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ORIGINAL RESEARCH

Development and Validation of a Nomogram for Predicting Tigecycline-Related Coagulopathy: A Retrospective Cohort Study

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Background: Although tigecycline is an effective drug against drug-resistant bacteria, it demonstrated a higher all-cause mortality than comparator antibiotics and a high incidence of coagulation disorders which can be accompanied by severe bleeding. At present, a predictive model for tigecycline-related coagulopathy is not readily available, and the prognostic value of coagulopathy in tigecycline-administered patients has not been elucidated. In this paper, we investigate the association between tigecycline-related coagulopathy and in-hospital mortality to develop a nomogram for the prediction of tigecycline-related coagulopathy.

Methods: This retrospective cohort study includes 311 adults prescribed with tigecycline from 2018 to 2020. The primary cohort and validation cohort were constructed by dividing the participants in a ratio of 7:3. The endpoint is tigecycline-related coagulopathy, defined as a condition with no abnormality in coagulation prior to tigecycline application but developed the following symptoms upon prescription: activated partial thromboplastin time (APTT) extended by >10 s than the upper limit of normal (ULN), prothrombin time (PT) prolonged for >3 s than the ULN or reduced serum level of fibrinogen to <2.0 g/L. A predictive nomogram based on logistic regression was subsequently constructed.

Results: Tigecycline intake for over 7 days, combined other antibiotics, initial PT, initial fibrinogen and estimated glomerular filtration rate (eGFR), are independent prognostic factors of tigecycline-related coagulopathy. The primary and validation cohort each has an area under the receiver operating characteristic curve (AUC) of 0.792 (0.732–0.851) and 0.730 (0.629–0.832) for nomogram, respectively. Furthermore, the fitted calibration curve illustrated adequate fit of the model, while the decision curve analysis demonstrated good clinical value. Survival curves showed a high mortality rate among patients with tigecycline-related coagulopathy.

Conclusion: This nomogram exhibited helpful clinical value in predicting tigecycline-related coagulopathy that could reduce the high mortality rate of patients prescribed with tigecycline.

Keywords: tigecycline, drug-resistant bacteria, coagulopathy, nomogram

Introduction

The multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens have attracted more and more public healthcare attention due to the high mortality rate, high morbidity rate and prolonged hospitalization.[1] It was estimated that antimicrobial resistance-associated deaths were as high as 1.27 million globally in 2019, among whom approximately 1 million cases were caused by the following six dominating bacteria: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus and Streptococcus pneumoniae*.[2]

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Additionally, *Acinetobacter baumannii* showed a very high carbapenem resistance rate (97%) in patients with ventilator-associated pneumonia in a clinical research conducted in Greece, Italy and Spain. At the same time, almost two-thirds of isolated strains were XDR or even pan-drug resistant.[3] With the high incidence and mortality rates of drug-resistant bacteria becoming increasingly concerning, the application of certain antimicrobial agents against MDR or XDR bacterial pathogens is becoming the focal point in clinical practice.

Tigecycline, the first glycylcycline antibiotic, is a 9-t-butylglycylamido derivative of minocycline.[4] Tigecycline and colistin are effective therapies for MDR and XDR, especially against *Acinetobacter* spp. and carbapenem-resistant *Enterobacterales*.[4–6] However, previous randomized controlled trials (RCT) showed that tigecycline has a higher all-cause mortality than comparator antibiotics,[7] although the exact reason remains unclear. Meanwhile, the impact of adverse reactions on the efficacy of tigecycline treatment is inevitable. Despite gastrointestinal reactions being recognized as the most common side effects,[8] tigecycline-associated coagulation disorders are gaining the attention of physicians nowadays. Hypofibrinogenemia, increased activated partial thromboplastin time (APTT), prolonged prothrombin time (PT) and increased international normalized ratio (INR) have incidence rates of nearly 50% during the administration of tigecycline according to previous studies.[9–12] About 11.3% of the patients with tigecycline-associated hypofibrinogenemia were reported to suffer from severe bleeding.[13] Prior studies revealed that age, gender, tigecycline dosage and course, baseline fibrinogen level and renal insufficiency may be relevant to the risk factors of hypofibrinogenemia associated with tigecycline.[13–15] However, those aforementioned risk factors are not good predictors of tigecycline-related coagulopathy. Besides, the prognostic value of coagulation dysfunction in patients administered with tigecycline has not been elucidated.

In this present study, we developed a nomogram as well as validating it to predict tigecycline-related coagulopathy based on the clinical records of patients prescribed with tigecycline. Furthermore, the association between coagulation dysfunction and in-hospital mortality among patients receiving tigecycline therapy was also investigated.

Method

Participants

A retrospective cohort study was conducted based on a protocol approved by the Ethics Review Board of Sun Yat-sen Memorial Hospital (Guangzhou, China, IRB number SYSEC-KY-KS-2022-009). This study includes adult patients who were prescribed with tigecycline for over 48 hours in Sun Yat-sen Memorial Hospital. The time span is from April 1st, 2018 to July 31st, 2020. Patients without information on coagulation indexes before or during tigecycline intake are excluded. Abnormalities in coagulation function or the occurrence of bleeding events before tigecycline prescription are also part of the exclusion criteria. A flow chart presents the inclusion and exclusion process (Figure 1). The upper normal limits (ULN) of PT and APTT in our laboratory are 14.4 s and 35 s, respectively. Tigecycline-related coagulopathy is defined as a condition with no abnormality in coagulation prior to tigecycline application but meets any of the following conditions for coagulation disturbance during drug administration: PT prolonged for >3 s than the ULN, APTT extended by >10 s than the ULN or serum level of fibrinogen <2.0 g/L. A total of 311 observations were selected for the investigation. The primary cohort and validation cohort were constructed by dividing the participants in a ratio of 7:3. The nomogram was built with the primary cohort and validated with the validation cohort.

Research Information Collection

The following information was collected within 10 days before tigecycline use: demographic data (age, gender, body mass index, in-hospital time, surgery, prescription department, smoke and alcohol abuse), comorbidity (abdominal tumor, pancreatitis, hypertension, coronary heart disease (CHD), apoplexy, diabetes, transplantation and source of infection), treatment (medication time, initial dose and cumulative dose of tigecycline, combined use of other antibiotics, glucocorticoid, ventilator use, anticoagulation or antiplatelet therapy, occurrence of tigecycline-related coagulopathy and in-hospital mortality), coagulation index (PT, INR, fibrinogen, APTT, plasma prothrombin activity (PTA) and D-dimer before tigecycline prescription) and lab results (blood routine examination, electrolyte, liver and kidney function). During tigecycline administration, all information on coagulation indexes was collected. The last measured coagulation indexes

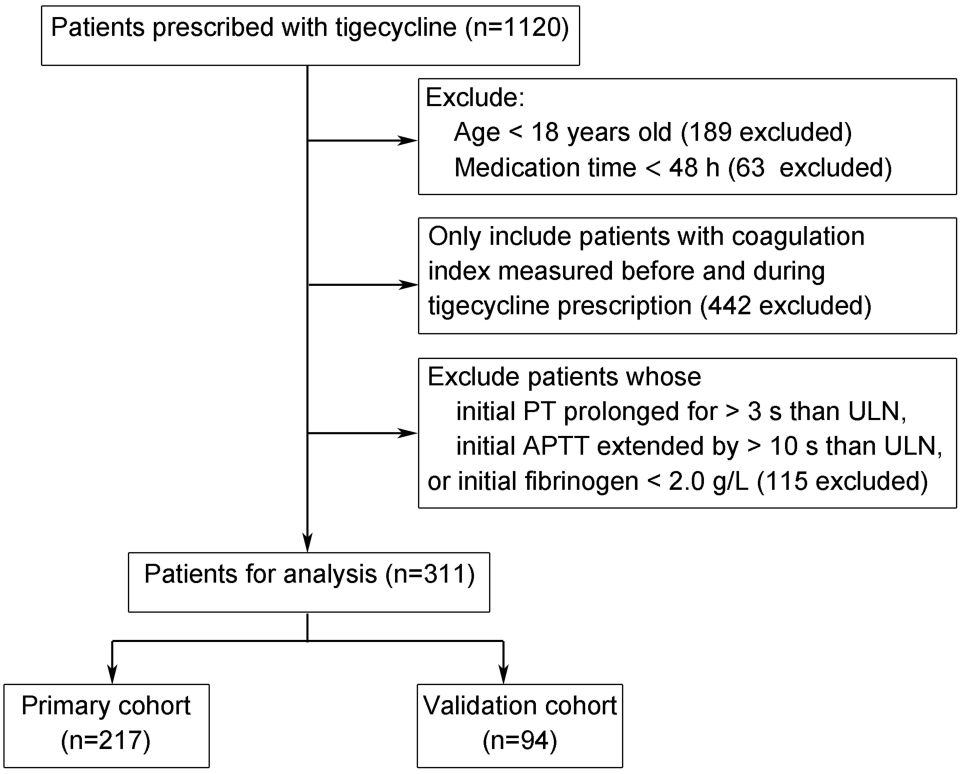

Figure 1 Study flow chart.
Abbreviations: PT, prothrombin time; ULN, upper limit of normal; APTT, activated partial thromboplastin time.

during the administration were regarded as the coagulation index level after prescription and displayed as the median [IQR] before being subsequently compared with initial coagulation indexes (Figure 2).

Statistical Method

The R (Vienna, Austria, ver. 4.1.0) software was used for statistical computation. The missing covariates were less than 10% and were filled by multiple imputation. The continuous variables of normal distribution and non-normal distribution are expressed as mean ± SD and median [IQR], respectively. The categorical variables are denoted as number (percentage). The comparison of continuous data is based on Student's *t*-test or the Wilcoxon rank sum test, whereas the comparison of categorical data is based on the chi-square test. For the purpose of developing a predictive model for the occurrence of tigecycline-related coagulopathy, a two-way stepwise logistic regression procedure was applied in the primary cohort based on Akaike information criterion to screen all biologically plausible variables for significant variables that meets general medical knowledge in univariate analysis. The variables identified were then entered into a multivariate logistic analysis. A two-sided $p < 0.05$ is considered statistically significant.

A nomogram was constructed based on results of the multivariable logistic analysis. We evaluated the performance of nomogram by adjusting its clinical value, calibration and discrimination.[16] The receiver operating characteristic curve (ROC) was applied to evaluated the predictive capacity of the prediction model by calculating the area under the curve (AUC). The fitted logistic calibration curve was used to analyze consistency between the actual state and the nomogram. Decision curve analysis (DCA) was applied to quantify the standardized net benefits at different threshold probabilities for assessing the clinical value of the predictive model. Additionally, the 30-day survival probability of both the primary and validation cohorts were compared between the patients with tigecycline-related coagulopathy and the non-coagulopathy patients on the survival curves, respectively.

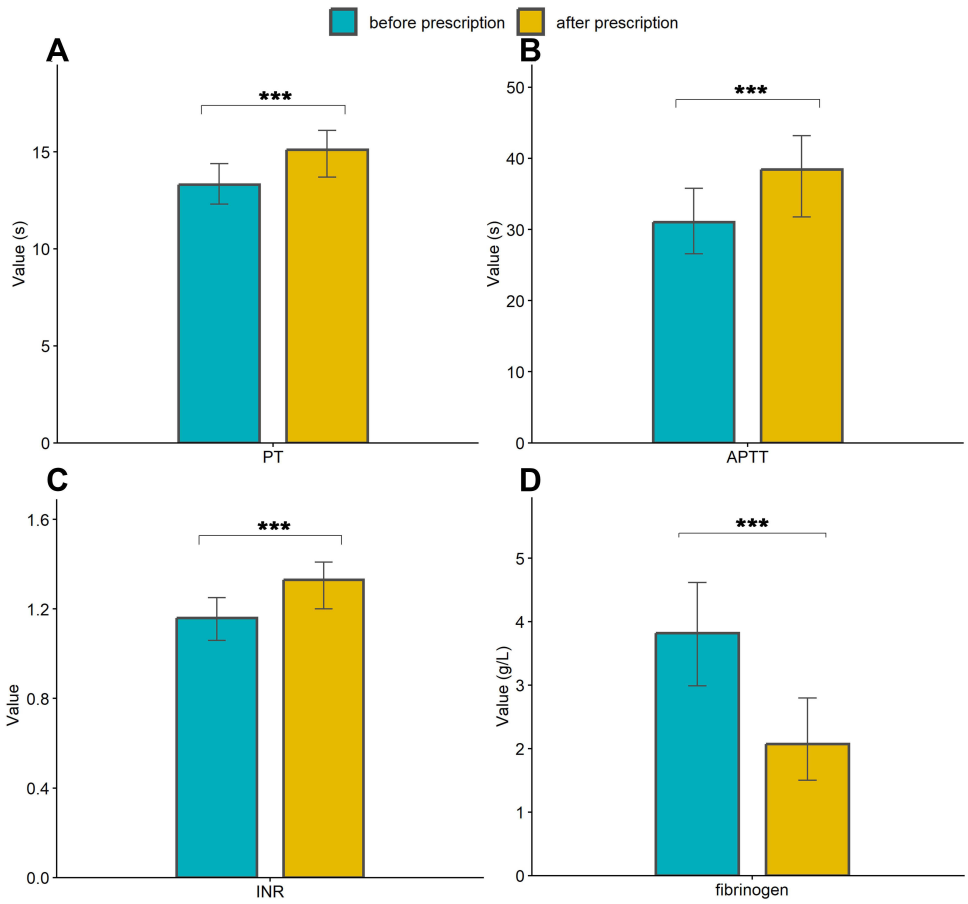

Figure 2 The variation of PT, APTT, INR and fibrinogen before and after tigecycline prescription.
Notes: (**A**–**D**) show the changes of PT, APTT, INR and fibrinogen before (yellow) and after (blue) tigecycline prescription, respectively. ***$p < 0.001$.
Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

Result

Baseline of the Primary and Validation Cohorts

A total of 311 individuals who met the inclusion criteria were divided into the primary cohort (n = 217) and the validation cohort (n = 94). The mean ages of the patients in the primary cohort and validation cohort were 58.36 ± 15.28 and 59.61 ± 16.98 years, respectively ($p > 0.05$). Males accounted for 62.7% in the primary cohort and 59.6% in the validation cohort ($p > 0.05$). The medication time and cumulative dose of tigecycline of the both cohorts showed no significant difference. The median in-hospital time of all patients was 33 days, while the medication time of tigecycline was 1–2 weeks. Cumulative dose of tigecycline can generally reach 0.8–1.8 g in the total course of treatment. In total, 78.8% of the patients were prescribed tigecycline in combination with other antibiotics (the summaries for the prescription department, pathogen, type of infection and antibiotics used in combination are visualized in Figures S1–S4). The median medication time when tigecycline-related coagulopathy occurred was 2 days, with an interquartile range of 1–4 days. Tigecycline-related coagulopathy has an incidence rate of around 50% in both cohorts. Bleeding events during tigecycline medication were observed in 24 patients, accounting for 7.9% within the sample population, whereas the in-hospital mortality rate was 19%. There was no significant difference in the baseline variables between the primary and validation cohorts (all $p > 0.05$) (Table 1).

Variation of Coagulation Indexes Before and After Tigecycline Prescription

Figure 2 demonstrates the variation of coagulation indexes in all patients. The level of PT, APTT and INR rose while the level of fibrinogen fell significantly after tigecycline prescription (all $p < 0.001$). The changes of the above indexes suggest that patients tend to bleed more easily after prescription.

Table 1 Comparison of Baseline Between the Primary Cohort and Validation Cohort

Variables	Primary Cohort N = 217	Validation Cohort N = 94	*P*-value
Demographic Data			
Age (years)	58.36 ± 15.28	59.61 ± 16.98	0.523
Male	136 (62.7%)	56 (59.6%)	0.697
Weight (kg)	59.00 [51.00, 67.00]	59.00 [50.00, 66.12]	0.818
Height (cm)	163.60 ± 7.63	163.17 ± 8.12	0.712
BMI (kg/m^2)	22.58 [20.07, 24.44]	22.04 [19.54, 24.92]	0.792
In-hospital Time (days)	32.00 [22.00, 47.00]	33.50 [21.25, 50.75]	0.865
Smoke	39 (18.2%)	13 (13.8%)	0.434
Alcohol Abuse	17 (7.9%)	11 (11.7%)	0.393
Comorbidity			
Abdominal Tumor	61 (28.1%)	34 (36.2%)	0.199
Pancreatitis	17 (7.8%)	7 (7.4%)	1.000
Hypertension	61 (28.1%)	31 (33.0%)	0.466
CHD	23 (10.6%)	8 (8.5%)	0.720
Apoplexy	34 (15.7%)	13 (13.8%)	0.808
Diabetes	41 (18.9%)	15 (16.0%)	0.647
Transplantation	11 (5.1%)	5 (5.3%)	1.000
Source of Infection			0.449
cIAI	120 (55.6%)	43 (47.3%)	
Pneumonia	70 (32.4%)	38 (41.8%)	
SSSI	4 (1.9%)	1 (1.1%)	
Others[a]	22 (10.2%)	9 (9.9%)	
Treatment			
Medication Time (days)	9.00 [6.00, 14.00]	10.00 [7.00, 14.00]	0.308
Medication Time over 7 days	142 (65.4%)	64 (68.1%)	0.747
Loading Dose for Initial Use	186 (74.8%)	82 (75.9%)	0.957
Treatment Scheme			0.833
<50 mg every 12 h	3 (1.4%)	1 (1.1%)	
50 mg every 12 h	154 (72.4%)	64 (68.1%)	
100 mg every 12 h	60 (27.6%)	29 (30.8%)	
Cumulative Dose of Tigecycline (g)	1.15 [0.80, 1.75]	1.23 [0.86, 1.89]	0.227
Combined Other Antibiotics	174 (80.2%)	71 (75.5%)	0.441
Glucocorticoid	54 (24.9%)	18 (19.1%)	0.340
Ventilator			0.609
Without	98 (45.2%)	46 (48.9%)	
Non-invasive	49 (22.6%)	23 (24.5%)	
Invasive	70 (32.3%)	25 (26.6%)	
Anticoagulant	39 (18.0%)	21 (22.3%)	0.459
Antiplatelet drug	3 (1.4%)	0 (0.0%)	0.607
Other drugs that may cause coagulation abnormality[b]	5 (2.3%)	5 (5.3%)	0.301
Surgery	141 (65.6%)	61 (64.9%)	1.000
Prescription in ICU	60 (27.6%)	25 (26.6%)	0.958
Medication Time when Tigecycline-related Coagulopathy Happened (days)	2.00 [1.00, 4.00]	2.00 [1.00, 4.50]	0.878
Time to Be Normalized after Withdrawal of Tigecycline (days)	5.00 [3.00, 6.00]	4.00 [2.00, 5.00]	0.239
Tigecycline-related Coagulopathy	114 (52.5%)	47 (50.0%)	0.774
Bleeding Events	19 (9.0%)	5 (5.4%)	0.414
In-hospital Mortality	43 (19.8%)	16 (17.0%)	0.675

(*Continued*)

Table 1 (Continued).

Variables	Primary Cohort N = 217	Validation Cohort N = 94	*P*-value
Coagulation Index			
Initial PT (s)	13.30 [12.30, 14.50]	13.20 [12.30, 14.10]	0.709
Initial INR	1.16 [1.06, 1.25]	1.14 [1.06, 1.24]	0.874
Initial fibrinogen (g/L)	3.83 [3.09, 4.98]	3.74 [2.94, 4.86]	0.794
Initial APTT (s)	31.20 [26.50, 35.80]	30.75 [26.85, 35.05]	0.476
Initial PTA (%)	72.60 [61.80, 90.35]	72.40 [64.40, 82.80]	0.912
Initial PTR	1.15 [1.06, 1.25]	1.14 [1.06, 1.23]	0.841
Initial TT (s)	16.50 [15.20, 17.65]	16.45 [15.60, 17.50]	0.646
Initial D-dimer (mg/L FEU)	4.26 [2.12, 7.97]	4.21 [2.26, 8.80]	0.689
Lab results			
CRP (mg/L)	75.30 [36.78, 109.80]	61.10 [45.10, 80.75]	0.632
HGB (g/L)	89.10 ± 23.64	85.51 ± 20.96	0.207
PLT ($\times10^9$/L)	201.57 ± 137.77	219.62 ± 141.69	0.297
HCT	0.26 [0.22, 0.30]	0.25 [0.21, 0.29]	0.274
LYM ($\times10^9$/L)	0.74 [0.45, 1.19]	0.79 [0.50, 1.30]	0.336
NEUT ($\times10^9$/L)	8.97 [5.32, 15.37]	8.61 [4.71, 13.47]	0.865
EOS ($\times10^9$/L)	0.03 [0.00, 0.15]	0.04 [0.00, 0.16]	0.449
BASO ($\times10^9$/L)	0.02 [0.01, 0.04]	0.02 [0.01, 0.04]	0.510
PCT (ng/mL)	1.25 [0.31, 8.39]	1.13 [0.22, 6.72]	0.822
ALT (U/L)	46.67 ± 61.00	47.76 ± 62.75	0.891
AST (U/L)	50.90 ± 75.93	57.90 ± 88.14	0.498
TBILI (μmol/L)	48.03 ± 85.88	51.49 ± 89.62	0.758
Cholinesterase (U/L)	3418.57 ± 1611.85	3478.27 ± 1852.82	0.775
ALB (g/L)	30.61 ± 6.25	30.51 ± 6.39	0.903
K (mmol/L)	4.19 ± 3.42	4.72 ± 7.43	0.409
Na (mmol/L)	136.91 ± 11.13	138.62 ± 5.10	0.175
Cr (μmol/L)	80.00 [62.25, 107.75]	81.50 [65.00, 132.25]	0.199
eGFR (mL/min/1.73 m^2)	98.41 [60.07, 121.32]	82.85 [45.02, 117.32]	0.050
CO2-CP (mmol/L)	23.41 ± 4.99	22.93 ± 4.86	0.457
GLU (mmol/L)	9.62 ± 15.74	8.56 ± 5.78	0.543
CK (U/L)	62.00 [35.00, 125.75]	51.00 [24.50, 102.50]	0.216
CK-MB (U/L)	12.00 [8.00, 16.00]	12.00 [8.00, 21.50]	0.294
LDH (U/L)	253.00 [184.50, 355.25]	275.00 [184.00, 421.50]	0.376

Notes: [a]Other infections include bacteremia, fever of unknown origin possibly related to infection, urinary tract infection, mediastinal infection, perianal infection and parapharyngeal space infection. [b]Other drugs include aminocaproic acid, tacrolimus, sirolimus, mycophenolate mofetil, pirarubicin, cyclosporine, levetiracetam and sodium valproate.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; cIAI, complicated intra-abdominal infection; SSSI, skin soft tissue infection; ICU, intensive care unit; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; PTA, plasma prothrombin activity; PTR, plasma prothrombin time ratio; TT, thrombin time; CRP, C-reactive protein; HGB, hemoglobin; PLT, platelet; HCT, hematocrit; LYM, lymphocyte; NEUT, neutrophil; EOS, eosinophil; BASO, basophil; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBILI, total bilirubin; ALB, albumin; K, potassium; Na, sodium; Cr, creatinine; eGFR, estimated glomerular filtration rate; CO2-CP, carbon dioxide combining power; GLU, glucose; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; LDH, lactate dehydrogenase.

Predicting Factors of Tigecycline-Related Coagulopathy

General demographics, comorbidities, coagulation indexes, lab results and treatments of the primary cohort were further examined using the stepwise logistic regression model to predict tigecycline-related coagulopathy. In the univariate analysis, the following variables were found to be associated with tigecycline-related coagulopathy: age, diabetes, the course of tigecycline medication over 7 days, cumulative dose of tigecycline, combined use with other antibiotics, initial PT, initial APTT, initial fibrinogen and eGFR. The following factors were identified to be independent prognostic factors of tigecycline-related coagulopathy in the multivariate logistic regression analysis: the course of tigecycline medication

Table 2 Univariate and Multivariate Logistic Regression Analysis for the Risk Factors of Tigecycline-Related Coagulopathy in the Primary Cohort

Variables	Univariate Logistic		Multivariate Logistic	
	OR	*P*-value	OR	*P*-value
Medication Time over 7 days	3.36 (1.86–6.05)	<0.01	3.11 (1.38–7.20)	0.01
Cumulative Dose of Tigecycline (g)	1.96 (1.32–2.90)	<0.01	1.38 (0.86–2.36)	0.20
Combined Other Antibiotics	4.22 (2.00–8.92)	<0.01	4.21 (1.86–10.21)	<0.01
Initial PT (s)	1.26 (1.05–1.51)	<0.01	1.24 (1.02–1.53)	0.03
Initial Fibrinogen (g/L)	0.76 (0.63–0.92)	0.02	0.71 (0.57–0.88)	<0.01
eGFR (mL/min/1.73 m^2)	0.99 (0.98–1.00)	<0.01	0.99 (0.98–0.99)	<0.01

Abbreviations: PT, prothrombin time; INR, international normalized ratio; eGFR, estimated glomerular filtration rate.

over 7 days, combined use with other antibiotics, initial PT, initial fibrinogen and eGFR (each $p < 0.05$) (Table 2). The detailed process of logistic regression can be checked in Tables S1–S4.

Establishment of a Nomogram

A predictive nomogram for tigecycline-related coagulopathy was established with the predictive factors gained from the multivariable logistic model. The nomogram was constructed using each of the independent predicting variables with weighted score. The score of combined antibiotics usage, medication over 7 days, baseline PT, eGFR and baseline fibrinogen ranges from 0 to 1, 0 to 1, 9.5 to 16.5, 240 to 0 and 10 to 2, respectively. A score of 35 points was identified as the highest total score. The scale of tigecycline-related coagulopathy probability ranges from 0.95 to 0.1. A higher total score in the nomogram represents a higher incidence of tigecycline-related coagulopathy (Figure 3).

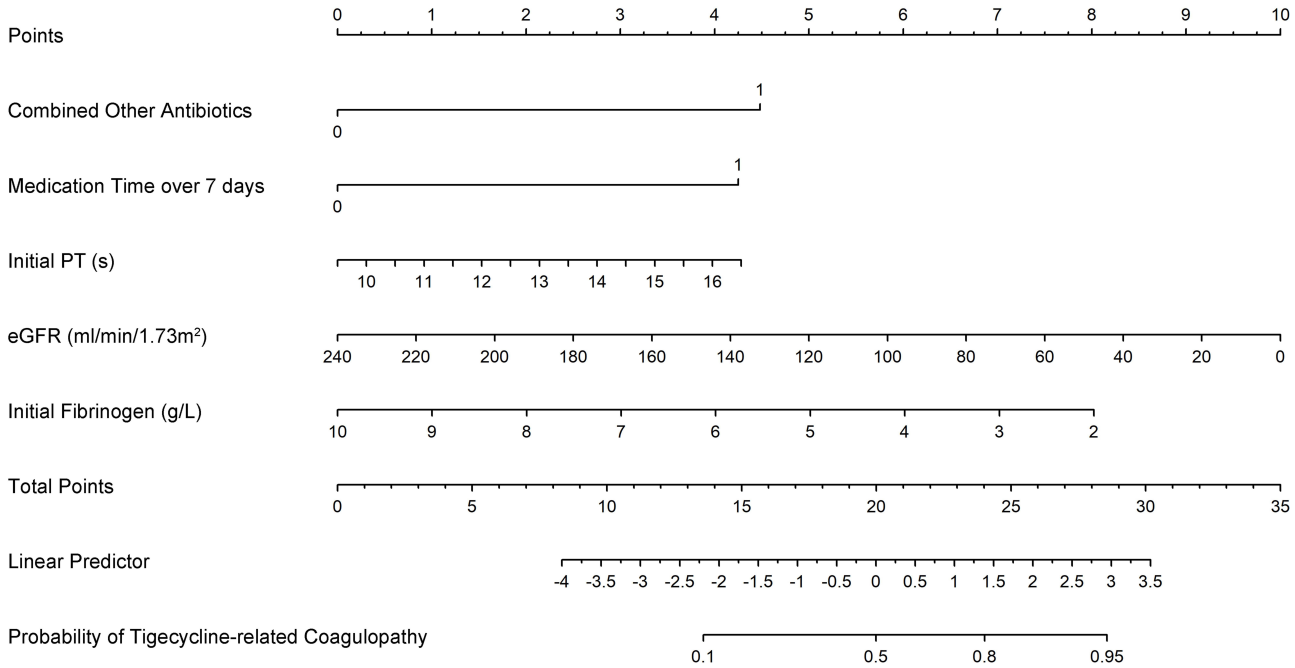

Figure 3 Nomogram to calculate probability of tigecycline-related coagulopathy after prescription of tigecycline based on the primary cohort.
Abbreviations: PT, prothrombin time; eGFR, estimated glomerular filtration rate.

Evaluation of the Nomogram

The predictive capacity of the nomogram was 0.792 (0.732–0.851) in the primary cohort and 0.730 (0.629–0.832) in the validation cohort according to the AUC (Figure 4). The fitted logistic calibration curve illustrated adequate fit of the predictive model for tigecycline-related coagulopathy in both cohorts (Figure 5). The net benefit obtained from the nomogram was 0.90 and 0.77 based on threshold probabilities for the primary cohort and validation cohort, respectively, as demonstrated by the decision curve analysis (Figure 6).

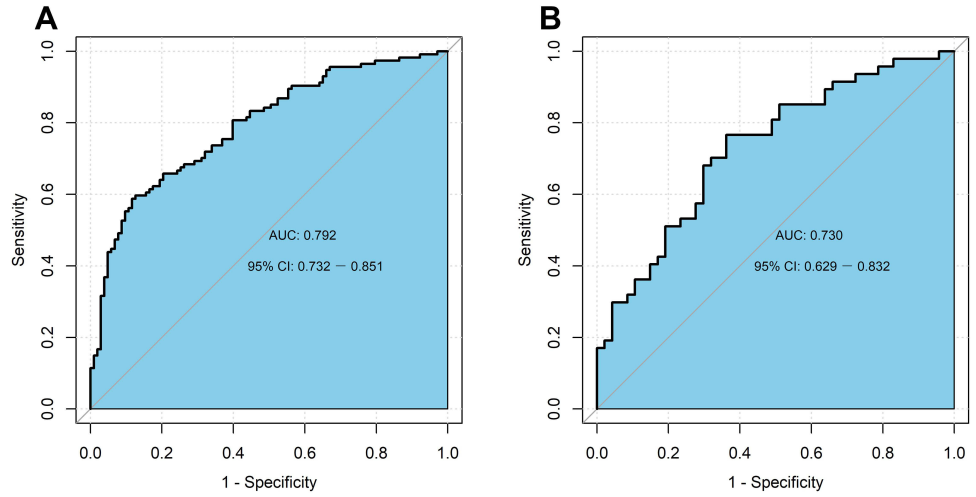

Figure 4 ROC to assess ability of the validation and primary population prescribed with tigecycline.
Note: (**A** and **B**) show the operating characteristic curve (ROC) of the primary cohort and validation cohort, respectively.

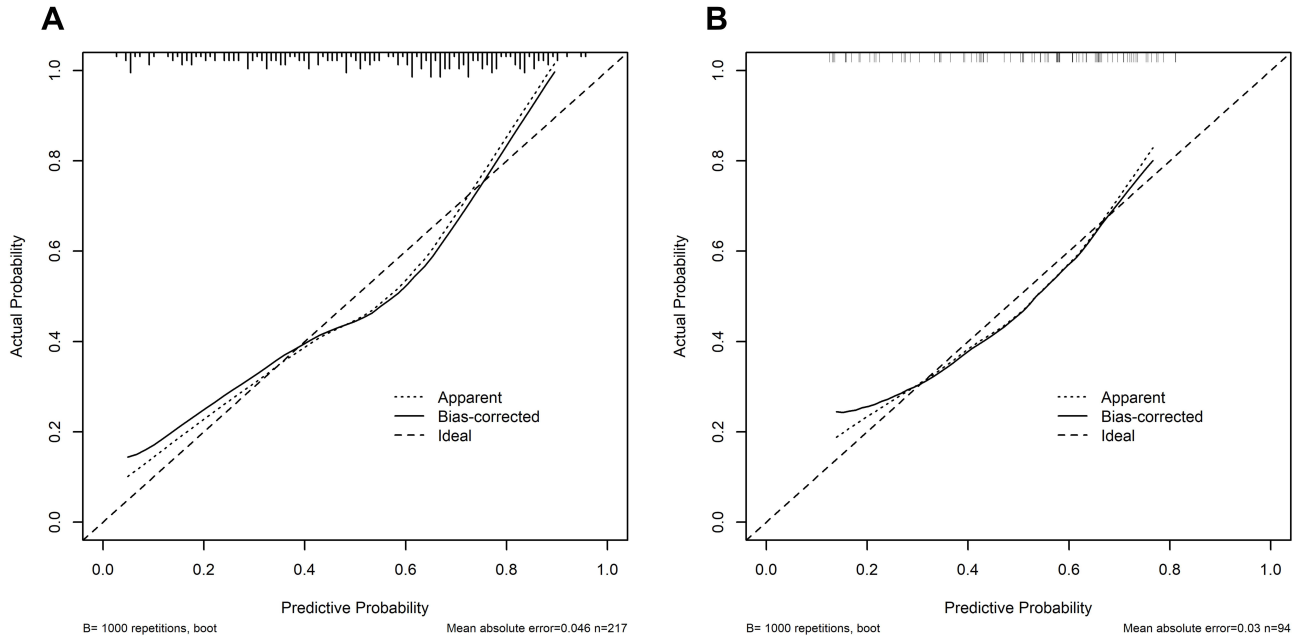

Figure 5 Fitted logistic calibration curve analysis in the primary and validation population.
Notes: (**A** and **B**) show the calibration curve of the primary cohort and validation cohort, respectively. The fitting degree of the solid line and diagonal line shows the prediction performance of the nomogram.

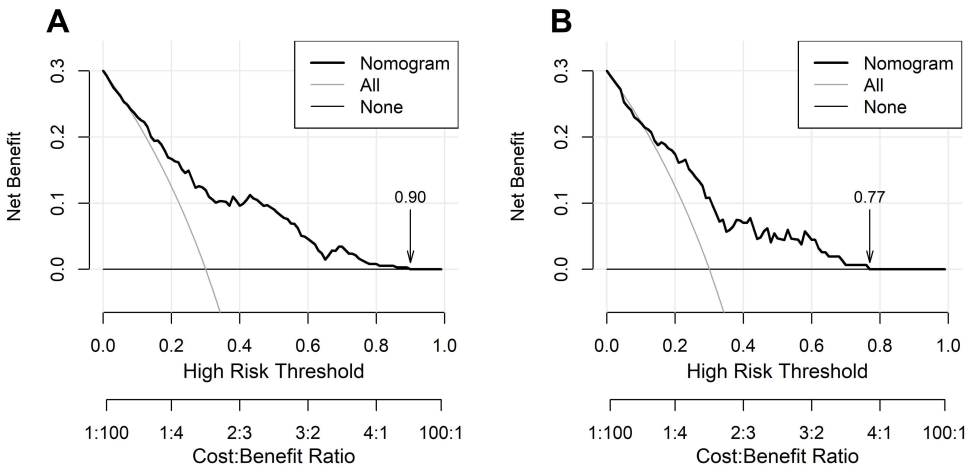

Figure 6 Decision curve analysis for the primary and validation.
Note: (**A** and **B**) demonstrate the decision curve of the primary cohort and validation cohort, respectively, demonstrating the net benefit with the application of the model.

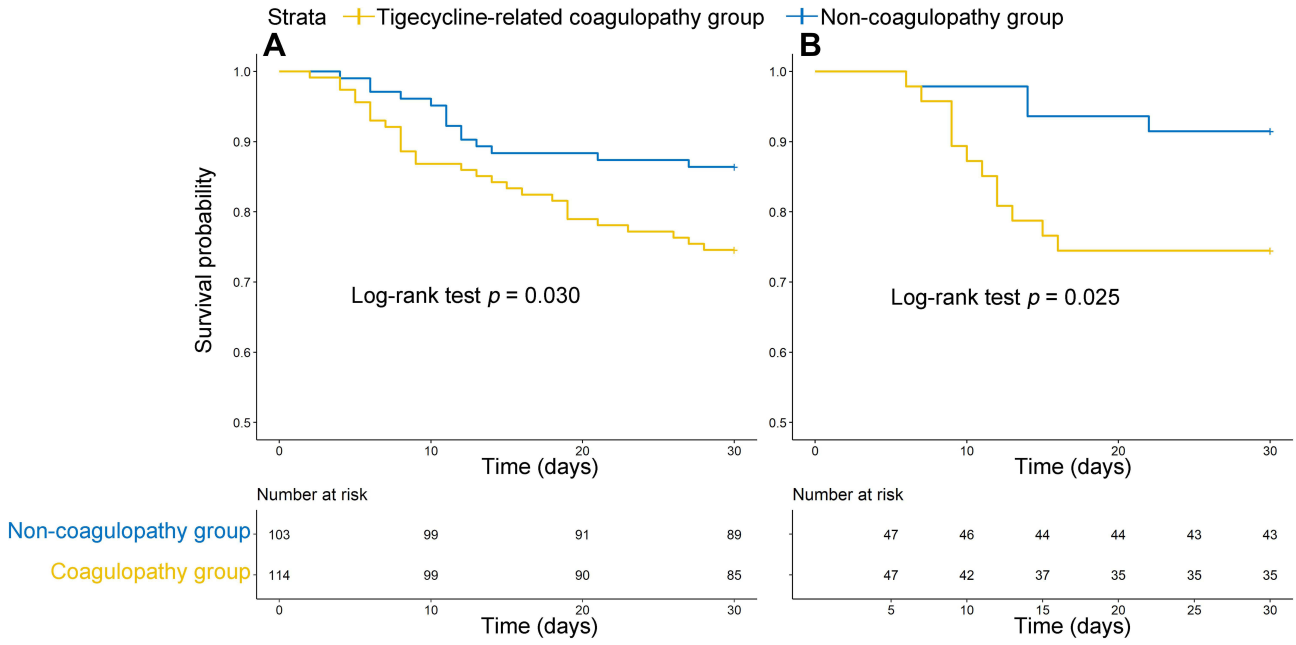

Figure 7 Survival analysis for the primary and validation cohort.
Note: (**A** and **B**) demonstrate the survival curve in the primary cohort and validation cohort, respectively.

The Association Between Coagulopathy and Mortality

To further analyze the association between tigecycline-related coagulopathy and in-hospital mortality, a log rank test based on survival curves was performed in both the primary and validation cohorts. The survival curves showed that patients with tigecycline-related coagulopathy under tigecycline prescription have a higher incidence of mortality ($p < 0.05$, log rank test) (Figure 7).

Discussion

In this study, a nomogram constructed on the basis of clinical characteristics as screened by the logistic regression model included cumulative dose, combined use with antibiotics, initial PT, initial fibrinogen and eGFR to predict tigecycline-related coagulopathy. As evaluated by the AUC, calibration curve as well as DCA, this model exhibits sound predictive

performance. Furthermore, the survivor curves revealed that patients suffering from tigecycline-related coagulopathy possess a higher risk of mortality. To our knowledge, this is the first model for predicting tigecycline-related coagulopathy.

Tigecycline, the first glycyl-tetracycline drug, obtained approval from the Food and Drug Administration (FDA) in June 2005 before entering the Chinese market in November 2011. The antibacterial spectrum of tigecycline covers Gram-positive bacteria, Gram-negative bacteria, atypical pathogens as well as anaerobic bacteria. Despite inactivity against *proteus* spp. and *Pseudomonas aeruginosa*, tigecycline exhibits powerful antibacterial activity against MDR and XDR, including the methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), carbapenem-resistant *Enterobacterales*, extended-spectrum β-lactamase-producing *Enterobacterales* and MDR *Acinetobacter* spp.[17–22] Tigecycline is recommended for community-acquired pneumonia, complicated intra-abdominal infections and complicated skin or soft tissue infections caused by sensitive bacteria, with its indications still rapidly expanding.

As the use of tigecycline increases, the side effects that it brings should be paid more attention as well. Based on information obtained from the FDA from 2004 to 2009, common adverse reactions associated with tigecycline include gastrointestinal effects, pancreatitis, hypoglycemia and liver injury.[23] Since the first case of tigecycline-induced hypofibrinogen was reported back in 2010,[24] tigecycline-related coagulopathy has attracted widespread attention. Subsequently, several case reports about coagulation disorders induced by tigecycline were published.[25–32] However, the accurate incidence of coagulopathy remains uncertain. A study based on the FDA adverse event reporting system (FAERS) database revealed that around 15% of patients prescribed with tigecycline developed coagulation disorder identified by Medical Dictionary for Regulatory Activities terms (V22.0).[33] The previous definitions of tigecycline-related coagulation disorder were not unified. Previous studies revealed that more than half of the patients who had undergone tigecycline therapy were presented with hypofibrinogen.[13–15] Moreover, the PT, APTT and INR were often applied for the research indicators to explore coagulopathy induced by tigecycline.[12,13,34] Cui et al summarized that tigecycline-induced coagulopathy usually manifests as prolongation of the prothrombin time and activated partial thromboplastin time and a reduction in the fibrinogen level.[9] In this study, the occurrence rate of coagulation dysfunction, defined as hypofibrinogen, increased APTT or increased PT, was around 50%. Differences in the incidence of various forms of coagulopathy are probably due to differences in definition and population.

Prior studies indicate that coagulopathy occurs within 2 weeks of tigecycline prescription, while the coagulation indicators could be restored several days after tigecycline withdrawal.[13,33] Besides, the incidence of bleeding in patients with coagulation dysfunction was documented to be approximately 10%.[15,33] This present study yielded highly similar results, where coagulopathy was shown to develop at a median of 2 days, and 7.9% of the patients involved in this study developed bleeding. Some researchers speculate that coagulopathy was associated with increased consumption or impaired synthesis of fibrinogen.[35] The liver is an important organ in synthesizing coagulation factors. Yet, liver function was hardly associated with coagulopathy as assessed by the logistic regression analysis in our study. In addition, the direct effect of tigecycline on coagulation function was not observed in vitro.[36] Therefore, other investigators inferred that it is likely for tigecycline to indirectly impact the fibrinogen level via suppressing the synthesis of interleukin-6 which has been proven to stimulate the expression of fibrinogen.[15] However, the underlying mechanism needs to be further elucidated.

In this present study, the risk factors of tigecycline-related coagulopathy as screened by a multivariable logistic model include cumulative dose of tigecycline, combined antibiotics, initial PT, initial fibrinogen and eGFR, all of which resonates with previous studies.[13–15] A predictive model for coagulopathy in the use of tigecycline was further constructed via the integration of relevant risk factors, and the model exhibits satisfactory performance as evaluated by the AUC, calibration curve as well as DCA. Nevertheless, the impact of tigecycline-related coagulopathy on survival outcome is still poorly studied. Herein, the association between coagulopathy and mortality was further evaluated (the potential causes for the higher mortality of patients with tigecycline-related coagulopathy can be checked in Tables S5 and S6). Patients with tigecycline-related coagulation dysfunction have a higher risk of mortality, thus implying the importance of a coagulation index monitor.

Several limitations to this study must, however, be mentioned. First, selection bias is inevitable in a retrospective study. The effect of tigecycline has not been studied in patients with coagulation disorder before prescription. Second, this is a single-center study with small sample size, which may affect the accuracy of the prediction model. Furthermore,

the definition of coagulopathy in this study includes the changes of PT, APTT and fibrinogen, irrespective of coagulation markers such as plasmin–α2-antiplasmin complex, thrombin–antithrombin-III complex and so on. Finally, validation from external database is currently absent for the nomogram.

Conclusion

In conclusion, a novel nomogram was constructed on the basis of relevant independent risk factors to predict the occurrence of tigecycline-related coagulopathy. This model possesses the potential as a useful tool in clinical practice, and is thus worthy of further scrutiny. Finally, tigecycline-related coagulopathy was also found to be associated with higher mortality, making it essential to monitor the occurrence of coagulation.

Data Sharing Statement

The data of this study can be obtained from the corresponding authors with reasonable requirement.

Ethics Approval

The whole process of this study is based on the Declaration of Helsinki. This study was conducted in concordance with a protocol approved by the Ethics Review Board of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (No. SYSEC-KY-KS-2022-009). Informed consents were obtained from all enrolled individuals.

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Disclosure

The authors report no conflicts of interest in this work.

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