Influence of Tigecycline on Liver Function in Adult Patients in the Intensive Care Unit

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Research Article

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Abstract

Background There are few studies investigating TGC-associated hepatotoxicity in ICU patients, and the pathogenesis of hepatotoxicity and identification of risk factors are limited.

Objectives To analyze the influence of tigecycline (TGC) on liver function in adult patients in the Intensive Care Unit to identify potential risk factors for tigecycline-induced liver injury (TILI).

Methods Patients receiving tigecycline treatment in ICU during January 2019 to October 2020 were retrospectively enrolled. The liver function parameters before and after tigecycline treatment were collected, and risk factors associated with TILI was identified by logistic regression analysis. The probability of 28-day mortality was determined in Cox regression analysis.

Results A total of 242 patients were enrolled, and TILI was identified in 24 patients (9.92%), of whom 75.0% had grade 1 liver injury, and 16.67%, 4.17%, 4.17% had grade 2 to 4 liver injury, respectively. The pattern of hepatotoxicity was hepatocellular in 16 patients (66.67%), cholestatic in 4 patients (16.67%), and mixed in 4 patients (16.67%). The median time from tigecycline start to symptoms was only 5 days (IQR, 3-7 days). Multivariate analysis identified tigecycline dose $\geq 200\text{mg/day}$, longer course of treatment and preexisting liver disease tend to be independently associated with TILI. In addition, APACHE II score > 15 , higher dose of tigecycline and TILI were independent risk factors of 28-day mortality, while longer course of tigecycline reduced this risk despite its association with TILI.

Conclusions The maintenance dose and course of tigecycline, as well as liver disease is considered as risk factors of hepatotoxicity. 28-day mortality tended to be higher in TILI patients. The relationships among tigecycline dose and course, TILI and mortality should be further investigated.

Impact Of Findings On Practice

- The incidence of TILI was high in ICU patients, mainly manifested by significantly increased bilirubin.
- Maintenance dose $\geq 200\text{mg/day}$, longer duration of treatment of TGC and preexisting liver disease tend to be independently associated with TILI.
- TILI was associated with an increase in 28-day mortality.

Introduction

Tigecycline (TGC) is the first glycylcycline antibiotic that has a broad antibacterial spectrum, strong antibacterial activity to most of the gram-positive (G^+) bacteria, gram-negative (G^-) bacteria, anaerobic bacteria and atypical pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), etc. [1, 2]. TGC was approved by the Food and Drug Administration (FDA) for the treatment of complex skin and soft tissue infections, complex abdominal infections and community-acquired pneumonia in adults [3, 4]. TGC is widely used in critically ill patients with severe infections in the intensive care unit (ICU) and several studies [5, 6] have shown that the

utilization of TGC has been on the rise over the past decade. ICU patients have unstable vital signs and complicated conditions, which cause lethal adverse effects when irrational medication happens [7]. With the increase in the utilization of TGC in recent years, the cases of adverse reactions (ADR) associated with TGC are also increasing, including hepatotoxicity [8–10]. However, there are few studies investigating TGC-associated hepatotoxicity in ICU patients, and the pathogenesis of hepatotoxicity and identification of risk factors are limited. In the present study, a single-center retrospective study was performed to evaluate TILI in ICU patients, which provide a reference for the rational drug use.

Material And Methods

Subjects

Chinese adult ICU inpatients in the first affiliated hospital of Sun Yat-sen University from January 2019 to October 2020 were retrospectively included. Inclusion criteria: (1) age 18 years or older; (2) length of stay in ICU for at least 3 days; (3) The duration of TGC treatment for at least 3 days; (4) with complete hospitalization records. The exclusion criteria were as follows: (1) liver transplantation was performed during treatment of TGC; (2) without complete hospitalization records. This study was approved by the local ethics committee of hospital, which need not to obtain informed consent.

Demographic and clinical data collection

The following demographic and clinical data were collected through the hospital information system: age, gender, acute physiology and chronic health II (APACHE II) score, sequential organ failure (SOFA) score, infection type, microbiological examination, dose of TGC, course of treatment, drug combination, infection indexes and liver function indexes.

Assessment of TILI

TILI was classified into 5 grades according to the classification of drug-induced liver injury (DILI) in CTCAE 5.0 [11](**Table 1**). The upper limit of normal (ULN) is 40 U/L for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), 100 U/L for alkaline phosphatase (ALP), 1.0 mg/dl (17.1 μ mol/L) for serum total bilirubin (TBIL), and 10 μ mol/L for total bile acid (TBA). If the patient had abnormal liver function before receiving TGC treatment, the baseline value before administration was taken as ULN.

Pattern of TILI was defined using the R value [$R = (\text{ALT} / \text{ALT ULN}) / (\text{ALP} / \text{ALT ULN})$] [12]: (1) hepatocellular pattern: $\text{ALT} \geq 3 \text{ ULN}$ and $R \geq 5$; (2) cholestatic pattern: $\text{ALP} \geq 2 \text{ ULN}$ and $R \leq 2$; (3) mixed pattern: $\text{ALP} \geq 3 \text{ ULN}$, $\text{ALT} \geq 2 \text{ ULN}$ and $2 < R < 5$.

The correlation between TGC and liver injury was retrospectively evaluated by RUCAM scale [12]. Based on the pattern of TILI, the RUCAM scale was scored according to medication duration, risk factors of TILI, possible drugs, etc., and ≥ 3 points indicated TILI.

Statistical analysis

Statistical analysis was performed by SPSS 25.0 statistical software. Continuous data were presented as median (interquartile range [IQR]) values and categorical data as proportions. Continuous data were compared by using the Wilcoxon test or Mann-Whitney *U* test. Proportions were compared by Chi-square test or Fisher exact test. The Log-rank test and Kaplan-Meier curve were used to analyze the time of TILI. Independent risk factors of TILI were identified by multivariate Logistic regression analysis. Factors with $P < 0.10$ from the univariate Logistic regression analysis and the strong confounding factors (age and gender) were included in the multivariate analysis. Cox regression analysis was used to evaluate the effect of TILI on 28-day mortality. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients

A total of 242 adult ICU inpatients were included in this study. Most of the patients were male (71.90%), with a median age of 58.0 years (IQR 46.0-72.0 years). Of those, 101 (41.74%) patients had liver disease. The demographic characteristics of patients were shown in **Table 2**. Besides, treatment regimens of TGC were shown in **Table 3**. The maintenance dose was 100mg/day in 159 (65.70%) patients, 150mg/day in 17 (7.02%) patients and ≥ 200 mg/day in 66 (27.27%) patients, all of them were given loading dose followed by maintenance dose in two divided administrations. 227 (93.80%) of patients used other antibacterial drugs in combination.

Liver function indexes

The values of liver function indexes in the baseline and maximum status after TGC treatment were compared. Abnormal elevation of ALP was found in 94 (38.84%) cases, ALT in 32 (13.22%) cases, AST in 69 (28.51%) cases, TBIL in 143 (59.09%) cases, and TBA in 113 (46.69%) cases. In the overall patient population, the values of ALP, TBIL and TBA after TGC treatment increased as compared to those in the baseline ($P < 0.05$), while no significances were found in ALT or AST. All liver function indexes in patients with TILI increased significantly ($P < 0.05$) (**Table 4**).

Classification and incidence of TILI

TILI was observed in 24 (9.92%) patients: grade 1 in 18 (75.0%) patients, grade 2 in 4 (16.67%) patients, grade 3 in 1 (4.17%) patient, and grade 4 in 1 (4.17%) patient. There were 16 (66.67%) patients with hepatocellular pattern, 4 (16.67%) with cholestatic pattern, and 4 (16.67%) with mixed pattern, as shown in the **Figure 1**. Kaplan-Meier curve indicated that TILI developed after a median time of 5 days (IQR, 3-7 days) (**Figure 2**).

Factors associated with TILI

As shown in **Table 5**, there were 24 independent variables were included in the univariate analysis. And ICU stay, liver disease, duration of TGC treatment, maintenance dose, azole antibiotics, amphotericin B and heparinase were significantly associated with TILI ($P < 0.05$). Multivariate logistic regression analysis

demonstrated that liver disease, duration of TGC treatment and maintenance dose were independent risk factors for TILI.

Subgroup analysis

TILI occurred in 16 (15.84%) of 101 patients with liver disease. The length of stay in ICU of TILI patients was longer than that of non-TILI patients ($P = 0.012$). The proportion of lung complicated with abdominal infection was higher in TILI patients ($P = 0.020$), while the proportion of abdominal cavity infections was lower ($P = 0.044$) (**Table 6**).

Secondary outcome

The 28-day mortality rate was 18.60% (45 of 242). In Cox regression analysis, APACHE II score > 15, TGC maintenance dose 150 mg/day and TILI were risk factors of mortality. The duration of TGC treatment ≥ 7 days was benefit to reduce mortality (**Table 7**).

Discussion

At present, the report about the risk factors of TILI in ICU patients was rare. This study retrospectively analyzed the changes of liver function in adult ICU inpatients with TGC treatment and the risk factors of TILI. It was observed the overall levels of ALP, TBIL and TBA, but not ALT or AST increased significantly, similar findings were also revealed in severely infected patients [13]. However, Chen [14] et al. observed that levels of ALT and TBIL increased in ICU patients with Ventilator-associated Pneumonia (VAP). The incidence of abnormal increase of liver enzyme in this study was close to a previous study [15] including 92.7% ICU patients (ALT 13.22% vs.18.8%, AST 28.51% vs. 25.0%), but the incidence of abnormal TBIL was reported lower than our study (6.7%vs. 59.09%). Another study [16] showed that TGC-associated serum transaminase elevations occurred in just 2%-5% of patients, which was lower than our study, suggesting that the incidence of abnormal liver enzyme level in ICU patients might be higher than that in general patients.

In the present study, 24 (9.92%) patients treated with TGC experienced TILI. The incidence is within the range reported in other studies [14, 17]. TILI severity graded as 1 to 2 were found in most of the patients. The incidence (0.41% of 242) of grade 4 (liver failure) is lower than that reported in a study including ICU patients with co-infection (1.20%) [18]. TILI is mostly cholestatic, similar to the results of Zhu et al. (62.50%) [19]. The mechanism of liver injury induced by TGC has not been clarified yet. It may be related to the increase of IL-18 level and hepatocyte apoptosis induced by TGC [20]. The concentration of TGC in bile is much higher than that in serum, and its prototype and metabolites are mainly excreted through the bile duct, which may cause cholestatic liver injury [20, 21].

Several studies [14, 22, 23] revealed that there was no significant difference in the incidence of TILI between high-dose and standard dose of TGC. However, a maintenance dose ≥ 200 mg/day was associated with TILI in our study. In addition, the extension of the duration of TGC treatment would also

increase the risk of TILI. A study [14] showed that the latest occurrence time of TILI in VAP patients in ICU was (10.28 ± 6.25) days. The median time of TILI in our study was 5 days (IQR 3–7 days), which may cause the attention to whether the patient has TILI in the early stage of TGC treatment. The liver function of patients with liver diseases had been impaired before receiving TGC, which were more likely to be further affected by potential hepatotoxic drugs, and in our study, preexisting liver disease increased the incidence of TILI by 3.2-fold. A pharmacokinetic study [24] demonstrated that variances were observed in $C_{\max}$ (55% higher), CL (55% lower) and AUC (105% higher) in the patients with Child-Pugh C or severely decompensated cirrhosis. Therefore, it is recommended that patients with liver function impairment should be prescribed with a loading dose of 100 mg followed by a reduced maintenance dose of 25 mg 12-hourly.

In the subgroup analysis of patients with liver disease, patients with TILI had longer ICU stay. Long-stay in ICU may aggravate the liver injury. Patients with TILI had a higher percentage of lung complicated with abdominal infections, which may be related to the higher dose of TGC.

Our study showed that patients with APACHE II score > 15, TILI and TGC maintenance dose 150 mg/day had higher risk of 28-day mortality. The development of TILI further aggravated the severity of the disease in ICU patients. This result suggests that the development of TILI should be reduced to avoid a worse outcome for ICU patients. The TGC maintenance dose ≥ 200 mg/day may increase the risk of TILI, but the effect on 28-day mortality was not statistically significant, this finding needs further study and discussion. Interesting, we also found TGC treatment duration ≥ 7 days was associated with a reduction in 28-day mortality. This was possibly because adequate treatment can help to treat infections and thus reduce the risk of death.

The present study had several limitations. Firstly, our study lacked PK evaluation. Nonetheless, according to the linear PK characteristics of TGC metabolism in the liver, the exposure will increase with the increase of dose, which is more likely to cause liver injury. Secondly, this study did not exclude patients with liver injury before TGC treatment. But the liver function ahead of TGC therapy was taken as baseline to evaluate the changes between before and after medication to exclude other factors as much as possible. In addition, we also performed a stratified analysis of patients with and without liver disease. Thirdly, this study was a retrospective study, the frequency and timing of liver examinations during TGC treatment were not constant due to retrospective design. Thus, prospective, randomized controlled studies are needed to further confirm the conclusions.

Conclusion

This study retrospectively analyzed the influence of TGC on the liver function of ICU patients and risk factors. For ICU patients, TGC has no significant effect on transaminase, but can cause a significant increase in TBIL. The incidence of TILI was higher in ICU patients, especially in those with preexisting liver diseases. Maintenance dose ≥ 200 mg/day, longer duration of treatment of TGC and liver disease tend to be independently associated with TILI, and TILI was associated with an increase in 28-day mortality.

Clinicians should reasonably select the dose and treatment duration of TGC and carefully monitor liver function during the treatment of TGC.

Declarations

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Conflict of Interests

The authors declare no conflict of interest that could appear to have influenced the submitted work.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jing-nan Song and Jia Li. The first draft of the manuscript was written by Jing-nan Song and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The study complies with current ethical consideration. As this study is a retrospective analysis, it was considered unnecessary to obtain the informed consent of the subjects.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Tables

Table 1 Grading for hepatotoxicity is according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0)

Liver function test	Grade score				
	1	2	3	4	5
ALP	1-2.5 ULN	2.5-5 ULN	5-20 ULN	> 20 ULN	Liver injury death
ALT	1-3 ULN	3-5 ULN	5-20 ULN	> 20 ULN	
AST	1-3 ULN	3-5 ULN	5-20 ULN	> 20 ULN	
TBIL	1-2 ULN	2-3 ULN	3-10 ULN	> 10 ULN	

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin.

Table 2 Clinical characteristics of study patients

Characteristics	Patients (n = 242)
Age $\geq$ 65 years, n (%)	58.00 (46.00-72.00)
Male, n (%)	174 (71.90)
APACHE II score > 15, n (%)	144 (59.50)
SOFA score > 7, n (%)	152 (62.81)
Complication, n (%)	
liver diseases	101 (41.74)
Cancer	70 (28.93)
Hypertension	60 (24.79)
Diabetes	40 (16.53)
Immunosuppression	25 (10.33)
Chronic renal failure	22 (9.10)
COPD	7 (2.89)
Length of ICU stay(days), median (IQR)	14 (8.0-26.0)
CRRT, n (%)	115 (47.52))
ECMO, n (%)	5 (2.07)
Infection site, n (%)	
Pulmonary infection	121 (50.00)
Abdominal infection	82 (33.88)
Lung complicated with abdominal infection	19 (7.85)
Skin infection	8 (3.31)
Others ^a	12 (4.96%)
Microbiological examination ^d , n (%)	
<i>Acinetobacter baumannii</i>	118 (40.27)
<i>Pseudomonas aeruginosa</i>	26 (8.87)
<i>Escherichia coli</i>	22 (7.51)
<i>Enterococcus</i>	19 (6.48)
<i>Stenotrophomonas maltophilia</i>	16 (5.46)
<i>Klebsiella pneumoniae</i>	15 (5.12)

<i>Burcraiholdella onion</i>	12 (4.10)
<i>Proteus mirabilis</i>	2 (0.68)
<i>Mogorgonian subspecies</i>	2 (0.68)
<i>Staphylococcus haemolyticus</i>	2 (0.68)
Other G ⁻ bacterias	11 (3.75)
Other G ⁺ bacterias	4 (1.37)

APACHE II: acute physiology and chronic health II; SOFA: sequential organ failure; ^a: Incision infection ($n = 4$), bloodstream infection ($n = 4$), urinary tract infection ($n = 3$), biliary tract infection ($n = 1$); COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

Table 3 Treatment regimen of TGC

Characteristics	Patients ($n = 242$)
TGC treatment duration (days), median (IQR)	7 (4-11)
TGC maintenance dose, n (%)	
100 mg/day	159 (65.70)
150 mg/day	17 (7.02)
≥ 200 mg/day	66 (27.27)
Drug combination, n (%)	227 (93.80)
Echinocandins	138 (57.02)
Azoles	81 (33.47)
Amphotericin B	26 (10.74)
β -lactams / β -lactamase inhibitors	116 (47.93)
Carbapenems	133 (54.96)
Quinolones	13 (5.37)
Sulfonamides	6 (2.48)
Vancomycin	5 (2.07)
Hepatinica, n (%)	122 (50.41)

Table 4 Changes in liver function within 14 days after treatment with TGC

Liver function test	All patients			TILI patients		
	Baseline value	After treatment	<i>P</i> -value	Baseline value	After treatment	<i>P</i> -value
ALP	95.00 (67.00-128.00)	114.50 (82.50-158.25)	< 0.001	102.50 (93.25-161.25)	173.50 (120.00-254.25)	0.001
ALT	21.00 (11.50-46.00)	23.00 (14.00-48.00)	0.153	32.00 (13.00-60.00)	96.50 (58.00-146.75)	< 0.001
AST	39.00 (24.00-67.25)	40.50 (24.00-88.25)	0.340	44.00 (32.50-83.75)	137.00 (85.25-362.75)	< 0.001
TBIL	23.10 (13.67-58.75)	34.70 (18.58-92.68)	< 0.001	33.05 (16.68-96.45)	132.80 (28.68-290.80)	0.014
TBA	5.20 (2.30-15.60)	12.75 (5.10-41.40)	< 0.001	7.90 (3.38-30.03)	86.05 (30.98-130.48)	< 0.001

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; TBA: Total bile acid.

Table 5 Single factor analysis and multi-factor analysis of TILI

Characteristic	Univariate analysis		Multivariate analysis	
	<i>P</i> -value	OR (95%CI)	<i>P</i> -value	OR (95%CI)
Age	0.467	1.008 (0.985-1.034)		
Male	0.727	0.847 (0.332-2.159)		
APACHE II score > 15	0.453	1.406 (0.577-3.426)		
SOFA score > 7	0.176	0.557 (0.239-1.299)		
Baseline value of liver indexes				
ALP	0.579	1.001 (0.996-1.007)		
ALT	0.736	0.999 (0.996-1.003)		
AST	0.773	1.000 (0.999-1.001)		
TBIL	0.295	1.002 (0.999-1.005)		
Length of ICU stay	0.076	1.017 (0.998-1.035)		
CRRT	0.127	1.967 (0.825-4.686)		
ECMO	0.459	2.326 (0.249-21.700)		
liver disease	0.012	3.129 (1.283-7.630)	0.015	3.202 (1.258-8.151)
Treatment duration of TGC	0.002	1.086 (1.030-1.144)	0.036	1.062(1.004-1.125)
Maintenance dose of TGC				
100 mg/day	0.035	0.400 (0.171-0.938)		
150 mg/day	0.569	0.549 (0.070-4.332)		
≥ 200 mg/day	0.011	3.037 (1.280-7.157)	0.027	2.832 (1.126-7.122)
Drug combination				
Echinocandins	0.766	0.879 (0.377-2.050)		
Azoles	0.009	3.155 (1.334-7.464)		
Amphotericin B	0.004	4.313 (1.590-11.701)		
β-lactams /β-lactamase inhibitors	0.828	0.911 (0.391-2.122)		
Carbapenems	0.106	2.135 (0.851-5.356)		

Quinolones	0.783	0.746 (0.093-6.004)
Sulfonamides	0.459	2.236 (0.249-21.700)
Hepatinica	0.099	2.113 (0.868-5.142)

APACHE II: acute physiology and chronic health II; SOFA: sequential organ failure; ICU: Intensive care unit; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; TAB: Total bile acid; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

Table 6 Subgroup analysis of patients with basic liver disease

Characteristic	Patients with preexisting liver disease			Patients without liver disease		
	Non-TILI (<i>n</i> = 85)	TILI (<i>n</i> = 16)	<i>P</i> - value	Non-TILI (<i>n</i> = 133)	TILI (<i>n</i> = 8)	<i>P</i> - value
Age (years), median (IQR)	56.00 (47.50- 64.00)	55.50 (45.50- 80.00)	0.063	61.00 (46.50- 76.00)	56.90 (41.50- 70.75)	0.449
Male, <i>n</i> (%)	65 (76.47)	11 (68.75)	0.550	95 (71.43)	3 (37.50)	0.103
APACHE II score > 15, <i>n</i> (%)	47 (55.29)	12 (75.00)	0.142	81 (60.90)	4 (50.00)	0.810
SOFA score > 7, <i>n</i> (%)	67 (78.82)	9 (56.25)	0.066 ^a	73 (54.98)	3 (37.50)	0.553
Child- Pugh classification, <i>n</i> (%)						
A	8 (9.41)	3 (18.75)	0.374 ^a	-	-	-
B	55 (64.71)	9 (56.25)	0.520	-	-	-
C	22 (25.88)	4 (25.00)	1.000 ^a	-	-	-
WBC > 10×10 ⁹ , <i>n</i> (%)	53 (61.60)	10 (62.50)	0.991	83 (62.41)	7 (87.50)	0.291
PCT ≥ 0.5 ng/ml, <i>n</i> (%)	76 (88.40)	14 (87.50)	0.230 ^a	102 (76.69)	5 (62.50)	0.627
Baseline values of liver indexes						
ALP	108.5 (84.0- 173.75)	127.0 (89.25- 167.75)	0.992	80.00 (61.00- 115.00)	96.50 (94.00- 113.50)	0.106
ALT	31.00 (13.00- 68.00)	48.00 (22.00- 79.00)	0.580	17.00 (10.00- 33.00)	20.50 (11.50- 38.75)	0.624
AST	56.00 (29.50- 157.00)	51.00 (34.00- 84.00)	0.926	32.00 (23.00- 50.00)	42.00 (29.25- 51.75)	0.220
TBIL	66.80 (20.30- 149.00)	50.80 (16.90- 262.70)	0.959	18.50 (12.40- 30.60)	19.05 (7.93- 37.90)	0.711
DBIL	39.80 (10.68- 92.20)	30.55 (8.10- 131.75)	0.683	6.40 (3.90- 14.60)	4.75(2.95- 15.05)	0.433

TAB	11.75 (4.40- 74.30)	9.80 (3.43- 60.45)	0.662	3.20 (1.80- 6.90)	5.15 (2.85- 13.75)	0.123
Complication, <i>n</i> (%)						
Cancer	28 (32.94)	5 (31.25)	0.895	36 (27.01)	1 (12.50)	0.620
Hypertension	17 (20.00)	4 (25.00)	0.738 ^a	38 (28.51)	1(12.50)	0.562
Diabetes	13 (15.29)	2 (12.50)	1.000 ^a	25 (18.80)	0 (0.00)	0.381
Immunosuppression	3 (3.53)	2 (12.50)	0.177 ^a	18 (13.53)	2 (25.00)	0.703
chronic renal failure	5 (5.88)	0 (0.00)	1.000 ^a	15 (11.28)	2 (25.00)	0.248 ^a
COPD	2(2.35)	1(6.25)	0.407 ^a	3 (2.26)	1 (12.50)	0.210 ^a
Infection site, <i>n</i> (%)						
Pulmonary infection	40(47.06)	9(56.25)	0.500	64 (48.12)	8 (100.00)	0.013
Abdominal infection	30(35.29)	1(6.25)	0.020 ^a	51 (38.35)	0 (0.00)	0.070
Lung complicated with abdominal infection	9(10.59)	5(31.25)	0.044 ^a	5 (3.76)	0 (0.00)	1.000 ^a
Length of ICU stay (days), median (IQR)	13(7.0- 22.0)	20.00(15.25- 33.50)	0.012	13.00 (7.00- 24.00)	25.00 (17.50- 36.25)	0.019
CRRT, <i>n</i> (%)	51(60.00)	11(68.75)	0.510	49 (36.84)	4 (50.00)	1.000
ECMO, <i>n</i> (%)	2(2.35)	0(0.00)	1.000 ^a	2 (1.50)	1 (12.50)	0.162 ^a
Treatment duration of TGC (days), median (IQR)	8.00(4.00- 11.00)	12.50(6.30- 15.80)	0.155	6.00 (4.00- 10.00)	12.50 (7.50- 18.75)	0.015
Maintenance dose of TGC, <i>n</i> (%)						
100mg/day	60(70.59)	8(50.00)	0.107	88 (66.17)	3 (37.50)	0.206
150mg/day	8(9.41)	1(6.25)	1.000 ^a	8 (6.02)	0 (0.00)	1.000 ^a
≥ 200mg/day	17(20.00)	7(4.38)	0.055 ^a	37 (27.82)	5 (62.50)	0.092

Drug combination, <i>n</i> (%)						
Echinocandins	53(62.35)	8(50.00)	0.354	72 (54.14)	5(62.50)	0.924
Azoles	33(38.82)	10(62.50)	0.079	34 (25.56)	4 (50.00)	0.270
Amphotericin B	12(14.12)	4(25.00)	0.276 ^a	7 (5.26)	3 (37.50)	0.012 ^a
β-lactam class/β-amide enzyme inhibitors	40(47.06)	10(62.50)	0.481	65 (48.87)	5 (62.50)	0.700
Carbapenems	52(61.18)	13(81.25)	0.124	64 (48.12)	4 (50.00)	1.000
Quinolones	4(4.71)	1(6.25)	0.586 ^a	8 (6.02)	0 (0.00)	1.000
Hepatinica, <i>n</i> (%)	57(67.06)	12(75.00)	0.531	49 (36.84)	4 (50.00)	0.711

APACHE II: acute physiology and chronic health II; SOFA: sequential organ failure; WBC: White blood cell count; PCT: Procalcitonin; ALT: Alanine transaminase; AST: Aspartate transaminase; TBIL: total bilirubin; TAB: Total bile acid; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; a. Fisher's exact test.

Table 7 Cox regression analysis for 28-day mortality

Variable	<i>P</i> -value	HR (95%CI)
Age ≥ 65 years	0.128	1.614 (0.871-2.989)
APACHE II score > 15	0.001	4.315 (1.894- 9.834)
Length of ICU > 30 days	0.073	0.430 (0.171- 1.080)
Preexisting liver disease	0.252	1.480 (0.757- 2.894)
TGC maintenance dose, mg/day		
150	0.023	3.128 (1.169- 8.369)
≥ 200	0.138	1.768 (0.833- 3.752)
TGC treatment duration, days		
7-14	0.020	0.443 (0.224- 0.878)
>14	0.020	0.229 (0.066- 0.796)
TILI	0.001	3.908 (1.694-9.018)

Figures

Figure 1

Severity of TILI observed in patients treated with TGC

Figure 2

Kaplan-Meier curve of the time of TIL after TGC treatment