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# Hypoalbuminemia, a significant risk factor for thrombocytopenia associated with tedizolid therapy

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**Abstract**

Recently, thrombocytopenia was found to be an adverse event associated with tedizolid therapy. However, there are few reports on the incidence rate and risk factors of thrombocytopenia associated with tedizolid therapy. Therefore, this study aimed to investigate the incidence rate and associated risk factors of thrombocytopenia associated with tedizolid therapy. Twenty-five patients who received tedizolid during hospitalization at Iwaki City Medical Center between May, 2018 and March, 2022 were enrolled in this study, and the development of thrombocytopenia was retrospectively investigated. Thrombocytopenia was defined as a decrease in platelet counts by $\geq 10 \times 10^4/\mu L$ or a reduction of platelet counts by ≥ 30% before treatment with tedizolid. Among the studied patients, thrombocytopenia was observed in six patients (24%). In the univariate analysis, using logistic regression analysis of objective variables, serum albumin (P =0.012), aspartate aminotransferase (P =0.038), blood urea nitrogen (P =0.002), estimated glomerular filtration rate (P=0.012), and white blood cell counts (P =0.039) were suggested as risk factors for thrombocytopenia associated with tedizolid therapy. Meanwhile, multivariate logistic regression analysis showed that hypoalbuminemia (albumin <2.5 g/dL) was the only significant risk factor for tedizolid-induced thrombocytopenia. These results suggest that thrombocytopenia is a common side-effect of tedizolid, and hypoalbuminemia is a significant risk factor for the development of thrombocytopenia. Therefore, platelet counts and serum albumin levels in patients who received tedizolid therapy should be closely monitored.

**Key Words**
Tedizolid; Thrombocytopenia; Hypoalbuminemia

## 1. Introduction

Oxazolidinone antibacterial agents are widely used to treat drug-resistant gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). The mechanism of action of this family of antimicrobials involves the inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunit.[1)]

Linezolid (LZD), the first member of the oxazolidinone class of antimicrobials, is known to induce thrombocytopenia due to its bone marrow suppression effect.[2)] Thrombocytopenia induced by LZD has been reported to be affected by the duration of its administration, renal function of the patients, and serum albumin (Alb) concentrations.[3,4)] Recently, tedizolid (TZD) was approved for clinical use as the second agent of this antimicrobial class after LZD, which is currently used in clinical practice against MRSA, and was listed in the National Health Insurance Drug Price List in May, 2018. TZD was thought to have a lower incidence of thrombocytopenia than LZD[5)] because of its low mitochondrial toxicity resulting from its low dosage administration and instability in the mitochondrial fraction of

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cells;[6] however, using data from the Food and Drug Administration Adverse Event Reporting System（FDA FAERS）, it was observed that the risks of thrombocytopenia were of similar magnitude in both LZD and TZD.[7] Since there are few reports on the factors associated with thrombocytopenia in TZD therapy, we investigated the risk factors associated with the development of thrombocytopenia in patients receiving TZD therapy in this study. Besides, to the best of our knowledge, this is the first study to report the risk factors for thrombocytopenia associated with TZD therapy.

## 2. Methods

### 2.1. Study subjects

Adult patients who received TZD（200 mg once daily intravenous infusion for 1 h）over 3 days during hospitalization at Iwaki City Medical Center from May, 2018 to March, 2022 were retrospectively studied.

### 2.2. Evaluation of thrombocytopenia

Patients' clinical laboratory data were collected from the patients' electronic medical charts. Thrombocytopenia was defined as a decrease in platelet counts（PLT）by ≥ $10 \times 10^4$/μL from the baseline or a reduction in PLT by ≥ 30% before initiating TZD therapy.[8] These patients were divided into the "thrombocytopenic" and "non-thrombocytopenic" groups. Age, duration of treatment, aspartate aminotransferase（AST）, alanine transaminase（ALT）, serum albumin（Alb）, total protein（TP）, sodium（Na）, potassium（K）, serum creatinine（Cr）and creatinine clearance（Ccr）, blood urea nitrogen（BUN）, estimated glomerular filtration rate（eGFR）, C-reactive protein（CRP）, white blood cells（WBC）counts, and red blood cells（RBC）counts of the patients were determined by F-test for equal variance, and comparisons were made using Student's t-test. Ccr was calculated using Cockcroft–Gault formula. The severity of thrombocytopenia was evaluated using the minimum PLT according to the Common Terminology Criteria for Adverse Events version 5.0（CTCAE v5.0）developed by the National Cancer Institute.

Furthermore, to examine the factors associated with the development of thrombocytopenia in patients receiving TZD therapy, univariate analysis using logistic regression was conducted on the 15 items mentioned above using the presence or absence of thrombocytopenia before and after TZD therapy as the objective variable. However, multivariate analysis was performed on five items: AST, Alb, BUN, eGFR, and WBC, which had P-values < 0.05 after the univariate analysis. For the collection of the "before TZD therapy" blood test data, the test results either immediately before therapy, on the day before, or on the day of TZD administration were used, and for the "after TZD therapy" data, the test results on the day after the end of TZD administration or on the day after the end of therapy were used.

### 2.3. Statistical analysis

Data were expressed as mean ± standard deviation. Comparisons between the two groups（thrombocytopenia and non-thrombocytopenia）were analyzed using Student's t-test. Univariate and multivariate logistic regression analyses were also performed to determine the odds ratios（OR）for thrombocytopenia. A P value of < 0.05 was considered to be statistically significant. Statistical analysis was performed using the State Mate V for the Win & Mac Hybrid（ATMS Co., Ltd., Tokyo, Japan）.

### 2.4. Ethical Approval

The protocol of this study conformed to the ethical guidelines for life science and medical research involving human subjects, and was approved by the Ethics Committee of the Iwaki City Medical Center（approval number: R4-26）.

## 3. Results

### 3.1. Study subjects

A total of 25 patients（15 men and 10 women）were included in this study. The mean age of the patients was 70.6 ± 16.9 years old. The mean duration of TZD therapy was 11.8 ± 7.1 days. PLT significantly decreased from 31.49 ± 14.27 x $10^4$/μL to 23.62 ± 13.13 x $10^4$/μL during the TZD therapy period（P=0.048）（Fig. 1）.

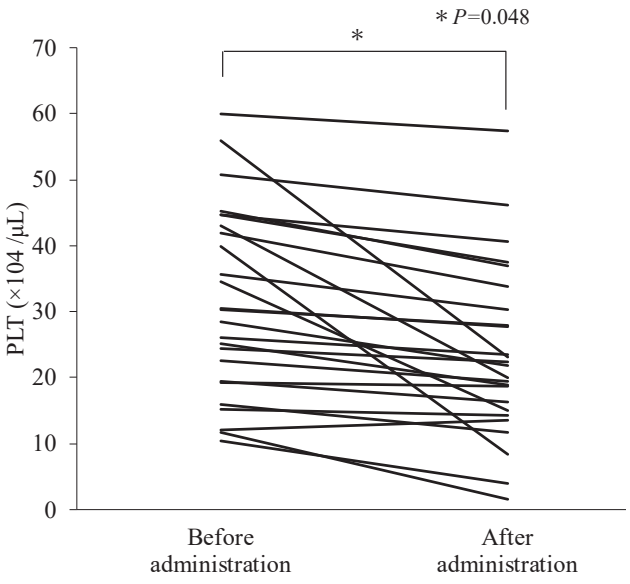


**Fig. 1　Changes in PLT with TZD therapy**

PLT were compared before and after TZD therapy. Columns of vertical bars represent mean ± standard deviation values（n=25）. *PLT after TZD therapy was significantly different from before therapy（Student's t-test, P = 0.048）. Before administration: Blood samples were collected immediately before dosing, on the day before, or on the day of dosing. After administration, blood samples were collected on the day of or the day after the end of TZD administration.
PLT: Platelet counts; TZD: Tedizolid.

### 3.2. Evaluation of thrombocytopenia

Among the 25 patients studied, thrombocytopenia occurred in 6（24%）. The patients with thrombocytopenia eventually recovered after treatment cessation. None of the patients required platelet transfusion. Next, we compared the basic data before TZD therapy between the thrombocytopenia and non-thrombocytopenia groups and found no significant differences in age, treatment duration, ALT, Na, K, Cr, CRP, WBC counts, and RBC counts. However, there were significant differences（P<0.01）in AST（P =0.018）, Alb（P =0.008）, TP（P =0.049）, BUN（P =0.013）, eGFR（P =0.018）, and Ccr（P =0.046）（Table 1）. Of the six patients with thrombocytopenia, grade 3 or higher（according to CTCAE v5.0）was seen in two patients（Table 2）. The before administration PLT of the two patients with grade 3 or higher were 10.4 x $10^4$ /μL and 11.6 x $10^4$ /μL, respectively. Notably,

**Table 1　Background physiological data of the patients with and without thrombocytopenia**

| Variables | Patients with thrombocytopenia | Patients without thrombocytopenia | P value |
|---|---|---|---|
| N | 6 | 19 | |
| Gender (Male) | 2 | 13 | |
| Age | 69.50 ± 17.90 | 70.15 ± 16.22 | 0.936 |
| Duration of TZD treatment (days) | 8.83 ± 5.18 | 12.68 ± 7.37 | 0.265 |
| Laboratory data at the start of treatment | | | |
| AST (IU/L) | 155.67 ± 206.98 | 28.78 ± 15.88 | 0.018* |
| ALT (IU/L) | 102.50 ± 169.10 | 22.32 ± 23.19 | 0.066 |
| Alb (g/dL) | 1.98 ± 0.15 | 3.17 ± 0.96 | 0.008** |
| TP (g/dL) | 5.81 ± 0.32 | 6.64 ± 0.92 | 0.049* |
| Na (mmol/L) | 143.33 ± 8.43 | 136.26 ± 7.58 | 0.076 |
| K (mmol/L) | 3.83 ± 1.01 | 4.20 ± 0.47 | 0.248 |
| Cr (mg/dL) | 2.82 ± 1.58 | 1.74 ± 2.61 | 0.363 |
| BUN (mg/dL) | 67.68 ± 47.92 | 29.56 ± 19.72 | 0.013* |
| eGFR (mL/min/1.73$m^2$) | 24.01 ± 15.88 | 68.43 ± 38.68 | 0.015* |
| Ccr (mL/min) | 24.07 ± 12.87 | 67.56 ± 47.86 | 0.046* |
| CRP (mg/dL) | 8.92 ± 6.53 | 12.75 ± 9.56 | 0.390 |
| WBC (x$10^2$/μL) | 72.67 ± 26.10 | 110.05 ± 52.50 | 0.117 |
| RBC (x$10^4$/μL) | 319.16 ± 52.74 | 325.73 ± 58.60 | 0.816 |

*P<0.05;**P<0.01

Data are presented as mean ± standard deviation. Statistical analyses were performed using the Student's t-test.

**Table 2 The severity of the thrombocytopenia suffered by the patients.**

| Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Number of patients | 4 | 0 | 0 | 1 | 1 |

The severity of thrombocytopenia was evaluated using the minimum PLT according to the Common Terminology Criteria for Adverse Events version 5.0 developed by the National Cancer Institute. The PLT ranges of each grade of thrombocytopenia were as follows: grade 0 (10> x $10^4$ platelets/μL, grade 1 (10-7.5 x $10^4$/μL), grade 2 (7.4-5 x $10^4$/μL), grade 3 (4.9-2.5 x $10^4$/μL), and grade 4 (<2.5 x $10^4$/μL). PLT: Platelet counts.

there was no significant difference in the WBC counts because TZD, like LZD, has an ameliorating effect on inflammation. Similarly, there was no significant difference between the groups with regard to the duration of administration, which had been reported to increase the risk of thrombocytopenia in patients on LZD. However, the thrombocytopenia group was administered TZD for shorter durations than the non-thrombocytopenia group（8.83 ± 5.18 vs. 12.68 ± 7.37 days）.

The univariate logistic regression analysis showed significant differences in the following five parameters: Alb（P = 0.012）, AST（P = 0.038）, BUN（P = 0.002）, eGFR（P = 0.012）, and WBC counts（P = 0.039）, with thrombocytopenia as the objective variable（Table 3）. Since Ccr <50 mL/min was previously identified as a risk factor

**Table 3 Univariate analysis with and without thrombocytopenia as objective variables.**

| Variables | OR | 95% CI | P value |
|---|---|---|---|
| Age | 0.99 | 0.94-1.05 | 0.936 |
| Duration of TZD treatment (days) | 0.90 | 0.77-1.05 | 0.208 |
| Laboratory data at the start of treatment | | | |
| AST (IU/L) | 1.03 | 1.00-1.07 | 0.038* |
| ALT (IU/L) | 1.01 | 0.99-1.03 | 0.152 |
| Cr (mg/dL) | 1.17 | 0.83-1.66 | 0.375 |
| Alb (g/dL) | 0.14 | 0.03-0.65 | 0.012* |
| TP (g/dL) | 0.49 | 0.18-1.31 | 0.059 |
| Na (mmol/L) | 1.17 | 1.03-1.33 | 0.060 |
| K (mmol/L) | 1.05 | 0.31-3.53 | 0.926 |
| BUN (mg/dL) | 1.03 | 1.01-1.06 | 0.002** |
| eGFR (mL/min/1.73$m^2$) | 0.95 | 0.91-0.99 | 0.010* |
| Ccr (mL/min) | 0.96 | 0.92-0.99 | 0.056 |
| Ccr (<50 mL/min) | 4.88 | 0.68-34.96 | 0.114 |
| CRP (mg/dL) | 0.95 | 0.86-1.05 | 0.309 |
| WBC (x$10^2$/μL) | 0.98 | 0.96-1.00 | 0.039* |
| RBC (x$10^4$/μL) | 0.99 | 0.98-1.00 | 0.349 |

**P<0.01; *P<0.05

Univariate analysis was performed using logistic regression analysis.

CI; confidence interval

for LZD, it was used as the variable. Ccr <50 mL/min, on the other hand, showed no significant difference. The ORs for the five parameters were as follows: 0.138 (95% confidence interval [CI], 0.030–0.68) for Alb, 1.03 (95% CI, 1.00–1.07) for AST, 1.03 (95% CI, 1.01–1.06) for BUN, 0.95 (95% CI, 0.91–0.99) for eGFR, and 0.98 (95% CI, 0.96–1.00) for WBC counts. Among these five parameters, three parameters, Alb, which is reported to be a risk factor for LZD (the same oxazolidinone antimicrobial agent), and eGFR and AST, which are indicators of renal and hepatic function, respectively, were used as variables in the multivariate analysis. The threshold values for each variable were set based on their respective reference values. The Alb threshold was set at 2.5 g/dL based on the trigger value for chronic hypoproteinemia in the Guidelines for the Use of Blood Products. The eGFR threshold was set at 30 mL/min/1.73 $m^2$, which is an indicator of severe decline in renal function in chronic kidney disease. Alb <2.5 g/dL showed a significant difference (P = 0.044), and the OR for Alb was 7.39 (95% CI, 0.36–147.80). Thus, an Alb level of < 2.5 g/dL was confirmed to be an independent risk factor for thrombocytopenia in patients undergoing TZD therapy (Table 4).

**Table 4　Multivariate analysis with and without thrombocytopenia as objective variables.**

| Variables | OR | 95% CI | P value |
|---|---|---|---|
| AST (>40 IU/L) | 0.88 | 0.08-9.47 | 0.191 |
| Alb (<2.5 g/dL) | 7.39 | 0.36-147.80 | 0.044* |
| eGFR (<30 mL/min/1.73$m^2$) | 6.98 | 0.76-64.12 | 0.086 |

The variables selected by univariate analysis (Table 3) were subjected to multivariate analysis using logistic regression analysis.

## 4. Discussion

Several publications have suggested that a lower incidence of thrombocytopenia can be attributed to TZD than to LZD (the first member of the oxazolidinone class of antimicrobials); however, using data from the FDA FAERS, Lee and Caffrey reported a significantly increased risk of thrombocytopenia of similar magnitude in both TZD and LZD.[7] Our present study also revealed a significant incidence of thrombocytopenia with TZD, and thrombocytopenia was observed in 6 (24%) of the 25 patients who received TZD therapy. Of these, grade 3 or higher thrombocytopenia, based on CTCAE v5.0, was observed in 8% of the patients. Therefore, it is assumed that thrombocytopenia is a common adverse effect of TZD as well as LZD.

Retrospective analysis of this study suggested that hypoalbuminemia (<2.5 g/dL) was a significant risk factor for TZD-induced thrombocytopenia. To the best of our knowledge, this is the first study to describe the risk factors for TZD-induced thrombocytopenia. It has been reported that TZD is a highly albumin-binding compound whose binding rate is approximately 85-90%.[9-11] Pharmacologically, Alb significantly affects the pharmacokinetics of many drugs because of the drug-albumin binding effect. In patients with hypoalbuminemia, the unbound proportion of highly protein-bound drugs increases because of the decrease in available binding sites.[12] This decline in Alb levels may have decreased the protein binding rate of TZD and increased the proportion of free TZD. However, the mechanism underlying the development of thrombocytopenia by TZD in hypoalbuminemia remains obscure. Further studies are needed to confirm this hypothesis.

It has been reported that impaired renal function is associated with an increased risk of LZD-

induced thrombocytopenia.[13,14] In this study, the laboratory value of eGFR and Ccr, markers of renal function, were significantly lower in patients with TZD-induced thrombocytopenia than in patients without thrombocytopenia. The multivariate analysis was performed based on an eGFR of <30 mL/min/1.73 $m^2$, which is an indicator of severe decline in renal function in chronic kidney disease. However, eGFR was excluded as a risk factor for TZD-induced thrombocytopenia in the multivariate analysis.

According to a study, TZD is primarily eliminated through a non-renal route.[15] TZD is metabolized in the liver to sulfate conjugates, which are excreted in the bile, and approximately 80% of the administered dose is eliminated in feces.[15] Thus, these results suggest that impaired renal function is not directly related to TZD-induced thrombocytopenia, and is consistent with a previous report that demonstarated that the pharmacokinetics of TZD are similar in subjects with severe renal impairment and controls.[16]

Although no significant differences were observed in the current study, multivariate analysis showed a relatively smaller P value（P=0.191）for AST -a marker of liver injury. Notably, thrombopoietin, a physiologically relevant regulator of platelet production, is primarily produced in the liver parenchymal cells, with smaller amounts being made in the kidney and bone marrow.[17,18] In addition to thrombopoietin, serum albumin is also synthesized in the liver parenchymal cells.[19] Thus, it can be inferred from the above explanation that reduced hepatic function may be partly related to TZD-induced thrombocytopenia. Further studies are required to clarify the relationship between hepatic damage and thrombocytopenia.

## 5. Conclusion

Thrombocytopenia is a common adverse effect of TZD, and hypoalbuminemia is a significant risk factor for TZD-induced thrombocytopenia. Therefore, platelet counts and serum albumin levels in patients who received TZD therapy should be closely monitored.

## 6. Competing Interests

There are no conflicts of interest to declare.

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