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RESEARCH

Assessment of linezolid-induced thrombocytopenia in older patients: reflections from a palliative care unit

Yaşlı hastalarda linezolide bağlı trombositopeninin incelenmesi: bir palyatif bakım ünitesinden yansımalar

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Abstract

Purpose: Linezolid (LZD) is an antibiotic which is effective against resistant gram-positive bacteria. The aim of this study was to investigate the characteristics and risk factors of linezolid-induced thrombocytopenia (LIT).

Materials and Methods: This monocentric and retrospective study comprised 93 older patients treated with LZD for a minimum of seven days in a palliative care unit. Thrombocytopenia was defined as a decrease in platelet count below 150x103/mm3 or a ≥ 50% decrease. Complete blood count (CBC) and biochemical analyses were performed on the first, third, seventh, last day of treatment and after treatment.

Results: The mean age of the patients was 73.7 years (±7.9 years). Thrombocytopenia was observed in 48 patients. The mean age, median duration of hospitalisation and LZD treatment were higher, and baseline serum albumin concentration and calcium level were lower in patients with LIT. In the groups aged ≥75 years, with albumin levels <25 g/L and platelet counts <200x103/mm, LIT was more frequent. Repeated measures ANOVA analysis was conducted, which revealed a significant interaction effect between platelet counts and the duration of exposure. Multivariate logistic regression analysis identified female gender, age ≥75 years, LZD treatment duration >14 days, serum baseline albumin <25g/L and platelet count <200x103/mm3 as risk factors for LIT.

Conclusion: Older patients receiving LZD treatment in a palliative care unit with risk factors should be closely monitored hematological. CBC should be performed once in the first week, and 14th day of treatment to prevent thrombocytopenic complications.

Keywords:. Linezolid, thrombocytopenia, older adults, palliative care

Öz

Amaç: Linezolid (LZD) dirençli gram-pozitif bakterilere karşı etkili bir antibiyotiktir. Bu çalışmada linezolide bağlı trombositopeninin (LIT) özelliklerini ve risk faktörlerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu tek merkezli ve retrospektif çalışmaya bir palyatif bakım ünitesinde en az 7 gün süreyle LZD ile tedavi edilen 93 yaşlı hasta dahil edildi. Trombositopeni, trombosit sayısının 150x103/mm3'ün altına düşmesi veya ≥ %50 azalması olarak tanımlandı. Tam kan sayımı (CBC) ve biyokimyasal analizler tedavinin ilk, 3., 7., son gününde ve tedavi sonrasında yapıldı.

Bulgular: Hastaların yaş ortalaması 73.7±7.9 yıl idi. Trombositopeni 48 hastada görüldü. LIT olan hastaların ortalama yaşı, ortalama hastanede yatış süresi ve LZD tedavisi daha yüksek, bazal serum albümin konsantrasyonu ve kalsiyum düzeyi daha düşüktü. LIT, yaşı ≥ 75 olan, bazal albümin düzeyi <25 g/L ve bazal trombosit sayısı <200x103/mm olan gruplarda anlamlı olarak daha sık görülmüştür. Tekrarlanan ölçümler ANOVA analizi, trombosit sayıları ve maruziyet süresi arasında anlamlı bir etkileşim etkisi olduğunu göstermiştir. Çok değişkenli lojistik regresyon analizine göre, kadın cinsiyet, yaş ≥75, LZD tedavi süresi >14 gün, serum bazal albümin <25g/L ve trombosit sayısı <200x103/mm3 LIT için risk faktörleri olarak belirlenmiştir.

Sonuç: Palyatif bakım ünitesinde LZD tedavisi alan ve risk faktörleri olan yaşlı hastalar hematolojik açıdan yakından izlenmelidir. Trombositopenik komplikasyonları önlemek için CBC tedavinin ilk haftasında bir kez ve 14. gününde yapılmalıdır.

Anahtar kelimeler: Linezolid, trombositopeni, yaşlı yetişkinler, palyatif bakım

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INTRODUCTION

Linezolid (LZD) represents the first antibiotic to be approved as a member of the oxazolidinone class, which is characterised by its ability to impede the initial stage of protein synthesis in bacterial cells. LZD is indicated for the treatment of vancomycin-resistant enterococcal (VRE) infection, nosocomial pneumonia, uncomplicated and complicated skin and skin-structure infections, and community-acquired pneumonia[1]. Furthermore, LZD is a highly efficacious second-line pharmaceutical agent employed in the management of multidrug-resistant tuberculosis.

Common side effects of LZD include gastrointestinal symptoms such as nausea and diarrhoea, myelosuppression, and neuropathy[2,3]. Moreover, rare side effects include hepatotoxicity, hypoglycaemia, and inappropriate antidiuretic hormone secretion syndrome[4, 5]. Furthermore, LZD has been identified as a risk factor for hospital-acquired thrombocytopenia[6]. The administration of drugs, including antimicrobial agents, has been demonstrated to induce haematological adverse effects by exerting an impact on the direct bone marrow or other organs. LZD is a well-recognised and defined antibiotic with haematological adverse effects, including anaemia, thrombocytopenia, and leukopenia.

Thrombocytopenia is a prevalent haematological disorder that has been observed to affect patients during their hospitalisation, resulting in diagnostic uncertainty among clinicians and the potential for fatal bleeding complications. It is imperative that a comprehensive review of all medications in the current treatment process is conducted, given the potential for drug-induced thrombocytopenia. Further investigation is necessary to accurately diagnose hematological diseases, and consultation with a hematologist is essential to ensure optimal patient care. In view of the fact that LZD is an effective treatment for the aforementioned resistant bacteria, and given the concomitant occurrence of thrombocytopenia, clinicians are obliged to exercise caution when administering the drug.

One such mechanism of LIT is based on studies which have observed an increase in megakaryocytes in the bone marrow or the presence of antiplatelet antibodies associated with the administration of a given drug. This condition is characterised by a rapid onset of platelet decline that occurs approximately three to seven days after the initiation of linezolid therapy[7]. A study conducted by Hanai et al. demonstrated that thrombocytopenia was identified at a higher frequency than anaemia (48.4% vs. 10.4%) during LZD treatment[8]. Moreover, a review of clinical trials demonstrated that LZD treatment exceeding two weeks was associated with an elevated risk of anemia and thrombocytopenia, but not neutropenia[9]. The prevalence of thrombocytopenia in adults treated with intravenous or oral linezolid varies considerably, with incidence rates ranging from 16.7% to 48.4%[10,11]. The determination of this condition is contingent upon the definition of thrombocytopenia employed.

In particular, the occurrence of drug-induced thrombocytopenia has been associated with an elevated mortality rate in certain studies of hospitalised patients[12]. As the human organism undergoes the process of ageing, there is a significant impact on the life cycle and function of platelets, which are vital components of the coagulation process, more commonly referred to as hemostasis. As megakaryocytes undergo changes in the altered bone marrow environment, platelet production is consequently affected. Therefore, older individuals are more vulnerable to factors affecting platelet counts. In instances where there is a high risk of clinically significant bleeding and/or a platelet count below 10,000/microL, the administration of platelet transfusions is recommended[13].

This study may contribute to the preparation and awareness of clinicians regarding potential risks associated with LIT. The aforementioned factor may also assist in distinguishing between elderly patients who require close monitoring and those who do not. A comprehensive understanding of these risk factors for LIT is imperative to enhance clinical outcomes and to establish guidelines for the safe utilisation of LZD.

MATERIALS AND METHODS

Sample

The present retrospective study was conducted in the palliative care unit of a university hospital and included 93 patients aged ≥65 years who had received a minimum of seven days of intravenous LZD 2X600 mg/day treatment between June 2017 and November 2022. Prior to the commencement of the study, a total of 627 patients' records were thoroughly reviewed, resulting in the exclusion of 534 patients

based on the evaluation of their clinical information. Exclusion criteria included individuals with haematological diseases (e.g. lymphoma, multiple myeloma, leukaemia, myeloproliferative disease), rheumatological disorders that may result in a decrease in platelet count (e.g. systemic lupus erythematosus [SLE]), myelosuppression, end-stage malignancy, sepsis, acute renal failure and chronic liver disease and under 65 years. Patients with malignancy and bone marrow metastasis, those who had received chemotherapy within the last three months, patients taking bone marrow suppressant drugs, platelet count below 100x103/mm3 and those with megaloblastic anaemia (caused by B12 or folate deficiency) were excluded from the study. Patients who had received any drugs with the potential to cause thrombocytopenia were excluded from the study. Examples of such drugs include amiodarone, acetylsalicylic acid, clopidogrel, digoxin, fluconazole, haloperidol, piperacillin, rifampin, trimethoprim-sulfamethoxazole, valproic acid and vancomycin. Acute kidney injury (AKI) was defined in accordance with the 2012 KDIGO (Kidney Disease Improving Global Outcomes) AKI Guideline, which is based on the repeating creatinine tests in clinical follow-up of the patients. A peripheral blood smear examination was conducted on patients diagnosed with thrombocytopenia.

Data collection

The retrospective blood analysis records of patients were obtained from five distinct time points, which were utilised in the present study. The initial record was obtained from the first day of LZD treatment. The second, third and fourth days were obtained from the third, seventh and last day of the LZD treatment, consequently (median [interquartile range] = 14th [11th] day). The fifth one was obtained from the median (interquartile range) 16th (8) day after LZD treatment. A comprehensive haematological profile was conducted, encompassing the complete blood count, as well as the assessment of haemoglobin, platelet count, C-reactive protein, creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, and uric acid levels. These parameters were meticulously documented on the first, third, seventh, and final day of LZD treatment. The estimated Glomerular Filtration Rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation, as updated in 2021. It is important to note that the values in question were only recorded if they could be accessed a minimum of 10 days after the last day of treatment. In addition, the albumin, phosphorus, calcium, and lactate dehydrogenase values at the commencement of treatment, as well as on the third and seventh days of treatment, were meticulously documented. Alanine aminotransferase and aspartate aminotransferase baseline values were also recorded. The presence of comorbidities and polypharmacy was determined by searching the national health record system, in which all health records for a minimum of eight years were kept. Polypharmacy was defined as the concurrent use of five or more medications. The duration of LZD treatment, the duration of treatment initiation after hospitalisation, the duration of thrombocytopenia resolution after the end of treatment, and the indication for LZD were retrieved from hospital information system data.

Definition of thrombocytopenia and resolution of thrombocytopenia

Each peripheral blood smear was referred to a haematologist for further investigation to exclude pseudothrombocytopenia. Numerous criteria have been used in different studies to define thrombocytopenia. Commonly, a 25-50% decrease in platelet count from baseline and/or a decrease in platelet count between 100x103/mm3-150x103/mm3 have been defined as the presence of thrombocytopenia. Two criteria were accepted for the definition of thrombocytopenia; criterion 1 was a platelet count <150 x 103/mm3 and criterion 2 was a 50% or greater decrease in platelet count during LZD treatment compared to baseline. The presence of either criterion was considered thrombocytopenia. Resolution of thrombocytopenia was defined as a platelet count above 150 x 103/mm3 for patients with thrombocytopenia according to criterion 1 and at least 50% above baseline for patients with thrombocytopenia according to criterion 2.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of the data. Independent samples t-test and Mann-Whitney U-test were used to compare two groups of independent variables. Chi-square test was used to assess the relationship between categorical variables. Repeated measures ANOVA analysis was used to analyse changes in platelet counts over time. Potential confounders of platelet count (age, sex, number of comorbidities,

polypharmacy, concomitant heparin use, chronic kidney disease, diabetes, hypertension, malignancy, etc.) were analysed, and confounders with VIF (variance inflation factor) > 5 were excluded from multivariate regression analysis because of the problem of collinearity.

G-Power software was used to calculate sample size. An a priori power analysis was performed using G*Power version 3.1.9.4 to determine the minimum sample size required to test the study hypothesis. The results showed that the sample size required to achieve 80% power to detect an effect size of 0.25 at the $\alpha = 0.05$ significance criterion was 78 for repeated measures ANOVA. Therefore, the resulting sample size of 93 is sufficient to test the study hypothesis. Missing data, statistically randomly distributed, were added to the dataset using the method of series averages. SPSS for Windows version 22.0 was used for statistical analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 73.7 years (±7.9) and 40.9% were aged 75 years and over. Of the patients, 44.1% were female and 51.6% had LIT. The median (interquartile range [IQR]) duration of LZD treatment was 14 (11) days, and the duration of hospitalisation was 32 (25) days. These variables were found to be higher in patients with LIT (p=0.004 and p<0.001, respectively). The median (IQR) time to resolution of thrombocytopenia was 16.5 (28) days, and thrombocytopenia did not resolve in two patients. As demonstrated in Table 1, no statistically significant differences were identified between the two groups with respect to gender, the number of comorbidities, and the frequency of patients with diabetes, hypertension, malignancy, concomitant heparin use, GFR<50ml/min, and polypharmacy. Furthermore, a higher mean age was observed in patients with LIT (p=0.036). Patients aged ≥75 years, with an albumin concentration <25g/L and a platelet count <200x103/mm3 were more likely to develop LIT (p=0.007) (Table 1).

Table 1. Comparison of categorical variables between patients with and without thrombocytopenia.

Variables n (%)	**Patients without Thrombocytopenia (n=45)**	**Patients with Thrombocytopenia (n=48)**	***p***
Gender			
Female	16 (35.6%)	25 (52.1%)	0.109
Male	29 (64.4%)	23 (47.9%)	
Age groups			
65-74 years	33 (73.3%)	22 (45.8%)	**0.007***
≥ 75 years	12 (26.7%)	26 (54.2%)	
Infection Location			
Skin and soft tissue infection	16 (35.6%)	16 (33.3%)	0.831
Pneumonia	5 (11.1%)	9 (18.8%)	0.389
Osteomyelitis	6 (13.3%)	6 (12.5%)	0.905
Urinary Infection	4 (8.9%)	3 (6.3%)	0.630
Bacteriemia	10 (22.2%)	8 (16.7%)	0.498
Comorbidities			
Hypertension	30 (66.7%)	34 (70.8%)	0.823
Diabetes mellitus	24(53.3%)	22 (45.8%)	0.536
Malignancy	7 (15.6%)	11 (22.9%)	0.437
Renal impairment (GFR< 50 ml/min)	15 (33.3%)	20 (41.7%)	0.407
Concomitant use of heparin	27 (60%)	31 (64.6%)	0.648
Serum albumin concentration < 25 g/L	2 (4.4%)	16 (34%)	**< 0.001***
Baseline Platelet < 200x10^{3}mm^3	2 (4.4%)	12 (25%)	**0.006***
Duration of LZD therapy			
7-14 days	27 (60%)	17 (35.4%)	**0.018***
>14 days	18 (40%)	31 (64.6%)	
Polypharmacy	34 (75.6%)	40 (83.3%)	0.353

*p<0.05 Chi-square test used for analysis of categorical variables. LZD, Linezolid; GFR, Glomerular Filtration Rate

The mean baseline haemoglobin level was lower in patients with LIT (p=0.037). A subsequent analysis of patients with different sites of infection (soft and hard tissue, pneumonia, osteomyelitis, urinary tract and bacteraemia) showed no significant difference between groups in the development of LIT. Biochemical analysis revealed that baseline albumin and calcium levels were lower in patients with LIT, whereas baseline sodium, potassium, magnesium and phosphorus levels did not differ significantly between the two groups (Table 2).

Table 2. Comparison of continuous variables between patients with and without thrombocytopenia

Variables	**Patients without thrombocytopenia (n=45)**	**Patients with thrombocytopenia (n=48)**	***p***
	Mean±SD	Mean±SD	
Age	71.9±7,5	75.3±8	0.036*
Number of comorbidities	4.38±2.37	4.88±2.2	0.297
Glomerular Filtration Rate (GFR) (ml/min)	70.1±34	59.6±34	0.138
CRP (mg/L)	126.7±71.2	135.2±109.2	0.657
Baseline Albumin(g/dl)	30.9±5.3	27.1±5.3	0.001*
Baseline Hemoglobin(gr/dl)	10.7±1.73	10±1.63	0.037*
Baseline Sodium (mmol/L)	135.3±5.1	135.8±4.3	
Baseline Potassium (mmol/L)	4.26±0.66	4.26±0.65	0.974
Baseline Calcium (mg/dl)	8.83±0.65	8.46±0.76	0.014*
	Median (IQR)	Median (IQR)	
Baseline Platelet Count x (10^3 /mm^3)	326 (113)	292 (234)	0.262
Duration of Hospitalization (days)	27 (22)	36 (27)	<0.001*
Duration of Linezolid therapy (days)	12 (9)	15 (12)	0.004*
Initial day of applying LZD from hospitalization	7 (13)	9 (17)	0.416
Baseline Phosphor (mg/dl)	3.1 (1.45)	3.25 (1.48)	0.785
Baseline Creatinine(mg/dl)	0.99 (0.29-6.13)	1.33 (0.25-7.69)	0.222
Baseline uric acid (mg/dl)	5.20(0.84)	5.7(1.29)	0.200
Post-treatment control time (days)	18(16.5)	15(5)	0.131

*p< 0.005. LZD, Linezolid. Chi-square analysis for categorical data, Student t test for normal distributed data and Mann Whitney U test fornon-normal distributed data. IQR: Interquartile range

A repeated measures ANOVA analysis revealed a significant interaction effect (partial eta squared: 0.285) between platelet counts measured at five different time points and period ($p < 0.001$) (Figure 1). A subsequent investigation into platelet counts, measured at five distinct time points, revealed that the mean platelet count at time point 4 was significantly lower than the mean of time points 1, 2, 3, and 5 ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively) (Figure 1). Figure 1 shows the change in platelet count over time during LZD treatment. In patients receiving LZD, platelet counts start to desrease on the 7th day of treatment and recover after treatment is discounted.

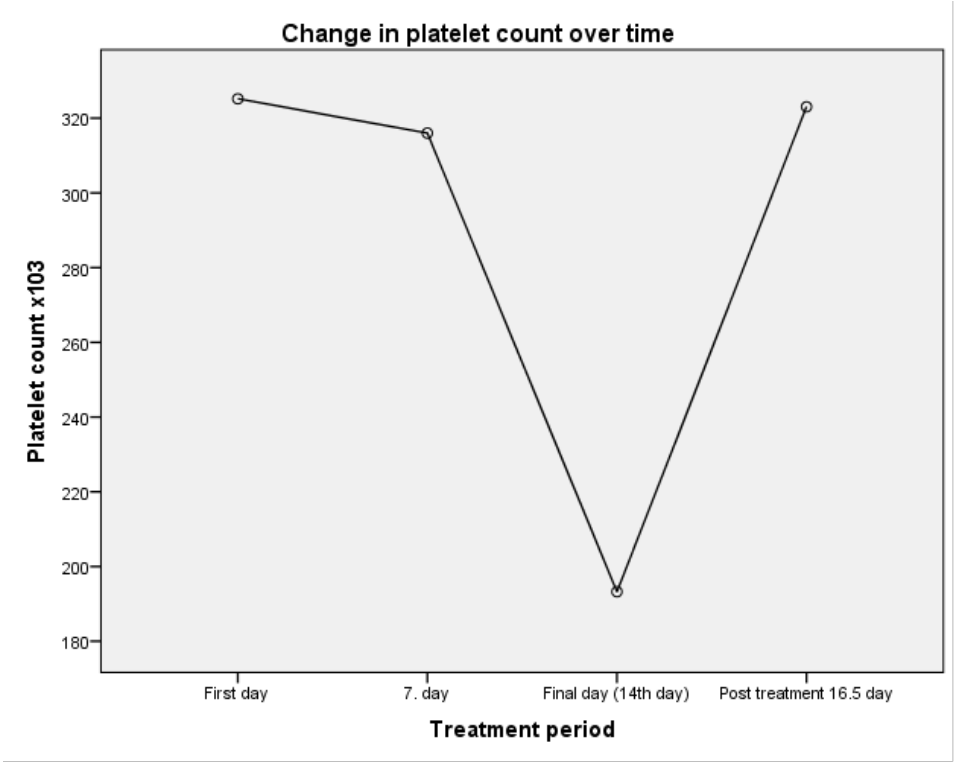

Figure 1. Change in platelet count over time

Confounders with a VIF greater than 5 were included in the multivariate regression analysis. The regression model incorporated a range of variables, including age, sex, the duration of LZD treatment, the use of heparin, baseline GFR, haemoglobin, albumin and platelet levels. Multivariate logistic regression analysis revealed that female sex, age 75 years and over, LZD treatment lasting more than 14 days, baseline serum albumin concentration less than 25 g/L, and platelet count less than 200 x $10^3/mm^3$ were all risk factors for the development of LIT ($p = 0.000$). The results of the statistical analysis are presented in Table 3.

Table 3. Multivariate logistic regression analysis results of the independent variables for LIT

	Linezolid Induced Thrombocytopenia	
Variable	**OR [95% CI]**	**P value**
Female gender	3.290 [1.106-9.785]	0.032*
≥75 years of age	3.440[1.114-10.322]	0.028*
>14 days of LZD therapy	5.164 [1.638-16.278]	0.005*
Baseline Albumin < 25 g/L	12.186 [2.188-67.853]	0.004*
Baseline platelet < 200x 103/mm3	18.041 [2.570-126.665]	0.004*

*p < 0.05 according to multivariate binary logistic regression analysis.
CI, confidence interval; OR, odds ratio; LZD, Linezolid; LIT, Linezolid Induced Thrombocytopenia

The odds ratio (OR) for the specified variables were determined to be 3.290 (95% confidence interval [CI]: 1.106–9.785), p = 0.028; 3.440 (95% CI: 1.114–10.322), p = 0.005; 5.164 (95% CI: 1.638–16.278), p = 0.004; 12.186 (95% CI: 2.188–67.853), p = 0.004; and 18.041 (95% CI: 2.570–126.665), p = 0.004, respectively. Receiver operating characteristic (ROC) curve analysis demonstrated that at the optimal cut-off value of 29.5 g/L for albumin, 73.5 years for age and 13.5 days for duration of LZD treatment, the area under the curve (AUC), cut-off points, sensitivity and specificity values are presented in Table 4.

The lowest platelet count observed during LZD treatment was 33x103/mm3, and no patients experienced a major bleeding event. A total of five patients required platelet transfusions, with one patient receiving one unit, two patients receiving two units, and two patients receiving three units.

Table 4. Area under the ROC curve, confidence interval, cut-off point, sensitivity, specificity values of the age, duration of LZD therapy, albumin level and platelet count

Risk Factor	AUC	Cut-off Value	95 % Confidence Interval	Sensitivity	Specificity	p
Age	0.643	73.5 years	0.528-0.758	61.7	73.30	**0.018***
Duration of LZD treatment	0.663	13.50 days	0.552-0.775	64.60	60.00	**0.007***
Albumin	0.677	29.50 g/L	0.568-0.785	61.7	60.00	**0.004***

*p < 0.05 AUC; Area under curve.

DISCUSSION

The present study set out to investigate the characteristics and risk factors for LIT. The investigation revealed that female gender, age ≥75 years, LZD treatment for ≥ 14 days, baseline albumin concentration lower than 25g/L, and baseline platelet count < 200x103/mm3 were found to be risk factors for LIT. In addition, a cut-off value of 73.5 years was identified for age, 29.5 mg/L for albumin, and 13.5 days for LZD treatment duration. The incidence of LIT varies across studies due to the utilisation of divergent definitions based on disparate criteria. The criteria employed for the definition of thrombocytopenia in the present study were also utilised in a recent study. The present study comprised 60 patients treated in the intensive care unit, with a mean age of 69.8 ± 11.9 years and a mean LZD treatment duration of 11.5 ± 5 days. A comparable incidence of LIT (48.3%) to that observed in this study was reported, however, a prolonged LZD treatment duration was not documented in patients with LIT in comparison to those without LIT[14]. Furthermore, Han X et al. also demonstrated that the incidence of LIT was 22.8% (defined as a platelet count decrease below 100x103/mm3) and 42.5% (defined as ≥ 25% decrease in platelet count from baseline). The present study comprised patients over the age of 18, with a mean age of 69.67 ± 16.39 years[15]. The study by Rabon et al. defined thrombocytopenia as a decrease in platelet count below 150x103/mm3 or 75% below the lower limit of normal value (112.5x 103/mm3) or a decrease in platelet count of ≥50% from the baseline value, and reported the incidence of LIT as 35.8%[16]. A study conducted in Japan revealed that thrombocytopenia was observed in 48.8% of patients with a mean age of 64.6 ± 14.5 years.

In the present study, the incidence of LIT was 51.6%, and patients received LZD treatment for a median (interquartile range [IQR]) duration of 14 (11) days. The extant literature addressing risk factors for LIT in the older adult population is, however, limited in scope. A retrospective cohort study involving older adults over 65 years of age demonstrated a greater decrease in platelet count in patients with renal impairment treated with LZD, but no risk factor for LIT was demonstrated[17]. Bi et al. conducted a study involving patients aged between 60 and 96 years, with a mean age of 81.4 years. The study demonstrated that baseline platelet count of less than 200 x 10^3 /mm^3 was a risk factor for LIT[18].

In contrast to the findings of this study, gender has not been identified as a risk factor for LIT in previous research[8,15,19]. The present study identified female gender as a risk factor for LIT. The observed result may be attributable to a number of factors. Firstly,

although the therapeutic dose range of LZD is wide, LZD clearance is affected by creatinine clearance[20]. Secondly, weight-adjusted renal clearance and non-renal clearance of LZD were 20% and 37% lower in women, respectively[21]. It was hypothesised that the female gender could be a risk factor for the development of LIT. This was due to the higher toxic effect of LZD resulting from gender-related differences in LZD clearance.

The association of long-term LZD treatment with an elevated risk of thrombocytopenia has been substantiated in numerous studies. As reported by Han et al., LZD treatment duration exceeding seven days was identified as a risk factor for thrombocytopenia. Similarly, Thirot et al. reported that a duration exceeding ten days and Takashi et al. reported a duration of at least fourteen days were associated with an increased risk of LIT[15,19,22]. Furthermore, Attassi et al. indicated that thrombocytopenia was observed in six of 19 patients treated with LZD for a period exceeding 10 days[23]. In the present study, it was found that a duration of LZD treatment of ≥ 14 days was an independent risk factor for LIT. Furthermore, the cut-off value of LZD treatment duration for the onset of thrombocytopenia was determined to be 13.5 days. Whilst Chen et al. determined the cut-off value for the duration of LZD treatment to be 10 days using the Youden index, we ascertained the cut-off value through the determination of optimal sensitivity and specificity values[24].

Aging has been demonstrated to be associated with progressive reductions in the functional reserve of several organs. These reductions have the potential to affect drug metabolism and pharmacokinetics. Furthermore, as individuals age, there is a possibility of substantial alterations in body composition, which may result in alterations in volume of distribution[25]. A number of studies have demonstrated an association between advanced age and LIT2,[15,24]. As Natsumoto et al. reported, older age was identified as a risk factor for LIT in patients over 20 years of age with a mean age of 64 years[26]. In the present study, it was determined that ≥75 years of age was a risk factor for LIT in older patients, with the cut-off value for the development of LIT being 73.5 years.

Linezolid demonstrates poor binding to serum albumin (31%)[27], suggesting that the relationship between albumin concentration and LIT would be limited. Although a number of studies[14,15,19,28] have presented findings that appear to support this expectation, a few studies[8,24,29] have demonstrated an association between low albumin concentration and LIT. Furthermore, Hanai et al. demonstrated that lower total protein value was a risk factor for early-onset LIT[8]. A single study was identified that reported low serum albumin concentration as a risk factor for LIT[24]. In this study, the cut-off value (determined by the Youden index) of serum albumin concentration for LIT was determined as 33.5 g/L, and it was reported that LIT rarely developed in patients who received human albumin. A cut-off value of 29.5 g/L was determined for the development of LIT. Furthermore, the present study found that LIT was significantly more prevalent in patients with serum albumin concentration <25 g/L, indicating that these patients were at risk for LIT. The hypothesis that lower calcium levels occurred due to lower albumin levels was investigated. It is recommended that serum albumin concentration be closely monitored. It is evident that further research is necessary to elucidate the mechanism by which low albumin levels augment the risk of LIT. Moreover, further research is necessary to ascertain the impact of albumin replacement on the development of LIT in older patients receiving LZD. The level of creatinine in the body is directly related to the muscle mass and age of the individual. Consequently, individuals afflicted with malnutrition and sarcopenia characteristically exhibit reduced creatinine levels relative to standard deviations. Moreover, it has been demonstrated that low albumin levels are associated with sarcopenia and malnutrition. The absence of a substantial discrepancy in creatinine levels between thrombocytopenic and non-thrombocytopenic patients may be attributed to the observation that thrombocytopenic patients were considerably older. In the present study, the GFR was assessed instead of creatinine levels to ensure that muscle mass did not influence the results. Despite the finding that GFR was lower in the non-thrombocytopenic group than in the thrombocytopenic group, this difference was not statistically significant.

A notable finding of the present study was that a platelet count of < 200x103/mm3 was predictive of LIT. The present study findings were consistent with those of previous studies[11,18,29,30], which determined a baseline platelet count value of < 200x103/mm3 as a risk factor for LIT.

The lowest mean platelet count was measured on the fourth measurement [median 14(11) days]. Furthermore, the time to resolution of

thrombocytopenia was found to be higher in the present study [16 (28) days] in comparison to the studies conducted by Rabon et al. [5 (2-9) days] and Takahashi et al. [12.3±7.8 days] [7]. In the present study, the resolution time was evaluated as the time between the withdrawal of LZD and the day of resolution of thrombocytopenia, in accordance with the approach of Takahashi et al. By contrast, Rabon et al. evaluated it as the time between the onset of thrombocytopenia and the day of resolution. In light of the findings, it is recommended that older adults be closely monitored for a period of at least two weeks following LZD treatment.

The underlying cause of thrombocytopenia remains challenging to ascertain, particularly when distinguishing between drug-induced thrombocytopenia and immune thrombocytopenic purpura (ITP)[12]. In light of the rapid onset of severe thrombocytopenia in drug-induced thrombocytopenia, the risk of severe bleeding, including intracranial haemorrhage, may be elevated in comparison to that observed in immune thrombocytopenia. In instances where there is a high risk of clinically significant bleeding and/or a platelet count below 10,000/microL, the administration of platelet transfusions is recommended[13]. In certain settings, such as fever, infection, GP IIb/IIIa or other antithrombotic agent, platelet transfusions should be considered at higher thresholds. In instances where platelet transfusions prove ineffective in stopping bleeding, the administration of IVIG may be considered as a therapeutic alternative[31]. In the present study, no instances of severe bleeding were observed; however, five patients did require platelet transfusions. The retrospective nature of the study constituted the primary limitation, while the second limitation was the unavailability of post-treatment measurement records for a proportion of patients. It is evident that the study results are not applicable to all older patients who have been hospitalised in the palliative care unit, owing to the high number of exclusion criteria. Notwithstanding the limitations of the study, it is notable that it possesses certain strengths. Firstly, all patients included in the study were aged ≥ 65 years. Secondly, potential causes of thrombocytopenia such as drugs and diseases were excluded. Furthermore, the results of data obtained from a palliative care unit were presented, and cut-off values for age, duration of LZD treatment, and albumin level for the development of LIT were determined.

It was observed that LIT was prevalent among older adults during LZD treatment. The following factors were identified as risk factors for the development of LIT: age ≥75 years, female sex, serum albumin concentration <25 g/L, LZD treatment ≥14 days, and baseline platelet count <200x103/mm3. Furthermore, the study identified cut-off values for age, duration of LZD treatment and albumin levels. In accordance with extant literature, a rapid decline in platelet count is anticipated within 3-7 days following the initiation of linezolid therapy in the event of a LIT. It was concluded that older adults undergoing LZD therapy with risk factors should undergo CBC (complete blood count) at least once in the first week and 14th day of treatment to prevent complications due to thrombocytopenia.

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