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Identification of Risk Factors and Predictive Indicators for Tigecycline-Associated Hypofibrinogenemia

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ABSTRACT

To investigate the prevalence, clinical manifestations, and risk factors of hypofibrinogenemia after tigecycline use, which can disrupt coagulation and potentially hinder antimicrobial therapy. This observational study was conducted from January to December 2021 at a tertiary general hospital in China. All patients over 18 years old who received tigecycline for more than 48 h were included. After treatment with tigecycline, patients were divided into two groups based on fibrinogen plasma concentrations of less than 2.0 g/L. Multivariable logistic regression was performed to identify risk factors for hypofibrinogenemia associated with tigecycline. A total of 50 patients (mean age 71.3 ± 20.2 years) were analyzed. The median duration of treatment was 8 days (range: 3 to 20 days). Among the 24 patients who developed hypofibrinogenemia, three gastrointestinal bleeding events were observed, and four of these patients required fibrinogen administration. We identified the total therapeutic dose (odds ratio (OR) = 15.28, 95% confidence interval (CI) 2.10–111.02, $p = 0.01$) and a baseline direct bilirubin level greater than 0.4 mg/dL (OR = 5.79, 95% CI 1.13–27.98, $p = 0.04$) as risk factors for tigecycline-induced hypofibrinogenemia. Conversely, a baseline fibrinogen level (OR = 0.53, 95% CI 0.29–0.97, $p = 0.04$) appeared to be a protective factor. Healthcare professionals should be aware that the administration of tigecycline may be associated with hypofibrinogenemia and severe adverse reactions. Regular monitoring of coagulation is essential, particularly for patients with liver dysfunction, low baseline fibrinogen levels, elevated baseline direct bilirubin levels, or those receiving higher total therapeutic doses.

1 | Introduction

Antimicrobial resistance (AMR) poses a significant global threat to human health, often resulting in prolonged and costly treatment regimens [1]. Tigecycline, the first drug in the glycylcyclines class, is a novel agent structurally akin to tetracyclines, exhibiting broad-spectrum antibacterial activity against a wide range of microbial pathogens, including gram-positive and gram-negative bacteria, anaerobic microorganisms, and non-tuberculous mycobacteria [2]. In China, tigecycline is utilized for treating complex skin and skin structure infections, complex abdominal infections, and community-acquired

Summary

- What is the current knowledge on the topic?
  - Current knowledge regarding tigecycline-associated hypofibrinogenemia is limited; however, it suggests that this antibiotic may induce coagulation disorders, particularly hypofibrinogenemia.
  - This condition can potentially hinder the administration of antimicrobial therapy and result in severe adverse reactions.
- What question did this study address?
  - We identified the total therapeutic dose and a baseline direct bilirubin level greater than 0.4 mg/dL as risk factors for tigecycline-induced hypofibrinogenemia.
  - Conversely, a higher baseline fibrinogen level appeared to be a protective factor according to our observational study.
- What does this study add to our knowledge?
  - This study enhances our understanding by identifying the total therapeutic dose of tigecycline and baseline direct bilirubin levels as risk factors for tigecycline-induced hypofibrinogenemia.
  - Furthermore, baseline fibrinogen levels were identified as a protective factor against this condition.
  - These findings offer valuable insights into the potential mechanisms and predictors of tigecycline-associated hypofibrinogenemia.
- How might this change clinical pharmacology or translational science?
  - This study may influence clinical pharmacology by alerting healthcare professionals to the potential risks of tigecycline-induced hypofibrinogenemia, particularly in patients with specific risk factors.
  - It underscores the importance of regular monitoring of coagulation parameters during tigecycline treatment.
  - Additionally, this study may contribute to translational science by providing a basis for future research into the mechanisms underlying tigecycline-associated coagulation disorders and potential interventions to mitigate these.

pneumonia [3], particularly those caused by carbapenem-resistant *Acinetobacter baumannii* or Enterobacterales, as well as Vancomycin-resistant *Enterococci* [4]. As one of the few therapeutic options for treating multi-drug resistant (MDR) and extensively drug-resistant (XDR) bacterial infections, tigecycline has a standard recommended dosage of 50 mg administered twice daily, preceded by an initial loading dose of 100 mg. In cases of severe infection, the dosage may be doubled [4]. However, recent surveillance data and studies have indicated that common adverse reactions to tigecycline include vomiting, diarrhea, abdominal pain, liver damage, and hematological changes [5]. Surveillance data on post-market adverse drug reactions (ADRs) associated with tigecycline [6], along with outcomes from a randomized controlled trial [7], have shown that tigecycline use can trigger coagulation abnormalities, particularly hypofibrinogenemia, with some cases reporting gastrointestinal bleeding [8–10]. Notably, the use of tigecycline has been associated with coagulation abnormalities, especially when high doses are administered or when treatment extends beyond 10 days [6, 8, 9]. In such cases, ADRs may occur more frequently and with greater severity than what is typically observed in clinical trials [8–10]. In light of this, we conducted a retrospective study to assess the likelihood of tigecycline-induced hypofibrinogenemia and to identify relevant clinical variables that could predict a high risk of these adverse events during treatment, with the ultimate goal of developing a risk prediction model.

2 | Material and Methods

2.1 | Study Objects

This retrospective study aimed to observe the occurrence of coagulation abnormalities, such as hypofibrinogenemia, during the administration of tigecycline at the First Hospital of Changsha, a tertiary general hospital in China. This study was conducted in accordance with all relevant principles of the Declaration of Helsinki. Approval was granted by the Medical Ethics Committee of the First Hospital of Changsha (approval no. 2023lks[ly]122), and written informed consent was not required.

2.2 | Methods

We searched the hospital information system and collected the medical records of all patients who were treated with tigecycline during their hospitalization from January 2021 to December 2021. This study included patients who met the following criteria: they were 18 years of age or older, had received tigecycline treatment for more than 48 h, and had undergone routine blood tests, coagulation function assessments, and other relevant measurements before, during, and after tigecycline treatment. The exclusion criteria were as follows: (1) patients with coagulation dysfunction prior to tigecycline treatment, such as hemophilia or active bleeding; (2) patients with fibrinogen levels less than 2.0 g/L before tigecycline treatment; (3) patients with incomplete clinical data; (4) patients who received other medications that could affect coagulation function, such as heparin and warfarin. Refer to Figure 1 for the flowchart outlining the case collection process.

Demographic data (age, gender), laboratory and clinical information (age-adjusted Charlson Comorbidity Index (aCCI), comorbidities, ICU admissions, infection sites and types), and tigecycline treatment details (dosage, treatment duration, and adverse reactions during treatment) were obtained from the hospital information system. We gathered clinical laboratory test results at various time points during tigecycline treatment, including baseline, every 2 days during administration, and after treatment discontinuation. Clinical pharmacists individually reviewed the collected records and evaluated the causality of adverse drug reactions based on the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system [11].

According to the tigecycline package insert [12], the initial recommended dosage is 100 mg, followed by subsequent doses of 50 mg every 12 h. For patients with severe liver impairment (Child-Pugh C), the dose should be reduced to 25 mg every 12 h. In our study, we defined high-dose tigecycline as 100 mg

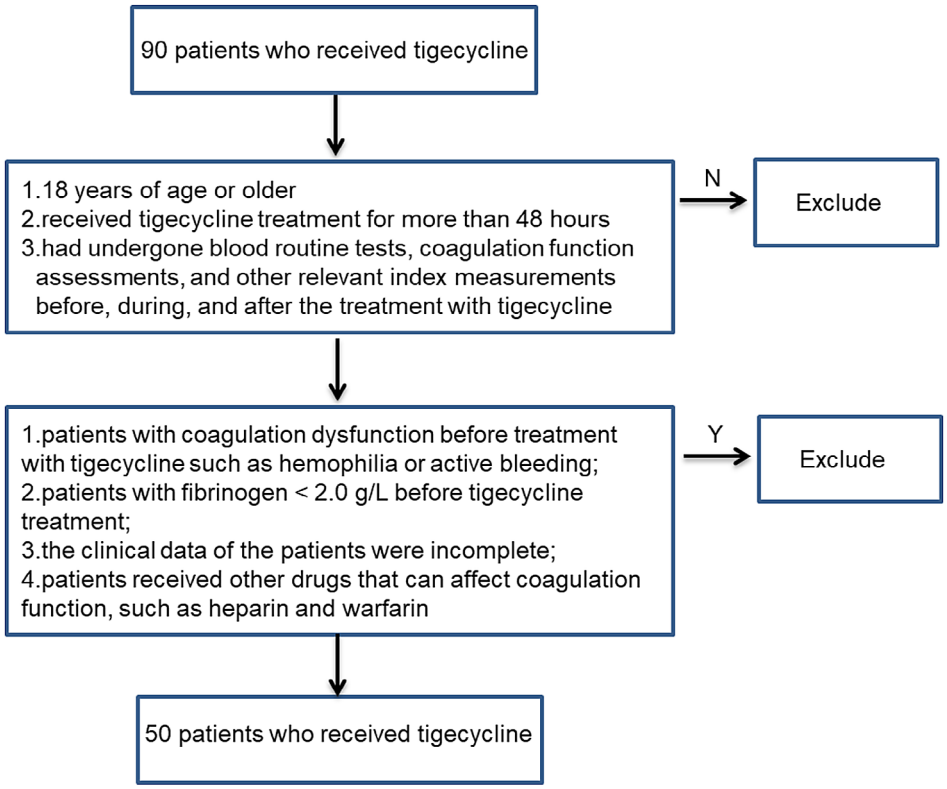

FIGURE 1 | Case collection process diagram.

administered twice daily [3], in contrast to the authorized low-dose of 50 mg twice daily, which we refer to as hypofibrinogenemia, defined as a plasma fibrinogen concentration of less than 2.0 g/L [13]. The total therapeutic dose is defined as the cumulative amount of tigecycline administered continuously over one treatment cycle.

The patients were categorized into a normal group and an abnormal group based on their fibrinogen plasma concentration following tigecycline treatment. In this study, we compared the differences in demographics, clinical, and laboratory data, and tigecycline treatment status between the two groups, aiming to identify potential risk factors associated with tigecycline-related hypofibrinogenemia through multivariate analysis.

2.3 | Statistical Analysis

The data were initially recorded in Microsoft Word and subsequently summarized in Microsoft Excel to create a database. Following the auditing process, the data were imported into the SPSS 20.0 statistical package (IBM Corp., Armonk, NY, USA) for statistical verification, collation, and analysis. Frequencies and proportions were reported for categorical variables, while the medians and interquartile ranges (IQR) were reported for continuous variables. Data with a normal distribution and homogeneous variance were analyzed using a *t*-test; data with unequal variance was analyzed using a corrected *t*-test; non-normally distributed data were analyzed using the Mann–Whitney *U*-test; and categorical data were analyzed using either the Chi-square test or Fisher's exact test. Multivariable logistic regression analyses were performed to incorporate risk factors identified in univariate analysis into multivariate models, using variables that were considered clinically relevant and statistically significant as covariates ($p < 0.05$). The joint prediction factor was calculated through a logistic regression model, and the Receiver Operating Characteristic (ROC) curves for independent influencing factors and joint prediction factors were generated. The Youden index was calculated based on the sensitivity and specificity of the ROC curve. All tests were two-tailed, with a $p < 0.05$ considered statistically significant.

3 | Results

3.1 | Demographics and Clinical Characteristics

A total of 50 patients who received tigecycline at the First Hospital of Changsha from January to December 2021 were identified as eligible for inclusion in the study. Table 1 showed the baseline characteristics of the patients at the onset of tigecycline treatment. The cohort comprised a higher proportion of males (82%) compared to females, with a mean age of 71.3 ± 20.2 years (48% of patients were over 80 years old), and the mean aCCI was 8.04 ± 3.11. The majority of patients (94%) were admitted to the intensive care unit (ICU) when tigecycline treatment commenced, and sepsis was diagnosed in 54% of the cases. Mixed infections were prevalent, occurring in 44% of the patients, with the most common site of infection being the lower respiratory tract (80%), followed by abdominal (26%) and skin and soft tissues (2%). Only four patients received high-dose tigecycline, and the median duration of

TABLE 1 | Demographic and clinical data for all patients included in the study [($\bar{x} \pm s$)/*N* (%)].

Variables	*N* = 50
Men [*N* (%)]	41 (82.0)
Age (years)	71.28 ± 20.22
Weight (kg)	57.92 ± 7.53
aCCI	8.04 ± 3.11
ICU admission (%)[a]	96
Sepsis (%)[a]	54
Creatinine clearance (mL/min/1.73m^2)[a]	40.2 (19.03, 78.85)
Alanine aminotransferase (UI/L)[a]	35.40 (11.72, 60.45)
Alkaline phosphatase (UI/L)[a]	37.45 (24.13, 67.48)
Total bilirubin (mg/dL)[a]	0.64 (0.37, 1.14)
Direct bilirubin (mg/dL)[a]	0.41 (0.20, 0.67)
Serum albumin (g/dL)[a]	2.94 ± 0.54
White blood cell count (×10^9/L)[a]	12.11 (9.5, 15.13)
Platelets count (×10^9/L)[a]	165 (85.25, 235.0)
Coagulation test[a]	
INR	1.22 ± 0.17
APTT(s)	36.9 ± 6.55
Fibrinogen(g/L)	4.48 ± 1.34
Tigecycline dose regimen	
High-dose tigecycline [*N* (%)]	4 (8.0)
Total therapeutic dose (mg)	850 (650, 1200)
Treatment course of tigecycline (days)	8.09 (5.85, 11.53)
The median time until the occurrence of hypofibrinogenemia events (days)	8.75 (6, 10)

Abbreviations: aCCI, Age-adjusted Charlson Comorbidity Index; APTT, activated partial thromboplastin time; ICU, Intensive Care Unit; INR, international normalized ratio.
[a]At the time of tigecycline treatment initiation.

treatment was 8 days, with an interquartile range of 6.0 to 11.0 days.

The risk factors associated with hypofibrinogenemia were listed in Table 2. Following treatment with tigecycline, patients were categorized into two groups based on their plasma fibrinogen concentration: the normal fibrinogen group (26 cases, 52%) and the abnormal fibrinogen group (24 cases, 48%). In the abnormal fibrinogen group, the median duration until hypofibrinogenemia occurred after medication was 8.75 days, with an interquartile range of 6.0 to 10.0 days. Of the cases in this group, 21 cases returned to normal after drug withdrawal, with recovery time ranging from 1 to 9 days. Additionally, six cases experienced liver function impairment, three cases had gastrointestinal bleeding, and four cases required intravenous administration of fibrinogen.

3.2 | Univariate Analysis of Hypofibrinogenemia Associated With Tigecycline Use

During tigecycline treatment, statistically significant changes in coagulation parameters were observed. Differences were noted in fibrinogen plasma level ($t = 9.57$, $p < 0.05$) and international standardized ratio (INR) levels ($t = 2.07$, $p < 0.05$) between the two groups. As shown in Table 2, the univariate analysis identified several factors related to hypofibrinogenemia, including direct bilirubin levels greater than 0.4 mg/dL (odds ratio (OR) = 3.78, 95% confidence interval (CI) 1.17–12.19, $p = 0.03$) and fibrinogen level (OR = 0.59, 95% CI 0.37–0.95, $p = 0.03$) at the time of tigecycline initiation, as well as the total therapeutic dose (OR = 4.17, 95% CI 1.14–15.26, $p = 0.03$).

3.3 | Multivariate Logistic Regression Analysis of Hypofibrinogenemia Associated With Tigecycline Use

Multivariate logistic regression analysis indicated that a baseline direct bilirubin level exceeding 0.4 mg/dL (OR = 5.79, 95% CI 1.13–27.98, $p = 0.04$) and the total therapeutic dose (OR = 15.28, 95% CI 2.10–111.02, $p = 0.01$) were risk factors for hypofibrinogenemia associated with tigecycline use. Conversely, a baseline fibrinogen level (OR = 0.53, 95% CI 0.29–0.97, $p = 0.04$) emerged as a likely protective factor against this condition. Notably, all other factors evaluated in this study were found to be unrelated to hypofibrinogenemia.

3.4 | Prediction Model of the Risk Factors of Hypofibrinogenemia Associated With Tigecycline Use

The logistic regression model was used to develop the mathematical equations of the prediction models, which calculate the joint prediction factor (Y joint) (see the equation). Subsequently, the ROC curve for each parameter was constructed to predict clinical response and to calculate the area under the curve (AUC) (see Figure 2). Sensitivity and specificity analyses of the predictive prognostic factors were performed using the ROC curve and AUC (see Figure 2 and Table 3). According to the results of the ROC curve analysis, baseline fibrinogen level emerged as the most accurate predictive factor, exhibiting a sensitivity of 87.5% and a specificity of 50% (AUC = 0.70, $p = 0.015$). The cut-off values for the total therapeutic dose and baseline fibrinogen were determined to be 1350 and 4, respectively (see Table 3).

When the AUC of the joint prediction factor reaches its maximum, it indicates higher prediction accuracy. The results showed that the combination of total therapeutic dose and baseline fibrinogen level provided better predictive accuracy for hypofibrinogenemia associated with tigecycline use (AUC = 0.771, $p = 0.001$). The Youden index, which combines sensitivity and specificity, reflects the effectiveness of the prediction; a larger

TABLE 2 | Factors related to hypofibrinogenemia associated with tigecycline use [$(\bar{x} \pm s)/N$].

Variables	Fibrinogen plasma concentration < 2.0 g/L		Univariate analysis		Mutivariate analysis	
	No ($n = 26$)	Yes ($n = 24$)	OR (95% CI)	p	OR (95% CI)	p
Age ≥ 80 years	15	11	0.62 (0.20–1.90)	0.4		
Male	23	18	0.39 (0.09–1.78)	0.23		
Weight ≥ 60 kg	13	8	0.50 (0.16–1.57)	0.24		
aCCI ≥ 9	10	11	1.35 (0.44–4.18)	0.6		
Sepsis	13	14	1.40 (0.46 ~ 4.28)	0.56		
Hepatic insufficiency	14	11	0.72 (0.24–2.21)	0.57		
Duration of medical hospitalization ≥ 30 days	14	15	1.43 (0.46–4.42)	0.54		
Before tigecycline administration						
Alanine aminotransferase > 40 UI/L	13	8	0.5 (0.16–1.57)	0.24		
Aspartate aminotransferase > 40 UI/L	14	10	0.61 (0.20–1.88)	0.39		
Total bilirubin > 1 mg/dL	7	8	1.36 (0.40–4.57)	0.622		
Direct bilirubin > 0.4 mg/dL*	9	16	3.78 (1.17–12.19)	0.03	5.79 (1.13–27.98)	0.04
Creatinine clearance > 90 mL/min	7	4	0.54 (0.14–2.16)	0.39		
White blood cell count > 10×10^9/L	18	16	0.89 (0.27–2.92)	0.85		
Platelet count < 100×10^9/L	4	9	3.3 (0.86–12.71)	0.08		
Fibrinogen*	4.88 ± 1.29	4.04 ± 1.28	0.59 (0.37, 0.95)	0.03	0.53 (0.29–0.97)	0.04
Concomitant drugs						
Cefoperazone/sulbactam	3	4	1.53 (0.306, 7.69)	0.60		
Vitamin K1	4	7	2.27 (0.57–9.02)	0.25		
Total therapeutic dose (mg)*	800 (487.50, 1000.00)	850 (762.50, 1712.50)	4.17 (1.14 ~ 5.26)	0.03	15.28 (2.10,111.02)	0.01

Note: *p value < 0.05 was considered statistically significant.
Abbreviations: aCCI, Age-adjusted Charlson comorbidity index; CI, confidence interval; OR, odds ratio.

index indicates a better predictive performance [14, 15]. The Youden index for the joint prediction factor is 0.475, with a corresponding threshold value of −1.31.

$$\text{Equation} = -0.7 + 0.003X1 - 0.63X2$$

where, X1: Total therapeutic doses; X2: Fibrinogen.

4 | Discussion

In our retrospective study, we observed that hypofibrinogenemia developed in 26 of the 50 patients (52%) following treatment with tigecycline. This finding underscores the necessity for further research to identify the underlying causes and predictors of this condition. Previous studies, including an analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, have also reported a high incidence of coagulation dysfunction, particularly hypofibrinogenemia, associated with tigecycline use [6]. Our findings aligned with those reports, indicating that the median duration until the onset of hypofibrinogenemia following medication administration was 8.75 days, which fell within the range of 5 to 10 days as previously reported in the literature [6, 9, 16–18]. The recovery of fibrinogen concentration after discontinuation of treatment further supports a causal relationship between tigecycline use and hypofibrinogenemia, consistent with conclusions drawn in previous research [8–10]. Notably, hypofibrinogenemia was less frequently detected in clinical trials, likely due to participants not receiving high doses and/or prolonged treatment with tigecycline [2]. This discrepancy emphasizes the importance of real-world data in identifying adverse events that may not be fully captured in controlled trial settings. Given the significant impact of adverse drug reactions (ADRs) on treatment adherence and outcomes, we conducted an analysis to identify the independent risk factors for hypofibrinogenemia in patients treated with tigecycline. Our results revealed that a baseline direct bilirubin level greater than 0.4 mg/dL and the total therapeutic dose of tigecycline were the independent risk factors, while the baseline fibrinogen level may serve as a protective factor.

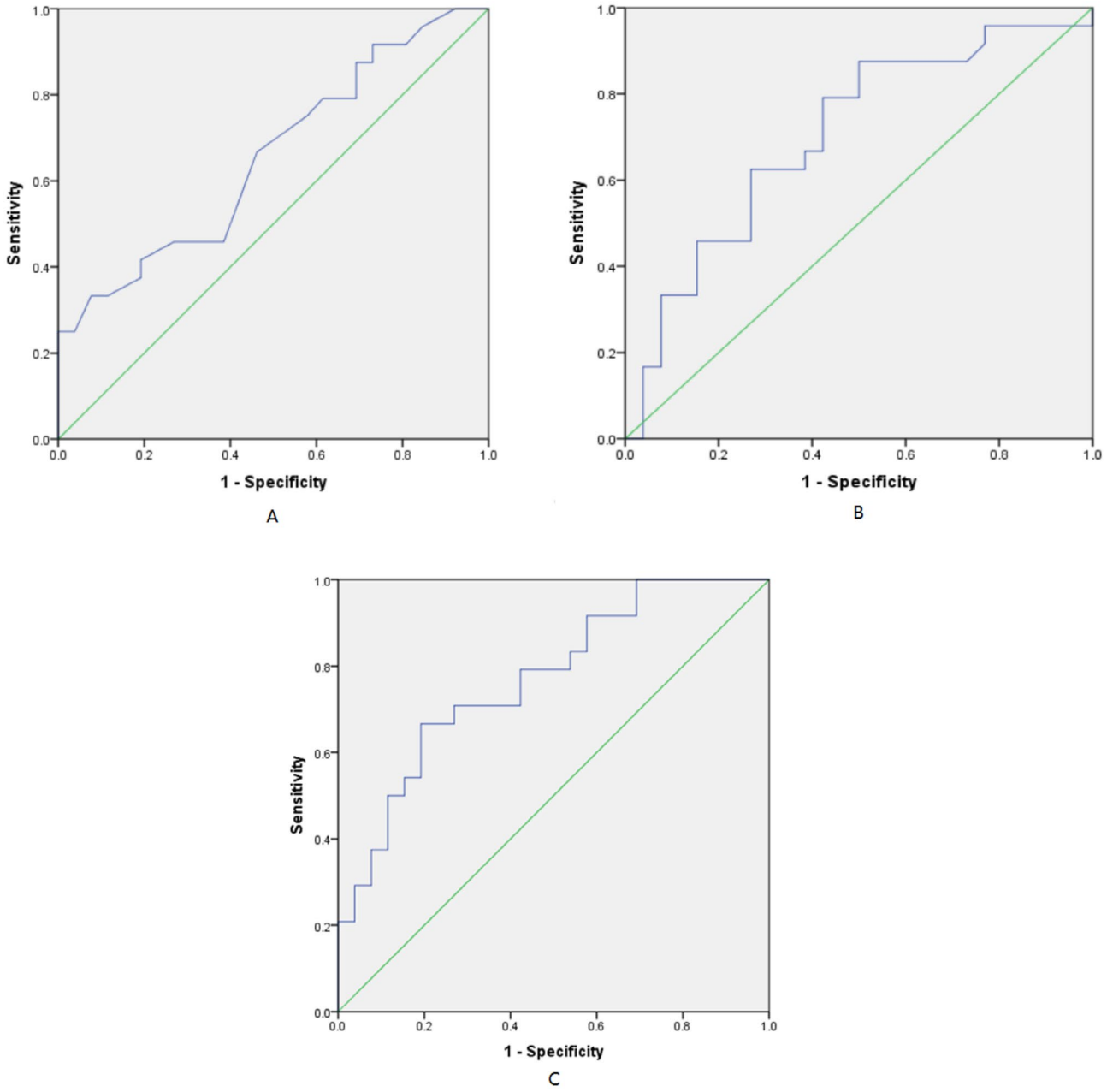

FIGURE 2 | The Receiver Operating Characteristic (ROC) curves used to compare the performance of different predictors for tigecycline-induced hypofibrinogenemia: (A) the ROC curve for the baseline fibrinogen level, (B) the ROC curve for the total therapeutic dose, (C) the ROC curve for the combination of risk factors. The ROC curves are evaluated based on their sensitivity (*y*-axis) and 1-specificity (*x*-axis) at various threshold settings. A predictor is considered more accurate if its line follows closely the left-hand border and then the top border of the ROC space. The Area Under the Curve (AUC) provides a quantitative measure of the overall accuracy for each predictor.

Fibrinogen, a glycosylated acute-phase protein synthesized by liver parenchymal cells, has a half-life of approximately 3 to 4 days. In healthy individuals, fibrinogen levels in the bloodstream typically range from 2 to 4 g/L. Hypofibrinogenemia, a condition characterized by abnormally low fibrinogen levels, can occur in patients with chronic inherited disorders such as afibrinogenaemia, dysfibrinogenemia, or hypodysfibrinogenemia. Additionally, acquired hepatic dysfunction, such as that seen in cirrhosis, hepatitis, and metastatic hepatoma, as well as severe malnutrition, can lead to hypofibrinogenemia. Acutely, hypofibrinogenemia has been associated with disseminated intravascular coagulation, severe sepsis, malignancy, and the administration of certain medications, such as valproic acid and allopurinol [9]. Through multivariate logistic regression analysis, we identified elevated direct bilirubin levels as an additional risk factor. Given that tigecycline is primarily metabolized by the liver, in vitro studies have shown that it may disrupt the polymerization ability of fibrinogen without directly interacting with the peripheral coagulation system [19]. Patients undergoing tigecycline treatment who exhibit decreased fibrinogen levels could either be related to heightened consumption or issues with hepatic synthesis. Furthermore, as liver injury deteriorates, abnormalities in blood coagulation may also become more pronounced. Therefore, we recommend increased monitoring of

TABLE 3 | Predictive value of each variable on the risk of hypofibrinogenemia associated with tigecycline use.

Variables	Threshold value	Sensitivity	Specificity	Youden index	AUC (95% CI)	*p*
Total therapeutic dose	1350	0.333	0.077	0.256	0.655 (0.504 ~ 0.807)	0.060
Baseline fibrinogen	4	0.875	0.5	0.375	0.701 (0.554 ~ 0.848)	0.015
Joint prediction factor	−1.31	0.667	0.192	0.475	0.771 (0.642 ~ 0.900)	0.001

Abbreviation: AUC, area under the curve.

patients with liver dysfunction, particularly those classified as Child-Pugh C, during tigecycline administration.

In this study, the total therapeutic dose of tigecycline was evaluated as a risk factor for the incidence of hypofibrinogenemia. As previously mentioned, the median duration until hypofibrinogenemia occurs following tigecycline administration was 8.75 days, with an interquartile range of 6.0 to 10.0 days. Additionally, prior research has reported a correlation between high-dose tigecycline and a reduction in fibrinogen levels [8, 20, 21]. Given that only four patients in our study received high-dose tigecycline, we were unable to draw a comparable conclusion. According to the manufacturer's instructions, the recommended daily dose of tigecycline is 100 mg. However, clinical practice has shown that a lower dose of tigecycline may be ineffective for certain patients with severe infections and could even promote the emergence of drug-resistant bacteria [21, 22]. An increased dosage has been shown to enhance the antibacterial efficacy of the drug [4], leading to the frequent use of high-dose tigecycline in clinical practice. Furthermore, some studies indicated that there was no significant difference in the incidence of adverse reactions, including coagulation abnormalities, between high-dose and standard-dose tigecycline treatments [22, 23]. Therefore, we emphasize the importance of closely monitoring coagulation indicators in patients undergoing tigecycline therapy, especially when the daily dose exceeds the recommended dosage, the treatment duration exceeds 8 days, or the total therapeutic dose is significant.

Since urine excretion accounts for 33% of tigecycline elimination [2], renal impairment may not lead to drug accumulation or increased toxicity. As a lipophilic drug, tigecycline exhibits a broader distribution in the body tissues of elderly patients, prolonging its retention time and increasing exposure. Furthermore, the metabolic and excretory function of the liver and kidneys decline with age, which exacerbates tigecycline's exposure and may lead to coagulation abnormalities. Additional factors, such as intra-abdominal infections and elevated protein C levels, have been identified as risk factors for tigecycline-associated hypofibrinogenemia in other studies [8, 9]. Conversely, hemoglobin levels have been reported as a protective factor against tigecycline-induced coagulation abnormalities [24]. A decrease in hemoglobin can impair the oxygen-carrying capacity of blood, thereby slowing down both cellular and tissue metabolism. Given tigecycline's extensive tissue distribution, this metabolic slowdown may further increase tigecycline concentration.

Regarding concomitant therapy, cefoperazone-sulbactam [25], sodium valproate [26], and asparaginase [27] have been reported to be associated with abnormal coagulation. In this study, we excluded patients who were receiving other medications that could potentially affect coagulation function, such as heparin and warfarin. No patient was using sodium valproate or asparaginase. When cefoperazone-sulbactam was administered, we did not observe an elevated risk of hypofibrinogenemia.

Hypofibrinogenemia associated with tigecycline typically manifests as dose-dependent prolongation of prothrombin time and activated partial thromboplastin time, accompanied by decreased fibrinogen levels. In this study, fibrinogen levels normalized in 87.5% of the patients within 1 to 9 days following drug withdrawal, similar to previous reports [16, 17, 21]. Currently, severe coagulation dysfunction induced by tigecycline can only be reversed through drug discontinuation and fibrinogen infusion. Fibrinogen replacement therapy is recommended either as a prophylactic measure against unprovoked bleeding in individuals with congenital or acquired fibrinogen deficiency, or as a therapeutic option for spontaneous bleeding events [28]. However, there remains a lack of effective preventive measures. This study found no significant difference in outcomes between patients with hypofibrinogenemia or those without when vitamin K injections were administered. Although it has been suggested that tigecycline reduces the gastrointestinal flora, resulting in decreased vitamin K production [29], this mechanism does not account for the observed reduction in plasma fibrinogen in this context.

The ROC curve stands as an ideal and classic method for evaluating diagnostic tests, with its AUC serving as a reliable indicator of diagnostic accuracy. As the AUC increases, so does the diagnostic efficiency [14, 15]. However, individual diagnostic indicators often exhibit limited sensitivity or specificity in identifying target diseases. To enhance predictive accuracy, it is beneficial to establish joint predictors using logistic regression models. These joint predictors can be derived by transforming the logistic regression model [14, 15]. As shown in Table 3, the joint predictor outperforms other individual influencing factors in terms of AUC, sensitivity, specificity, and the Youden index. Therefore, it is advisable to select the joint predictor as the primary predictor. Notably, a threshold value of −1.31 for the joint predictor indicates a significantly increased risk of hypofibrinogenemia.

4.1 | Limitations

This study has several limitations. Primarily, its retrospective nature may have introduced biases related to sample size and selection. Due to this retrospective design, the study did not comprehensively encompass numerous influencing factors of hypofibrinogenemia, such as multidrug therapy and the stratification analysis of different levels of initial fibrinogen. Additionally, the variability among patients posed challenges to statistical

analysis, despite the diligent efforts of the researchers to minimize confounding factors. The heterogeneity of the patient population likely contributed to the complexity of the data and limited the ability to draw definitive conclusions. Furthermore, the data were exclusively sourced from inpatient settings, which underscore the potential value of extending research to prospective randomized controlled trials involving larger patient populations. Such trials would provide a more robust platform for assessing the impact of tigecycline on fibrinogen levels and could help validate the findings of this study. Nevertheless, the study successfully identified several clinical characteristics and risk factors associated with tigecycline-induced hypofibrinogenemia, undoubtedly propelling advancements in this field.

5 | Conclusions

Currently, the mechanism underlying hypofibrinogenemia associated with tigecycline use remains unclear. Key findings from our analysis revealed that independent risk factors include a baseline direct bilirubin level exceeding 0.4 mg/dL and the total therapeutic dose of tigecycline administered. Conversely, a baseline fibrinogen level may serve as a protective factor. These findings have significant implications for risk stratification and the formulation of personalized treatment strategies in patients undergoing tigecycline therapy. In light of these findings, clinicians should exercise caution when prescribing tigecycline, particularly in patients with liver dysfunction, low baseline fibrinogen levels, or elevated baseline direct bilirubin levels. Additionally, patients receiving daily doses that exceed the recommended dosage, treatment durations longer than 8 days, or higher total therapeutic doses should be closely monitored. Therefore, it is essential to enhance the regular monitoring of coagulation parameters in such cases to promptly detect and manage hypofibrinogenemia.

Author Contributions

X.L. and J.L. wrote the manuscript. J.L. designed the research. L.W., Q.S., and X.T., performed the research. X.Y. analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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