

# Clinical Manifestations and Risk Factors of Tigecycline-Associated Thrombocytopenia

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**Background:** Thrombocytopenia, characterized by a diminished platelet count, emerged as the most frequently reported coagulation dysfunction event according to the FDA Adverse Event Reporting System (FAERS) database. In recent years, numerous clinical studies have investigated the potential link between tigecycline usage and the occurrence of hypofibrinogenemia. However, a research gap remains in comprehensively examining the association between tigecycline and thrombocytopenia in real-world settings.

**Methods:** This study was conducted to explore the incidence and clinical manifestations of tigecycline-associated thrombocytopenia. A retrospective case-control study of patients treated with tigecycline was conducted between January 2018 and June 2022.

**Results:** In total, 373 patients were included in this study. Among these patients, 12.3% experienced thrombocytopenia. The onset of thrombocytopenia occurred within a range of 2 to 22 days after the initiation of tigecycline, with a median period (25–75th percentile) of 9 (6–11) days. Among the patients manifesting thrombocytopenia, 60.9% exhibited mild-to-moderate cases (grades 1–2) while 39.1% endured severe cases (grades 3–4). Multivariate analysis delineated several factors as independent risk factors for thrombocytopenia. Notably, advanced age ( $\geq 74$  years) ( $p=0.028$ ), risk of malnutrition ( $p<0.001$ ), tigecycline therapy for  $\geq 7$  days ( $p=0.003$ ),  $\text{DBIL}>8.1\mu\text{mol/L}$  ( $p<0.001$ ),  $\text{BUN}>8.1\text{mmol/L}$  ( $p=0.002$ ) emerged as independent risk factors associated with thrombocytopenia. When comparing the control group to the thrombocytopenia group, 70.7% of patients in the control group exhibited 0–2 risk factors, while all patients in the thrombocytopenia group demonstrated risk factors. Specifically, 95.7% of patients in the thrombocytopenia group presented with three to five risk factors, with only 4.4% having 0–2 risk factors.

**Conclusion:** Tigecycline administration is associated with thrombocytopenia. Healthcare professionals should exercise vigilance, particularly in cases of severe tigecycline-associated thrombocytopenia, and undertake routine monitoring of patients' platelet counts, especially for those who possess three or more risk factors.

**Keywords:** tigecycline, thrombocytopenia, risk factor, pharmacovigilance, coagulation disorder

## Introduction

Tigecycline, a novel glycylcycline antibacterial agent, has shown remarkable efficacy against a wide spectrum of bacterial pathogens.<sup>1</sup> Its potent activity extends across Gram-positive, Gram-negative and anaerobic bacteria, including methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant enterococci, KPC-producing *Klebsiella pneumoniae*, extended-spectrum  $\beta$ -lactamase (ESBL)-producing Enterobacteriaceae, and other multidrug-resistant (MDR) Gram-negative bacteria.<sup>2,3</sup>

The escalating prevalence of drug-resistant bacterial infections as a serious concern aggravated by the scarcity of efficacious antibacterial agents. Since its approval by the US FDA in 2005, tigecycline has gained recognition as an exceptionally potent antimicrobials agent. In China, tigecycline has received approval for the treatment of community-acquired pneumonia (CAP), complicated intra-abdominal infections (cIAIs) and complicated skin and skin structure infections (cSSSIs). Additionally, tigecycline exhibits the advantage of obviating the necessity for dose adjustment in patients with renal impairment and has minimal proclivity for drug interactions, thereby underscoring its viability as a reasonable option for managing severe bacterial infections.<sup>3</sup>

Clinical trials have provided evidence acknowledging the general tolerability of tigecycline. Within these trials, which enrolled 1415 patients, the prevailing adverse events included nausea (29.5%), vomiting (19.7%), diarrhea (12.7%), infection (8.3%), thrombocytopenia (6.1%), ALT increase (5.6%), AST increase (4.3%), rash (2.4%) and bilirubinemia (2.3%).<sup>4</sup> While occurrences of tigecycline-induced thrombocytopenia have been sporadically documented, they have frequently been overlooked by physicians. The first documented case of tigecycline-induced thrombocytopenia was in 2017.<sup>5</sup> However, recent pharmacovigilance data have raised apprehension regarding this adverse event.<sup>6</sup> According to data from the FDA Adverse Event Reporting System, thrombocytopenia, hypofibrinogenemia, increased international normalized ratio (INR), prolonged activated partial thromboplastin time (APTT), and prolonged prothrombin time emerged as the most common coagulation disorder associated with tigecycline. Although several clinical studies have focused on tigecycline-associated hypofibrinogenemia and coagulopathy, this present study represents the inaugural endeavor to specifically investigate tigecycline-associated thrombocytopenia in real-world patients undergoing tigecycline therapy, and to identify any clinical factors that may increase the susceptibility to this particular adverse event.

## Materials and Methods

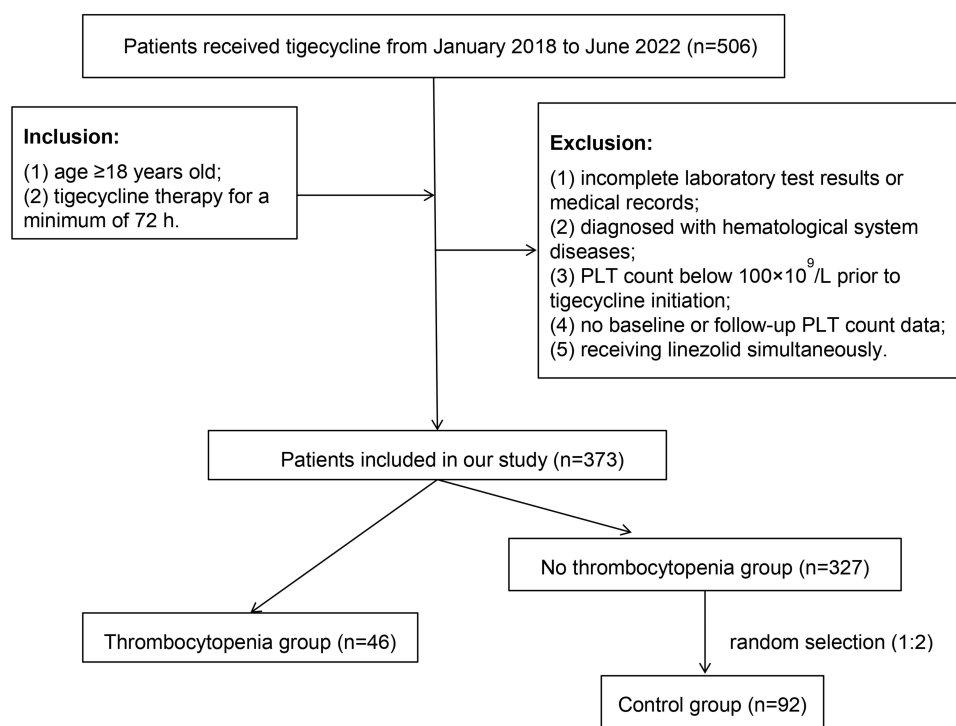
### Study Population

This retrospective, single-center, observational study was conducted at Beijing Hospital between January 2018 and June 2022. The study included patients of 18 years or above who had undergone tigecycline treatment for a minimum duration of 72 hours. Patient data were retrieved from the Pharmacy Department Database. Patients with incomplete laboratory test results or medical records, a confirmed diagnosis of hematological diseases, pre-treatment PLT count below  $100 \times 10^9/L$ , absence of baseline information or follow-up PLT count data, or concomitant administration of linezolid were excluded from the study. This study was approved by the Beijing Hospital Ethics Committee.

For a comprehensive schematic of the patient screening process, refer to [Figure 1](#).

### Data Collection

Patient's information was extracted from their medical records, encompassing the following data: (1) demographic information (eg, age, gender, weight, diet, and comorbidities), (2) primary underlying disease, (3) the dose, frequency



**Figure 1** The schematic of the patient selection process.

and duration of tigecycline treatment, (4) the occurrence time, symptoms, signs and grading of adverse reaction related to thrombocytopenia, and (5) clinical laboratory test results, including liver function indicators [aspartate transaminase (AST), alanine transaminase (ALT), direct bilirubin (DBIL), total bilirubin (TBIL)], renal function indicators [serum creatinine (SCR), blood urea nitrogen (BUN)], coagulation function indicators [fibrinogen concentration, international normalized ratio (INR)], platelet (PLT) count, blood albumin (ALB), white blood cell (WBC) count, C reactive protein (CRP), and procalcitonin (PCT).

## Adverse Events Definitions and Severity Grading

Thrombocytopenia was precisely delineated in accordance with the criteria laid out in the Common Adverse Event Evaluation Criteria (CTCAE) version 5.0.<sup>7</sup> Thrombocytopenia was characterized by a PLT count  $<100 \times 10^9/L$ . The severity of thrombocytopenia was stratified into four grades: Grade 1 (PLT count of  $75\text{--}100 \times 10^9/L$ ), Grade 2 (PLT count of  $50\text{--}75 \times 10^9/L$ ), Grade 3 (PLT count of  $25\text{--}50 \times 10^9/L$ ), and Grade 4 (PLT count below  $25 \times 10^9/L$ ).

The primary outcome of the study was to determine the incidence and severity of thrombocytopenia after tigecycline treatment. As a secondary outcome, the study also aimed to evaluate the incidence of coagulation disorders, specifically hypofibrinogenemia and INR elevation. Additionally, the study examined the concomitant medications that might potentially correlate with the incidence of thrombocytopenia.

## Statistical Analysis

Statistical analyses were performed using SPSS Statistics 17.0. Continuous variables were presented as mean  $\pm$  standard deviation (SD) in cases of normal distribution, or as median and interquartile range for variables exhibiting non-normal distribution. Categorical variables were reported in terms of percentages. The comparison of laboratory indicators before and after tigecycline treatment was carried out using a paired *t*-test. To access disparities between the control and non-thrombocytopenia groups, either the *t*-test or Chi-square test was employed as appropriate. To identify risks factors associated with thrombocytopenia, binary logistic regression analysis was performed. For variables that exhibited significance in univariate analyses, stepwise multiple logistic analysis was conducted to identify independent risk factors. Statistical significance was established at  $P < 0.05$ .

## Ethics

This study, which was in compliance with the Declaration of Helsinki, received ethical approval from the Ethics Committee of Beijing Hospital (Permit Number: 2022BJYYEC-312-02). As neither individual data were published nor any intervention was performed on patients, patient consent was waived by the Ethics Committee of Beijing Hospital.

## Results

### Clinical Features of Patients with Thrombocytopenia

Figure 1 illustrates the schematic representation of the patient selection process. A cohort of 506 patients who received tigecycline underwent preliminary screening for potential inclusion in the study. Following this screening, 373 patients fulfilled the inclusion criteria for participation and were included in the study. The average age of the enrolled patients was ( $75.4 \pm 14.7$ ) years. Among these patients, 46 individuals experienced thrombocytopenia and were subsequently categorized into the thrombocytopenia group. The remaining 321 patients were classified into the no-thrombocytopenia group. Within the no-thrombocytopenia group, a subset of 96 patients were randomly selected and designated as the control group. There were no significant differences in demographic characteristics between the two groups. The above findings are elaborated upon in Table 1.

Thrombocytopenia manifested within the thrombocytopenia group over a span of 2 to 22 days after the initiation of tigecycline treatment, with a median onset occurring at 9 days (25–75th percentile) (Figure 2). A total of 9 patients discontinued tigecycline treatment due to thrombocytopenia. Furthermore, within the patient cohort, 25 patients exhibited a return of platelet count levels to normal prior to their discharge from the hospital (Figure 3). The classification of thrombocytopenia severity is shown in Table 2. The incidence of tigecycline-associated thrombocytopenia was 12.3%

**Table 1** Demographic of Control Group and No Thrombocytopenia Group

Variable	Control Group (n=92)	No Thrombocytopenia Group (n=327)	T/ $\chi^2$ value	P-value
Sex				
Male	62	222	0.233	0.629
Female	30	105		
Age, years	73.7 $\pm$ 14.0	74.2 $\pm$ 15.1	-0.289	0.773
Hospital length of stay, d	33.2 $\pm$ 17.0	32.7 $\pm$ 22.4	0.209	0.834

(46/373). The severity of thrombocytopenia varied among the patients, with 60.9% (28/46) experiencing mild-to-moderate thrombocytopenia, while 39.1% (18/46) experienced severe thrombocytopenia. Eight patients died within 30 days after receiving tigecycline treatment.

The analysis extended to coagulation indicators within both the thrombocytopenia and control groups (Table 3). When compared to the control group, patients in the thrombocytopenia group displayed an increased likelihood of elevated INR (82.6% (38/46) vs 37.0% (34/92),  $\chi^2=24.444$ ,  $p<0.001$ ) and hypofibrinogenemia (69.6% (32/46) vs 33.7% (31/92),  $\chi^2=15.903$ ,  $p<0.001$ ).

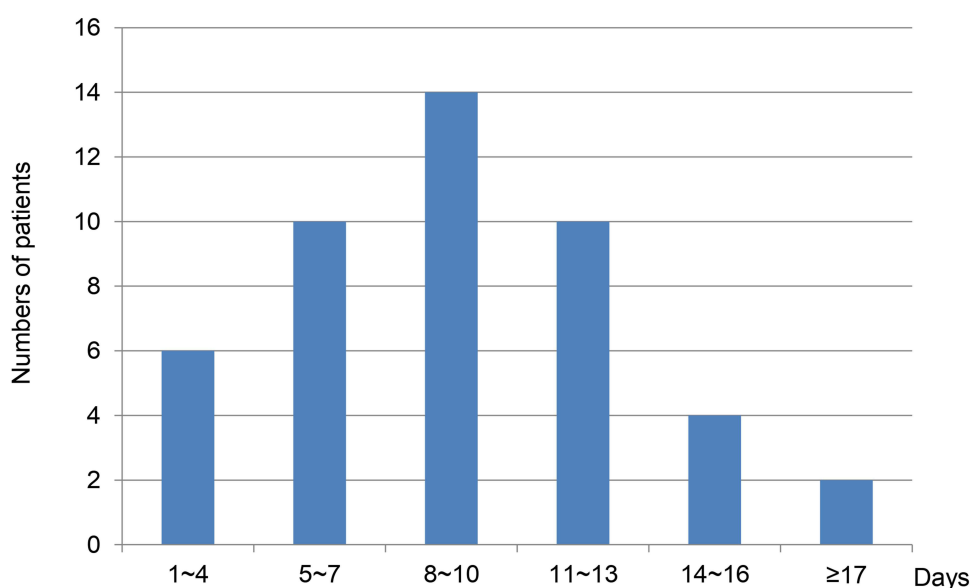
## Risk Factors for Thrombocytopenia Group

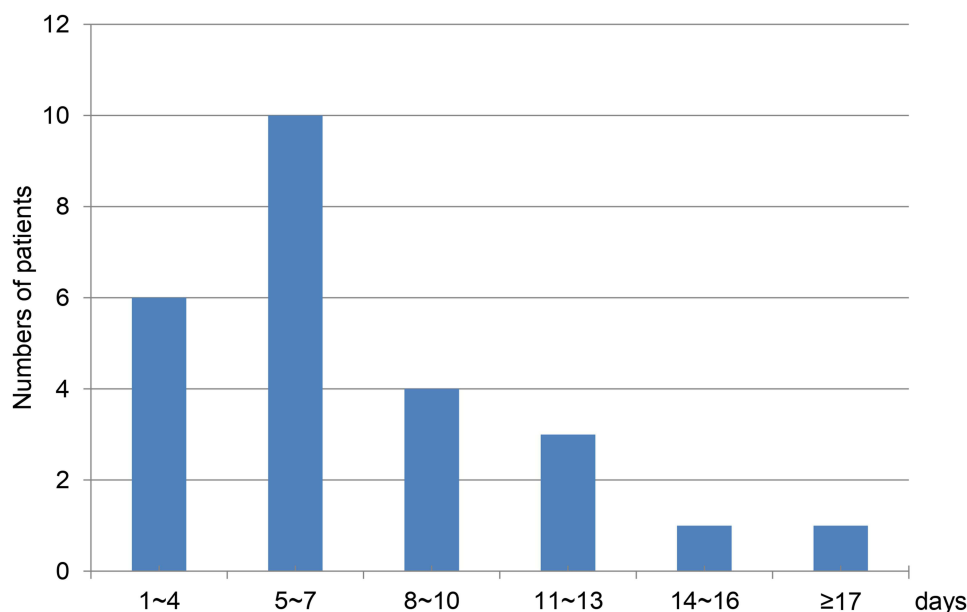
The baseline characteristics and clinical features of both the thrombocytopenia and control groups are displayed in Table 3.

In the univariate analysis, several factors exhibited statistically significant associations with thrombocytopenia, including advanced age ( $\geq 74$  years), emergency ward admission, risk of malnutrition, tigecycline therapy for  $\geq 7$  days, DBIL  $>8.1\mu\text{mol/L}$ , TBIL  $>17.1\mu\text{mol/L}$  and BUN  $>8.1\text{mmol/L}$  ( $P<0.05$ ).

Conversely, no significant differences were detected between the thrombocytopenia group and the control group in terms of other indicators, such as AST, ALT, SCR, PLT count, ALB, WBC count, CRP and PCT.

No substantial association was identified between tigecycline-induced thrombocytopenia and concomitant medications acknowledged for their potential association with the risk of thrombocytopenia, including aspirin, clopidogrel, cefoperazone/sulbactam, piperacillin/tazobactam, imipenem/cilastatin, meropenem, amikacin, or ceftazidime.

**Figure 2** Days from tigecycline initiation to thrombocytopenia.



**Figure 3** Days until the platelet count levels return to normal after the discontinuation of tigecycline.

Considering the intrinsic relationship between DBIL and TBIL, DBIL was chosen as an independent variable in the multivariate logistic regression analysis with other risk factors. According to multivariate analysis, advanced age ( $\geq 74$  years), risk of malnutrition, tigecycline therapy for  $\geq 7$  days,  $\text{DBIL} > 8.1 \mu\text{mol/L}$ ,  $\text{BUN} > 8.1 \text{mmol/L}$  emerged as independent risk factors associated with thrombocytopenia (Table 4).

Furthermore, an assessment of the quantity of coexisting risk factors among patients was conducted (Table 5). In the control group, 70.7% (65/92) of the patients exhibited a range of 0 to 2 risk factors. In contrast, all patients in the thrombocytopenia group presented with accompanying risk factors, with a notable 95.7% (44/46) of them manifesting three to five risk factors.

## Tigecycline Effects on Laboratory Test

Based on our analysis, we found significant elevations in DBIL, TBIL and BUN level in both thrombocytopenia group and control group ( $p < 0.05$ ) (Table 6). Conversely, we observed no significant changes in AST, ALT, SCR or eGFR levels associated with the treatment ( $p > 0.05$ ). Additionally, the levels of ALB and HGB decreased in the thrombocytopenia group ( $p < 0.05$ ), but not in the control group ( $p > 0.05$ ).

**Table 2** Grade and Incidence of Tigecycline-Associated Thrombocytopenia

Grade of Thrombocytopenia	Patients (n)	Incidence in Thrombocytopenia Patients ( $n/46 \times 100\%$ )	Incidence in all Enrolled Patients ( $n/373 \times 100\%$ )
1	13	28.3	3.5
2	15	32.6	4.0
3	15	32.6	4.0
4	3	6.5	0.8
Total	46	100.0	12.3

**Table 3** Univariate Analysis of Risk Factors for Tigecycline-Associated Thrombocytopenia

Characteristics	Thrombocytopenia Group (n=46)	Control Group (n=92)	OR (95% CI)	P-value
Sex				
Male	31	60	1.000 (0.470–2.128)	1
Female	15	32		
Age (years)	84.2±7.7	73.7±14.0	0.906 (0.864–0.949)	<0.001
≥74 (%)	42	41	8.077 (2.674–24.394)	<0.001
Underlying disease				
Malignant tumors	12	18	1.451 (0.629–3.347)	0.383
Cardiovascular disease	11	17	1.493 (0.628–3.543)	0.364
Respiratory disease	10	19	0.939 (0.400–2.204)	0.855
Neurological disease	4	15	0.489 (0.152–1.568)	0.229
Urinary tract disease	3	7	1.000 (0.238–4.198)	1
Digestive diseases	3	6	1.000 (0.238–4.193)	1
Others	3	10	0.643 (0.166–2.501)	0.524
Emergency ward admission	12	10	2.901 (1.180–7.129)	0.02
Bedridden	18	26	1.632 (0.774–3.441)	0.198
Risk of malnutrition				
Yes	32	18	8.782 (3.923–19.657)	<0.001
No	14	74		
BMI <sup>a</sup> (kg/m <sup>2</sup> )	21.5±4.6	23.7±4.1	1.105 (0.971–1.162)	0.067
Hyponatraemia	15	26	1.169 (0.543–2.497)	0.695
Site of infection				
Respiratory disease	36	67	1.799 (0.766–4.221)	0.177
Urinary tract infection	10	19	1.067 (0.450–2.531)	0.883
Intra-abdominal infection	7	18	0.865 (0.365–2.172)	0.758
Bloodstream infection	6	7	2.573 (0.811–8.159)	0.109
Skin and soft tissue infection	1	2	0.659 (0.067–6.519)	0.722
Tigecycline monotherapy	9	14	1.173 (0.453–3.037)	0.742
Tigecycline daily dose	114.1±37.1	104.9±20.9	0.991 (0.979–1.003)	0.126
Concomitant drugs associated with				
Aspirin and/or clopidogrel	5	17	0.579 (0.198–1.695)	0.319
Cefoperazone/sulbactam	12	22	1.172 (0.507–2.710)	0.711
Piperacillin/tazobactam	5	8	1.160 (0.361–1.727)	0.803
All β-Lactam Antibiotics + β-lactamase inhibitor	19	30	1.502 (0.694–3.251)	0.302
Meropenem	14	18	1.929 (0.834–4.462)	0.125
Imipenem/cilastatin	1	4	0.500 (0.520–20.306)	0.542
Biapenem	3	2	3.250 (0.180–5.865)	0.207
Amikacin	1	4	0.395 (0.045–3.500)	0.404
Ceftazidime	1	10	0.378 (0.079–1.818)	0.225
Others	9	13	1.700 (0.648–4.463)	0.281
Pathogenic microorganism				
<i>Acinetobacter baumannii</i>	15	28	1.112 (0.491–2.521)	0.799
<i>Klebsiella pneumoniae</i>	19	46	0.594 (0.260–1.356)	0.216
Gram positive coccus	8	8	2.370 (0.806–6.968)	0.117
Others	1	2	1.029 (0.090–11.754)	0.981
Duration of tigecycline therapy (days)	12.2±6.5	8.4±4.4	0.891 (0.829–0.957)	0.002
≥7 days	11	20		<0.001
Hospitalization duration (days)	34.1±28.1	33.2±17.0	0.998 (0.980–1.016)	0.83

(Continued)

**Table 3** (Continued).

Characteristics	Thrombocytopenia Group (n=46)	Control Group (n=92)	OR (95% CI)	P-value
Baseline laboratory data				
PLT ( $10 \times 10^9/L$ )	192.4±77.6	226.5±85.2	0.999 (0.995–1.004)	0.689
ALT (U/L)	27.0±45.8	23.5±30.9	0.997 (0.988–1.007)	0.593
AST (U/L)	39.2±48.5	27.8±27.8	0.992 (0.982–1.002)	0.105
DBIL ( $\mu\text{mol/L}$ )	12.5±16.6	6.1±6.8	0.935 (0.889–0.984)	0.009
DBIL>8.1 $\mu\text{mol/L}$	24	10	8.945 (3.729–21.460)	<0.001
TBIL ( $\mu\text{mol/L}$ )	18.5±19.8	10.9±9.1	0.950 (0.913–0.988)	0.011
>17.1 $\mu\text{mol/L}$	19	8	7.389 (2.907–18.782)	<0.001
BUN (mmol/L)	15.8±11.1	10.8±8.1	0.941 (0.902–0.982)	0.005
BUN>8.1 mmol/L	38	41	0.261 (0.095–0.713)	<0.001
SCR ( $\mu\text{mol/L}$ )	131.1±137.4	107.3±106.0	0.998 (0.995–1.001)	0.242
eGFR (mL/min/1.73m <sup>2</sup> )	64.3±31.4	74.8±35.6	1.009 (0.999–1.020)	0.081
ALB (g/L)	30.6±4.3	31.8±4.3	0.990 (0.972–1.008)	0.271
HGB (g/L)	90.3±16.1	92.5±16.6	1.005 (0.984–1.025)	0.65
WBC ( $10 \times 10^9/L$ )	11.9±6.3	10.5±5.2	0.977 (0.922–1.035)	0.424
CRP (mg/L)	16.1±22.4	17.6±29.8	1.002 (0.989–1.016)	0.751
PCT (ng/mL)	4.6±10.2	3.1±18.4	0.995 (0.974–1.016)	0.609

**Notes:** a, 28 patients in the thrombocytopenia group and 66 patients in the control group have BMI data.

**Abbreviations:** OR, odds ratio; CI, confidence interval; ALT, aspartate transaminase; AST, alanine transaminase; PLT, platelet count; DBIL, direct bilirubin; TBIL, total bilirubin; BUN, blood urea nitrogen; SCR, serum creatinine; eGFR, estimated Glomerular Filtration Rate; ALB, blood albumin; HGB, hemoglobin; WBC, white blood cell count; CRP, C reactive protein, PCT, procalcitonin.

**Table 4** Multivariate Analysis of Risk Factors for Tigecycline-Associated Thrombocytopenia

Variables	OR (95% CI)	Wald	P-value
Age≥74 years	4.767 (1.184–19.196)	4.827	0.028
Emergency ward admission	1.384 (0.343–5.574)	0.209	0.648
Risk of malnutrition	8.124 (2.728–24.195)	14.154	<0.001
Tigecycline duration ≥7 days	8.829 (2.074–37.580)	8.686	0.003
DBIL>8.1 $\mu\text{mol/L}$	7.367 (2.200–24.664)	10.494	0.001
BUN>8.1 mmol/L	7.136 (2.028–25.118)	9.37	0.002

**Abbreviations:** DBIL, direct bilirubin; BUN, blood urea nitrogen.

**Table 5** Number of Combined Risk Factors in 2 Groups (n, %)

Number of Combined Risk Factors	Thrombocytopenia Group (n=46)	Control Group (n=92)
0	0 (0.0)	4 (4.3)
1	1 (2.2)	31 (33.7)
2	2 (2.2)	30 (32.6)
3	12 (26.1)	21 (22.8)
4	21 (45.7)	6 (6.5)
5	11 (23.9)	0 (0.0)



**Table 6** Effect of Tigecycline on Laboratory Tests

Laboratory Indexes	Thrombocytopenia Group (n=46)			Control group (n=92)		
	Before Treatment	After Treatment	P-value	Before Treatment	After Treatment	P-value
PLT ( $10 \times 10^9/L$ )	192.4±77.6	56.9±22.1	<0.001	226.5±85.2	222.0±88.1	0.460
ALT (U/L)	27.0±45.8	29.6±36.4	0.525	23.5±30.9	21.6±18.7	0.527
AST (U/L)	39.2±48.5	66.4±109.2	0.082	27.8±27.8	35.5±62.9	0.159
DBIL (umol/L)	12.5±16.6	23.2±27.1	0.001	6.1±6.8	7.6±6.6	0.028
TBIL (umol/L)	18.5±19.8	33.6±34.0	<0.001	10.9±9.1	13.9±10.1	0.005
BUN (mmol/L)	15.8±11.1	22.0±15.7	0.019	10.8±8.1	13.9±11.9	<0.001
SCR (umol/L)	131.1±137.4	147.4±133.6	0.467	107.3±106.0	113.0±134.9	0.364
eGFR (ml/min/1.73m <sup>2</sup> )	64.3±31.4	56.0±32.6	0.054	74.8±35.6	77.0±37.2	0.147
ALB (g/L)	30.6±4.3	28.6±4.8	0.011	31.8±4.3	30.8±4.8	0.053
HGB (g/L)	90.3±16.1	83.0±14.4	0.002	92.5±16.6	95.1±16.8	0.067

**Abbreviations:** PLT, platelet count; ALT, aspartate transaminase; AST, alanine transaminase; DBIL, direct bilirubin; TBIL, total bilirubin; BUN, blood urea nitrogen; SCR, serum creatinine; eGFR, estimated Glomerular Filtration Rate; ALB, blood albumin; HGB, hemoglobin.

## Discussion

Drug induced thrombocytopenia (DIT) necessitates special attention due to its relatively high incidence, particularly among critically ill patients. The prevalence of DIT is estimated at around 25% in critically ill patients.<sup>8</sup> Various antimicrobial agents can trigger DIT through diverse mechanisms, including both immune-mediated and non-immune-mediated pathways.<sup>9</sup> DIT primarily falls into two main categories: decreased platelet (PLT) production due to bone marrow suppression, and increased PLT destruction, often mediated by the immune pathway.<sup>10</sup>

The precise mechanism of tigecycline-induced DIT remains ambiguous. Our research revealed that thrombocytopenia developed within a timeframe spanning 2 to 22 days following the initiation of tigecycline treatment, with a median onset occurring at 9 days. Most patients demonstrated recovery of PLT counts upon discontinuation of tigecycline. Based on mechanism insights, non-immune-mediated thrombocytopenia tends to evolve gradually over a few weeks, linked to suppressed megakaryocytes leading to reduced PLT production. Conversely, immune-mediated thrombocytopenia typically emerges more rapidly, often after 7 to 14 days of treatment. In patients with prior exposure, its onset can occur within 1 to 3 days. Recovery of PLT levels after discontinuation of the medication may occur within days for immune-mediated DIT, whereas non-immune DIT may require an extended recovery duration.<sup>11</sup> Considering the potential mechanism of tigecycline-induced thrombocytopenia, it is possible that this drug elicits thrombocytopenia through the immune-mediated pathway. A few studies have demonstrated that the relative occurrence of immune-mediated DIT, including hapten-dependent antibodies, quinine-type antibodies and autoantibodies.<sup>9,11</sup> Therefore, conducting laboratory tests to identify platelet-reactive antibodies in suspected patients might prove valuable in investigating tigecycline-induced DIT. It is our anticipation that future research will shed more light on the association between tigecycline and thrombocytopenia.

Furthermore, in a two-week animal study, researchers observed that tigecycline induced bone marrow hypo-cellularity in rats and dogs at doses 8 and 10 times higher than the equivalent human daily dose, respectively. These effects demonstrated reversibility after a two-week administration period, implying that tigecycline may suppress bone marrow function.<sup>12</sup> In a murine model, antibiotic therapy was found to suppress various types of hematopoietic progenitors, including HSCs and common lymphoid progenitors, indicating that the antibiotic-mediated myelopoiesis suppression relies on microbiome depletion. Therefore, preserving the microbiome could potentially mitigate the occurrence of tigecycline-associated bone marrow suppression.<sup>13</sup>

In our research, a comparison of concomitant medication between the thrombocytopenia group and the control group was conducted. The outcomes of univariate analysis revealed no discernible disparity in medication utilization pattern between the two groups, suggesting that the occurrence of thrombocytopenia was not associated with concomitant medications.



However, it is important to acknowledge that numerous non-pharmaceutical factors may also contribute to thrombocytopenia. In severely infected populations, conditions such as DIC and HIT should be considered in the differential diagnosis. The risk factors we identified in our study also demonstrated associations with aggravated sepsis and poor prognosis. Notably, eight patients in the thrombocytopenia group died, potentially hinting at a correlation with the occurrence of thrombocytopenia. Recent research has additionally proposed a potential role of Covid-19 in the development of thrombocytopenia.<sup>14</sup>

In our study, the incidence of tigecycline-associated thrombocytopenia was 12.3%, which is higher than that reported in previous studies. Specifically, a thrombocytopenia rate of 6.0% (49/817) was reported in a Phase III studies.<sup>15</sup> This difference may be attributed to the advanced age and underlying health conditions characterizing our study's patient cohort. The average age of the enrolled patients in our study was ( $75.4 \pm 14.7$ ) years, in contrast to the average age of ( $47.1 \pm 18.6$ ) years reported in the aforementioned phase III trial. Moreover, patients with significant hepatic or renal disease were excluded from the phase III study but deliberately included in our research. Our results demonstrated that advanced age ( $\geq 74$  years), risk of malnutrition, tigecycline therapy for  $\geq 7$  days,  $\text{DBIL} > 8.1 \mu\text{mol/L}$ ,  $\text{BUN} > 8.1 \text{mmol/L}$  were independent risk factor for tigecycline-associated thrombocytopenia. These findings are consistent with earlier studies that also identified older age and prolonged tigecycline exposure as risk factors for hypofibrinogenemia associated with tigecycline.<sup>16</sup> Furthermore, a retrospective study investigating linezolid-induced thrombocytopenia found that renal insufficiency ( $\text{crCL} < 60 \text{ mL/min}$ ), hemodialysis, and the extended linezolid therapy duration represented significant risk factors for thrombocytopenia associated with linezolid.<sup>17</sup>

The primary route of tigecycline elimination is biliary excretion (59%), wherein the compound is excreted unaltered. Renal excretion serves as a secondary route.<sup>18</sup> An impairment in biliary excretion can prolong the tigecycline excretion time, leading to drug accumulation and potential overdosage. In addition, we observed that tigecycline therapy could elicit elevated bilirubin levels, particularly noticeable in patients with thrombocytopenia ( $\text{DBIL}$ : ( $12.5 \pm 16.6$ ) vs ( $23.2 \pm 27.1$ ),  $p=0.001$ ;  $\text{TBIL}$ : ( $18.5 \pm 19.8$ ) vs ( $33.6 \pm 34.0$ ),  $p<0.001$ ). Our study did not establish a relationship between eGFR and thrombocytopenia, a finding divergent from linezolid-induced thrombocytopenia.<sup>16</sup> This suggests that renal function may not play a significant role in the development of thrombocytopenia during tigecycline therapy.<sup>19</sup>

In terms of risk factors for thrombocytopenia, our analysis highlighted that elevated BUN, distinct from SCR, emerged as an independent risk factor. BUN, modulated by both renal and non-renal factors, has exhibited predictive value for long-term mortality among critically ill patients, even when creatinine levels are within the normal range.<sup>20</sup> Hyper-catabolism and nutrition support have demonstrated correlation with increased BUN levels and can potentially lead to compromised immune function.<sup>21,22</sup> Additionally, malnourished patients receiving nutritional support after admission are prone to experience hyper-catabolism, thereby contributing to elevated BUN levels.

In contrast to the control group, patients in the thrombocytopenia group exhibit a heightened susceptibility towards underlying coagulation disorder, such as elevated INR or hypofibrinogenemia. This observation could potentially elucidate the rationale behind the reduction of ALB and HGB in the thrombocytopenia group. The serious consequences of erythropenia, neutropenia and thrombocytopenia underline the necessity for vigilant monitoring of bleeding manifestations and coagulation disorders during tigecycline therapy.<sup>23</sup>

Currently, scarce evidence supports the efficacy of specific treatment for DIT apart from discontinuation of the causative drug. Previous research addressing vancomycin-induced thrombocytopenia have indicated that interventions such as platelet transfusions, corticosteroids, plasma exchange, intravenous immunoglobulin, and anti-Rh immune globulin did not consistently elevate platelet levels in most patients until vancomycin was stopped.<sup>24</sup> In our research, 95.7% of thrombocytopenic patients exhibited 3 to 5 risk factors. Thus, in cases where patients exhibit multiple risk factors for DIT, prudent consideration of alternative antimicrobials agent becomes paramount. However, if tigecycline remains imperative, we recommend routine blood examinations every three days to monitor platelet levels.

Several limitations warrant consideration. Firstly, this investigation adopted a retrospective case-control design, making it susceptible to selection bias. Secondly, despite the study's execution within a substantial hospital setting, the findings may lack generalizability to all patient populations. Lastly, it is important to acknowledge that other factors, beyond tigecycline, can contribute to thrombocytopenia.

## Conclusion

Thrombocytopenia constitutes a prevalent and potentially life-threatening adverse event linked to tigecycline, yet often remained underestimated. Through our analysis, advanced age ( $\geq 74$  years), risk of malnutrition, tigecycline therapy for  $\geq 7$  days, DBIL  $> 8.1 \mu\text{mol/L}$  and BUN  $> 8.1 \text{mmol/L}$  emerged as independent risk factors for tigecycline-induced thrombocytopenia. Therefore, healthcare professionals should be vigilant to discern potential bleeding and regularly monitor platelet counts every three days throughout tigecycline therapy, particularly in patients with multiple risk factors. In scenarios where a decline in platelet levels becomes evident, deliberation over alternative antimicrobials should be considered.

## Data Sharing Statement

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study, which was in compliance with the Declaration of Helsinki, received ethical approval from the Ethics Committee of Beijing Hospital (Permit Number: 2022BJYYEC-312-02).

The manuscript strictly omits any identifying information of human participants. As neither individual data were published nor any intervention was performed on patients, patient consent was waived by the Ethics Committee of Beijing Hospital.

Our research received ethical exemption from patient informed consent, granted by the Ethics Committee of Beijing Hospital (Permit Number: 2022BJYYEC-312-02).

## Consent for Publication

All authors approved the final manuscript and the submission to this journal.

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## Disclosure

The authors declare the absence of known competing financial interests or personal relationships that could potentially influence the work reported in this paper.

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