0.111$) mortalities compared with those with mean VTC < 10 mg/L in the univariable logistic regression analyses. After multivariable adjustment, mean VTC 10–15 mg/L was not correlated with ICU mortality ($P = 0.160$), and mean VTCs of 15–20 and > 20 mg/L were associated with higher ICU mortality (1.946 [1.106–3.424]; 2.314 [1.296–4.132]) compared with mean VTC of < 10 mg/L. Additionally, the hospital mortality in the groups with mean VTCs of 10–15, 15–20 and > 20 mg/L ($P = 0.494$; $P = 0.154$; $P = 0.061$) were not significantly different from those with mean VTC of < 10 mg/L (Table 2). Restricted cubic splines visually

showed that the risks of ICU (A) and hospital (B) mortalities increased with an increasing mean VTC (Additional file 1: Fig. 1).

Table 2
Logistic Analysis for the Association of Mean VTC with Mortality

	ICU Mortality		**Hospital Mortality**	
VTC Variable	**OR (95% CI)**	P **Value**	OR (95% CI)	P Value
Univariable Model				
Continuous variable	1.073 (1.050,1.096)	< 0.001	1.052 (1.033,1.070)	< 0.001
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.722 (0.995,2.982)	0.052	1.364 (0.931,1.997)	0.111
15–20 mg/L	2.782 (1.634,4.738)	< 0.001	1.942 (1.339,2.815)	< 0.001
> 20 mg/L	3.564 (2.077,6.115)	< 0.001	2.271 (1.550,3.329)	< 0.001
Multivariable Model				
Continuous variable	1.042 (1.017,1.068)	0.001	1.025 (1.004,1.046)	0.017
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.512 (0.849,2.694)	0.160	1.154 (0.766,1.739)	0.494
15–20 mg/L	1.946 (1.106,3.424)	0.021	1.342 (0.896,2.011)	0.154
> 20 mg/L	2.314 (1.296,4.132)	0.005	1.496 (0.981,2.281)	0.061

Multivariable model: adjusted for age (category), sex, ethnicity, BMI, APACHE IV score, CCl, the use of ventilation, dialysis, hypotensor and hyperensort, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure)
VTC, vancomycin trough concentration; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; CCl, creatinine clearance; COPD, chronic obstructive pulmonary disease.

Association of Mean VTC with Mortality in Different Subgroups

We further analyzed the association between mean VTC and mortality in different predefined subgroups: APACHE IV score ≤ 64 (n = 1,736) and APACHE IV score > 64 (n = 1,628) or CCl ≤ 80 ml/min (n = 1,460) and CCl > 80 ml/min (n = 1,904). We found no interaction between APACHE IV score (category) and mean VTC (ICU mortality, $P_{interaction}$ = 0.721; hospital mortality, $P_{interaction}$ = 0.067). Similarly, no interaction was found between mean VTC and CCl for ICU ($P_{interaction}$ = 0.807) and hospital ($P_{interaction}$ = 0.756) mortalities. Notably, the multivariable logistical regression results were still robust across different subgroups. We observed that mean VTC, as a continuous variable, was significantly correlated with both ICU and hospital mortalities in APACHE IV score > 64 (P < 0.001; P < 0.001) and CCl ≤ 80 ml/min (P = 0.017; P = 0.002) subgroups. When mean VTC was used as a categorical variable, the groups with mean VTCs of 15–20 and > 20 mg/L exhibited a statistical difference in ICU (P = 0.041; P = 0.005) and hospital (P = 0.017; P = 0.003) mortalities compared to those with mean VTC < 10 mg/L in APACHE IV score > 64 subgroups.

Similarly, mean VTC > 20 mg/L was an independent risk factor for ICU mortality (P = 0.012) in CCl ≤ 80 ml/min subgroup (Table 3; Table 4).

Table 3
Multivariable Analysis for Association of Mean VTC with Mortality in APACHE IV Score Subgroups

	ICU Mortality		Hospital Mortality	
VTC Variable	**OR (95% CI)**	P **Value**	**OR (95% CI)**	P **Value**
APACHE IV score ≤ 64				
Continuous variable	1.001 (0.957,1.048)	0.958	0.979 (0.944,1.015)	0.241
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.268 (0.496,3.245)	0.620	0.801 (0.441,1.456)	0.467
15–20 mg/L	1.486 (0.591,3.737)	0.400	0.798 (0.440,1.448)	0.459
> 20 mg/L	1.458 (0.545,3.896)	0.452	0.772 (0.399,1.491)	0.441
APACHE IV score > 64				
Continuous variable	1.061 (1.030,1.092)	< 0.001	1.049 (1.024,1.075)	< 0.001
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.589 (0.770,3.278)	0.210	1.534 (0.882,2.667)	0.130
15–20 mg/L	2.095 (1.032,4.254)	0.041	1.944 (1.128,3.349)	0.017
> 20 mg/L	2.770 (1.350,5.683)	0.005	2.304 (1.319,4.025)	0.003

Multivariable model: adjusted for age (category), sex, ethnicity, BMI, CCl, the use of ventilation, dialysis, hypotensor and hyperensort, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure)
VTC, vancomycin trough concentration; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; BMI, body mass index; CCl, creatinine clearance; COPD, chronic obstructive pulmonary disease.

Table 4
Multivariable Analysis for Association of Mean VTC with Mortality in CCl Subgroups

	ICU Mortality		Hospital Mortality	
VTC Variable	**OR (95% CI)**	P **Value**	OR (95% CI)	P Value
CCl ≤ 80ml/min				
Continuous variable	1.049 (1.018,1.082)	0.002	1.032 (1.006,1.060)	0.017
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.612 (0.706,3.683)	0.257	0.986 (0.541,1.797)	0.963
15–20 mg/L	2.133 (0.956,4.758)	0.064	1.295 (0.724,2.317)	0.384
> 20 mg/L	2.813 (1.251,6.325)	0.012	1.461 (0.807,2.643)	0.211
CCl > 80ml/min				
Continuous variable	1.035 (0.993,1.079)	0.100	1.016 (0.984,1.049)	0.335
Categorical variable				
< 10 mg/L	1		1	
10–15 mg/L	1.437 (0.637,3.237)	0.382	1.330 (0.755,2.344)	0.323
15–20 mg/L	1.905 (0.8541,4.248)	0.115	1.383 (0.782,2.446)	0.265
> 20 mg/L	1.800 (0.757,4.282)	0.184	1.465 (0.784,2.738)	0.231

Multivariable model: adjusted for age (category), sex, ethnicity, BMI, APACHE IV score, the use of ventilation, dialysis, hypotensor and hyperensort, and diagnoses at ICU admission (tumor, hepatic failure, COPD, heart failure, diabetes, gastrointestinal bleed, pancreatitis, burns, pneumonia, sepsis, and renal failure)
VTC, vancomycin trough concentration; CCl, creatinine clearance; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease.

Discussion

In this retrospective multicenter cohort study, we recruited a total of 3,364 critically ill patients with two or more VTC monitoring records after vancomycin therapy from 335 different ICUs at 208 hospitals in the eICU-CRD. Mean VTC was calculated by dividing the sum of all collected VTC by the frequency of monitoring for each patient. Our study showed that mean VTCs of 10–15, 15–20 and > 20 mg/L failed to reduce the ICU and hospital mortalities for critically ill patients. Patients with mean VTCs of 15–20 and > 20 mg/L were found to be exposed to even higher risks of ICU mortality. The results indicated that maintaining high serum VTC throughout the entire course of vancomycin therapy failed to demonstrate benefit for ICU and hospital mortalities in critically ill patients.

As serum VTC has been suggested as a surrogate marker for the AUC/MIC index to monitor vancomycin efficacy, several studies have been designed to verify the association of VTC with clinical and microbiological outcomes in critically ill patients [10]. Surprisingly, most studies found no statistical difference in treatment outcomes according to the VTC level. Two retrospective studies have shown that VTC alone is not a good indicator for vancomycin treatment success among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia [7, 8]. Two other

retrospective cohort studies have demonstrated that VTC > 15 mg/L fails to improve the outcomes of patients with MRSA infection [17, 18]. Additionally, two prospective, multicenter, observational studies have demonstrated no significant association between VTC level and vancomycin treatment response in a Chinese population diagnosed with gram-positive bacterial infections [11, 19]. Moreover, the latest consensus suggests that there are minimal to no data to support the safety and efficacy of a target VTC of 15–20 mg/L in patients with serious MRSA infections [9]. However, those aforementioned studies only explored the relationship between single steady-state VTC and outcomes. In a retrospective study of 76 critically ill patients confirmed MRSA infections, *Cheong* reported that the initial VTC was not associated with treatment response, which was consistent with the results of the other studies. Surprisingly, a corrected VTC, calculated as dividing the sum of each measured VTC multiplied by the number of days at that level by the total number of days under treatment, was higher among patients with improved clinical presentation and laboratory results than among those with poor clinical outcomes [20]. Because of the lack of large-scale population studies on multiple VTC records after receiving vancomycin therapy, which may represent personalized PK/PD profiles of vancomycin, whether the mean VTC derived from the entire course of therapy is of potential benefit for critically ill patients remains unclear.

In this study, the mean VTC was estimated using all collected VTCs throughout the therapy course, providing an overall level of VTC during the ICU stay. The chord diagram showed initial VTC and mean VTC was inconsistent in 55% of all patients. 19.48% of patients with initial VTC < 10 mg/L, 44.3% of patients with initial VTC 10–15 mg/L, and 27.4% of patients with initial VTC > 20 mg/L, had reached a mean VTC 15–20 mg/L eventually, which indicated that initial subtherapeutic or excessive VTC had been adjusted to achieve suggested VTC. Therefore, mean VTC could reflect exposure dosage of vancomycin after adjustment for those with lower or higher initial VTC, to some extent. We further found that mean VTC of 15–20 and > 20 mg/L were significantly correlated with higher ICU mortality (1.946-fold and 2.314-fold) than a mean VTC of < 10 mg/L. Moreover, mean VTCs of 10–15 and 15–20 mg/L had no benefit for hospital mortality. Therefore, this present study is one in a growing number of studies demonstrating that maintaining suggested VTC might not ensure vancomycin efficacy for critically ill patients.

The APACHE IV score is useful for assessing the severity of illness and predicting outcomes in ICU patients [21, 22]. To diminish the influence of disease severity itself, all individuals were divided into two subgroups for further investigations based on the median first APACHE IV score (≤ 64 or > 64). Mean VTCs of 10–15 and 15–20 mg/L might not offer a survival advantage in APACHE IV score ≤ 64 subgroup. In APACHE IV score > 64 subgroup, mean VTCs of 10–15 and 15–20 mg/L were risk factors for ICU and hospital mortalities. Therefore, regardless of the severity of critically ill patients, high mean VTC might not be beneficial for patients receiving the vancomycin.

Vancomycin is eliminated primarily via the renal route, with > 80–90% recovered unchanged in urine within 24 h after administration of a single dose [4]. A decrease in the glomerular filtration rate for any cause would increase the VTC, making the association between mortality and VTC difficult to assess [23]. To exclude the influence of renal function on outcomes, we classified the patients into two groups according to CCl (≤ 80 or > 80 ml/min) to assess this relationship. The results showed that mean VTCs of 10–15 and 15–20 mg/L failed to reduce ICU and hospital mortalities for ICU patients in both the CCl > 80 and ≤ 80 ml/min subgroups. Moreover, a mean VTC of > 20 mg/L might serve as an independent risk factor for ICU mortality in the CCl ≤ 80 ml/min subgroup. Based on these results, other index of TDM for vancomycin management, such as AUC/MIC or Bayesian AUC-only estimation, should be considered to improve prognosis.

A few underlying mechanisms may explain our results. First, Patel et al. reported that patients with a VTC of 15–20 mg/L could achieve an AUC_{0-24}/MIC ratio of ≥ 400 when the MIC value is ≤ 1 [24]. However, several studies have demonstrated a poor correlation between VTC and AUC_{0-24} because of high inter-individual variability [25–28]. A 3-

year, prospective study indicated that 68% of adults who were administered vancomycin with an $AUC_{0-24} \geq 400$ mg·h/L had a trough concentration of < 15 mg/L [29]. Additionally, a prospective study of Chinese patients suggested that C_{max}, AUC_{0-24}, and $AUC_{0-24\,h}$/MIC are not significantly associated with clinical and microbiological outcomes based on multivariable logistic regression analysis [19]. Second, vancomycin has been associated with several adverse events. A multicenter prospective clinical trial that included 288 adult patients indicated that a VTC of > 15 mg/L is associated with a 3-fold increased risk of nephrotoxicity [30]. Another prospective multicenter clinical study in Chinese patients observed that vancomycin nephrotoxicity is significantly correlated with its trough concentration and the cut-off is 13 mg/L [11]. The optimal TDM of vancomycin in ICU patients warrants further investigation.

Limitations

Our study has some limitations. First, given the retrospective nature of the study, the risk of unmeasured confounding effects and introduction of bias were unavoidable. However, this multicenter study of VTC included the largest sample size to date, allowing the findings to be generalized. Second, there is no available information on microbiological outcomes after vancomycin treatment in eICU-CRD. Nevertheless, mortality may represent clinical outcomes to confirm the prognostic value of VTC, as critically ill patients with gram-positive bacterial infections have a high mortality, particularly owing to MRSA infection [31]. Third, we can provide only the association between mean VTC and mortality rather than causality. In the future, a well-designed randomized controlled trial should be considered to evaluate causality between VTC and mortality.

Conclusions

In conclusion, increasing mean serum VTC showed no benefit for ICU and hospital mortalities in critically ill patients, independent of the disease severity or renal function. Therefore, our results suggested that continuous VTC monitoring might not ensure vancomycin efficacy for ICU patients. TDM for vancomycin management using AUC/MIC or Bayesian AUC-only estimation should be studied in the future.

Abbreviations

TDM, therapeutic drug monitoring; ICU, intensive care unit; PK/PD, pharmacokinetic/pharmacodynamics; AUC0–24h/MIC, area under the concentration-time curve over 24 hours/minimum inhibitory concentration; VTC, vancomycin trough concentration; eICU-CRD, eICU Collaborative Research Database; APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; Scr, serum creatinine; CCl, creatinine clearance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus.*

Declarations

Ethical approval and consent to participate

As all protected patient health-related information in the eICU had been deleted, the requirement for individual patient consent was waived. The database is 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).

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets generated and analyzed during the current study is available in the eICU repository, https://doi.org/10.13026/C2WM1R[13].

Competing interests:

The authors declare that they have no competing interests.

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Author contributions:

GW, YH, and JR conceived of the study. GW provided funding for the study. GW, XL and XW provided critical appraisal and revision. JL, RL, YG, XJ, JZ, and JR extracted and collected data from eICU-CRD. YH, XJ, and JL performed statistical analysis. YH and JR wrote the manuscript. YH, JR, JL, XJ, YG, RL, and JZ revised the manuscript. All authors read and approved the final manuscript.

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Figures

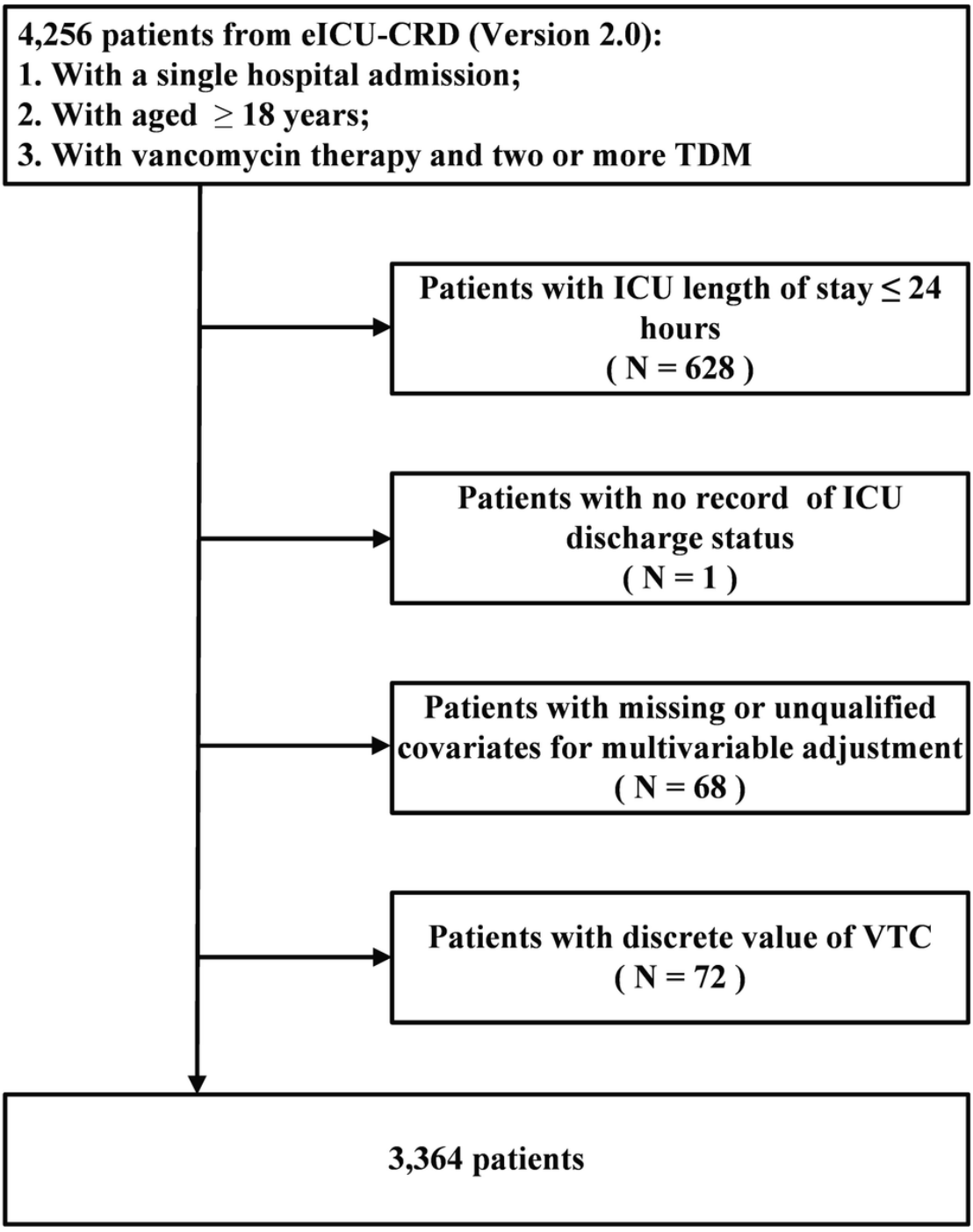

Figure 1

Flow chart of participant selection. Cohort selection and criteria for exclusion, a total of 3,364 patients were included in the analysis. eICU-CRD, eICU Collaborative Research Database; ICU, intensive care unit; TDM, therapeutic drug monitoring; VTC, vancomycin trough concentration.

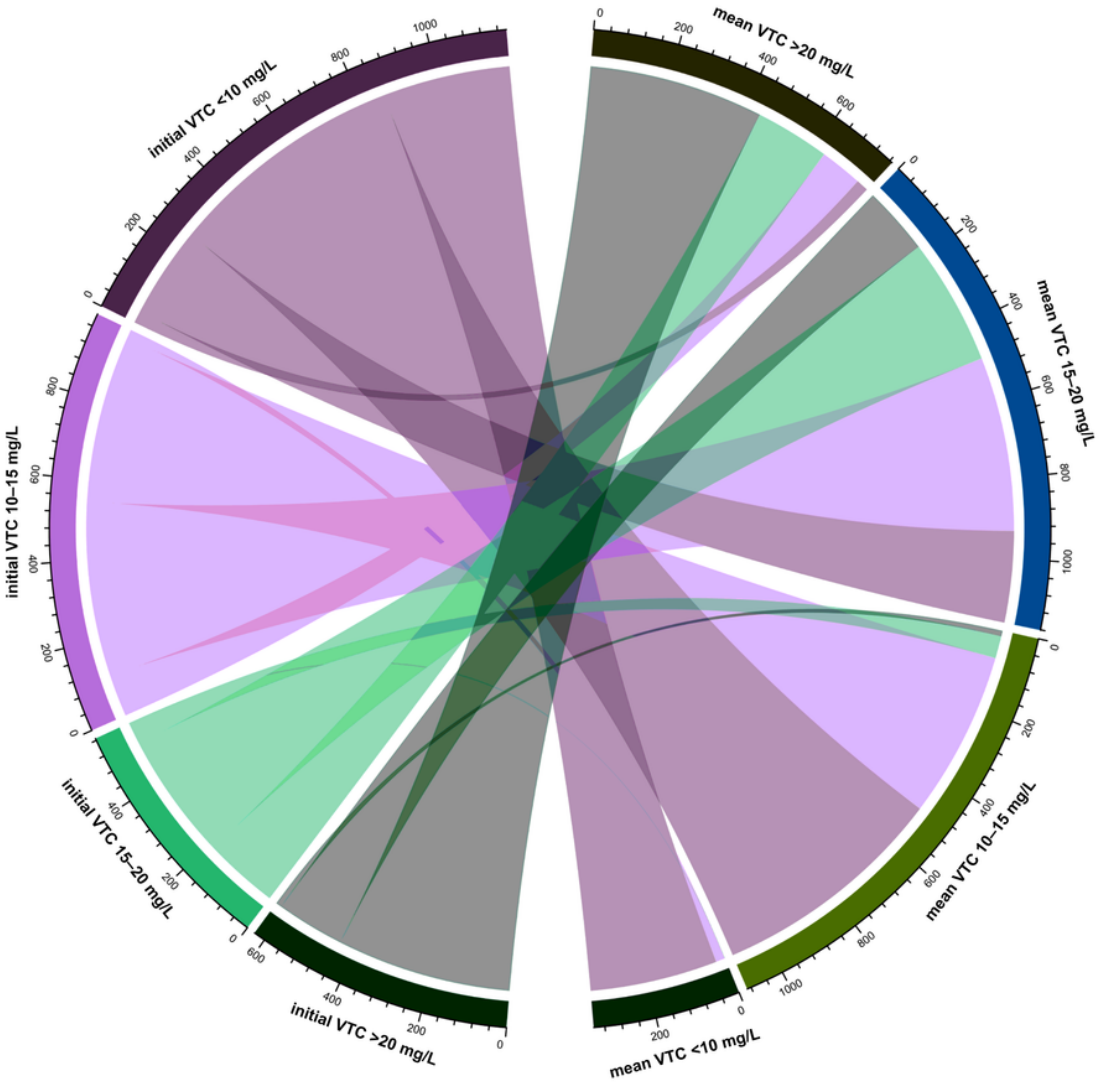

Figure 2

Connection between the mean VTC and initial VTC. A chord diagram presented the difference of the mean VTC with initial VTC for each patient. VTC, vancomycin trough concentration

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