RESEARCH ARTICLE

Risk factors for linezolid-induced thrombocytopenia in adult inpatients

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Abstract

Background Previous reports about risk factors for linezolid-induced thrombocytopenia have been insufficient, often due to the variability in study design and population, and some factors have not yet been studied. *Aim* The aims of this study are to determine potential risk factors for linezolid-induced thrombocytopenia, and to analyze the influencing factors of different thrombocytopenia definitions. *Method* This retrospective study involved patients who were administered intravenous linezolid for ≥ 1 day between January 1, 2015 and January 1, 2021. Their demographic and clinical data were extracted from electronic medical records. Thrombocytopenia was defined as: ①thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count (criterion 1); ②thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline (criterion 2). Risk factors were determined via binary logistic regression analysis. *Results* This study included 320 patients. Binary logistic regression analysis indicated that baseline platelet count ($p < 0.001$), linezolid therapy duration ($p = 0.001$) and shock (patients require vasoactive medications) ($p = 0.019$) were independent risk factors for criterion-1thrombocytopenia, while linezolid therapy duration ($p < 0.001$) and shock ($p = 0.015$) were independent risk factors for criterion-2 thrombocytopenia. There was also a significant correlation between shock and early-onset thrombocytopenia ($p = 0.005$ and 0.019 for criterion 1 and criterion 2, respectively). *Conclusion* Linezolid therapy duration and shock were common causes of different thrombocytopenia definitions; shock was correlated with early-onset thrombocytopenia. Platelet count should be monitored during linezolid therapy especially during long-duration therapy and in shock patients.

Keywords Linezolid · Thrombocytopenia · Risk factor · Shock

Impacts on practice

1. Linezolid therapy duration and shock patients requiring vasoactive drugs were risk factors of linezolid-induced thrombocytopenia.
2. Shock was correlated with early-onset thrombocytopenia.
3. Platelet count should be monitored during linezolid therapy especially during long-duration linezolid therapy and in shock patients.

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Introduction

Linezolid, a new oxazolidinone antimicrobial drug, has been used against Gram-positive bacterial infections such as methicillin-resistant staphylococci and vancomycin-resistant enterococci [1]. The antimicrobial mechanism of linezolid prevents the formation of a 70S initiation complex by binding to a site near the central region of domain V of the 23S ribosomal RNA in the 50S subunit, which includes fMet transfer RNA, messenger RNA and the two ribosomal subunits [2, 3]. Cross-resistance does not occur, since no other known antimicrobial agent inhibits this process. Recent studies have indicated that linezolid has a positive effect on Mycobacterium tuberculosis (TB), and has been suggested to provide statistically significant treatment benefits to adult patients exhibiting extensive drug resistance [4]. In 2016, the World Health Organization recommended linezolid as a core second-line medicine in multidrug resistant tuberculosis (MDR-TB) regimen [5]. Linezolid has became widely used

alongside the increasing prevalence of multidrug-resistant bacteria.

Linezolid is well tolerated, but myelosuppression in the form of thrombocytopenia and anaemia is a significant adverse drug reaction, of which thrombocytopenia has the highest risk. Reported risk factors of linezolid-induced thrombocytopenia included linezolid therapy duration [6–10], decreased creatinine clearance [6–13], baseline platelet count [6, 8, 11, 14, 15], concomitant drugs with thrombocytopenic adverse effects [8, 11, 13], chronic disease complications [10] and low body weight [8, 15]. However, the studies of these risk factors were insufficient and often limited due to variability in study design, patient population and thrombocytopenia definitions. In clinical practice, critically ill patients, especially shock patients requiring vasoactive medications suffered severe thrombocytopenia shortly after linezolid treatment. So these further potential risk factors for linezolid-induced thrombocytopenia should be investigated.

Aim of the study

The aims of this study are to determine potential risk factors for linezolid-induced thrombocytopenia, including early onset thrombocytopenia, and to analyze the influencing factors of different thrombocytopenia definitions.

Ethics approval

This study was approved by the medical ethics committee of Xi'an Central Hospital (No. LW-2021–011). Data was de-identified prior to analysis so patient consent was not required.

Method

Study design and population

This retrospective study was conducted on patients from Xi'an Central Hospital, which is a 1,000-bed tertiary-care teaching hospital in China. The population consisted of hospitalized patients aged ≥ 18 years who received intravenous linezolid (0.6 g, q12h) for ≥ 1 day between January 1, 2015 and January 1, 2021. Patients were excluded if they had haemato-oncologic diseases, myelosuppression, chemotherapy, COVID-19 or other viral disease, or incomplete baseline data.

Data collection and thrombocytopenia definition

Demographic and clinical data of each patient were collected, including sex, age, admission department, primary diagnosis, comorbidities, hospitalization days, the dose of linezolid and the frequency used, concurrent medications and baseline laboratory data prior to the first day of linezolid treatment including creatinine, total bilirubin, alanine aminotransferase, glutamic oxaloacetic transaminase, total protein, serum albumin, platelet count, haemoglobin level, intensive care, shock and linezolid treatment duration. Platelet count data were also collected after day 1 of linezolid treatment until discharge.

Thrombocytopenia was defined as two different criteria: ①thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count (criterion 1); ②thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline (criterion 2). Early-onset thrombocytopenia was defined as thrombocytopenia occurrence within 6 days of linezolid treatment initiation.

Statistical analyses

All analyses were conducted using IBM SPSS (version 23.0). Continuous data were expressed as mean $\pm$ SD values; and categorical data were expressed as frequencies. The differences in thrombocytopenia frequency as a function of sociodemographic characteristics were examined using independent-samples t-tests and Pearson's chi-square test. Binary logistic regression model was used to evaluate the factors associated with thrombocytopenia. The cumulative incidence of thrombocytopenia was compared between patients with different clinical conditions using a log-rank test and presented as Kaplan–Meier curves. Two-tailed probability values of $p < 0.05$ were considered statistically significant.

Results

Demographics and clinical characteristics

Table 1 listed the characteristics of the study population. After excluding 116 participants with haemato-oncologic diseases, myelosuppression, chemotherapy, incomplete clinical data or aged < 18 years, 320 patients who received intravenous linezolid treatment between January 1, 2015 and January 1, 2021 were included in this study. The age of the patients was 69.67 ± 16.39 years, and 69.06% of the population was male. The duration of hospitalization

Table 1 Demographic and clinical characteristics of the study patients (n = 320)

Characteristics	Value
Age (years), mean ± SD	69.67 ± 16.39
Male, n (%)	221 (69.06%)
Hospitalization days, mean ± SD	24.57 ± 15.58
Linezolid therapy duration, days, mean ± SD	7.40 ± 5.75
Creatinine clearance, mL/min	
≥ 60 ml/min	193 (60.3%)
≥ 30, < 60 ml/min	75 (23.4%)
< 30 ml/min	52 (16.3%)
Baseline laboratory data, mean ± SD	
Total bilirubin (µmol/L)	20.31 ± 49.81
ALT (U/L)	74.04 ± 173.2
AST (U/L)	85.37 ± 217.5
Total protein (g/L)	59.54 ± 9.66
Serum albumin (g/L)	31.6 ± 5.46
Platelet count (10^9/L)	240.47 ± 120.65
Haemoglobin (g/L)	109.32 ± 22.99
Intensive care, n (%)	168 (52.5%)
Shock[a], n (%)	107 (33.4%)
Comorbid diseases, n (%)	
Hypertension	174 (54.4%)
Diabetes	75 (23.4%)
Malignant tumor	19 (5.9%)
Stroke	93 (29.0%)
Cardiac insufficiency	97 (30.3%)
Chronic lung disease	25 (7.8%)
Concurrent medications, n (%)	
Aspirin	45 (14.1%)
Clopidogrel	38 (11.8%)
Low molecular weight heparins	79 (24.7%)

ALT alanine aminotransferase; *AST* glutamic oxaloacetic transaminase

[a]Shock patients require vasoactive medications

was 24.57 ± 15.58 days and linezolid therapy duration was 7.40 ± 5.75 days. (Table 1).

Comparison of the clinical characteristics between thrombocytopenia group and non thrombocytopenia group

The thrombocytopenia patients were classified into 73 cases (22.8%) and 136 cases (42.5%) defined by criterion 1 and 2, respectively. Among the 320 patients included in this study, 18 patients stopped linezolid due to severe thrombocytopenia, of which, the platelet count of 16 patients dropped to 25–49 × 10⁹/L, and two patients dropped to less than 25 × 10⁹/L. Table 2 compared the clinical characteristics between thrombocytopenia group and non thrombocytopenia

group including sex, age, hospitalization duration, bilirubin level, creatinine clearance, intensive care, shock, linezolid therapy duration, comorbidities and concurrent medications. Patients were divided into three groups according to creatinine clearance rate (≥ 60 mL/min, ≥ 30 and < 60 mL/min, and < 30 mL/min), and also according to linezolid therapy duration (< 7 days, ≥ 7 and < 14 days, and ≥ 14 days). The independent-samples t-test and Pearson's chi-square test showed that there were significant differences in age ($p = 0.015$), baseline platelet count ($p < 0.001$), creatinine clearance ($p = 0.005$), shock ($p = 0.007$), linezolid therapy duration ($p = 0.002$) and cardiac insufficiency ($p = 0.004$) between thrombocytopenia group and non thrombocytopenia group(criterion-1); the analysis also indicated significant differences for age ($p = 0.026$), hospitalization days ($p = 0.024$), shock ($p = 0.012$) and linezolid therapy duration ($p < 0.001$) between thrombocytopenia group and non thrombocytopenia group(criterion-2) (Table 2).

Risk factors for linezolid-induced thrombocytopenia

Age, sex, creatinine clearance, baseline platelet count, linezolid therapy duration and shock were analyzed as covariates in binary logistic regression model, with results indicating that criterion-1 thrombocytopenia was associated with baseline platelet count (OR = 0.992, 95% CI = 0.988–0.995, $p < 0.001$), linezolid therapy duration (≥ 7 and < 14 days: OR = 3.463, 95% CI = 1.796–6.676, $p < 0.001$; ≥ 14 days: OR = 2.508, 95% CI = 1.047–6.006, $p = 0.039$) and shock (OR = 2.091, 95% CI = 1.127–3.880, $P = 0.019$), while criterion-2 thrombocytopenia was associated with linezolid therapy duration (≥ 7 and < 14 days: OR = 3.767, 95% CI = 2.213–6.413, $p < 0.001$; ≥ 14 days: OR = 2.615, 95% CI = 1.260–5.429, $p = 0.010$) and shock (OR = 1.907, 95% CI = 1.132–3.213, $p = 0.015$) (Table 3).

Since shock was a common risk factor for both thrombocytopenia definitions, the cumulative incidence of thrombocytopenia was compared in patients with and without shock using a log-rank test and presented as Kaplan–Meier curves. Kaplan–Meier analysis also indicated a higher cumulative thrombocytopenia incidence in shock patients than in those without shock (Fig. 1). The *p* values of log-rank tests for the different thrombocytopenia definitions (criterion 1, criterion 2, early-onset criterion-1 and early-onset criterion-2 thrombocytopenia) were 0.006, 0.021, 0.001 and 0.004, respectively (Fig. 1).

Comparison of shock between early-onset thrombocytopenia and no thrombocytopenia

Table 4 compared shock patients requiring vasoactive drugs in terms of early-onset thrombocytopenia or no thrombocytopenia. Pearson's chi-square test indicated significant

Table 2 Comparison of clinical characteristics between thrombocytopenia and no thrombocytopenia

Variables	Platelet count $< 100 \times 10^9$/L[a]			The drop decrease of platelet count was $\geq 25\%$[b]		
	No thrombocytopenia	Thrombocytopenia[a]	p	No thrombocytopenia	Thrombocytopenia[a]	p
Total, n (%)	247 (77.2%)	73 (22.8%)		184 (57.5%)	136 (42.5%)	
Sex, n (%)			0.302			0.214
Male	167 (75.6%)	54 (24.4%)		122 (55.2%)	99 (44.8%)	
Female	80 (80.8%)	19 (19.2%)		62 (62.6%)	37 (37.4%)	
Age (years)	68.47 ± 16.12	73.78 ± 16.77	**0.015**	67.93 ± 16.15	72.05 ± 16.48	**0.026**
Hospitalization days	24.19 ± 15.29	25.84 ± 16.57	0.429	22.82 ± 14.00	26.93 ± 17.26	**0.024**
Total bilirubin level	18.18 ± 39.06	27.53 ± 75.58	0.312	20.03 ± 44.94	20.69 ± 55.91	0.908
ALT	61.69 ± 154.05	115.84 ± 222.65	0.055	70.92 ± 175.82	78.26 ± 170.21	0.709
AST	70.35 ± 207.09	136.19 ± 244.14	0.039	81.45 ± 238.08	90.68 ± 186.70	0.708
Total protein (g/L)	59.51 ± 9.41	59.64 ± 10.53	0.923	59.39 ± 9.66	59.75 ± 9.69	0.740
Serum albumin (g/L)	31.89 ± 5.51	30.77 ± 5.23	0.125	32.13 ± 5.40	30.96 ± 5.48	0.059
Haemoglobin (g/L)	108.03 ± 23.00	110.95 ± 27.72	0.366	108.48 ± 23.80	109.00 ± 24.69	0.848
Platelet count (10^9/L)	236.45. ± 118.15	162.12 ± 81.53	**0.000**	214.66 ± 113.35	225.88 ± 117.42	0.390
Creatinine clearance, mL/min			**0.005**			0.113
≥ 60	159 (82.4%)	34 (17.6%)		120 (62.2%)	73 (37.8%)	
$\geq 30, < 60$	56 (74.7%)	19 (25.3%)		38 (50.7%)	37 (49.3%)	
< 30	32 (61.5%)	20 (38.5%)		26 (50.0%)	26 (50.0%)	
Intensive care, n (%)			0.327			0.205
No intensive care	121 (79.6%)	31 (20.4%)		93 (61.2%)	59 (38.8%)	
Intensive care	126 (75.0%)	42 (25.0%)		91 (54.2%)	77 (45.8%)	
Shock[c], n (%)			**0.007**			**0.012**
No shock	174 (81.7%)	39 (18.3%)		133 (62.4%)	80 (37.6%)	
Shock	73 (68.2%)	34 (31.8%)		51 (47.7%)	56 (52.3%)	
Linezolid therapy duration days, mean ± SD	6.93 ± 5.47	9.01 ± 6.41	**0.006**	6.93 ± 5.47	9.01 ± 6.41	**0.006**
Linezolid therapy duration, days,			**0.002**			**0.000**
< 7d	145 (84.8%)	26 (15.2%)		121 (70.7%)	50 (29.3%)	
$\geq 7, < 14$d	74 (67.9%)	35 (32.1%)		45 (41.3%)	64 (58.7%)	
≥ 14d	28 (70.0%)	12 (30.0%)		18 (45.0%)	22 (55.0%)	
Comorbid diseases, n (%)						
Malignant tumor	15 (78.9%)	4 (21.1%)	0.850	12 (63.2%)	7 (36.8%)	0.607
Hypertension	135 (77.6%)	39 (22.4%)	0.853	102 (58.6%)	72 (41.4%)	0.658
Cardiac insufficiency	65 (67.0%)	32 (33.0%)	**0.004**	48 (49.5%)	49 (50.5%)	0.056
Diabetes	58 (77.3%)	17 (22.7%)	0.973	48 (64.0%)	27 (36.0%)	0.193
Stroke	77 (82.8%)	16 (17.2%)	0.126	58 (62.4%)	35 (37.6%)	0.260
Chronic lung disease	18 (72.0%)	7 (28.0%)	0.520	15 (60.0%)	10 (40.0%)	0.792
Concurrent medications						
Aspirin	24 (53.3%)	21 (46.7%)	0.542	23 (51.1%)	22 (48.9%)	0.541
Clopidogrel	32 (84.2%)	6 (15.8%)	0.272	26 (68.4%)	12 (31.6%)	0.147
Low molecular weight heparin	56 (70.9%)	23 (29.1%)	0.124	42 (53.2%)	37 (46.8%)	0.369

ALT Alanine aminotransferase, *AST* Glutamic oxaloacetic transaminase

Bold values show statistical significance of differences

[a]Thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count

[b]Thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline

[c]Shock patients require vasoactive medications

Table 3 Binary logistic regression analysis of determinants associated with thrombocytopenia

Variables	Platelet count $< 100 \times 10^9$/L[a]			The drop decrease of platelet count was $\geq 25\%$[b]		
	OR	95%CI	P	OR	95%CI	P
Age (years)	1.015	0.995–1.035	0.139	1.013	0.997–1.030	0.105
Sex	0.631	0.324–1.230	0.176	0.649	0.380–1.108	0.113
CrCl, mL/min						
≥ 60 (reference)	1.000	–	–	1.000	–	–
$\geq 30, < 60$	0.975	0.464–2.048	0.947	1.231	0.668–2.266	0.505
< 30	1.876	0.864–4.071	0.112	1.550	0.766–3.135	0.223
Baseline platelet count (10^9/L)	0.992	0.988–0.995	**0.000**	1.001	0.999–1.004	0.201
Linezolid therapy duration, days,						
< 7	1.000	–	–	1.000	–	–
$\geq 7, < 14$	3.463	1.796–6.676	**0.000**	3.767	2.213–6.413	**0.000**
≥ 14	2.508	1.047–6.006	**0.039**	2.615	1.260–5.429	**0.010**
Shock[c]	2.091	1.127–3.880	**0.019**	1.907	1.132–3.213	**0.015**

CrCL creatinine clearance rate

Bold values show statistical significance of differences

[a]Thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count

[b]Thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline

[c]Shock patients require vasoactive medications

differences for shock between early-onset criterion-1 thrombocytopenia and no thrombocytopenia ($P = 0.001$), and between early-onset criterion-2 thrombocytopenia and no thrombocytopenia ($p = 0.005$).

## Correlation between shock and early-onset thrombocytopenia

We analyzed the correlation between shock and early-onset thrombocytopenia after adjusting for the confounding factors of age, hospitalization days, creatinine clearance rate and baseline platelet count in the regression model. Binary logistic regression analysis indicated a significant correlation between shock and early-onset criterion-1 thrombocytopenia (adjusted OR = 2.709, 95% CI = 1.359–5.398, $p = 0.005$), and early-onset criterion-2 thrombocytopenia (adjusted OR = 1.900, 95% CI = 1.113–3.243, $p = 0.019$) after eliminating the confounding factors (Table 5).

Discussion

This study indicated that thrombocytopenia incidence and risk factors differed according to its definition. The criterion-1 thrombocytopenia incidence was 22.8%, baseline platelet count, linezolid therapy duration and shock were independent risk factors. The criterion-2 thrombocytopenia

incidence was 42.5%, linezolid therapy duration and shock were independent risk factors. Linezolid therapy duration and shock were common causes of thrombocytopenia regardless of the definition. Kaplan–Meier analysis also indicated that the cumulative thrombocytopenia incidence was higher in shock patients. The binary logistic regression analysis indicated a significant correlation between shock and early-onset thrombocytopenia. As far as we know, this is the first study of that has elucidated the relationship between shock and thrombocytopenia risk.

A previous study that included only intensive-care unit (ICU) patients found a thrombocytopenia incidence of 48.3% [16], which was higher than in other studies involving patients in general ward. However, there was no difference in thrombocytopenia incidence between ICU patients and non-ICU patients in our study, and shock was indicated as an independent risk factor. Immunosuppression occurs both early and late in the shock response. Patients who survive septic shock often have prolonged clinical trajectories and exhibit chronic immune suppression [17, 18]. The mechanisms of linezolid-induced thrombocytopenia may be related to myelosuppression and immune-mediated platelet destruction [19–21]. In clinical practice, patients with shock requiring vasoactive medications often develop thrombocytopenia after only 1 or 2 days of linezolid treatment, and recover gradually after linezolid discontinuation. Onset and recovery times are consistent with immune-mediated drug-induced thrombocytopenia [19, 20]. In the present study, 24
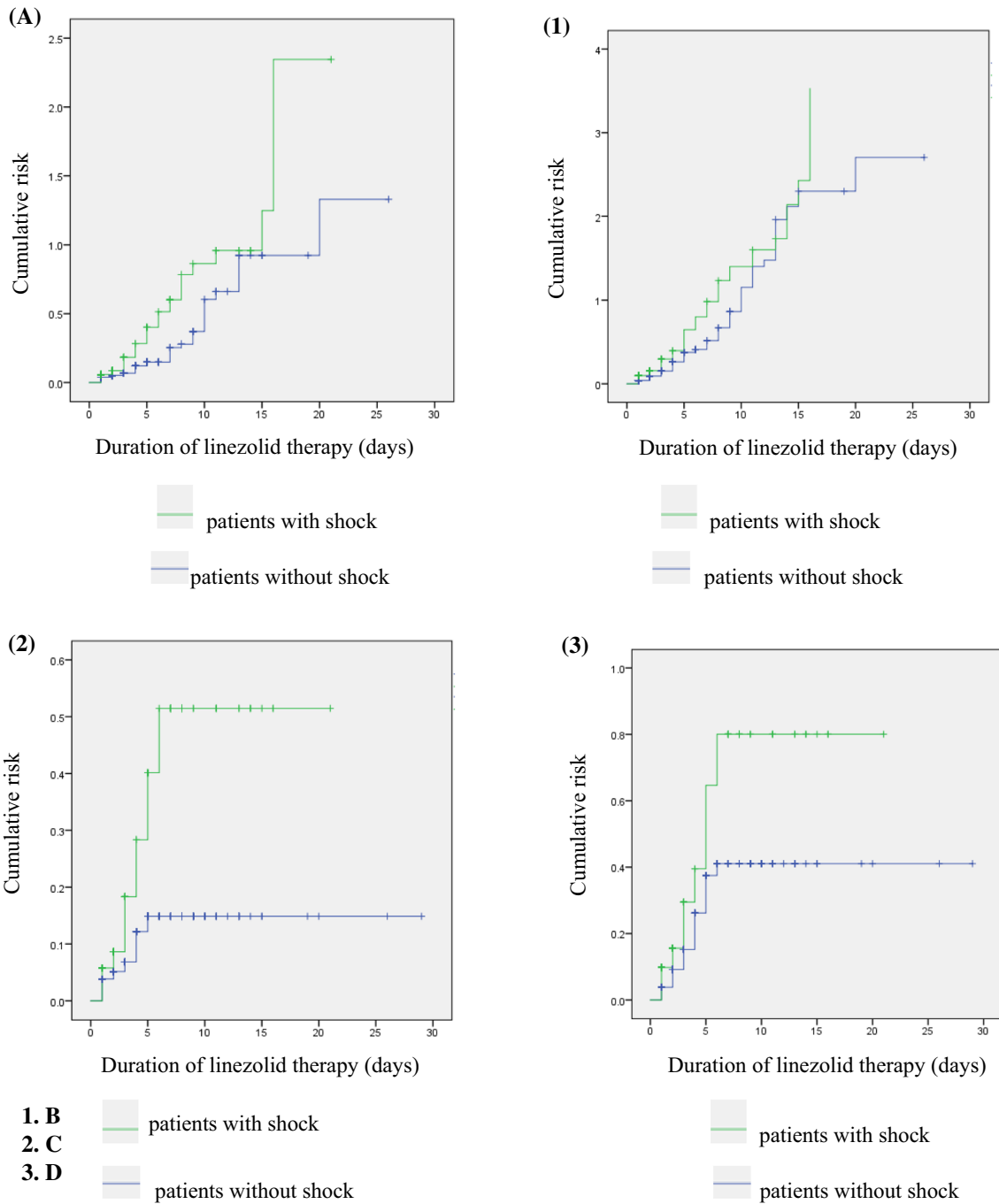
Fig. 1 Kaplan–Meier estimates of the cumulative incidence of linezolid—induced thrombocytopenia in patients with shock and patients without shock. **a** Criterion-1thrombocytopenia: thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count; **b** Criterion-2 thrombocytopenia: thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline; **c** Early-onset criterion-1 thrombocytopenia: criterion-1 thrombocytopenia occurrence within 6 days of linezolid treatment initiation; **d** Early-onset criterion-2 thrombocytopenia: criterion-2 thrombocytopenia occurrence within 6 days of initiating linezolid therapy

cases (22.4%) and 37 cases (34.6%) shock patients developed early-onset thrombocytopenia according to criterion 1 and criterion 2, respectively. The binary logistic regression analysis indicated a significant correlation between shock and early-onset thrombocytopenia.

Baseline platelet count has been reported as a risk factor for thrombocytopenia. Our study indicated that the risk

Table 4 Comparison of shock between early-onset thrombocytopenia and no thrombocytopenia

	Platelet count $< 100 \times 10^9$/L[a]			The drop decrease of platelet count was $\geq 25\%$[b]		
	No thrombocytopenia	Early-onset thrombocytopenia[c]	p	No thrombocytopenia	Early-onset thrombocytopenia[c]	p
Shock[d], n (%)			**0.001**			**0.005**
No shock	194 (91.1%)	19 (8.9%)		170 (79.8%)	43 (20.2%)	
Shock	83 (77.6%)	24 (22.4%)		70 (65.4%)	37 (34.6%)	

Bold values show statistical significance of differences

[a]Thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count

[b]Thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline

[c]Early-onset thrombocytopenia: thrombocytopenia occurrence within 6 days of linezolid treatment initiation

[d]Shock patients require vasoactive medications

Table 5 Binary logistic regression analysis: the correlation between shock[a] and early-onset thrombocytopenia

Variables	Early-onset thrombocytopenia[b] (platelet count $< 100 \times 10^9$/L[c])			Early-onset thrombocytopenia (the drop decrease of platelet count was $\geq 25\%$[d])		
	OR	95%CI	P	OR	95%CI	P
Crude	2.952	1.534–5.681	**0.001**	2.090	1.242–3.516	**0.005**
Adjusted[e]	2.709	1.359–5.398	**0.005**	1.900	1.113–3.243	**0.019**

Bold values show statistical significance of differences

[a]Shock patients require vasoactive medications

[b]Early-onset thrombocytopenia: thrombocytopenia occurrence within 6 days of linezolid treatment initiation

[c]Thrombocytopenia with platelet count $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count

[d]Thrombocytopenia due to a platelet count drop decrease of 25% or more from baseline

[e]Age, hospitalization days, creatinine clearance rate, baseline platelet count were adjusted for in the regression model as the confounding factors

factors for linezolid-induced thrombocytopenia differed according to its definition. Baseline platelet count was an independent risk factor when thrombocytopenia was defined as a platelet count of $< 100 \times 10^9$/L (whether patients with baseline platelet counts $< 100 \times 10^9$/L were excluded or not), but not when it was defined as a decrease of $\geq 25\%$ in baseline platelet count, which was consistent with previous reports [6–15]. There is currently no unified diagnostic criterion for linezolid-induced thrombocytopenia. In some previous studies, thrombocytopenia was defined as a platelet count of $< 100 \times 10^9$/L after treatment (patients with baseline platelet counts $< 100 \times 10^9$/L were excluded in some studies), while in others thrombocytopenia was defined as a decrease of $\geq 25\%$ or 30% in baseline platelet count. According to the drug-related thrombocytopenia criteria adopted by the University of Oklahoma Health Sciences Center [22], when platelet counts are lower than the lower limit of normal ($< 100 \times 10^9$/L) after treatment, it is considered thrombocytopenia. This criterion better reflects platelet counts after linezolid treatment to indicate severe linezolid-induced thrombocytopenia, but it includes some patients with small

decreases in platelet counts. For example, the baseline platelet count of some patients is 101×10^9/L, and the platelet count is 98×10^9/L after treatment (which is defined as thrombocytopenia), but this decrease has no clinical significance, which will result in an artificially higher thrombocytopenia incidence. We therefore defined thrombocytopenia as either a platelet count of $< 100 \times 10^9$/L and a decrease in 25% or more from baseline of the platelet count, or a platelet count drop decrease of 25% or more from baseline.

Patients included in this study were divided into three groups according to creatinine clearance rate (≥ 60 mL/min, ≥ 30 and < 60 mL/min, and < 30 mL/min), and Pearson's chi-square test results indicated a significant difference in creatinine clearance rate between patients with criterion-1 thrombocytopenia and patients without thrombocytopenia. However, binary logistic regression analysis indicated that the creatinine clearance rate was not a risk factor for criterion-1 thrombocytopenia, which was not consistent with previous reports [6–13]. Such differences may be at least partially attributable to the inclusion of patients from different racial groups, different clinical conditions and different

definitions of thrombocytopenia. A standard definition is necessary to facilitate comparisons between studies.

Linezolid treatment duration was an independent risk factor for thrombocytopenia, which is consistent with previous reports. The recommended duration for linezolid treatment is 10–14 days for pneumonia and skin and soft-tissue infections, and 14–28 days for vancomycin-resistant enterococci. Gerson et al. [23] reported that thrombocytopenia was evident after > 2 weeks of linezolid treatment. Our study indicated that the relative risks of thrombocytopenia among patients receiving linezolid therapy for 7–14 days were 3.463 and 3.767 times higher than in patients receiving linezolid therapy for < 7 days for criterion-1 and -2 thrombocytopenia, respectively, and among patients receiving linezolid therapy for ≥ 14 days were 2.508 and 2.615 times for criterion-1 and -2 thrombocytopenia, respectively. The increased thrombocytopenia incidence was not proportional to linezolid therapy duration, this is consistent with the literature that thrombocytopenia usually occurs within 10–14 d after initiation of therapy [24, 25], which may be due to the mechanisms of linezolid-induced thrombocytopenia resulting from myelosuppression and immune-mediated platelet destruction. Our findings indicated the necessity for monitoring platelet counts frequently in all patients who received linezolid treatment for longer than 7 days.

Our study had three limitations. Firstly, we could not control for all confounding factors due to the retrospective design of the study. Secondly, patient selection bias may have occurred since the study was only conducted within our hospital, which limits the generalizability of the results. Thirdly, the sample of our study was small. Further multicenter prospective studies with large samples would be required for to ensure adequate statistical power in the analyses. However, our study indicated that shock was a risk factor for thrombocytopenia, which will be useful for establishing an appropriate drug utilization strategy in linezolid therapy.

Conclusions

This study found that thrombocytopenia incidence and risk factors differed according to its definition. Baseline platelet count was an independent risk factor when thrombocytopenia was defined as a platelet count of $< 100 \times 10^9$/L (whether or not patients with baseline platelet counts $< 100 \times 10^9$/L were excluded), but not when defined as a decrease of $\geq 25\%$ in baseline platelet count. Linezolid therapy duration and shock patients require vasoactive medications were common causes of thrombocytopenia, regardless of its definition. Shock was correlated with early-onset thrombocytopenia. Platelet count should be monitored during linezolid therapy

especially during long-duration linezolid therapy and in patients with shock requiring vasoactive medications.

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