

ARTICLE

Development and Validation of a Risk Prediction Model of Vancomycin-Associated Nephrotoxicity in Elderly Patients: A Pilot Study

Chen Pan^{1,†}, Aiping Wen^{1,†}, Xingang Li¹, Dandan Li¹, Yang Zhang¹, Yin Liao¹, Yue Ren¹ and Su Shen^{1,*}

This exploratory study aimed to develop a risk prediction model of vancomycin-associated nephrotoxicity (VANT) in elderly patients. Clinical information of elderly patients who received vancomycin therapy from January 2016 to June 2018 was retrieved. A total of 255 patients were included in this study. Univariate analysis and multivariable logistic regression analysis revealed that vancomycin trough concentration ≥ 20 mg/L (odds ratio (OR) = 3.009; 95% confidence interval (CI) 1.345–6.732), surgery (OR = 3.357; 95% CI 1.309–8.605), the Charlson Comorbidities Index ≥ 4 points (OR = 2.604; 95% CI 1.172–5.787), concomitant use of cardiotoxic drug (OR = 3.283; 95% CI 1.340–8.042), plasma volume expander (OR = 3.459; 95% CI 1.428–8.382), and piperacillin/tazobactam (OR = 2.547; 95% CI 1.680–6.007) were risk factors for VANT in elderly patients. Furthermore, a VANT risk prediction model was developed, which had good discriminative power and was well-calibrated.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Vancomycin-associated nephrotoxicity (VANT) is a common adverse drug reaction of vancomycin. Elderly patients with specific physiological parameters are more likely to develop VANT. However, to our knowledge, there are few reports about developing a risk prediction model of VANT in elderly patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Our study aimed to answer the questions of (i) which factors would affect the incidence of VANT in elderly patients, and (ii) whether it was possible to construct a risk prediction model of VANT in these patients.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Except for vancomycin trough concentration ≥ 20 mg/L and concomitant usage of piperacillin/tazobactam, we found that surgery, the Charlson Comorbidities Index ≥ 4 points, concomitant usage of cardiotoxic drugs, and plasma volume expander were also risk factors for VANT in elderly patients. Moreover, a risk prediction model for VANT in elderly patients was developed and validated.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ Our model might be used to identify high-risk elderly patients for close monitoring in practice as an assessment tool, although further investigations were needed to verify it.

Vancomycin is used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections.^{1,2} Vancomycin-associated nephrotoxicity (VANT)³ is a common adverse drug reaction, and is linked to the need for renal replacement therapy, prolonged hospitalization, higher healthcare costs, and increased mortality.⁴ Elderly patients are more likely to develop VANT^{5–7} due to multiple illnesses and complicated medications. The incidence of VANT in the general adult patients was 4.7–15.4%,^{8–11} whereas the rate was 15.8–29% in elderly patients.^{6,12} With the aging of our society, VANT in elderly patients is worthy of more attention.¹²

Previous studies indicate that age,⁷ mechanical ventilation,¹² intensive care unit (ICU) admittance,¹³ vancomycin

trough concentration,^{9,14–17} dose,¹⁵ length of therapy,^{9,17} infusion method (continuous or intermittent infusions),^{18,19} cirrhosis,¹⁴ hypertension,²⁰ hyperuricemia,¹² shock,⁶ heart failure,⁶ concomitant medications, vasopressor drugs,^{16,17} aminoglycosides,^{9,21} contrast agents,^{22,23} piperacillin/tazobactam (PTZ),^{24,25} furosemide,^{3,11} amphotericin B,²⁶ and the Acute Physiology and Chronic Health Evaluation II (APACHE-II)^{21,27} are risk factors associated with VANT. However, only two studies reported VANT risk factors in elderly patients.^{6,12} Additionally, there are few reports on developing risk prediction models of VANT in elderly patients. Therefore, we attempted to explore clinical predictors of VANT to construct a risk prediction model of VANT in elderly patients.

†Chen Pan and Aiping Wen contributed equally to this work.

¹Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, China. *Correspondence: Su Shen (shensu11022000@163.com)

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METHODS

Study population

This was a retrospective study performed at Beijing Friendship Hospital, Capital Medical University. Inpatients treated with vancomycin from January 2016 to June 2018 were recruited. The inclusion criteria were: (i) ≥ 60 years old; and (ii) receiving vancomycin therapeutic drug monitoring (TDM). Patients were excluded if: (i) receiving vancomycin therapy < 48 hour; (ii) stage 5 chronic kidney disease; (iii) receiving renal replacement therapy; and (iv) lack of enough serum creatinine (SCr) information to assess VANT. This study was approved by the ethics committee of Beijing Friendship Hospital (Reference No. 2019-P2-168-01).

Data extraction

Patients' clinical parameters were extracted mainly based on previous studies.^{3,6,7,9,12-23,26,27} Data extracted from the hospital's electronic database included sex, weight, date of birth, admission dates and diagnosis, serum lactic acid, serum creatinine and serum albumin, the start and stop dates of vancomycin, vancomycin dosage and interval, and concomitant medications, including angiotensin converting enzyme inhibitors, angiotensin receptor blocker, aminoglycoside, carbapenem, quinolones, antiviral drugs, diuretics, immunosuppressant, proton pump inhibitors, cardiotoxic drugs, vasopressor, plasma volume expander, contrast agent, fluconazole, voriconazole, caspofungin, amphotericin B, PTZ, mannitol, sulfamethoxazole, and aescinate. Other information extracted included if patients were transferred to the ICU, had surgery, and/or mechanical ventilation while on vancomycin therapy. Charlson Comorbidities Index (CCI) was calculated based on admission diagnosis.²⁸ All vancomycin trough concentrations were recorded. For patients who developed VANT, only trough concentrations, serum lactic acid, serum creatinine, and serum albumin collected before the occurrence of VANT were analyzed. If multiple vancomycin trough serum concentrations were measured, the maximum concentration was chosen for analysis.¹⁴

Dosing of vancomycin

Local vancomycin dosing protocol is 0.5 g q8h for elderly patients with intermittent infusion at rate of 500 mg/hour. Vancomycin trough level is measured for TDM, with blood sample taken 30 minutes before the next dose. TDM is conducted 48 hours after vancomycin therapy or dose adjustment. Clinicians adjust vancomycin dose based on infection parameters, adverse reactions, and the results of TDM.

Definition of VANT

VANT was defined as acute kidney injury that occurred during vancomycin therapy or within 2 days of discontinuing of vancomycin. Acute kidney injury was selected as the major screening criterion based on the Kidney Disease: Improving Global Outcomes definition: an increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours or increase in SCr to ≥ 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days.²⁹

Data analysis

By simple randomization, all eligible patients were randomized into a train set and a validation set (4:1 ratio). Based on the train data set, a risk model and a risk score system were developed sequentially.

Normally distributed continuous variables were expressed as the mean \pm SD, and groups were compared using the independent *t*-test. Non-normally distributed continuous variables were presented as the median (interquartile range), and groups were compared using the rank-sum test. Categorical variables were expressed as number (percentage) and analyzed using the χ^2 test or Fisher's exact test.

For a clearer expression, age was divided into 60–79 and ≥ 80 years, serum albumin valley was divided into < 25 and ≥ 25 g/L, CCI score was divided into < 4 and ≥ 4 points, the vancomycin trough concentration was divided into 4 groups: < 10 mg/L, 10–15 mg/L, 15–20 mg/L, and ≥ 20 mg/L.

Variables that were significant at $P < 0.1$ in the univariate analyses and of clinical importance were entered into a stepwise multivariable logistic regression model. Variables retained in the final model were used to construct the risk model. According to the multivariable logistic regression model, a risk score was developed. To evaluate the discrimination of the risk model, receiver operating characteristic (ROC) curves were constructed, and area under the curve (AUC) was calculated. The calibration of the risk model was evaluated by the Hosmer-Lemeshow test and calibration plot. All data analyses were performed using SAS version 9.4 (SAS Institute). A two-sided $P < 0.05$ was considered significant.

RESULTS

Basic information

As shown in **Figure 1**, of the 2,008 patients who received vancomycin, 255 were included in the study. The most common reason for patient exclusion was stage 5 chronic kidney disease (68.25%; 86/126). Of the 1,110 elderly inpatients who received vancomycin, 34.32% (381/1110) received vancomycin TDM. Among the 255 patients, 63 (24.71%) experienced VANT. Forty-seven of the 204 patients (23.04%) experienced VANT in the train set, whereas 16 of 51 (31%) experienced VANT in the validation set. All factors considered except sex and age were balanced between the train and validation sets (**Table 1**).

Univariate analysis

A comparison of patient characteristics in the train set was shown in **Table S1**. A total of 15 variables were significant ($P < 0.1$) in the univariate analyses (**Table 2**). After excluding concomitant immunosuppressant (as the number of cases was too low), 14 variables finally entered into multivariable logistic regression analysis, including: age, surgery, ICU admittance, mechanical ventilation, serum albumin valley, CCI score, respiratory failure, sepsis, trough concentration, aminoglycoside, cardiotoxic drug, vasopressor, plasma volume expander, and PTZ.

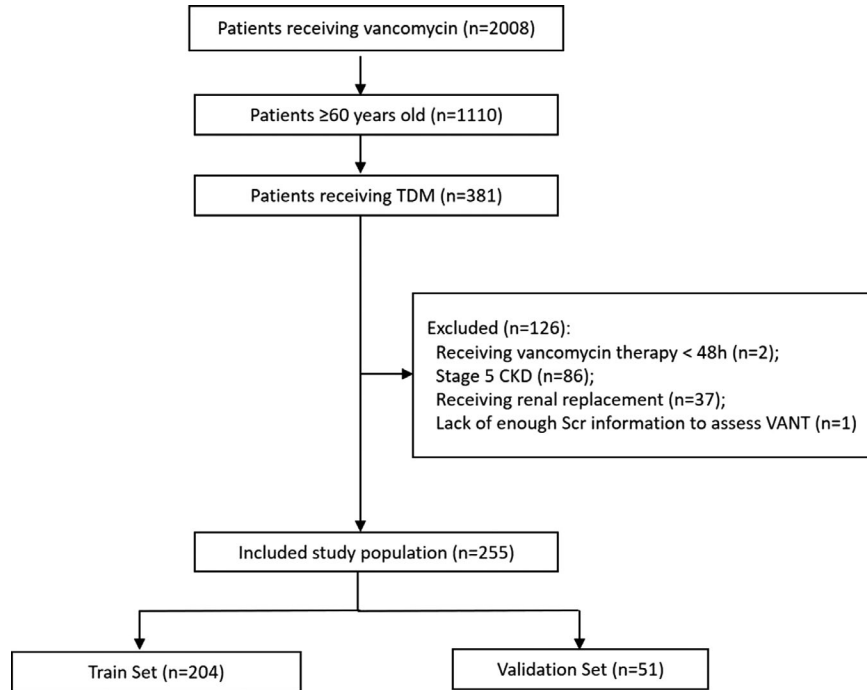


Figure 1 Flowchart of patients included in this study. CKD, chronic kidney disease; SCr, serum creatinine; TDM, therapeutic drug monitoring; VANT, vancomycin-associated nephrotoxicity.

The vancomycin trough concentration was originally divided into 4 groups: < 10 mg/L, 10–15 mg/L, 15–20 mg/L, and ≥ 20 mg/L. Univariate logistic regression analysis showed that VANT was associated with vancomycin trough concentration ≥ 20 mg/L (odds ratio (OR) = 3.450; 95% confidence interval (CI) 1.146–10.390; **Table S2**). Hence, vancomycin trough concentration was divided into two groups of < 20 or ≥ 20 mg/L in the multivariable logistic regression analysis.

Multivariable logistic regression model

Multiple logistic regression analysis revealed that vancomycin trough concentration ≥ 20 mg/L (OR = 3.009; 95% CI 1.345–6.732), surgery (OR = 3.357; 95% CI 1.309–8.605), CCI score ≥ 4 (OR = 2.604; 95% CI 1.172–5.787), concomitant cardiotoxic drug (OR = 3.283; 95% CI 1.340–8.042), plasma volume expander (OR = 3.459; 95% CI 1.428–8.382), and PTZ (OR = 2.547; 95% CI 1.680–6.007) were risk factors for VANT (**Table 3**). On the basis of a multiple logistic regression model, a risk VANT prediction model in elderly patients was constructed:

$$\text{logit}(P) = -5.3349 + 1.2109 \times \text{surgery} + 1.1016 \times (\text{vancomycin trough concentration}) + 0.9572 \times \text{CCI} + 1.1887 \times (\text{cardiotoxic drug}) + 1.2410 \times (\text{plasma volume expander}) + 0.9350 \times \text{PTZ} \quad (1)$$

where surgery, yes = 1, no = 0; vancomycin trough concentration, < 20 mg/L = 1 and ≥ 20 mg/L = 2; CCI score, < 4 = 1 and ≥ 4 = 2; cardiotoxic drug, yes = 1, no = 0; plasma volume expander, yes = 1, no = 0; and PTZ, yes = 1, no = 0.

In the train set, the risk model had excellent discriminative power, with the AUC of 0.8278 (95% CI 0.7577–0.8979) and was well-calibrated with the Hosmer-Lemeshow χ^2 statistic of 1.4791 ($P = 0.9830$; **Figure 2**).

Risk score development

To facilitate the clinical application, each risk factor was assigned a risk score according to the VANT risk assessment model (**Table 4**). The total risk score ranged from 0 to 6, with corresponding predicted probabilities of VANT ranging from 3.64–91.16% (0, 3.64%; 1, 8.78%; 2, 19.68%; 3, 38.44%; 4, 61.39%; 5, 80.20%; and 6, 91.16%). The incidence of VANT by risk assignment was depicted in **Figure S1**. In the train set, the trend of higher risk score linking to a higher incidence of VANT was apparent.

The risk scores were categorized into three levels to enhance the clinical use of the risk score model. Three risk levels were provided: low-risk (score 0–2, VANT incidence 12.3%), moderate-risk (score 3–4, VANT incidence 63.2%), and high-risk (score 5–6, VANT incidence 75.0%). In the train set, the trend of higher risk level linking to a higher incidence of VANT was apparent (**Figure S2**).

Model validation

The VANT risk model demonstrated good discriminative power in the validation population, with AUC of 0.7357 (95% CI 0.5813–0.8901; **Figure 2**). The incidence of VANT in the validation set showed evident increasing trend across each score value (**Figure S1**). In the validation set, the incidence of VANT of the low-risk, moderate-risk, and high-risk levels were, respectively, 22.5%, 55.6%, and 100.0%, which

Table 1 Demographic and clinical data of the patients in the train and validation sets

Variable	Train set (N = 204)	Validation set (N = 51)	P value
Demographic characteristics			
Sex (male/female)	143/61	25/26	0.0045
Age (years)	84.0 (75.0, 90.0)	82.0 (73.0, 88.0)	0.0619
60–79 n (%)	64 (31.4%)	24 (47%)	0.0351
≥ 80 n (%)	140 (68.6%)	27 (53%)	
Surgery n (%)	43 (21.1%)	11 (22%)	0.9389
ICU admittance n (%)	47 (23.0%)	14 (28%)	0.5089
Mechanical ventilation n (%)	53 (26.0%)	13 (26%)	0.9430
Laboratory variables			
Baseline SCr (μmol/L) ^a	74.9 (62.4, 91.5)	70.5 (54.5, 103.6)	0.9655
Peak serum lactic acid (mmol/L) ^b	2.5 (1.8, 3.3)	2.5 (2.0, 3.5)	0.9746
Serum albumin valley (g/L)	25.7 ± 4.67	25.5 ± 5.41	0.7959
< 25 n (%)	83 (40.7%)	22 (44%)	0.7504
≥ 25 n (%)	121 (59.3%)	29 (57%)	
Comorbidity			
CCI score	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	0.6589
< 4 n (%)	123 (60.3%)	32 (63%)	0.7485
≥ 4 n (%)	81 (39.7%)	19 (37.3%)	
Vancomycin therapy			
Daily dose (g/day)	1.5 (1.1, 1.9)	1.3 (1.1, 1.9)	0.7899
< 1.5 n (%)	103 (50.5%)	30 (59%)	0.4501
1.5–2 n (%)	52 (25.5%)	9 (18%)	
≥ 2 n (%)	49 (24.0%)	12 (24%)	
Length of therapy (days)	12.0 (8.0, 15.0)	10.0 (7.0, 14.0)	0.0677
2–5 n (%)	6 (2.9%)	3 (6%)	0.4279
5–10 n (%)	68 (33.3%)	22 (43%)	
10–15 n (%)	69 (33.8%)	16 (31%)	
15–20 n (%)	39 (19.1%)	7 (14%)	
≥ 20 n (%)	22 (10.8%)	3 (6%)	
Trough concentration (mg/L)	16.1 (12.7, 20.7)	16.8 (12.1, 26.0)	0.5037
< 10 n (%)	28 (13.7%)	5 (10%)	0.4025
10–15 n (%)	53 (26.0%)	16 (31%)	
15–20 n (%)	67 (32.8%)	12 (24%)	
≥ 20 n (%)	56 (27.5%)	18 (35%)	

CCI, Charlson comorbidities index; ICU, Intensive Care Unit; SCr, serum creatinine.

^aEleven patients lacked baseline SCr.

^bFive patients lacked peak serum lactic acid.

showed a noticeable trend of higher risk level linking to a higher incidence of VANT (**Figure S2**).

DISCUSSION

In this study, we found vancomycin trough concentration ≥ 20 mg/L, surgery, CCI score ≥ 4, concomitant cardiotoxic drug, plasma volume expander, and PTZ were risk factors for VANT in elderly patients. Based on this, we developed

Table 2 Association of characteristics and VANT (train set, univariate analysis, P < 0.1)

Variable	VANT (N = 47)	NO-VANT (N = 157)	P value
Demographic characteristics			
Age (years)	80.0 (69.0, 87.0)	86.0 (79.0, 90.0)	0.0014
60–79 n (%)	22 (47%)	42 (26.8%)	0.0093
≥ 80 n (%)	25 (53%)	115 (73.2%)	
Surgery n (%)	20 (43%)	23 (14.6%)	< 0.0001
ICU admittance n (%)	21 (45%)	26 (16.6%)	< 0.0001
Mechanical ventilation n (%)	23 (49%)	30 (19.1%)	< 0.0001
Laboratory variables			
Serum albumin valley (g/L)	23.0 ± 4.89	26.5 ± 4.30	< 0.0001
< 25 n (%)	30 (64%)	53 (33.8%)	0.0002
≥ 25 n (%)	17 (36%)	104 (66.2%)	
Comorbidity			
CCI score	4.0 (2.0, 5.0)	3.0 (2.0, 4.0)	0.0493
< 4 n (%)	20 (43%)	103 (65.6%)	0.0046
≥ 4 n (%)	27 (57%)	54 (34.4%)	
Respiratory failure n (%)	18 (38%)	38 (24.2%)	0.0575
Sepsis n (%)	20 (43%)	37 (23.6%)	0.0109
Vancomycin therapy			
Trough concentration (mg/L)	20.1 (15.4, 28.0)	15.5 (12.2, 18.8)	0.0001
< 10 n (%)	5 (11%)	23 (14.6%)	0.0003
10–15 n (%)	5 (11%)	48 (30.6%)	
15–20 n (%)	13 (28%)	54 (34.4%)	
≥ 20 n (%)	24 (51%)	32 (20.4%)	
Concomitant drugs			
Aminoglycoside n (%)	7 (15%)	7 (4.5%)	0.0208
Cardiotonic drug n (%)	18 (38%)	20 (12.7%)	< 0.0001
Immunosuppressant n (%)	4 (9%)	3 (1.9%)	0.0507
Vasopressor n (%)	22 (47%)	25 (15.9%)	< 0.0001
Plasma volume expander n (%)	24 (51%)	23 (14.6%)	< 0.0001
PTZ n (%)	16 (34%)	34 (21.7%)	< 0.0001

CCI, Charlson Comorbidities Index; ICU, intensive care unit; PTZ, piperacillin/tazobactam; VANT, vancomycin-associated nephrotoxicity.

and validated a risk prediction model for elderly patients. To the best of our knowledge, our study is the first to attempt to develop a risk prediction model of VANT in elderly patients.

Many studies not particularly for elderly patients report vancomycin trough concentration is an important risk factor for VANT,^{9,20,27} which is consistent with this study. The guideline recommends keeping trough levels of 10–15 mg/L in adult patients and 10–20 mg/L in adult patients with serious MRSA infections.³⁰ However, the guideline does not explicate vancomycin trough concentration range for elderly patients. We made further efforts to assess vancomycin trough concentration by using a logistic regression analysis model to predict the probabilities of VANT. The predicted

Table 3 Multivariable analysis of risk factors for VANT

Factors	β	SE	Wald χ^2	P value	OR	95% CI
Intercept	-5.3349	0.9008	35.0748	< 0.0001		
Vancomycin trough concentration \geq 20 mg/L	1.1016	0.4108	7.1895	0.0073	3.009	1.345–6.732
Surgery	1.2109	0.4803	6.3559	0.0117	3.357	1.309–8.605
CCI \geq 4	0.9572	0.4073	5.5233	0.0188	2.604	1.172–5.787
Cardiotonic drug	1.1887	0.4571	6.7612	0.0093	3.283	1.340–8.042
Plasma volume expander	1.2410	0.4516	7.5524	0.0060	3.459	1.428–8.382
PTZ	0.9350	0.4436	4.4429	0.0350	2.547	1.680–6.077

95% CI, 95% confidence interval; CCI, Charlson Comorbidities Index; OR, odds ratio; PTZ, piperacillin/tazobactam; VANT, vancomycin-associated nephrotoxicity.

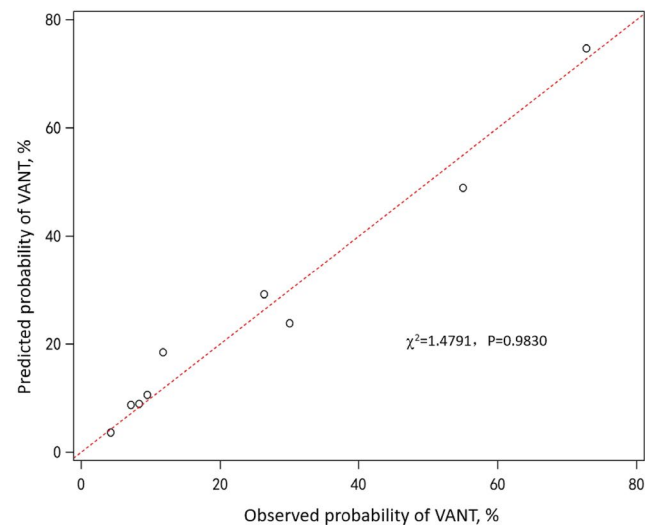
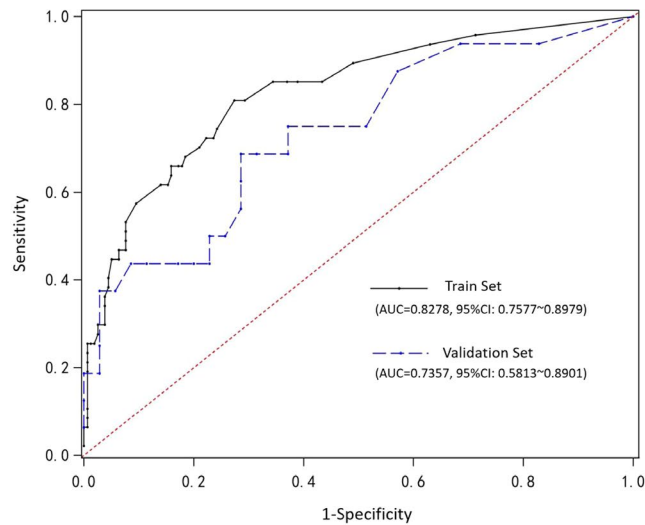


Figure 2 Receiver operating characteristic curves for the vancomycin-associated nephrotoxicity risk model using the train and validation sets (up panel). Calibration chart for predicted vs. observed risk in the train set (down panel). AUC, area under the curve; 95% CI, 95% confidence interval.

Table 4 Risk scores for all predictors

Risk factors	Score
Surgery	
No	0
Yes	1
Vancomycin trough concentration	
< 20 mg/L	0
\geq 20 mg/L	1
CCI	
< 4	0
\geq 4	1
Cardiotonic drug	
No	0
Yes	1
Plasma volume expander	
No	0
Yes	1
PTZ	
No	0
Yes	1

CCI, Charlson Comorbidities Index; PTZ, piperacillin/tazobactam.

probability curve showed that the probability of VANT risk increased as the vancomycin trough concentration increased. Receiver operating characteristic analysis identified 18.1 mg/L as the vancomycin trough concentration with the greatest sensitivity and specificity for VANT in elderly patients (**Figures S3** and **S4**). This result shows that high trough concentration recommended by the guideline might increase the incidence of VANT for elderly patients with serious MRSA infections. The guideline recommends that TDM should be performed in elderly patients, whereas the rate of TDM in our study was relatively low (32.5%).³⁰ However, the latest guideline recommended AUC instead of trough concentration as the pharmacokinetic/pharmacodynamic marker of vancomycin, which may reduce the adverse impact of trough concentration on VANT.

CCI has been widely utilized to measure the burden of disease and predict mortality.³¹ Many elderly patients have multiple comorbidities, therefore, we tried to explore the effect of CCI to VANT in elderly patients. This study showed

that CCI was a risk factor for VANT, which indicates that elderly patients with poor physical condition are more likely to develop VANT. This is the first study to explore the effect of CCI to VANT in elderly patients. We also found surgery was a risk factor, which is consistent with the result of CCI.

Elderly patients usually take various concomitant medications.³² Thirteen kinds and eight varieties of drugs which may cause nephrotoxicity or affect renal function were included, and the results of our study demonstrated that concomitant cardiotoxic drugs and plasma volume expander were risk factors for VANT in elderly patients. These two categories of medication are for patients with heart failure and circulatory shock, respectively. The results suggest that the cardiac function and circulation of the patients would affect the occurrence of VANT, which should be handled before vancomycin therapy. PTZ was extensively studied in previous studies and proved to be an important risk factor for VANT.^{24,25} We found similar results in elderly patients. PTZ might lead to vancomycin's accumulation within nephron by decreasing its clearance.

Our study developed and validated a risk prediction model of VANT for elderly patients, and the risk scores were divided into three levels of low, moderate, and high-risk groups for assessing VANT risk in elderly patients. This provided a relatively practical tool for clinicians to identify patients with high-risk VANT for close monitoring. For these patients, prompt measures could be taken, such as reducing the dosage of vancomycin or ceasing vancomycin therapy to reduce its trough concentration, monitoring the patient's renal function, and avoiding combined use of other nephrotoxic drugs.^{2,33}

Two limitations should be addressed. First, this was a retrospective single-center study, and the validation was conducted with retrospective data. This might have generated biases and the results are subjected to future prospective multicenter studies. Second, the sample size was relatively small to develop a classical risk prediction model, and the validation data sets were not independent samples, which may lead to the instability of our model. However, the results of our model were inspiring, which had good discriminative power. Therefore, we want to share our exploratory results and hope our model can be further validated.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Table S1. Association of characteristics and VANT (train set, univariate analysis).

Table S2. Univariate logistic regression analysis of vancomycin trough concentration (train set, $n = 204$).

Figure S1. Incidence of VANT with increasing risk score in the train set and the validation set. The individual risk score was calculated as the sum of each weighted score for the six predictive factors of VANT. Solid bars = train set; open bars = validation set.

Figure S2. Incidence of VANT according to the three risk classes in the train set and the validation set. Solid bars = train set; open bars = validation set.

Figure S3. Logistic regression analysis model of the relationship between vancomycin trough concentrations and the predicted probabilities of VANT associated with these concentrations.

Figure S4. ROC curve to evaluate the predictive value of vancomycin trough concentration to VANT using the train sets. ROC curves, receiver operating characteristic curves.

Data Set S1. Example model code and data sets of risk prediction model of VANT in elderly patients.

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