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Jia Wang, Chuzhu Huang, Yan Chen, Yilin Huang & Zhuomin Wu

Vancomycin Therapeutic Drug Monitoring is Associated with Reduced Toxicity in ICU Patients: A MIMIC-IV Retrospective Study

Author information

Jia Wang: The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China

18664446825@163.com

Chuzhu Huang: The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China stcz1234@163.com

Yan Chen: The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China chenyan980115@163.com

Yilin Huang: The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China ylhuang495@163.com

Zhuomin Wu: The First Affiliated Hospital of Shantou University Medical College, Shantou 515041, China [Corresponding Author], wuzhuomin_2012@163.com

Abstract

Background: Vancomycin is a first-line treatment for methicillin-resistant Staphylococcus aureus (MRSA) infections but is associated with risks of nephrotoxicity (5–43%), hepatotoxicity, and hematotoxicity. Therapeutic drug monitoring (TDM) is recommended to optimize dosing, yet its impact on multi-organ toxicity and mortality in intensive care unit (ICU) patients remains controversial because of conflicting evidence and methodological limitations in prior studies.

Methods: Data were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.1) database for a retrospective cohort analysis of 28,451 ICU patients receiving intravenous vancomycin. The primary outcomes were vancomycin-associated nephrotoxicity (AKI according to the KDIGO criteria), hepatotoxicity (ALT/AST ≥120 U/L or bilirubin ≥2.5 mg/dL), and hematotoxicity (thrombocytopenia, anemia, or leukopenia); secondary outcomes included ICU / hospital mortality. Propensity score matching (PSM, 1:1 nearest neighbor with caliper=0.1) balanced 32 baseline covariates, including demographics. The associations between TDM and outcomes were evaluated via multivariable logistic regression and Cox proportional hazards models, with the results validated through subgroup analyses (stratified by comorbidities and concomitant medications) and sensitivity analyses.

Results: Data from 28,451 ICU patients receiving intravenous vancomycin were extracted from the MIMIC-IV database, with 10,758 (37.8%) receiving TDM and 17,693 (62.2%) not receiving TDM. Before PSM, the TDM group presented higher baseline illness severity scores (e.g., SOFA, APS III) and more comorbidities. Unadjusted analyses revealed increased risks of adverse outcomes in the TDM group (AKI: OR = 2.98, 95% CI: 2.83–3.15; hematotoxicity: OR = 1.97, 95% CI: 1.88–2.07; hepatotoxicity: OR = 2.34, 95% CI: 2.19–2.50; all $P <$ 0.001). However, with progressive adjustment for confounders, these associations attenuated significantly (Model 3: AKI OR = 1.93, hematotoxicity OR = 1.55, hepatotoxicity OR = 1.25; all $P < 0.001$). After PSM, the TDM group demonstrated significantly reduced risks of AKI (OR = 0.580, 95% CI: 0.540–0.610, $P = 0.001$), hematotoxicity (OR = 0.760, 95% CI: 0.710–0.800, $P = 0.001$), and hepatotoxicity (OR = 0.800, 95% CI: 0.750–0.860, $P = 0.001$). Secondary outcomes also favored TDM, with lower in-hospital mortality (OR = 0.672, 95% CI: 0.570–0.790, $P = 0.001$) and ICU mortality (OR = 0.691, 95% CI: 0.580–0.820, $P = 0.001$). Kaplan-Meier analysis further confirmed the survival benefits of TDM in both ICU and hospital settings (log-rank $P <$ 0.001). Subgroup analyses revealed that hypertension, type 2 diabetes mellitus (T2DM), cancer, cerebral bleeding (CB), and concomitant use of aspirin or antibiotics were significant risk factors for nephrotoxicity, hematotoxicity and hepatotoxicity.

Conclusion: This study demonstrated that vancomycin TDM is significantly associated with reduced toxicity risks (nephrotoxicity, hepatotoxicity, hematotoxicity) and mortality in intensive care unit (ICU) patients, supporting its routine use in critically ill populations.

Keywords: Vancomycin, therapeutic drug monitoring, ICU, nephrotoxicity, hepatotoxicity, hematotoxicity, MIMIC-IV

1 Introduction

Vancomycin is the first-line antibiotic for treating methicillin-resistant Staphylococcus aureus (MRSA) infections and is also employed in the management of other severe gram-positive bacterial infections[1]. As one of the most widely used antibiotics in the United States, vancomycin has been in clinical use for nearly 50 years [2]. Nonetheless, its application has long been complicated by a narrow therapeutic window and the risk of toxicity. Research has indicated that *S. aureus* infections, particularly MRSA infections, significantly increase patient morbidity, mortality, and healthcare burdens [3][4][5][6][7]. Moreover, vancomycin therapy can cause various adverse reactions, including vancomycin infusion reaction [8], nephrotoxicity [8][9][10], and ototoxicity [11][12]. The incidence of acute kidney injury (AKI) associated with vancomycin ranges from 5% to 43% [13], with a 2.45-fold higher risk of nephrotoxicity than that associated with non-glycopeptide antibiotics [14]. Importantly, this increased risk exists independently of other confounding factors. There is substantial evidence linking vancomycin to nephrotoxicity, demonstrating this association even when vancomycin is not explicitly classified as nephrotoxic in guidelines [15].

To optimize therapeutic efficacy while minimizing toxicity, therapeutic drug monitoring (TDM) of vancomycin is currently recommended by organizations such as the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Japanese Society of Chemotherapy [2][16]. However, the evidence supporting these recommendations remains contentious. On the one hand, the TDM criteria in these guidelines are primarily based on pharmacodynamic targets, such as the area under the concentration–time curve to minimum inhibitory concentration ratio (AUC/MIC), which may not be fully applicable to patients in ICU, whose pathophysiological states can significantly vary. On the other hand, several studies have reported that TDM implementation has not markedly improved clinical outcomes or decreased the incidence of nephrotoxicity [2]. Moreover, some research indicates that the cost-effectiveness of TDM may be limited to specific high-risk populations, including ICU patients, those receiving concomitant nephrotoxic drugs, or oncology patients [17]. This ongoing debate highlights a critical issue: without high-quality evidence, the clinical value of vancomycin TDM remains to be conclusively established.

Current research on vancomycin TDM has notable limitations. Most studies have focused primarily on nephrotoxicity and have often neglected other critical adverse effects, such as hepatotoxicity and hematologic toxicity. Additionally, there is a paucity of research specifically targeting ICU populations, with existing studies confounded by factors such as concomitant nephrotoxic drugs, hemodynamic fluctuations, and underlying diseases. Therefore, this study aimed to evaluate the impact of vancomycin TDM on clinical outcomes in critically ill ICU patients using the MIMIC-IV database. The primary aim was to assess the association between vancomycin TDM and the risk of vancomycin-associated nephrotoxicity, hepatotoxicity, and hematotoxicity. The secondary aim was to investigate the effect of TDM on ICU and in-hospital mortality, as well as to explore potential effect modifiers through subgroup and sensitivity analyses.

2 Materials and methods

2.1 Sources of Data

This retrospective study utilized health-related data obtained from the MIMIC-IV (version 3.1) database, a comprehensive and extensive resource developed and managed by the MIT Computational Physiology Laboratory. This database comprises high-quality medical MIMIC-IV contains de-identified clinical data corresponding to all medical record numbers of patients admitted to the ICU or emergency department between 2008 and 2022 records of patients admitted to the intensive care units of the Beth Israel Deaconess Medical Center. MIMIC-IV contains de-identified clinical data corresponding to all medical record numbers of patients admitted to the ICU or emergency department between 2008 and 2022 [18]. Jia Wang, one of the authors, collected clinical data from the MIMIC database (certification number: 42257067), including patient demographic information, laboratory findings, and medication usage. This project adhered to the principles of the Helsinki Declaration, and approval from the ethics committee was not required because of participant anonymity and data standardization within the database.

2.2 Study population

All adult patients (≥18 years) admitted to the ICU recorded in the MIMIC-IV database were screened for this study. We included patients who were administered vancomycin intravenously after ICU admission. Vancomycin TDM was defined as at least one measurement of the blood vancomycin concentration in laboratory indices at MIMIC-IV during ICU hospitalization. We categorized patients who were or were not treated with vancomycin TDM into a vancomycin group (TDM group) and a control group (non-TDM group). For patients with multiple ICU admissions, only data from their first ICU stay were analyzed. The patient enrollment process for this study is depicted in **Figure 1.**

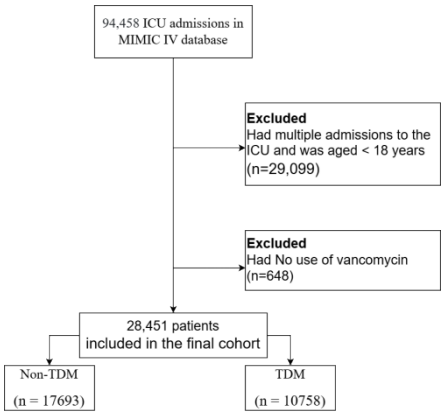

Figure 1. Patient inclusion flow chart.

2.3 Data collection and definitions

Structured Query Language (SQL) was employed to extract data via Navicat Premium software (version 15) on the basis of unique patient identifiers (e.g., stay_id). We collected demographic information, including age, sex, BMI, and race. Disease severity and laboratory indices were assessed via the SOFA score, APS III score, SAPS II score, OASIS score, GCS score, Charlson comorbidity index, and APACHE II score within the first 24 hours of ICU admission. The SIRS criteria were also evaluated. Comorbidities were identified using ICD-9/10 codes, including hypertension, liver cirrhosis, hepatitis, CVA, CKD, cancer, T1DM and T2DM, obesity, sepsis, CB, HF, MI, and IHD, were identified via ICD-9/10 codes. The use of medications, including aspirin and antibiotics, was documented. The laboratory variables collected included RDW, red blood cell count, creatinine, BUN, calcium, chloride, and glucose.

In this study, nephrotoxicity was defined according to the AKI criteria [19], with patients considered positive if they exhibited either an absolute serum creatinine (Cr) increase ≥0.3 mg/dL or a ≥50% Cr elevation from baseline (highest value within 3 days prevancomycin) during treatment [13][20], confirmed by two consecutive measurements. Hematotoxicity was identified by laboratory abnormalities: thrombocytopenia (platelet count $<100\times10^9$/L), leukopenia (white-blood-cell count $<3\times10^9$/L), neutropenia (absolute neutrophil count $<1\times10^9$/L), or anemia (hemoglobin <10 g/dL). Hepatotoxicity required elevations in alanine aminotransferase (ALT ≥120 U/L), aspartate aminotransferase (AST ≥120 U/L), or total bilirubin (≥2.5 mg/dL). All thresholds correspond to Grade ≥2 of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [21], ensuring a standardized and clinically relevant definition. Laboratory values were obtained from baseline samples drawn within 24 h of ICU admission or before any study treatment; patients meeting any single criterion were classified as having the respective toxicity.

2.4 Outcomes

This study aimed to investigate the impact of TDM on medication safety

during vancomycin administration in ICU patients. The primary safety endpoints studied include nephrotoxicity, hematotoxicity, and hepatotoxicity. Secondary outcomes focus on the associations between TDM and in-hospital mortality and ICU mortality. In addition, the study will assess the impact of different comorbidities (e.g., hypertension, liver cirrhosis, hepatitis, etc.). on the effect of TDM through subgroup analyses, with a special focus on whether concomitant use of nephrotoxic medications (e.g., aspirin, antibiotics) affects the safety profile of vancomycin.

2.5 Statistical analysis

Continuous variables were non-normally distributed and are presented as medians with interquartile ranges (IQRs). Categorical variables are summarized as frequencies and percentages. Baseline characteristics between the TDM and non-TDM groups were compared using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Variables with less than 20% missing data were retained, and missing values were handled using multiple imputation in SPSS version 27.

To evaluate the association between vancomycin TDM and clinical outcomes, multivariable regression analyses were conducted. Logistic regression models were used to assess associations with binary outcomes, including AKI, hematotoxicity, and hepatotoxicity. Cox proportional hazards models were applied to estimate the association between TDM use and time-to-event outcomes, including in-hospital and ICU mortality. Effect estimates are reported as odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

Three hierarchical models were constructed: Model 1 (crude), which included no covariate adjustment; Model 2, adjusted for demographic characteristics, major comorbidities, and concomitant medications (race, hypertension, liver cirrhosis, cerebrovascular accident, chronic kidney disease, cancer, type 1 and type 2 diabetes mellitus, obesity, sepsis, chronic bronchitis, heart failure, myocardial infarction, ischemic heart disease, aspirin use, and antibiotics); and Model 3 (fully adjusted), which further included disease severity scores and laboratory parameters (age, BMI, hepatitis, systemic inflammatory response syndrome, SOFA score, APS III, SAPS II, OASIS, GCS, Charlson comorbidity index, APACHE II score, RDW, red blood cell count, creatinine, blood urea nitrogen, calcium, chloride, and glucose).

To control for potential confounding by indication, we used propensity score matching (PSM). PSM was chosen over other adjustment methods, such as multivariable regression or inverse probability weighting (IPW), for its ability to approximate the baseline balance of a randomized controlled trial and facilitate more intuitive outcome comparisons, including the visualization of survival data with Kaplan-Meier curves. The propensity score, representing the probability of receiving TDM, was estimated using a multivariable logistic regression model for which covariates were selected via a principled, two-stage process: we included

both clinically established risk factors for vancomycin toxicity and variables showing a univariate association ($P < 0.10$) with the outcome or exposure. This comprehensive strategy, ultimately including 33 baseline covariates, was intended to reflect the complex clinical reality of ICU patients where multiple physiological parameters—such as direct markers of renal function (creatinine, BUN), indicators of metabolic disturbance (calcium, glucose), and markers of systemic inflammation (RDW)—can act as confounders (see Supplementary Table S2 for a full rationale). Consistent with our data handling strategy, missing values were addressed prior to score estimation using the previously described multiple imputation method (SPSS version 27). Subsequently, we performed 1:1 nearest-neighbor matching without replacement, using a caliper of 0.1 standard deviations of the logit-transformed propensity score. Covariate balance was assessed using standardized mean differences (SMDs), with a value < 0.1 indicating adequate balance.

Following matching, the association between TDM use and clinical outcomes was evaluated within the matched cohort. Logistic regression models were used to assess binary safety outcomes (AKI, hematotoxicity, and hepatotoxicity), while Cox proportional hazards models were applied to estimate associations with time-to-event outcomes (in-hospital and ICU mortality). To account for the paired data structure from matching, all regression models were fitted using robust sandwich variance estimators. Furthermore, we prespecified a doubly robust approach: any clinically important covariates that exhibited residual statistical imbalance ($P < 0.05$) after matching would be included as adjustment variables in these final regression models.

Prespecified subgroup analyses were conducted to explore potential effect modification by clinically relevant factors, including comorbidities (e.g., hypertension, liver cirrhosis, hepatitis, cerebrovascular accident, chronic kidney disease, cancer, diabetes, obesity, sepsis, chronic bronchitis, heart failure, myocardial infarction, and ischemic heart disease) and concomitant medications (e.g., aspirin and antibiotics).

All statistical analyses were performed using R version 4.4.1 and SPSS version 27. A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

A total of 28,451 ICU patients receiving intravenous vancomycin were included, with 10,758 (37.8%) undergoing TDM (**Table 1**)(**Supplementary Table S1**). Prior to matching, patients selected for TDM had a higher baseline risk profile, being significantly older and exhibiting greater disease severity (e.g., higher APS III scores) and comorbidity burden (all $P < 0.001$; **Table 1**). This pattern is consistent with clinical practice where monitoring is prioritized for sicker patients.

Propensity score matching successfully yielded 9,785 pairs of patients. A total of 8,887 patients were excluded due to the lack of a suitable match. After

matching, all 36 baseline covariates were well-balanced based on the standardized mean difference criterion (all SMDs < 0.1; **Figure 2**). Notably, while balance was achieved by the SMD threshold, small but statistically significant differences persisted for age (SMD = 0.08, $P < 0.001$) and baseline creatinine (SMD = 0.09, $P = 0.002$) (**Table 1**).

In this matched cohort, the TDM group demonstrated a lower incidence of AKI (23.21% vs. 34.95%, $P < 0.001$), with reduced AKI severity (stage 3: 43.20% vs. 27.57%, $P < 0.001$). Hematotoxicity was less common in the TDM group (45.03% vs. 52.36%, $P < 0.001$), whereas hepatotoxicity was more common (23.33% vs. 18.48%, $P < 0.001$). The hospital length of stay was longer in the TDM group (median 9.73 vs. 8.88 days, $P < 0.001$), as was the ICU stay (median 1.76 vs. 1.62 days, $P < 0.001$).

Table 1. Baseline characteristics of patients before and after propensity score matching

Variables	Before PSM				After PSM			
	Total (n = 28451)	Non TDM (n = 17693)	TDM (n = 10758)	*P*	Total (n = 19570)	Non TDM (n = 9785)	TDM (n = 9785)	*P*
Patient characteristics								
Age, M (Q_1, Q_3)	68.00 (57.00, 79.00)	69.00 (59.00, 79.00)	66.00 (55.00, 77.00)	<.001	67.00 (56.00, 78.00)	68.00 (57.00, 79.00)	67.00 (55.00, 78.00)	<.001
BMI, M (Q_1, Q_3)	27.76 (24.06, 32.32)	27.68 (24.06, 32.01)	27.96 (24.02, 32.91)	<.001	27.73 (23.95, 32.43)	27.65 (23.92, 32.20)	27.85 (23.98, 32.72)	0.002
Gender, n(%)				0.243				0.235
F	11597 (40.76)	7165 (40.50)	4432 (41.20)		8198 (41.89)	4140 (42.31)	4058 (41.47)	
M	16854 (59.24)	10528 (59.50)	6326 (58.80)		11372 (58.11)	5645 (57.69)	5727 (58.53)	
Race, n(%)				<.001				0.029
OTHER	11970	7926	4044		7213	3533	3680	

Variables	Before PSM				After PSM			
	Total (n = 28451)	Non TDM (n = 17693)	TDM (n = 10758)	*P*	Total (n = 19570)	Non TDM (n = 9785)	TDM (n = 9785)	*P*
	(42.07)	(44.80)	(37.59)		(36.86)	(36.11)	(37.61)	
WHITE	16481 (57.93)	9767 (55.20)	6714 (62.41)		12357 (63.14)	6252 (63.89)	6105 (62.39)	
Laboratory Index								
SOFA, M (Q_1, Q_3)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	0.574	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	0.407
APS III, M (Q_1, Q_3)	37.00 (28.00, 46.00)	36.00 (28.00, 45.00)	38.00 (29.00, 47.00)	<.001	38.00 (29.00, 46.00)	37.00 (29.00, 46.00)	38.00 (29.00, 47.00)	0.082
SAPS II, M (Q_1, Q_3)	32.00 (25.00, 40.00)	32.00 (25.00, 40.00)	32.00 (24.00, 40.00)	0.001	32.00 (24.00, 40.00)	32.00 (24.00, 40.00)	32.00 (24.00, 40.00)	0.057
OASIS, M (Q_1, Q_3)	28.00 (23.00, 33.00)	28.00 (23.00, 33.00)	28.00 (23.00, 33.00)	0.357	28.00 (23.00, 33.00)	28.00 (23.00, 33.00)	28.00 (23.00, 33.00)	0.169
GCS, M (Q_1, Q_3)	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	<.001	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	0.007
Charlson, M (Q_1, Q_3)	5.00 (3.00, 7.00)	5.00 (3.00, 7.00)	5.00 (3.00, 8.00)	0.003	5.00 (3.00, 8.00)	5.00 (3.00, 8.00)	5.00 (3.00, 8.00)	0.067
APACHE II, M (Q_1, Q_3)	15.00 (11.00, 19.00)	15.00 (11.00, 19.00)	15.00 (11.00, 20.00)	0.391	15.00 (11.00, 19.00)	15.00 (11.00, 19.00)	15.00 (11.00, 19.00)	0.597
SIRS, n(%)				<.001				0.122
0	205	147	58		114	60 (0.61)	54	

Variables	Before PSM				After PSM			
	Total (n = 28451)	Non TDM (n = 17693)	TDM (n = 10758)	*P*	Total (n = 19570)	Non TDM (n = 9785)	TDM (n = 9785)	*P*
	(0.72)	(0.83)	(0.54)		(0.58)		(0.55)	
1	3115 (10.95)	1955 (11.05)	1160 (10.78)		2176 (11.12)	1104 (11.28)	1072 (10.96)	
2	9693 (34.07)	6158 (34.80)	3535 (32.86)		6642 (33.94)	3385 (34.59)	3257 (33.29)	
3	12358 (43.44)	7631 (43.13)	4727 (43.94)		8458 (43.22)	4188 (42.80)	4270 (43.64)	
4	3080 (10.83)	1802 (10.18)	1278 (11.88)		2180 (11.14)	1048 (10.71)	1132 (11.57)	
Primary Outcomes								
AKI, n(%)				<.001				<.001
0	10888 (38.27)	8391 (47.43)	2497 (23.21)		5732 (29.29)	3420 (34.95)	2312 (23.63)	
1	17563 (61.73)	9302 (52.57)	8261 (76.79)		13838 (70.71)	6365 (65.05)	7473 (76.37)	
Aki Stage, n(%)				<.001				<.001
1	4180 (23.80)	2770 (29.78)	1410 (17.07)		2948 (21.30)	1663 (26.13)	1285 (17.20)	
2	7725 (43.98)	4443 (47.76)	3282 (39.73)		6002 (43.37)	2947 (46.30)	3055 (40.88)	
3	5658 (32.22)	2089 (22.46)	3569 (43.20)		4888 (35.32)	1755 (27.57)	3133 (41.92)	
Hematotoxicity, n(%)				<.00				<.00

Variables	Before PSM				After PSM			
	Total (n = 28451)	Non TDM (n = 17693)	TDM (n = 10758)	*P*	Total (n = 19570)	Non TDM (n = 9785)	TDM (n = 9785)	*P*
				1				1
0	15775 (55.45)	10931 (61.78)	4844 (45.03)		9563 (48.87)	5123 (52.36)	4440 (45.38)	
1	12676 (44.55)	6762 (38.22)	5914 (54.97)		10007 (51.13)	4662 (47.64)	5345 (54.62)	
Hepatotoxicity, n(%)				<.001				<.001
0	23905 (84.02)	15657 (88.49)	8248 (76.67)		15602 (79.72)	7977 (81.52)	7625 (77.93)	
1	4546 (15.98)	2036 (11.51)	2510 (23.33)		3968 (20.28)	1808 (18.48)	2160 (22.07)	
Secondary outcomes								
Hosp Day, M (Q_1, Q_3)	8.78 (5.63, 16.65)	8.15 (5.38, 14.95)	9.73 (6.01, 20.14)	<.001	9.11 (5.80, 17.94)	8.88 (5.63, 16.82)	9.67 (6.00, 19.17)	<.001
Icu Day, M (Q_1, Q_3)	1.55 (1.00, 3.18)	1.46 (0.99, 2.88)	1.76 (1.04, 4.06)	<.001	1.66 (1.01, 3.53)	1.62 (1.00, 3.23)	1.71 (1.02, 3.83)	<.001

Z: Mann–Whitney test, χ^2: Chi–square test

M: Median, Q_1: 1st quartile, Q_3: 3rd quartile

Body mass index (BMI), Sequential Organ Failure Assessment (SOFA), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II), Systemic Inflammatory Response Syndrome (SIRS), cerebrovascular accident (CVA), chronic kidney disease (CKD), type 1 and type 2 diabetes mellitus (T1DM, T2DM), cerebral bleeding (CB), heart failure (HF), myocardial infarction (MI), ischemiaemic heart disease (IHD), red cell distribution width (RDW), blood urea nitrogen (BUN), acute kidney injury (AKI), hospital length of stay (Hosp Day), and ICU length of stay (Icu Day)

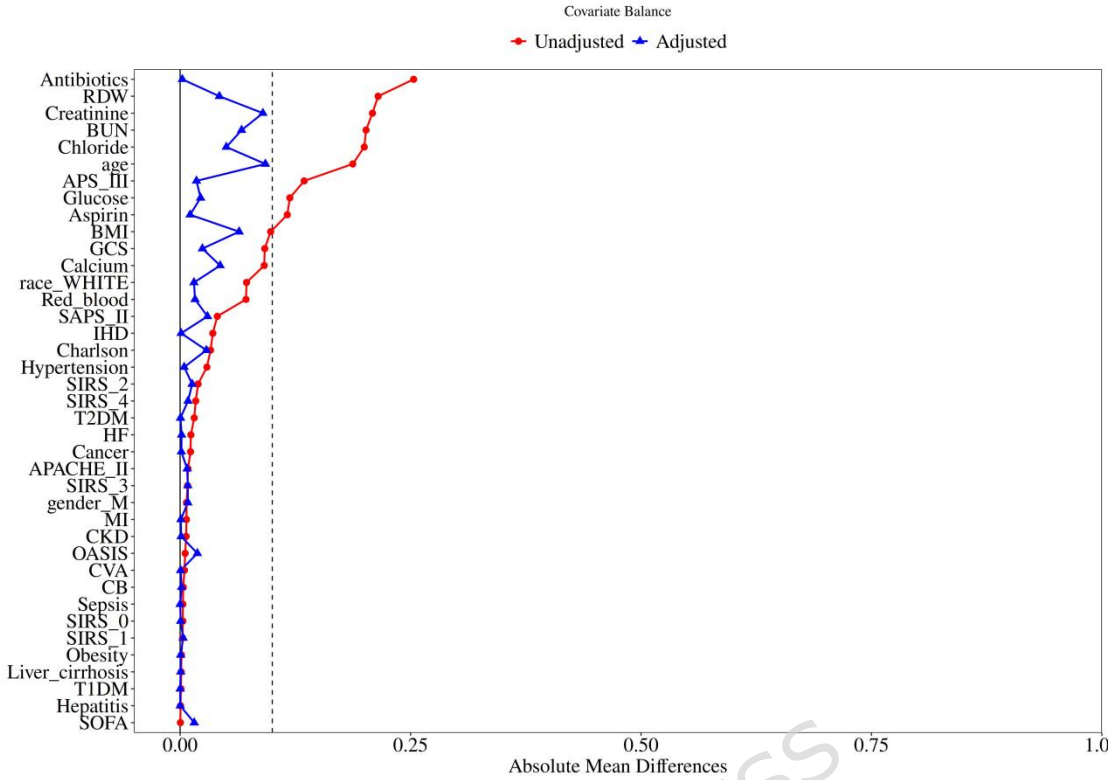

Figure 2: Love plot of standardized mean differences for covariate balance

3.2 Multivariable logistic and Cox regression analyses

Table 2 presents the evolution of the association between vancomycin TDM and clinical outcomes in the full cohort through sequential multivariable adjustment. In the unadjusted analysis (Model 1), TDM was paradoxically associated with substantially higher risks of all adverse events compared to non-TDM, including AKI (OR = 2.98, 95% CI = 2.83–3.15), hematotoxicity (OR = 1.97, 95% CI = 1.88–2.07), and hepatotoxicity (OR = 2.34, 95% CI = 2.19–2.50) (all $P < 0.001$). However, with progressive adjustment for potential confounders—first for demographics and comorbidities (Model 2), and then comprehensively for disease severity and laboratory parameters (Model 3)—these associations attenuated markedly. In the fully adjusted model (Model 3), the point estimates for toxicity risks were substantially reduced (AKI OR = 1.93; hematotoxicity OR = 1.55; hepatotoxicity OR = 1.25; all $P < 0.001$), indicating that a significant portion of the initial risk was attributable to baseline patient differences.

Notably, for the key secondary outcomes, the direction of association reversed upon full adjustment. In Model 3, TDM was associated with significantly lower in-hospital mortality (OR = 0.63, 95% CI = 0.54–0.74, $P < 0.001$) and ICU mortality (OR = 0.72, 95% CI = 0.62–0.85, $P < 0.001$). This pattern—where adjustment transforms an apparently harmful association into a beneficial one—powerfully illustrates the presence of severe confounding by

indication and underscores the necessity of rigorous statistical control in observational studies of TDM.

Table 2. Multivariate-Adjusted Associations between Vancomycin TDM Use and Clinical Outcomes

Variables	TDM		Model 1		Model 2		Model 3	
	Non use (n = 17693)	Use (n = 10758)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Primary Outcomes								
AKI	9302 (52.57)	8261 (76.79)	2.98 (2.83 ~ 3.15)	<.001	1.99 (1.87 ~ 2.12)	<.001	1.93 (1.81 ~ 2.06)	<.001
Hematotoxicity	6762 (38.22)	5914 (54.97)	1.97 (1.88 ~ 2.07)	<.001	1.39 (1.32 ~ 1.47)	<.001	1.55 (1.46 ~ 1.65)	<.001
Hepatotoxicity	2036 (11.51)	2510 (23.33)	2.34 (2.19 ~ 2.50)	<.001	1.49 (1.39 ~ 1.59)	<.001	1.25 (1.16 ~ 1.34)	<.001
Secondary outcomes								
In-Hospital Mortality	8.15 (5.38, 14.95)	9.73 (6.01, 20.14)	0.49 (0.42 ~ 0.57)	<.001	0.58 (0.49 ~ 0.67)	<.001	0.63 (0.54 ~ 0.74)	<.001
In-ICU Mortality	1.46 (0.99, 2.88)	1.76 (1.04, 4.06)	0.51 (0.44 ~ 0.59)	<.001	0.64 (0.55 ~ 0.75)	<.001	0.72 (0.62 ~ 0.85)	<.001

OR: Odds Ratio, CI: Confidence Interval

Model 1: Crude

Model 2: Adjust: race, Hypertension, Liver_cirrhosis, CVA, CKD, Cancer, T2DM, T1DM, Obesity, Sepsis, CB, HF, MI, IHD, Aspirin, Antibiotics

Variables	TDM		Model 1		Model 2		Model 3	
	Non use (n = 17693)	Use (n = 10758)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*

Model 3: Adjust: race, Hypertension, Liver_cirrhosis, Hepatitis, CVA, CKD, Cancer, T2DM, T1DM, Obesity, Sepsis, CB, HF, MI, IHD, SIRS, Aspirin, Antibiotics, age, BMI, SOFA, APS III, SAPS II, OASIS, GCS, Charlson, APACHE II, RDW, Red_blood, Creatinine, BUN, Calcium, Chloride, Glucose

3.3 Sensitivity analysis

Logistic regression analysis after PSM demonstrated significant associations between vancomycin TDM and clinical outcomes (**Figure 3**). For primary safety outcomes, TDM was associated with reduced risks of AKI (OR = 0.580, 95% CI = 0.540–0.610; *P* = 0.001), hematotoxicity (OR = 0.760, 95% CI = 0.710–0.800; *P* = 0.001), and hepatotoxicity (OR = 0.800, 95% CI = 0.750–0.860; *P* = 0.001).

With respect to secondary outcomes, TDM had protective effects on in-hospital mortality (OR: 0.672, 95% CI: 0.570–0.790; *P* = 0.001) and ICU mortality (OR = 0.691, 95% CI = 0.580–0.820; *P* = 0.001). All associations were statistically significant, with *P* values of 0.001 and odds ratios consistently below 1.0, indicating beneficial effects of TDM across all measured outcomes.

The narrow confidence intervals for each outcome suggest precise effect estimates, supporting the robustness of these findings. The consistency in direction and significance across both primary and secondary outcomes reinforces the clinical benefits associated with vancomycin TDM in this patient population.

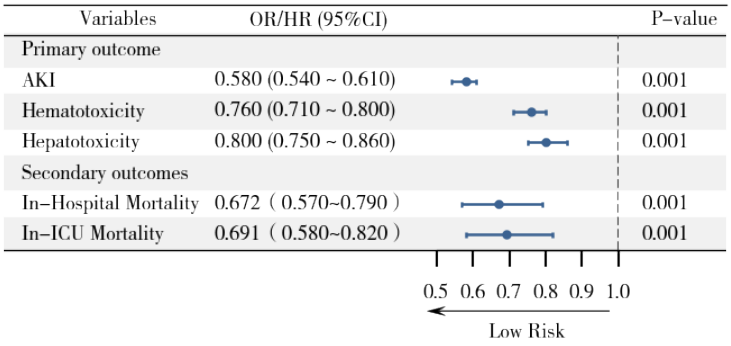

Figure 3. Forest plot: TDM-associated outcomes after PSM analysis

3.4 Subgroup analysis

Subgroup analyses identified distinct and shared risk profiles for vancomycin-associated toxicities (**Figure 4**). Concomitant medication use emerged as a pervasive risk factor: both aspirin and antibiotic use were consistently associated with significantly increased odds across all primary toxicity endpoints (AKI, hematotoxicity, and hepatotoxicity). Condition-specific risks were also prominent. For nephrotoxicity (AKI), the strongest associations were observed with pre-existing cerebral bleeding (OR = 4.96) and cancer (OR = 2.64), alongside hypertension (OR = 2.14). In contrast, the risk profile for hematotoxicity was uniquely characterized by a very strong association with hepatitis (OR = 20.47) and a specific link with type 2 diabetes mellitus (OR = 1.16). Hypertension was again a significant risk factor for hematotoxicity (OR = 1.62). Notably, several variables (e.g., liver cirrhosis, CVA) yielded extreme point estimates with wide confidence intervals, a pattern suggestive of instability due to small subgroup sample sizes. The consistent and significant associations of aspirin and antibiotics with multiple forms of toxicity underscore their clinically important role as potential effect modifiers and risk amplifiers during vancomycin therapy.

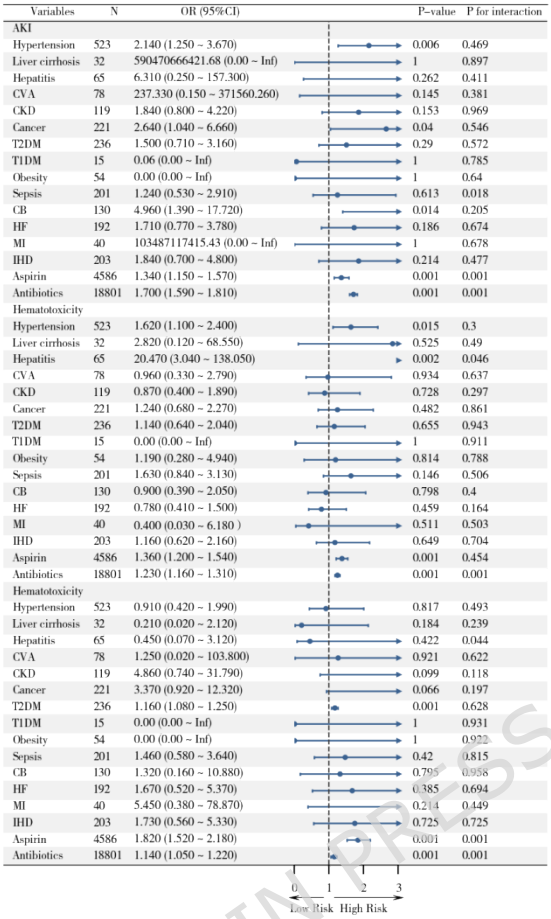

Figure 4. Forest plot: Subgroup analysis of the effects of TDM on vancomycin-associated AKI, cardiotoxicity and hepatotoxicity in ICU patients

3.5 Kaplan–Meier analysis

Kaplan-Meier survival analyses conducted within the propensity score-matched cohort consistently demonstrated significant survival benefits associated with vancomycin TDM (**Figure 5**). This graphical assessment revealed early and sustained separation of the survival curves, favoring the TDM group throughout both the ICU and total hospital follow-up periods. Quantitatively, this visual advantage translated into a substantial and significant reduction in mortality risk. For ICU survival, the TDM group exhibited a 29% lower hazard of death (HR = 0.69, 95% CI = 0.59–0.82, log-rank $P < 0.001$). Similarly, for in-hospital survival, TDM was associated with a 33% reduction in mortality hazard (HR = 0.67, 95% CI = 0.57–0.79, log-rank $P < 0.001$). The robustness of these findings is further supported by the consistently higher number of patients remaining at risk in the TDM group at successive time points (e.g., in-hospital: TDM vs. non-TDM, 9774 vs. 9778 at baseline; 4673 vs. 4246 at later assessments). Together, the clear separation of curves, highly

significant log-rank *P* values, and hazard ratios substantially below 1.0 provide congruent and compelling evidence that vancomycin TDM is associated with significantly improved survival outcomes in critically ill patients.

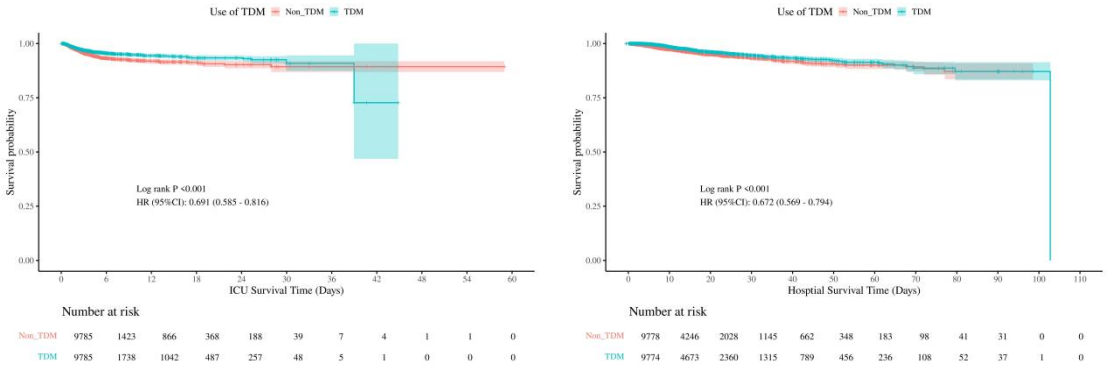

Figure 5. After PSM survival analysis (left: ICU mortality; right: in-hospital mortality)

4. Discussion

The results of this study demonstrate that after rigorous control for confounding, vancomycin TDM is consistently associated with enhanced medication safety in ICU patients. Although initial multivariable regression analyses suggested no safety advantage for the TDM group (OR > 1), this finding must be interpreted in light of substantial baseline differences. Patients selected for TDM had significantly higher disease severity scores and worse clinical status, indicating a classic case of confounding by indication. The progressive attenuation of the odds ratios with sequential covariate adjustment, culminating in a protective association after PSM, provides a powerful methodological lesson. It demonstrates that the initial, seemingly unfavorable results were primarily driven by these pre-existing patient disparities rather than a true lack of TDM benefit. This analytical progression—from a confounded to an adjusted association—effectively isolates the signal of TDM's effect from the noise of clinical selection bias. Consequently, the protective associations observed in the balanced, matched cohort (OR < 1 for all safety outcomes) likely reflect the true relationship between TDM and reduced toxicity. This study thus provides compelling evidence to support the routine implementation of vancomycin TDM in ICU patients. The findings underscore that the clinical practice of reserving TDM for sicker patients, while rational, can obscure its benefits in observational research unless meticulously controlled for.

To place our findings in context, they align with several meta-analyses supporting TDM’s nephroprotective effect, but contrast with some single-center

studies. For example, Yang et al.[22] reported no statistically significant association between vancomycin TDM and a reduced incidence of nephrotoxicity, whereas our study revealed that TDM is significantly associated with a decreased risk of nephrotoxicity in ICU patients. This discrepancy may be attributed to several factors: although Yang's study included 971 treatment sessions, the intervention group comprised only 207 cases, and the follow-up period was short (one year), potentially limiting statistical validity. Additionally, as a single-center retrospective study, it may have suffered from selection bias and inadequate control of ICU-specific confounders such as SOFA scores and vasoactive medication use. Notably, multiple studies support our findings; for example, a systematic review and meta-analysis [23] confirmed that TDM significantly reduces nephrotoxicity risk (HR = 0.25, 95% CI = 0.13–0.48; P <0.0001). Several researchers have also demonstrated that vancomycin therapeutic drug monitoring is associated with shorter treatment durations and lower total doses [2][24][25][26]. Regarding mortality outcomes, evidence from the MIMIC-IV database corroborates our finding that TDM is linked to reduced mortality, despite differences in database versions (3.1 vs. 2.1) [27]. The strengths of this study include the use of multicenter, large-sample ICU data from the MIMIC-IV, rigorous propensity score matching, multiple regression analyses, and sensitivity tests that validate the robustness of our results. These methodological strengths provide a greater level of evidence supporting an association between TDM and nephroprotection in critically ill patients.

A key contribution of our study is the parallel analysis of mechanistically distinct toxicities: while vancomycin ' s nephrotoxicity is dose-dependent, hepatotoxicity and hematotoxicity are often immune-mediated. Our findings in a propensity score-matched cohort revealed that TDM was associated with a reduced risk of both hepatotoxicity and hematotoxicity. This observed association aligns with TDM's primary goal of optimizing dosage to mitigate the overall toxicity burden. However, a deeper understanding of the pathophysiology of these adverse events is crucial for clinical vigilance. Vancomycin-induced liver injury is typically an idiosyncratic, immune-mediated hypersensitivity reaction (e.g., as part of DRESS syndrome) and is associated with prolonged treatment and genetic factors (e.g., HLA-A*32:01 allele), not elevated serum levels [28][29][30]. Likewise, hematological toxicities like thrombocytopenia are mainly caused by drug-dependent antibodies leading to rapid cell clearance, a mechanism contingent on individual immune sensitization rather than drug concentration [31][32][33]. Consequently, patients in our cohort who received TDM likely had more severe infections requiring prolonged exposure to vancomycin. This extended duration is an independent risk factor for the immune sensitization underlying these reactions [30][34][35]. Therefore, our results present a critical nuance: although TDM is associated with a protective effect, likely mediated by the avoidance of excessive drug concentrations, clinicians must recognize that rare, immune-mediated toxicities can still arise from different pathways. This conclusion underscores the clinical significance of our

work, highlighting that the development of hepatotoxicity or hematotoxicity should prompt an investigation into an immune-mediated cause, thereby ensuring thorough patient monitoring.

In this study, we systematically analyzed the risk factors associated with vancomycin-related toxicity. We found that hypertension, malignancy, CB, aspirin use, and antibiotic coadministration were significantly linked to an increased risk of nephrotoxicity. Conversely, hypertension, hepatitis, aspirin, and antibiotic use were significantly associated with hematologic toxicity. Notably, type 2 diabetes was specifically associated with hepatotoxicity, and the combination of aspirin with antibiotics consistently demonstrated significant correlations across all toxicity analyses. Previous studies have identified key risk factors for vancomycin-associated nephrotoxicity, including the concurrent use of nephrotoxic drugs (e.g., aminoglycosides, amphotericin B) [36][37][38], prolongation of treatment duration [36][39], and the use of vasoactive medications [39]. Vancomycin exhibits considerable interindividual variability in pharmacokinetics among adults [40], a variation that is particularly pronounced in critically ill populations such as patients with severe sepsis, those undergoing continuous veno-venous hemodialysis, patients with malignancies, neonates, and severe burn victims [10][14][41][42][43][44][45][46][47]. Moreover, predicting blood levels in specific high-risk groups—such as patients with heart failure [48], obesity [49], or renal insufficiency[36][39][50]—is challenging, underscoring the importance of TDM in these populations. Some studies [51] have also suggested that TDM provides limited clinical benefit in patients with normal renal function. Our findings confirm known risk factors and, importantly, for the first time, systematically reveal a potential synergistic effect of aspirin across multiple forms of vancomycin toxicity. This novel insight may inform more rational and evidence-based clinical use of vancomycin.

Although the present study was limited by the use of the MIMIC-IV database, which precluded the collection of data on ototoxicity and vancomycin infusion reaction, the literature offers valuable insights into these adverse reactions. Research indicates that vancomycin infusion reaction is primarily mediated by histamine release and manifests clinically as flushing and tingling sensations in the face, neck, and upper body [8]. Its occurrence is closely related to the infusion rate, with a significantly increased risk when doses exceeding 500 mg are infused rapidly over 30 minutes [11][17][52]. Consequently, clinical guidelines recommend controlling the infusion time for 1 g doses to at least 1 hour [53] and for higher doses (e.g., 2 g) to extend to 1.5–2 hours [54]. These standardized practices effectively prevent the syndrome. With respect to ototoxicity, available studies depict a more complex picture. Early reports by Bailie et al. [55], covering studies from 1956--1986, linked ototoxicity mainly to vancomycin preparations with high impurity levels. Notably, several studies have failed to establish a clear association between vancomycin blood levels and ototoxicity [2][53], and the incidence of ototoxicity when vancomycin is used alone appears to be very low [2]. Age has emerged as a significant risk factor

[56], with a retrospective study demonstrating a higher incidence in patients aged ≥53 years than in younger patients ($P = 0.008$) [57]. Additionally, coadministration of other ototoxic agents (e.g., aminoglycosides and certain diuretics) may result in synergistic toxicity. On the basis of current evidence, heightened vigilance remains necessary for high-risk groups, such as elderly individuals, individuals with pre-existing hearing loss, and those receiving multiple ototoxic medications [58]. These findings increase our understanding of the adverse effects of vancomycin. Although this study's database limitations prevented direct analysis of these outcomes, existing evidence suggests that these drug-related risks can be effectively managed through infusion standardization and identification of at-risk populations.

Although vancomycin dose and trough concentration data were not directly analyzed in this study, the available evidence indicates that these parameters are strongly associated with safety. The literature consistently demonstrates that elevated serum trough concentrations and prolonged vancomycin treatment duration increase the risk of nephrotoxicity [59]. Older age, longer treatment courses, and lower serum vancomycin concentrations (30–65 mg/L) are significant risk factors for vancomycin-induced nephrotoxicity [60]. Notably, treatment durations exceeding one week can increase nephrotoxicity risk from 6% to 30% [61], and concomitant use of nephrotoxic agents (e.g., aminoglycosides) can increase the incidence from 5–7% to as high as 22% with monotherapy [2][11][37]. The pharmacokinetic properties of vancomycin, which accounts for approximately 80–90% of vancomycin renally excreted [20], underscore the importance of precise dose adjustment in patients with renal impairment [62]. Multiple studies have shown that higher doses significantly increase nephrotoxicity risk, with rates reaching 12–42.7% [10][11][36][63][64]. While clinical guidelines for MRSA infection management [65] and the vancomycin TDM consensus [2] recommend maintaining trough levels between 15–20 μg/mL and Australian guidelines suggest 12–18 μg/mL [66] (to ensure an AUC/MIC ≥400 [2]), recent research indicates that these ranges may heighten the risk of acute kidney injury [67][68]. In high-risk populations, such as pediatric, renal failure, or critically ill patients [20][69][70][71], individualized dosing via TDM is essential because of significant pharmacokinetic variability [72]. With respect to administration mode, studies comparing continuous versus intermittent infusion have yielded mixed results. Although some reports suggest potential advantages of continuous infusion, there is no conclusive evidence that it is superior in terms of clinical outcomes [73][74][75]. Consequently, current guidelines continue to endorse intermittent infusion as the standard. These findings underscore the critical role of TDM in balancing efficacy and safety, particularly in high-risk groups.

This study has several notable strengths. Its primary strength is the use of a large, real-world cohort, which enhances the generalizability of our findings. Furthermore, a key methodological strength lies in our rigorous and transparent

approach to confounder adjustment. While including numerous covariates in our regression models (**Table 2**, Model 3) could theoretically increase the risk of overfitting, our large sample size (n = 28,451) provides substantial statistical power to mitigate this concern. More importantly, the sequential presentation of Models 1-3 was intentionally designed to transparently demonstrate how effect estimates changed with progressive adjustment, thereby illustrating the powerful impact of confounding. This detailed, stepwise approach, as detailed in Supplementary Table S2, reinforces the robustness of our conclusions while maintaining methodological rigor. However, our study also has limitations. First, although we used AKI based on the KDIGO criteria as a surrogate for nephrotoxicity — which is consistent with most literature [2][76] — this may introduce bias in assessing drug-related nephrotoxicity in clinical practice [77]. Second, owing to database constraints, we could not differentiate between types of TDM modalities (e.g., AUC monitoring versus trough concentration monitoring alone) or access specific TDM protocols (e.g., sampling times, dose adjustment criteria) at individual centers, potentially affecting result interpretation. Third, despite the use of multivariate adjustment and propensity score matching (with a caliper of 0.1), residual confounding may persist in this retrospective design. Fourth, while PSM balanced a wide array of observed confounders, the exclusion of a substantial number of patients (n = 8,887) who could not be matched introduces a potential for selection bias. This may limit the generalizability of our findings. Fifth, the large sample size in this study necessitates careful interpretation of statistical significance. For instance, the statistically significant difference in hospital length of stay (< 1 day) is of limited clinical relevance. We applied this principle consistently: the persistence of statistically significant *P* values for age and creatinine after matching, despite excellent balance as measured by SMDs (< 0.1), is more likely attributable to high statistical power than to residual confounding of clinical importance. This consistency in interpretation reinforces the rationale behind our a priori decision to prioritize the SMD—a sample-size-independent metric—for assessing covariate balance. It is important to note that despite rigorous adjustment through propensity score matching, our study retains the inherent limitations of an observational design. Although we observed strong associations between TDM and reduced toxicity risks, residual confounding by indication may persist, as the clinical decision to implement TDM was not randomized. Therefore, our findings should be interpreted as demonstrating significant associations rather than establishing definitive causal relationships. Additionally, the database included only hospitalization data, preventing the assessment of delayed adverse events such as permanent hearing impairment that may manifest postdischarge. Finally, this study did not evaluate the economic aspects of TDM implementation; however, existing evidence suggests [17][47] that TDM can be cost-effective — particularly in critically ill, oncologic, or patients receiving conephrotoxic agents — a crucial consideration for future research and clinical decision-making.

5. conclusion

This study confirms that implementation of vancomycin TDM in ICU patients is significantly associated with enhanced medication safety. Cohort analysis demonstrated that TDM is associated with a substantial reduction in vancomycin-related nephrotoxicity, hematotoxicity, and hepatotoxicity, as well as a notable decrease in ICU and in-hospital mortality. Importantly, TDM also benefits high-risk patients, including those with hypertension or those receiving nephrotoxic comedications. These findings underscore the importance of routine vancomycin TDM in critically ill populations.

Declarations

Abbreviations

Abbreviation	Full Term
AKI	Acute kidney injury
APS III	Acute Physiology Score III
APACHE II	Acute Physiology and Chronic Health Evaluation II
ASHP	American Society of Health-System Pharmacists
BMI	Body mass index
BUN	Blood urea nitrogen
CB	Cerebral bleeding
CI	Confidence interval
CKD	Chronic kidney disease
Cr	Serum creatinine
CVA	Cerebrovascular accident
GCS	Glasgow Coma Scale
HF	Heart failure
Hosp Day	Hospital length of stay
Icu Day	ICU length of stay
ICD	Ischemic heart disease

Abbreviation	Full Term
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
MIMIC-IV	Medical Information Mart for Intensive Care IV
MI	Myocardial infarction
MRSA	Methicillin-resistant Staphylococcus aureus
OASIS	Oxford Acute Severity of Illness Score
OR	Odds ratio
PSM	Propensity score matching
RDW	Red cell distribution width
SAPS II	Simplified Acute Physiology Score II
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SQL	Structured Query Language
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TDM	Therapeutic drug monitoring

Data declarations

The research involving human participants was approved, and the need for further ethical approval was waived by the Clinical Research Ethics Committee of the First Affiliated Hospital of Shantou University Medical College, Shantou. This exemption was granted because ethical approval for the MIMIC-IV database had already been obtained from the institutional review boards (IRBs) of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The study complied with local regulations and institutional standards. Furthermore, written informed consent from participants or their legal guardians / next of kin was waived by the ethics committee / institutional review board, as the research followed applicable legal and institutional policies, and the database contains no protected health information.

Consent for publication

All authors have read and approved the final manuscript and consent to its publication in this journal.

Availability of data and materials

The MIMIC-IV database used in this study is publicly available to researchers who meet the criteria for access. Detailed instructions for obtaining the data can be found at https://mimic-iv.mit.edu/.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

This short text acknowledges the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors. All the authors contributed to the study conception and design. Project design, patient information verification, and data cleaning, W.J.; paper writing and data checking, W.Z.M.; data inclusion and cleaning, H.C.Z.; data organization and statistical analysis, C.Y.; and data statistics, H.Y.L. All the authors have read and agreed to the published version of the manuscript.

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