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Serum concentration as a predictor of tigecycline-induced hypofibrinogenemia in critically ill patients: A retrospective cohort study

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ABSTRACT

Objectives: This study aimed to determine the thresholds of serum concentration as a predictor of tigecycline (TGC)-induced hypofibrinogenemia (HF) in critically ill patients.
Methods: A retrospective cohort study was conducted in intensive care unit patients treated with TGC. The clinical data and serum concentration were extracted from the patients' electronic medical records. Patients were divided into an HF group and a normal group according to fibrinogen value. The receiver operating characteristic curves and logistic regression were used to derive serum concentration thresholds and quantify the association between exposure thresholds and HF while adjusting for confounders.
Results: In total, 100 patients were included. The receiver operating characteristic curves analysis showed that TGC concentration parameters were strongly predictive of HF. Adjusting for duration of TGC, serum concentration at the 6 hours after the dosing ($C_{1/2}$) ≥ 0.645 mg/l, area under the concentration-time curve over a 24-hour period ($AUC_{0\text{-}24}$) ≥ 20.76 mg·h/l, and serum concentration of 30 minutes before next dose (C_{min}) ≥ 0.455 mg/l were associated with a three- to five-fold increased risk of TGC-induced HF in logistic regression.
Conclusion: The findings from this study provide evidence that TGC exposure is highly predictive of HF, with an approximately three- to five-fold increased risk. Serum concentration at the 6 hours after the dosing ($C_{1/2}$) ≥ 0.645 mg/l with best area under the receiver operating characteristic curve and negative predictive value appears to be the most appropriate toxicity threshold.

Introduction

Tigecycline (TGC) is the first glycylcycline antibacterial drug that inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking the entry of amino-acyl tRNA molecules into the A site of the ribosome. TGC has been shown to exhibit a wide range of activity against aerobic and anaerobic gram-positive and gram-negative bacteria, including polymicrobial multidrug resistance strains, and was approved by the Food and Drug Administration for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia at a dose of 50 mg twice daily, after a 100 mg loading dose (Kaewpoowat and Ostrosky-Zeichner, 2015; Muralidharan *et al.*, 2005; Slover *et al.*, 2007; Yaghoubi *et al.*, 2022). TGC has been regarded as the last resort to treat multidrug resistance bacteria owing to its powerful antibacterial activity (Xie *et al.*, 2014).

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According to a review, the most common TGC-associated adverse reactions include nausea, vomiting, liver impairment, and elevations in alanine aminotransferase, bilirubin, alkaline phosphatase, and aspartate aminotransferase (Kadoyama *et al.*, 2012). Although many studies have found that TGC has minimal adverse effects and is well tolerated in patients (Mei *et al.*, 2019; Zha *et al.*, 2020), there is increasing evidence that coagulopathy associated with treatment with TGC has been underestimated. Coagulopathy caused by TGC has been reported with a low incidence in a phase 3 clinical trial (at a frequency of < 2%) (Ellis-Grosse *et al.*, 2005). Nevertheless, high doses of TGC (100 mg twice daily) and longer treatments have been used frequently in clinical settings over the past few years; thus, adverse events might be more frequent and severe than those observed in clinical trials. In a large study of 426 patients, 50.5% of patients developed hypofibrinogenemia (HF), and 10.1% suffered bleeding after the TGC treatment (Zhang *et al.*, 2020). Campany-Herrero *et al.* (2020) likewise showed that TGC caused a decrease in fibrinogen (FIB), which was 30% lower than the initial value after treatment. TGC-induced HF, which is a potentially life-threatening coagulation disorder, can lead to adverse outcomes such as prolonged hospital stays and an increased burden of additional treatment, especially in critically ill patients (Levy *et al.*, 2014; McMahan and Moenster, 2017). Consequently, a predictor is urgently needed to prevent TGC-induced HF.

Therapeutic drug monitoring (TDM) uses drug concentration to manage the patient's dosing regimen and optimize outcomes, allowing advanced prediction of efficacy and safety (Gross, 2001). The TDM program at our institution was established in 2016 to optimize the dosage for patients. TGC TDM to ensure the anti-infective efficacy is one of our routine procedures. The pharmacokinetic-pharmacodynamic relationship of TGC has been extensively researched to improve efficacy optimization, and the dose is adjusted according to the ratio of the area under the concentration-time curve ($AUC_{0\text{-}24}$) to the minimum inhibitory concentration for the bacteria (Meagher *et al.*, 2007; Passarell *et al.*, 2008; Rubino *et al.*, 2012; Xu *et al.*, 2019). However, TGC exposure-toxicity thresholds, especially the serum concentration upper value of TGC-induced HF, are unknown. This study aimed to determine the thresholds of serum concentration that would predict TGC-induced HF in critically ill patients and thus enhance the safety of TGC.

Materials and methods

Study design

This was a single-center, retrospective, cohort study of critically ill patients from October 2019 and October 2021 at the intensive care unit of Drum Tower Hospital affiliated with the Medical School of Nanjing University. All patients received an intravenous loading dose of 100 mg followed by 50 mg of TGC (Standard dose) or a loading dose of 200 mg followed by 100 mg (High dose) of TGC every 12 hours, depending on the doctors' decisions. Patients aged ≥ 18 years receiving ≥ 72 hours of TGC therapy and coagulation monitoring more than three times during treatment were eligible for inclusion. Pregnant women, patients with an FIB level lower than 2.0 g/l before receiving TGC, and patients with incomplete medical records were excluded from the study.

Data collection and definitions

Demographics and clinical data were extracted from the electronic medical records, which included age, sex, infected site, bacterial type, dose, treatment duration, and combination therapy. The severity of illness was quantified using the Acute Physiology and Chronic Health Evaluation II score and the sequential organ failure assessment score. The laboratory examinations included coagulation function, hepatic function, renal function, and infection index before TGC medication was obtained. The serum concentration parameters were also collected from electronic medical records. The 0–12-hour area under the time-concentration curve ($AUC_{0\text{-}12}$) was determined by the linear trapezoidal rule. TGC $AUC_{0\text{-}24}$ was calculated as double the 0–12-hour area under the time-concentration curve. The day of automatic discharge or death was the endpoint of the observation, and the follow-up endpoint was 21 days after the administration and 10 days after TGC discontinuation.

FIB < 2.0 mg/l was defined as HF in this context. The disseminated intravascular coagulation was diagnosed by the International Society for Thrombosis and Hemostasis (ISTH) score. The ISTH diagnostic score for overt disseminated intravascular coagulation is calculated based on platelet count (< 100×10^9 /l but > 50×10^9 /l score 1; < 50×10^9 /l score 2), PT (Prolonged > 3 s but < 6 s score 1; > 6 s score 2), FIB level (FIB < 1 g/l score 1), and FIB/fibrin degradation peptides (D-dimer) (Moderate increase score 2; Strong increase score 3) in conjunction with clinical considerations. If the score is ≥ 5, it is compatible with overt disseminated intravascular coagulation (Popescu *et al.*, 2022). For all patients, the TGC-induced HF was defined by the following conditions, based on the WHO-Uppsala Monitoring Centre causality assessment criteria (https://www.who.int/publications/m/item/WHO-causality-assessment): (i) FIB < 2 g/l occurred at least 48 hours after the commencement of TGC therapy; and (ii) there was no alternative cause for HF, such as anticoagulant therapy. Each case involving a suspected adverse event was reviewed independently by two investigators (an antimicrobial clinical pharmacist and an infectious disease physician). At least "possible" (one of the criteria was fulfilled) was defined as TGC-induced HF in this study.

Measurement of TGC serum concentration

TGC-plasma concentrations were measured at our department of pharmacy. Blood samples were undertaken after at least six doses (on day 4 of treatment) of TGC to achieve a steady state. At least three blood samples were taken from each patient: C_{min} (serum concentration of 30 mins before next dose), $C_{1/2}$ (serum concentration at the 6 hours after the dosing), and C_{max} (serum concentration of 30 mins after dose). A 200 μl sample of plasma was treated with 600 μl of a solution of 8% perchloric acid. The mixture was vortexed for 30 seconds and centrifuged at room temperature for 8 minutes at 15000 × g; next, a 200 μl aliquot of the supernatant was injected into the analytical system. TGC concentration was determined using a validated two-dimensional liquid chromatographic system, which consisted of the first separation system and second separation system (Zhou *et al.*, 2021). The first separation system was performed on column ASTON SNX5 (4.6 × 50 mm, 5 μm, ANAX, Changsha, Hunan China) at a constant temperature of 40 °C for chromatographic separation. The mobile phase of first separation system was a 55:45 (V/V) solution of 20.0 mmol/l phosphoric acid: methanol (pH adjusted to 7.95 by ammonium hydroxide), with a flow rate of 1.0 ml/min. The second separation system was performed on column ASTON SCB (4.6 × 250 mm, 5 μm, ANAX, Changsha, Hunan China) at a constant temperature of 40°C. The mobile phase of second separation system was an 80:20 (V/V) solution of 20.0 mmol/l phosphoric acid: acetonitrile (pH adjusted to 5.18 by ammonium hydroxide), with a flow rate of 1.2 ml/min. The UV detector was set at 340 nm. The overall run time was 10 minutes. The method was linear for TGC concentrations ranging from 0.048 to 6.516 mg/l. Within-run and between-run accuracy and precision (% coefficient of variance) for the serum quality control samples were 4.7% and 5.8%, respectively. The cal-

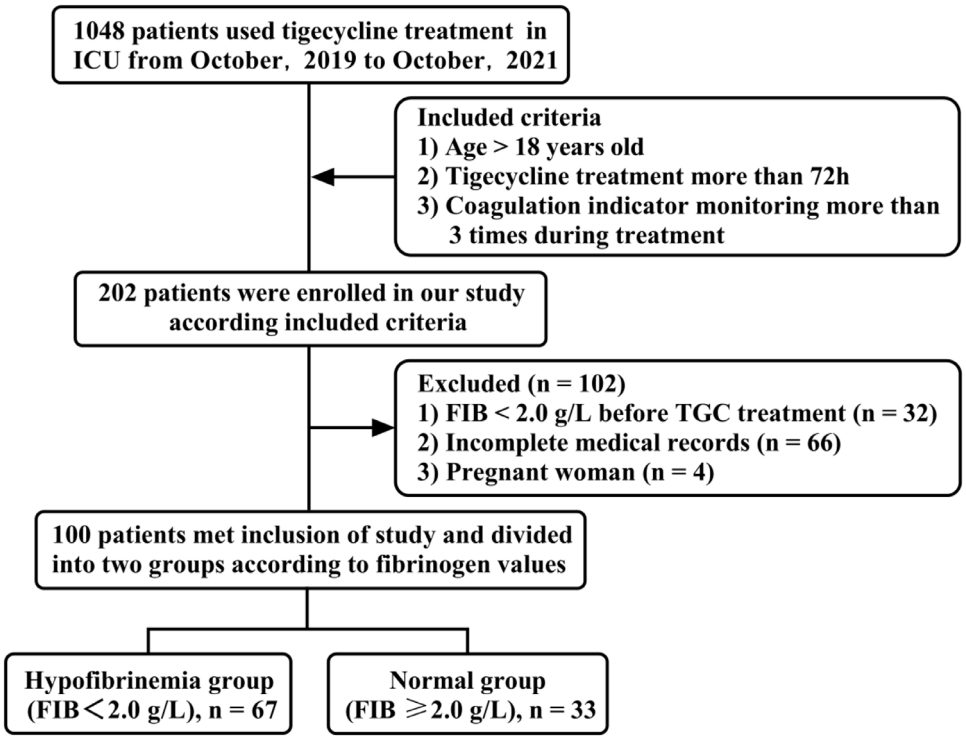

Figure 1. Flowchart of patients included in this study.
FIB, fibrinogen; ICU, intensive care unit; TGC, tigecycline.

ibrator of 0.048 mg/l of TGC was chosen for the lower limit of quantification.

Statistical analyses

Continuous variables were expressed as mean ± SD (normal distribution) or median and Interquartile range (IQR) (non-normal distribution) and evaluated by the Student's *t*-test or Mann-Whitney U test, whereas categorical variables were expressed as number (%) and were compared using a Pearson chi-square test or Fisher's exact tests, as appropriate. A Wilcoxon test was used to compare FIB levels before, during, and after TGC treatment. The receiver operating characteristic (ROC) was performed to derive the concentration thresholds that predict TGC-induced HF. The predictive performance of candidate thresholds was evaluated using the area under the ROC curves along with negative predictive value (NPV) and positive predictive value (PPV). Multivariable logistic analyses were performed to determine the independent association between the concentration variable and TGC-induced HF while adjusting for confounding variables. Each concentration variable was assessed in a separate logistic regression model. Variables with a *P*-value < 0.1 in the baseline variables analyses and concentration parameters were included in the multivariable model at model entry, and variables were excluded from the model using a backward stepwise approach. A *P*-value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics version 26.0.0.

Result

Demographics and clinical characteristics

A total of 100 patients who fulfilled the inclusion and exclusion criteria were considered for the retrospective analysis (Figure 1). The cohort was predominantly male (66%), with a mean ± SD age of 60.9 ± 16.5 years. The median (IQR) duration of therapy was 13.0 (8.2-19.7), and the mean ± SD of the FIB baseline level was 4.4 ± 1.4g/L. The most prevalent infection site was pulmonary infections (52%), and 21 patients (21%) had two or more sites of infections. Regarding the pathogenic microorganism, *Acinetobacter baumannii* (49%) was the most frequent focus, followed by two or more pathogenic microorganisms (35%) and *Klebsiella pneumonia* (13%). A total of 67 patients showed a decrease in FIB to less than 2 g/l during treatment and were classified as the HF group, and 33 patients whose FIB was ≥ 2 g/l were classified as the normal group. Bivariate comparisons between patients who experienced HF or did not experience HF are listed in Table 1. Patients who experienced HF had significantly longer duration of TGC therapy [median (IQR) 14.0 (11.0-21.0) vs 9 (7.5-15.0) days, $P < 0.001$]. In addition, more patients used the high dose in the HF group ($P = 0.015$).

Effect of TGC treatment on FIB

All patients demonstrated a significant decrease in FIB level during TGC therapy. The mean ± SD values of FIB levels before TGC treatment and during treatment were 4.4 ± 1.4 g/l and 1.7 ± 0.8 g/l ($P < 0.001$), respectively. The FIB levels increased after TGC cessation, with a mean ± SD value of 3.5 ± 1.4 g/l, but there was no statistical difference from the during-TGC treatment (Figure 2). The Kaplan-Meier plot revealed that the median time from the initiation of therapy to the development of TGC-induced HF was 7 days (Figure 3). The number of patients with HF gradually increased with the extension of medication time. After 7 days of TGC treatment, 36.17% of patients experienced HF. Subsequently, 68.67% of patients developed HF after 14 days and 83.72% of patients after 21 days of medication (TGC was discontinued according to the clinical cure, the patient was discharged automatically

Table 1
Bivariate comparisons of clinical characteristics between normal groups and HF groups

Variables	Total (n=100)	HF groups (n=67)	Normal groups (n=33)	*P*-value
Age, years, mean ± SD	60.9 ± 16.5	60.3 ± 17.0	62.0 ± 15.6	0.627[a]
Sex, female, n (%)	34.0 (34.0)	25.0 (37.3)	9.0 (27.2)	0.319[b]
SOFA score, median (IQR)	8.0 (6.0-11.7)	7.0 (6.0-12.0)	10.0 (6.0-11.0)	0.717[b]
APACHE II score, mean ± SD	24.4 ± 8.0	25.6 ± 8.0	24.1± 8.1	0.397[a]
FIB baseline level (g/l), mean ± SD	4.4 ± 1.4	4.2 ± 1.4	4.7 ± 1.5	0.093[a]
Duration of TGC therapy, day, median (IQR)	13.0 (8.2-19.7)	14.0 (11.0-21.0)	9.0 (7.5-15.0)	< 0.001[b]
Dose, 100/50 mg q12h	78/22	57/10	21/12	0.015[c]
DIC n (%)	11 (11.0)	8 (11.9)	3 (9.1)	1.000[d]
Infected site n (%)				
Pneumonia infection	52 (52.0)	35 (52.2)	17 (51.5)	0.946[c]
Skin and skin-structures infection	3 (3.0)	2 (6.0)	1 (1.5)	0.253[d]
Intra-abdominal infection	16 (16.0)	13 (19.4)	3 (9.1)	0.186[d]
Central nervous system infection	8 (8.0)	3 (9.1)	5 (7.5)	1.000[d]
Two or more than	21 (21.0)	13 (19.4)	8 (24.2)	0.576[c]
Pathogenic microorganism n (%)				
Klebsiella pneumoniae	13 (13.0)	9 (13.4)	4 (12.1)	0.854[d]
Acinetobacter baumannii	49 (49.0)	29 (43.3)	20 (60.6)	0.103[c]
Stenotrophomonas maltophilia	1 (1.0)	1 (1.5)	0	0.481[d]
Escherichia coli	2 (2.0)	1 (1.5)	1 (3.0)	0.606[d]
Two or more than	35 (35.0)	27 (40.3)	8 (24.2)	0.113[c]
Baseline laboratory data, median (IQR)				
WBC, × 10^9/l	10.9 (6.7-15.4)	10.2 (6.7-14.5)	11.3 (7.4-15.7)	0.494[b]
Neu %	84.0 (79.1-90.4)	85.3 (79.0-90.5)	82.0 (72.5-90.4)	0.274[b]
CRP, mg/l	77.6 (33.0-119.7)	84.6 (44.1-142.2)	73.8 (15.1-127.0)	0.267[b]
PCT, ng/ml	0.7 (0.2-2.2)	0.9 (0.2-3.1)	0.3 (0.1-1.8)	0.160[b]
ALT, U/l	29.1 (14.4-60.4)	28.6 (14.9-51.9)	42.7 (14.9-62.2)	0.783[b]
AST, U/l	29.7 (20.3-49.1)	29.2 (17.4-58.4)	34.8 (24.2-67.6)	0.288[b]
BUN, mmol/l	11.2 (7.3-17.4)	11.1 (6.8-13.7)	12.1 (8.4-22.5)	0.215[b]
Cr, μmol/l	78.0 (45.0-175.0)	80.0 (35.0-163.5)	84.0 (45.0-183.5)	0.606[b]
TB, μmol/l	12.3 (6.3-30.7)	9.5 (5.4-39.3)	14.6 (6.9-34.7)	0.624[b]
Albumin, g/l	33.2 (30.3-37.0)	32.2 (29.7-36.6)	34.2 (30.8-37.3)	0.475[b]
Outcome n (%)				
Recovering	67 (67.0)	45 (67.2)	22 (66.7)	0.960[c]
Automatic discharge	16 (16.0)	10 (14.9)	6 (18.2)	0.676[c]
Death	17 (17.0)	12 (17.9)	5 (15.2)	0.730[c]
Combination n (%)				
Anticoagulants	64 (64.0)	41 (61.2)	23 (69.7)	0.405[c]
Antiplatelet agents	14 (14.0)	10 (14.9)	4 (12.1)	0.941[d]
Cefoperazone/sulbacatam	46 (46.0)	31 (46.3)	15 (45.5)	0.939[c]

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, serum creatinine; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; FIB, fibrinogen; FIB baseline level, FIB level before tigecycline medication; HF, hypofibrinogenemia; IQR, interquartile range; Neu%, neutrophil percentage; PCT, procalcitonin; SOFA, sequential organ failure assessment; TB, total bilirubin; TGC, Tigecycline; WBC, white blood cell count.
[a] Student *t*-test.
[b] Mann-Whitney U.
[c] Pearson chi-square test.
[d] Fisher's exact tests.

or died, 83 patients were treated for 14 days, and 43 patients were treated for 21 days).

Tigecycline serum concentration

As shown in Figure 4a, the calculated $AUC_{0\text{-}24}$ value, C_{max}, $C_{1/2}$, and C_{min} were significantly higher in the high dose group [median (IQR) 19.92 (16.64-27.66) vs 13.74 (10.55-18.24)) mg·h/l, 1.62 (1.25-2.26) vs 0.99 (0.73-1.31) mg/l, 0.61 (0.45-1.06) vs 0.45 (0.39-0.52) mg/l, 0.45 (0.31-0.76 vs 0.31(0.25-0.41) mg/l, all P <0.05)]. The concentration parameters of TGC in the HF group and normal group are shown in Figure 4b. The calculated $AUC_{0\text{-}24}$ value was significantly higher in the HF group [median (IQR) 20.04 (15.60-29.94) vs 17.16 (11.64-20.01) mg·h/l, P=0.003]. Similarly, statistical differences were observed in C_{max}, $C_{1/2}$, and C_{min} of patients treated with TGC. C_{max}, $C_{1/2}$, and C_{min} were higher in the HF group than in the normal group [median (IQR) 1.59 (1.24-2.29) vs 1.37 (0.82-1.68) mg/l, 0.69 (0.45-1.12) vs 0.46 (0.40-0.59) mg/l, 0.46 (0.30-0.78) vs 0.36 (0.26-0.45 mg/l, all P < 0.05)].

Concentration thresholds of tigecycline-induced hypofibrinogenemia

ROC curves of $AUC_{0\text{-}24}$, C_{max}, $C_{1/2}$, and C_{min} were plotted to obtain the cut-off values for HF (Figure 5). The thresholds and predictive performance by ROC curves analysis are listed in Table 2. The $C_{1/2} \geq 0.645$ mg/l had the maximal area under the ROC curve with 0.690 (95% CI, 0.586-0.793), followed by $AUC_{0\text{-}24} \geq 20.76$ mg·h/l with an area under the ROC curve of 0.684 (95% CI, 0.577-0.790), $C_{max} \geq 1.065$ mg/l with an area under the ROC curve of 0.651 (95% CI, 0.534-0.769), and $C_{min} \geq 0.455$ mg/l with an area under the ROC curve of 0.641 (95% CI, 0.531-0.750). The NPV was high across thresholds for $C_{1/2}$, $AUC_{0\text{-}24}$, and C_{min} with 84.85%, 81.81%, and 78.79%, whereas PPV was lower with 52.24%, 49.25%, and 50.75%, respectively. Compared with other thresholds, the C_{max} threshold of ≥ 1.065 mg/l had a lower NPV (42.42%) but a higher PPV (88.06%). The final logistic regression models are listed in Table 3. Adjusting for the duration of TGC, the $AUC_{0\text{-}24} \geq 20.76$ mg·h/l and $C_{min} \geq 0.455$ mg/l were associated with a more than three-fold increased risk of TGC-induced HF (odds ratio [OR], 3.779; 95% CI, 1.327-10.758 and OR, 3.627;95% CI, 1.328-9.903) and $C_{1/2} \geq 0.645$

Table 2
Predictive performance of ROC curve and other candidate thresholds

Variables	Sensitivity	NPV (%)	Specificity	PPV (%)	Area under ROC curve (95% CI)	*P*-value
$AUC_{0\text{-}24} \geq 20.76$ mg·h/l	0.493	81.81	0.818	49.25	0.684 (0.577-0.790)	0.003
$C_{1/2} \geq 0.645$ mg/l	0.522	84.85	0.848	52.24	0.690 (0.586-0.793)	0.002
$C_{max} \geq 1.065$ mg/l	0.881	42.42	0.424	88.06	0.651 (0.534-0.769)	0.014
$C_{min} \geq 0.455$ mg/l	0.507	78.79	0.788	50.75	0.641 (0.531-0.750)	0.023

$AUC_{0\text{-}24}$, area under the concentration-time curve; $C_{1/2}$, serum concentration of the 6 hours after the dosing; C_{max}, serum concentration of 30 minutes after dose; C_{min}, serum concentration of 30 minutes before next dose; over a 24-hour period; NPV, negative predictive value; PPV, positive predicted value; ROC, receiver operating characteristic.

Table 3
Logistic regression analysis of the risk factors for TGC-induced hypofibrinogenemia.

Variables	Odds ratio (95% IC)		*P*-value
	Unadjusted	Adjusted	
$AUC_{0\text{-}24} \geq 20.76$ mg·h/l			
$AUC_{0\text{-}24} \geq 20.76$ mg·h/l	4.368 (1.597-11.943)	3.779 (1.327-10.758)	0.013
Duration of TGC, day	1.146 (1.052-1.249)	1.130 (1.037-1.232)	0.005
$C_{1/2} \geq 0.645$ mg/l			
$C_{1/2} \geq 0.645$ mg/l	6.125 (2.110-17.777)	5.289 (1.760-15.898)	0.003
Duration of TGC, day	1.146 (1.052-1.249)	1.125 (1.033-1.225)	0.007
$C_{max} \geq 1.065$ mg/l			
$C_{max} \geq 1.065$ mg/l	5.434 (1.978-14.933)	5.443 (1.790-16.548)	0.003
Fibrinogen baseline level, g/l	0.687 (0.481-0.983)	0.687 (0.481-0.983)	0.040
Duration of TGC, day	1.146 (1.052-1.249)	1.130 (1.031-1.237)	0.009
$C_{min} \geq 0.455$ mg/l			
$C_{min} \geq 0.455$ mg/l	3.827 (1.462-10.017)	3.627 (1.328-9.903)	0.012
Duration of TGC, day	1.146 (1.052-1.249)	1.135 (1.042-1.236)	0.004

$AUC_{0\text{-}24}$, area under the concentration-time curve over a 24-hour period; $C_{1/2}$, serum concentration of the 6 hours after the dosing; C_{max}, serum concentration of 30 minutes after dose; C_{min}, serum concentration of 30 minutes before next dose; TGC, tigecycline

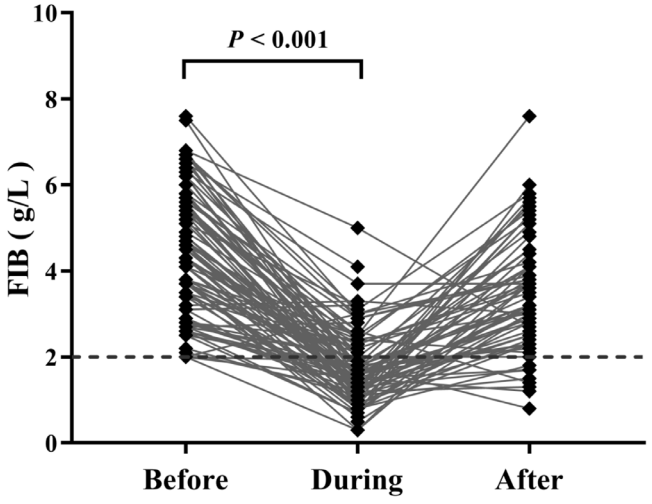

Figure 2. Comparison of FIB values before, during TGC treatment, and after TGC discontinuation. Only 66 patients were collected after discontinuation due to patient discharge or death.
TGC, tigecycline.
FIB, fibrinogen; TGC, tigecycline.

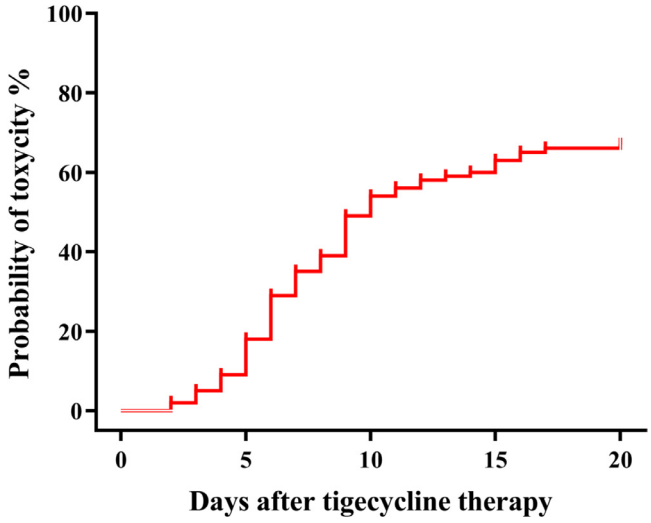

Figure 3. Kaplan-Meier plot showing the time from the initiation of tigecycline therapy to the development of hypofibrinogenemia.

mg/l with a more than five-fold increased risk (OR, 5.289; 95% CI, 1.760-15.898). Adjusting for duration of TGC and FIB baseline level, a $C_{max} \geq 1.065$ mg/l was associated with a more than five-fold increased risk of TGC-induced HF (OR, 5.443; 95% CI, 1.790-16.548).

Discussion

Given the important role of TDM in the efficacy and safety of antibacterial agents, this study sought to determine TGC exposure-toxicity thresholds to predict TGC-induced HF. To our knowledge, this is the first study on the relationship between serum concentration and TGC-induced HF.

Previously published studies focused on concentration parameters as a predictor of efficacy (Leng *et al.*, 2021; Xie *et al.*, 2017). Only a safety analysis reported that 289 patients with TGC treatment had an incidence of nausea/vomiting of 40.4%, when $AUC_{0\text{-}24}$ values were above the threshold value of 6.87 mg·h/l (Rubino *et al.*, 2012). In this study, concentration thresholds of TGC-induced HF were derived from ROC curves with NPV and PPV to detect threshold predictive performance. The area under the ROC curves of C_{min}, C_{max}, $AUC_{0\text{-}24}$, and $C_{1/2}$ was between 0.641 and 0.690. C_{min},

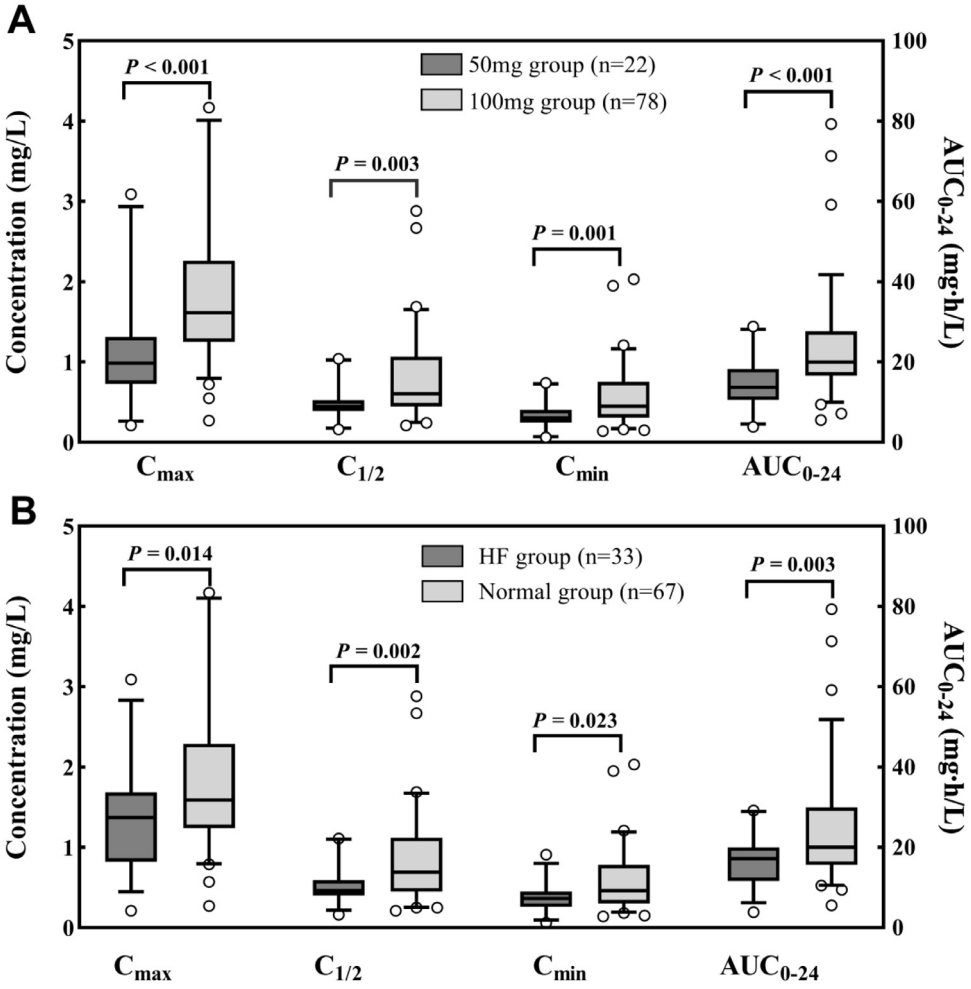

Figure 4. (a) Comparison of C_{max}, $C_{1/2}$, C_{min}, and $AUC_{0\text{-}24}$ between 50 mg group and 100 mg groups. (b) Comparison of C_{max}, $C_{1/2}$, C_{min}, and $AUC_{0\text{-}24}$ between HF group and normal groups.
$AUC_{0\text{-}24}$, area under the concentration-time curve over a 24-hour period; C_{max}, peak serum concentration of TGC; $C_{1/2}$, serum concentration of the 6 hours after the dosing; C_{min}, trough serum concentration of TGC; HF, hypofibrinogenemia; TGC, tigecycline.

$AUC_{0\text{-}24}$, and $C_{1/2}$ had higher NPV between 78.79% and 84.85% but lower PPV, whereas C_{max} presented higher PPV with 88.06% and lower NPV with 42.42%. The major advantage of higher NPV is in identifying patients without HF and reducing the false negative rate. This is desirable when establishing an upper range of recommended TGC exposure for multidrug resistance bacterial infections in which morbidity and mortality concerns may outweigh toxicity concerns. According to the maximal area under the ROC curve and NPV, the $C_{1/2}$ threshold of $\geq$ 0.645 mg/l could be the optimal choice to predict TGC-induced HF. When $C_{1/2}$ values are above the threshold value of $\geq$ 0.645 mg/l, the incidence of HF is more than five times below this threshold. In addition, the threshold of an $AUC_{0\text{-}24} \geq$ 20.76 mg·h/l has been proposed as a suboptimal choice based on the second highest area under the ROC curve and NPV; meanwhile, $AUC_{0\text{-}24}$ is also an indicator of TGC effectiveness in our routine TDM. Although the area under the ROC curves and NPV is inferior to $AUC_{0\text{-}24}$ and $C_{1/2}$, C_{min} is more easily obtained without considering dosing time and cumbersome AUC estimation. Accordingly, $C_{min} \geq$ 0.455 mg/l is only recommended when institutions cannot obtain $C_{1/2}$ or $AUC_{0\text{-}24}$. Nevertheless, owing to the lower NPV, C_{max} is not recommended as a predictor because it may provide too many false negatives.

It was notable that the duration of TGC is another independent risk factor for TGC-induced HF in the final logistic regression models, in addition to the concentration thresholds. The time from the initiation of therapy to the development of HF was 7 days (median), based on the Kaplan-Meier plot in this retrospective study with 100 patients, which was close to that reported by others. The median of 6 days after TGC treatment developed HF was reported by Hu *et al.* (Hu *et al.*, 2020). Moreover, the FIB baseline level was included as the independent risk factor in the final logistic regression models with $C_{max} \geq$1.065mg/l. The duration of TGC and FIB baseline levels were likewise reported in the previous studies as independent risk factors for TGC-induced HF (Zhang *et al.*, 2020). In addition, there was a difference in the $AUC_{0\text{-}24}$ value, C_{max}, $C_{1/2}$, and C_{min} between the high and standard dose groups. Therefore, the dose was included in the initial multivariable model as a covariate but was excluded from the final logistic regression models using a backward stepwise approach.

This study is limited in several aspects. Owing to the retrospective nature of this study, medical surveillance bias cannot be excluded. For example, not all patients were monitored for FIB levels daily. Another limitation is the thresholds attained based on the predictive model may limit the applicability of some of our conclusions. In addition, thresholds for TGC-induced HF should be confirmed prospectively with a large sample. Despite these limitations, our findings provide valuable information about TGC-induced HF limiting thresholds in real-world patients.

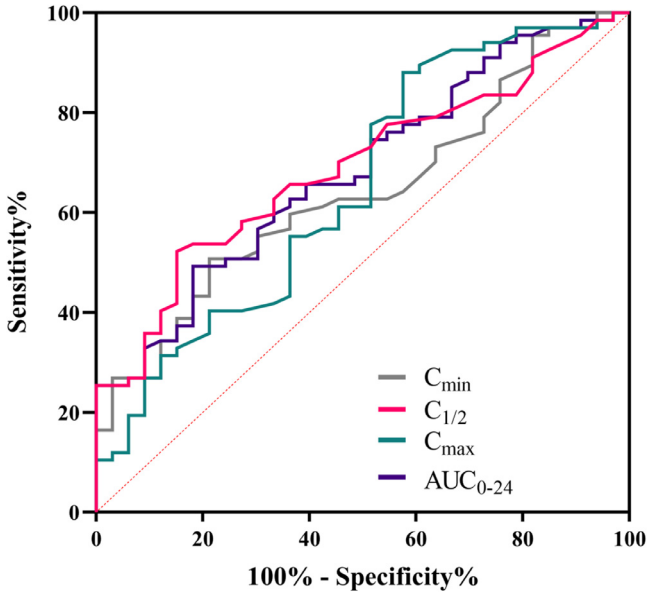

Figure 5. Receiver operating characteristic curve analysis of tigecycline-induced hypofibrinogenemia concentration thresholds.
$AUC_{0\text{-}24}$, area under the concentration-time curve over a 24-hour period; C_{max}, peak serum concentration of TGC; $C_{1/2}$, serum concentration of the 6 hours after the dosing; C_{min}, trough serum concentration of TGC; TGC, tigecycline.

Conclusions

This study derived TGC-induced HF thresholds in $AUC_{0\text{-}24}$, C_{max}, $C_{1/2}$, and C_{min} of steady state. The predictive performance of the $AUC_{0\text{-}24}$, C_{min}, and $C_{1/2}$ thresholds was reliable. TGC $C_{min} \geq 0.455$ mg/l, $AUC_{0\text{-}24} \geq 20.76$ mg·h/l, and $C_{1/2} \geq 0.645$ mg/l were associated with an approximately three- to five-fold increased HF risk. $C_{1/2} \geq 0.645$ mg/l with the best area under the ROC curve and NPV appears to be the most appropriate toxicity threshold.

CRediT authorship contribution statement

Xiaoxuan Yang: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Lu Jin:** Conceptualization, Writing – original draft, Writing – review & editing. **Xuemei Luo:** Validation, Writing – review & editing. **Min Wang:** Data curation, Formal analysis, Writing – review & editing. **Huaijun Zhu:** Investigation, Writing – review & editing. **Yujie Zhou:** Investigation, Writing – review & editing. **Weihong Ge:** Conceptualization, Writing – review & editing.

Conflicts of interest

The authors have no competing interests to declare.

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Ethics and data management

This study was approved by the Ethical Committee of Drum Tower Hospital affiliated with the Medical School of Nanjing University (NO.2021-552-02) and registered on Chinese Clinical Trial Registry (ChiCTR2100053866) (http://www.chictr.org.cn).

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