

Pretreatment Platelet Count and Neutrophil/Lymphocyte Ratio Are Predictive Markers for Carboplatin Plus Pemetrexed Therapy-induced Thrombocytopenia

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Abstract. *Background/Aim:* This study aimed to identify the predictive markers for carboplatin-induced severe thrombocytopenia. *Patients and Methods:* We conducted a retrospective cohort analysis of inpatients who received carboplatin and pemetrexed. *Results:* Among the 106 eligible patients, the incidence rate of grade ≥ 3 thrombocytopenia was 29.2% (31/106). Multivariate analysis revealed that grade ≥ 3 thrombocytopenia was associated with platelet count $\leq 26.6 \times 10^4/\text{mm}^3$ [odds ratio (OR)=24.70, 95% confidence interval (CI)=5.75-106.00; $p < 0.001$], neutrophil/lymphocyte ratio (NLR) > 2.856 (OR=15.10, 95%CI=2.89-78.60; $p = 0.0013$) and prognostic nutritional index ≤ 42.511 (OR=6.25, 95%CI=1.53-25.60; $p = 0.011$). In particular, patients with both platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$ and NLR > 2.856 presented with significantly higher frequencies of thrombocytopenia compared to those without these two factors [23/34 patients (67.6%) vs. 8/72 patients (11.1%), OR=16.1, 95%CI=5.40-53.6; $p < 0.001$]. *Conclusion:* Platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$ and NLR > 2.856 are predictive markers for carboplatin-induced thrombocytopenia.

Carboplatin, a platinum-based anticancer drug, has long been administered to many lung cancer patients. Thrombocytopenia is a major dose-limiting carboplatin toxicity and is correlated with the area under the concentration curve (AUC). Therefore, its dose is regularly calculated using the following Calvert

formula: Dose (mg)=target AUC (mg \times min/ml) \times [measured glomerular filtration rate (GFR) + 25] (ml/min) (1).

Since measuring GFR is complicated and impractical, creatinine clearance (CrCL) estimated by the Cockcroft–Gault (CG) formula was often substituted for clinically measured GFR. The CG formula was based on serum creatine measured by the kinetic Jaffe method. Meanwhile, serum creatine has been recently measured accurately using the enzymatic peroxidase–antiperoxidase (PAP) or isotope dilution mass spectrometry (IDMS) methods (2, 3). Since using the more accurate method yields overestimated results, the revised CG formula that is adjusted by adding 0.2 mg/dl to the serum creatinine level or estimated GFR was substituted for measured GFR using the Calvert formula (2-4). Meanwhile, another study reported that the desirable value for non-renal clearance of carboplatin using the Calvert formula was 15 ml/min instead of 25 ml/min (5). Although extensive research has recently been done, no consensus has been reached on what formula to apply in clinical practice. In this situation, the Food and Drug Administration and the National Cancer Institute recommended only that values should not exceed 125 ml/min to avoid extreme overdose of carboplatin (6). A recent report mentioned that carboplatin dosing, which is estimated by the capped CG formula in the era of IDMS-creatinine, resulted in 11% of patients being underdosed and 19% overestimated by $> 20\%$ as compared to when applying CG formula according to measured GFR (3). Although the following non-revised Calvert formula based on the CG formula, which used values obtained from a more accurate method of serum creatinine has such problems, new carboplatin-containing regimens using the formula have been increasingly established: Dose (mg)=target AUC (mg \times min/ml) \times (CrCL + 25) (ml/min) (7, 8)

Therefore, using the revised Calvert formula for all patients receiving carboplatin is not desirable as it may lead to more frequent carboplatin underdosing with the new

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regimens. To avoid both unnecessary underdosing and severe thrombocytopenia, predictive markers for carboplatin-induced thrombocytopenia may be useful for identifying patients requiring decreased carboplatin doses. However, predictive markers for carboplatin-induced severe thrombocytopenia have not yet been identified.

Thrombocytopenia induced by carboplatin plus pemetrexed would suffer from the largest influence of carboplatin in frequently used carboplatin-based doublet regimens for lung cancer. Although risk factors for severe neutropenia and hematologic toxicities in these patients have already been reported (9, 10), those specific for thrombocytopenia remain unknown. Therefore, this retrospective study aimed to detect predictive markers for carboplatin-induced severe thrombocytopenia in patients receiving carboplatin plus pemetrexed therapy in the era of enzymatic PAP or IDMS-creatinine.

Patients and Methods

Study design and participants. We performed a retrospective cohort analysis of patients aged 18 years and older who received combination chemotherapy with carboplatin (AUC 6 mg/ml-min) and pemetrexed (500 mg/m²) without molecular-targeted drugs for the first time between January 2010 and March 2020 at Osaka City University Hospital (Osaka, Japan). The carboplatin dose was calculated using Calvert formula and CrCL was based on the CG formula. The AUC of 6 mg/ml-min included AUC of 5.5 to 6.5 mg/ml-min, recalculated by the value just before administration. In our institution, the maximum dose of carboplatin was set to 1,000 mg.

Exclusion criteria included the following: (i) outpatients receiving chemotherapy, (ii) lack of essential laboratory data within 7 days before the initial administration, (iii) loss to follow-up within 21 days after chemotherapy for any reason. This study was approved by the institutional ethics committee, who waived the requirement of informed consent. Participants were also free to opt-out.

Data collection. The following data were collected from the patients' medical records: age, sex, Eastern Cooperative Oncology Group performance status, body weight, body mass index, body surface area (BSA), smoking history, underlying disease, concomitant use of drugs, prior chemotherapy, chemotherapy dose, white blood cell count, differential white blood count, hemoglobin, platelet count, albumin, C-reactive protein (CRP) levels, aspartate transaminase levels, alanine transaminase levels, total bilirubin levels, and serum creatinine levels based on the enzymatic PAP method.

Toxicities. Adverse effects of thrombocytopenia were assessed for 21 days after carboplatin and pemetrexed administration. The severity of toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (11).

AUC estimation. The estimated AUC was calculated using the modified Calvert formula as follows: estimated AUC = Dose/(measured GFR + non-renal clearance) (1). In this study, measured GFR values were substituted with values obtained using the following formulas: GFR: CrCL = (140 - age) × body weight / (72 × serum creatinine) (Note: ×0.85 if female), CrCL_(sCr+0.2) = (140 -

age) × Body Weight / [72 × (serum creatinine + 0.2)] (Note: ×0.85 if female), or estimated GFR = BSA × 194 × serum creatinine^{-1.094} × Age^{-0.287} / 1.73 (Note: ×0.739 if female) (4, 12, 13). Non-renal clearance values of 15 ml/min or 25 ml/min were applied in the estimated AUC.

Assessment of systemic inflammation markers. Modified Glasgow Prognostic Score (GPS) was assigned as follows: (i) GPS 2, both CRP levels >1.0 mg/dl and serum albumin levels <3.5 g/dl; (ii) GPS 1, either CRP levels >1.0 mg/dl or albumin <3.5 g/dl, but not both; and (iii) GPS 0, both CRP levels ≤1.0 mg/dl and serum albumin levels ≥3.5 g/dl. The prognostic nutritional index (PNI) was calculated as 10 × serum albumin levels (g/dl) + 0.005 × peripheral lymphocyte count (per mm³). The NLR was calculated as the ratio of neutrophils to lymphocytes. Platelet/lymphocyte ratio was calculated as the ratio of platelet count to lymphocyte count. Lymphocyte/monocyte ratio (LMR) was calculated as the ratio of lymphocytes to monocytes. CRP/albumin ratio was calculated by dividing the CRP level (mg/dl) by the serum albumin level (g/dl).

Statistical analysis. Fisher's exact tests were used to compare categorical data and the Mann-Whitney *U*-test was used to compare continuous variables. *p*-Values <0.05 were considered statistically significant. To evaluate the putative association between carboplatin-induced thrombocytopenia and clinical characteristics, various estimated AUCs, or systemic inflammation markers, we compared these factors in patients with and without grade ≥3 thrombocytopenia. In cases where toxicity was found to be significantly associated with continuous variables, receiver operating characteristics (ROC) curve analysis was performed to determine its optimal cutoff value. Subsequently, eligible patients were divided into two groups according to the cut-off values. The categorical variables with a *p*-value of <0.05 in the univariate analysis were included in the multivariate logistic regression analysis. The significant factors in multivariate analysis were considered to be independently associated with the outcome. We constructed a scoring system to predict the thrombocytopenia using a simple integer based on each variable's β coefficient. The total predictive score was then generated by summing together the individual scores for each variable.

All statistical analyses were performed with EZR version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (14).

Results

Patient characteristics. A flow chart of participant recruitment is shown in Figure 1. Combination chemotherapy with carboplatin (AUC 6 mg/ml-min) and pemetrexed (500 mg/m²) was administered for the first time to 117 patients between January 2010 and March 2020. Although a capping dose of carboplatin was administered to three patients, the AUC of carboplatin was not below 5.5 mg/ml-min. However, 11 patients met the exclusion criteria, which led to a total of 106 eligible patients.

The incidence of grade 3 or 4 thrombocytopenia during the carboplatin plus pemetrexed therapy was 29.2% (31/106). The

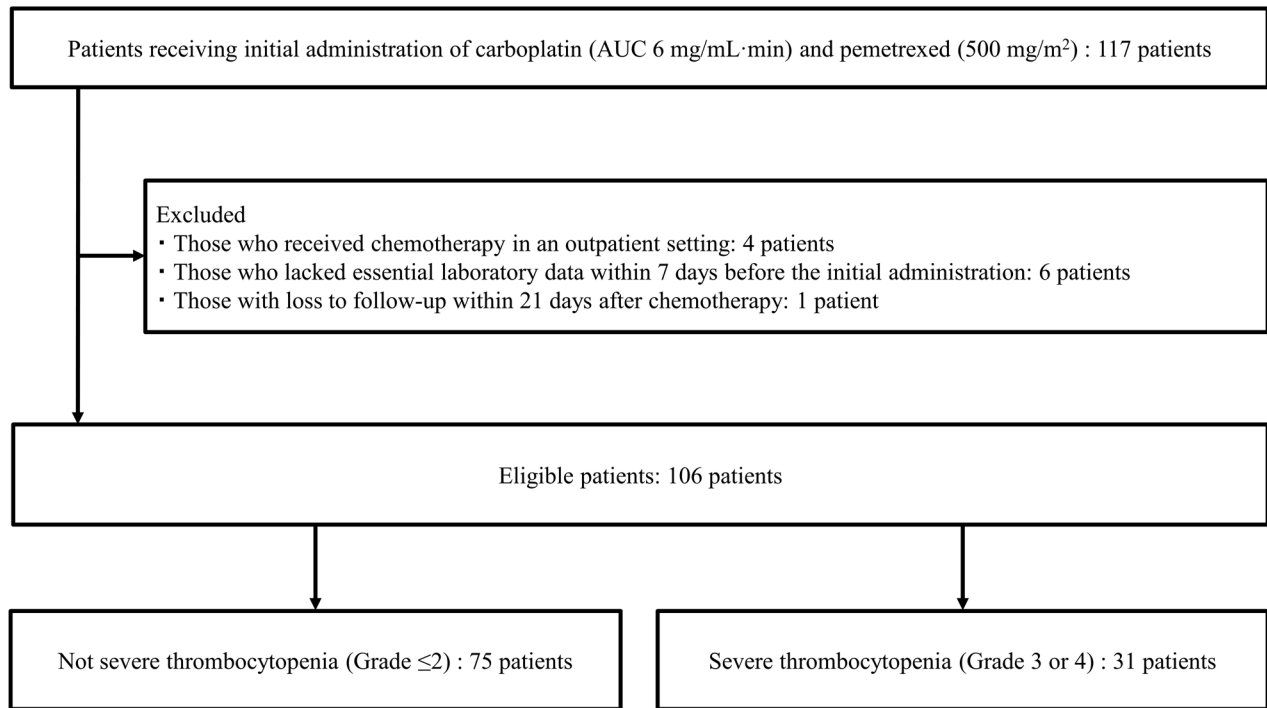


Figure 1. Flow chart of participant recruitment.

associations among the background data of the patients and laboratory values before the combination chemotherapy with carboplatin and pemetrexed are summarized in Table I. The platelet count was significantly lower in the thrombocytopenia group than in the non-thrombocytopenia group ($p<0.001$).

Association between carboplatin-induced thrombocytopenia and estimated AUC or systemic inflammation markers. Table II presents the association between carboplatin-induced thrombocytopenia and various estimated AUC or systemic inflammation markers. Univariate analysis revealed that there were no associations among various estimated AUC values and thrombocytopenia. Among the six systemic inflammation markers, PNI and NLR were significantly associated with thrombocytopenia ($p=0.039$ and $p=0.004$, respectively).

ROC analysis. We used the platelet count, NLR or PNI before combination chemotherapy as the test variables and grade 3 or 4 thrombocytopenia as the state variable. When we used the ROC curve to investigate the cutoff value for the platelet count, NLR, or PNI, we found that the appropriate cutoff values were $26.6 \times 10^4/\text{mm}^3$ (specificity: 51.1%; sensitivity: 82.9%), 2.856 (specificity: 44.4%; sensitivity: 91.4%), and 42.511 (specificity: 74.7%; sensitivity: 54.8%) for platelet count, NLR, and PNI, respectively (Figure 2). The areas under the ROC curves for the platelet count, NLR, and PNI

were 0.725 (95%CI=0.625-0.824), 0.659 (95%CI=0.569-0.749) and 0.628 (95%CI=0.512-0.743), respectively.

Comparison of the incidence of grade 3 or 4 thrombocytopenia between patients with platelet count, NLR or PNI values below and above the cutoff values. Table III presents the incidence of grade 3 or 4 thrombocytopenia in patients with platelet count, NLR, or PNI values below and above the cutoff values. The incidence was significantly higher in patients with platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$ compared to patients with platelet counts $> 26.6 \times 10^4/\text{mm}^3$ [25/55 patients (45.5%) vs. 6/51 patients (11.8%), OR=6.14, 95%CI=2.13-20.6; $p<0.001$]. The incidence of grade 3 or 4 thrombocytopenia was significantly higher in patients with an NLR > 2.856 value compared to patients with an NLR ≤ 2.856 [29/74 patients (39.2%) vs. 2/32 patients (6.3%), OR=9.51, 95%CI=2.13-88.3; $p<0.001$]. Similarly, the incidence of grade 3 or 4 thrombocytopenia was significantly higher in patients with PNI ≤ 42.511 compared to patients with a PNI > 42.511 [16/35 patients (45.7%) vs. 15/71 patients (21.1%), OR=3.11, 95%CI=1.19-8.25; $p=0.012$]. The platelet count, NLR, and PNI values below and above the cutoff values were included in a multivariate model. The multivariate logistic regression analysis revealed that the platelet count $\leq 26.6 \times 10^4/\text{mm}^3$ (OR=24.70, 95%CI=5.75-106.00; $p<0.001$), NLR > 2.856 (OR=15.10, 95%CI=2.89-

Table I. Baseline demographic and clinical characteristics.

Factors	Not severe thrombocytopenia (n=75)	Severe thrombocytopenia (n=31)	p-Value
Age (years), median [IQR]	70.0 [65.5, 73.0]	69.0 [63.5, 73.0]	0.666
Gender			
Male	51 (68.0%)	23 (74.2%)	0.644 ^a
Female	24 (32.0%)	8 (25.8%)	
ECOG PS			
0-1	68 (90.7%)	27 (87.1%)	0.727 ^a
≥2	7 (9.3%)	4 (12.9%)	
Body weight (kg), median [IQR]	57.40 [47.85, 64.60]	54.50 [52.25, 63.30]	0.532
BMI (kg/m ²), median [IQR]	21.64 [19.71, 24.67]	21.32 [20.28, 22.77]	0.981
BSA (m ²), median [IQR]	1.58 [1.45, 1.68]	1.62 [1.53, 1.73]	0.245
Underlying disease			
Non-small cell lung cancer	70 (93.3%)	29 (93.5%)	1 ^a
Malignant mesothelioma	5 (6.7%)	2 (6.5%)	
Smoking history			
Yes	49 (65.3%)	21 (67.7%)	1 ^a
No	26 (34.7%)	10 (32.3%)	
Concomitant use of NSAIDs			
Yes	7 (9.3%)	3 (9.7%)	1 ^a
No	68 (90.7%)	28 (90.3%)	
Prior chemotherapy history			
Untreated	52 (69.3%)	20 (64.5%)	0.556 ^a
EGFR-TKI	10 (13.3%)	3 (9.7%)	
Platinum-based drugs	7 (9.3%)	4 (12.9%)	
ALKI	2 (2.7%)	0 (0.0%)	
Platinum-based drugs and EGFR-TKI	1 (1.3%)	0 (0.0%)	
Other	3 (4.0%)	4 (12.9%)	
Carboplatin dosing (mg/body)			
median [IQR]	587.4 [509.5, 691.2]	546.6 [484.7, 638.7]	0.215
>900 mg	5 (6.7%)	2 (6.5%)	1 ^a
≤900 mg	70 (93.3%)	29 (93.5%)	
Laboratory values before carboplatin and pemetrexed			
White blood cell count (/mm ³), median [IQR]	7,400 [6,500, 9,550]	6800 [5,500, 8,500]	0.116
Hemoglobin (g/dl), median [IQR]	12.70 [11.75, 13.95]	12.70 [11.30, 13.65]	0.459
Platelet count (×10 ⁴ /mm ³), median [IQR]	29.70 [23.05, 35.05]	21.00 [15.20, 26.30]	<0.001
Albumin (g/dl), median [IQR]	3.80 [3.40, 4.10]	3.70 [3.50, 4.10]	0.961
AST (U/l), median [IQR]	19.0 [15.5, 25.0]	19.0 [16.0, 30.0]	0.308
ALT (U/l), median [IQR]	14.0 [11.0, 21.0]	15.0 [11.0, 20.0]	0.947
Total bilirubin (mg/dl), median [IQR]	0.40 [0.30, 0.60]	0.50 [0.40, 0.65]	0.121
CrCL (ml/min), median [IQR]	72.94 [60.46, 91.63]	66.46 [55.86, 82.15]	0.277

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: body mass index; BSA: Body Surface Area; NSAIDs: non-steroidal anti-inflammatory drugs; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor; ALKI: anaplastic lymphoma kinase inhibitors; AST: aspartate transaminase; ALT: alanine transaminase; CrCL: creatinine clearance. ^aFisher's exact test; the rest: Mann-Whitney *U*-test.

78.60; $p=0.0013$) and PNI ≤ 42.511 (OR=6.25, 95%CI=1.53-25.60; $p=0.011$) were significantly associated with grade 3 or 4 thrombocytopenia.

Prediction model for thrombocytopenia. We created a predictive scoring model for thrombocytopenia by rounding up β coefficients values (Table III). The predictive scores of platelet count $\leq 26.6 \times 10^4/\text{mm}^3$, NLR > 2.856 , PNI ≤ 42.511 and others were 4, 3, 2, and 0, respectively. We next constructed an ROC curve evaluating the relationship between predictive scores and grade 3 or 4 thrombocytopenia and found that the appropriate

cutoff value for the predictive score was 7 (specificity: 85.3%; sensitivity: 74.2%) (Figure 3). The incidence of grade 3 or 4 thrombocytopenia was significantly higher in patients with predictive score ≥ 7 compared to patients with a predictive score < 7 [23/34 patients (67.6%) vs. 8/72 patients (11.1%), OR=16.1, 95%CI=5.40-53.6; $p<0.001$] (Table IV).

Discussion

The present study retrospectively evaluated the risk factors for carboplatin-induced thrombocytopenia in patients with thoracic

Table II. Univariate analysis of estimated AUC and systemic inflammation markers for severe thrombocytopenia.

Estimated AUC			
AUC estimation formula	Not severe thrombocytopenia (n=75)	Severe thrombocytopenia (n=31)	p-Value
Dose _{CBDCA} /(CrCL+25), median [IQR]	6.00 [5.96, 6.00]	6.00 [5.92, 6.00]	0.403
Dose _{CBDCA} /(CrCL+15), median [IQR]	6.65 [6.53, 6.84]	6.73 [6.54, 6.83]	0.639
Dose _{CBDCA} /[CrCL _(sCr+0.2) +25], median [IQR]	7.85 [7.36, 8.08]	7.61 [7.39, 7.87]	0.16
Dose _{CBDCA} /[CrCL _(sCr+0.2) +15], median [IQR]	9.04 [8.68, 9.22]	8.82 [8.54, 9.07]	0.136
Dose _{CBDCA} /(eGFR+25), median [IQR]	6.27 [5.84, 6.64]	6.25 [5.95, 6.45]	0.898
Dose _{CBDCA} /(eGFR+15), median [IQR]	7.07 [6.48, 7.40]	7.17 [6.72, 7.39]	0.481
Systemic inflammation markers			
Factors	Not severe thrombocytopenia (n=75)	Severe thrombocytopenia (n=31)	p-Value
Modified GPS			
0	41 (54.7%)	16 (51.6%)	0.714 ^a
1	16 (21.3%)	9 (29.0%)	
2	18 (24.0%)	6 (19.4%)	
PNI, median [IQR]	45.68 [42.48, 48.44]	42.18 [39.96, 46.01]	0.039
NLR, median [IQR]	3.26 [2.43, 4.79]	4.40 [3.38, 5.99]	0.004
PLR, median [IQR]	1.88 [1.36, 2.67]	2.04 [1.41, 2.62]	0.947
LMR, median [IQR]	3.01 [2.15, 3.97]	2.40 [1.89, 3.28]	0.098
CAR, median [IQR]	0.12 [0.02, 0.78]	0.25 [0.02, 1.24]	0.593

CrCL=(140-age) × Body Weight/(72 × serum creatinine) (Note: ×0.85 if female). CrCL_(sCr+0.2)=(140-age) × Body Weight/[72 × (serum creatinine+0.2)] (Note: ×0.85 if female). eGFR=Body surface area × 194 × serum creatinine^{-1.094} × Age^{-0.287}/1.73 (Note: ×0.739 if female). IQR: Interquartile range; AUC: area under the plasma concentration curve; GPS: Glasgow prognostic score; PNI: prognostic nutritional index; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; CAR: CRP/Albumin ratio. ^aFisher's exact test; the rest: Mann-Whitney *U*-test.

malignant tumors undergoing carboplatin plus pemetrexed therapy. We found that platelet count, NLR, and PNI at baseline were associated with carboplatin-induced grade 3 or 4 thrombocytopenia. As platelet count $\leq 26.6 \times 10^4/\text{mm}^3$ and NLR > 2.856 of the three factors were essential for the predictive score ≥ 7 , the final prediction model for thrombocytopenia was enough to meet both two factors. Therefore, patients with both platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$ and NLR > 2.856 frequently presented grade 3 or 4 thrombocytopenia, the combination of the two factors can identify patients who are very likely to present with grade 3 or 4 thrombocytopenia. Notably, these two factors could be estimated conveniently by blood sampling, which is routinely clinically measured.

This study showed that the incidence of grade 3 or 4 thrombocytopenia was 29.2% for all eligible patients. Although our result was slightly lower than previously reported results, which showed that 41.3% of Japanese patients presented with grade 3 or 4 thrombocytopenia (15), as the previous study included up to four cycles, it is reasonable to assume that this study's profile of adverse effects is comparable to the previous study.

Our study showed that CrCL and various estimated AUCs were not significantly associated with grade 3 or 4

thrombocytopenia induced by carboplatin plus pemetrexed. In fact, although a previous study also reported that the average carboplatin dose was significantly higher, the frequency of grade 3 thrombocytopenia was not statistically significantly different between the pre-IDMS and post-IDMS treatment groups (16). Since carboplatin dose > 900 mg was not a risk factor in this study, it might not prevent grade 3 or 4 thrombocytopenia, only to set the capping dose of carboplatin at 900 mg/body under the recommendations of the Food and Drug Administration and the National Cancer Institute. As the difference in the methods used for carboplatin dosing was not enough to have an effect on thrombocytopenia, it was conceivable that there were other risk factors.

We also found that platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$, NLR > 2.856 , and PNI ≤ 42.511 were associated with grade 3 or 4 thrombocytopenia. As the percentage platelet count reduction linearly correlates with the AUC of carboplatin, it is reasonable that patients with platelet counts $\leq 26.6 \times 10^4/\text{mm}^3$ have a higher risk of severe thrombocytopenia than those without (1). On the contrary, it is widely known that NLR and PNI are easily measurable parameters of systemic inflammation, which are related to reduced survival and poor chemotherapy outcome in lung cancer patients (17–19). Additionally, it has been recently reported that reduced drug clearance due to changes in drug

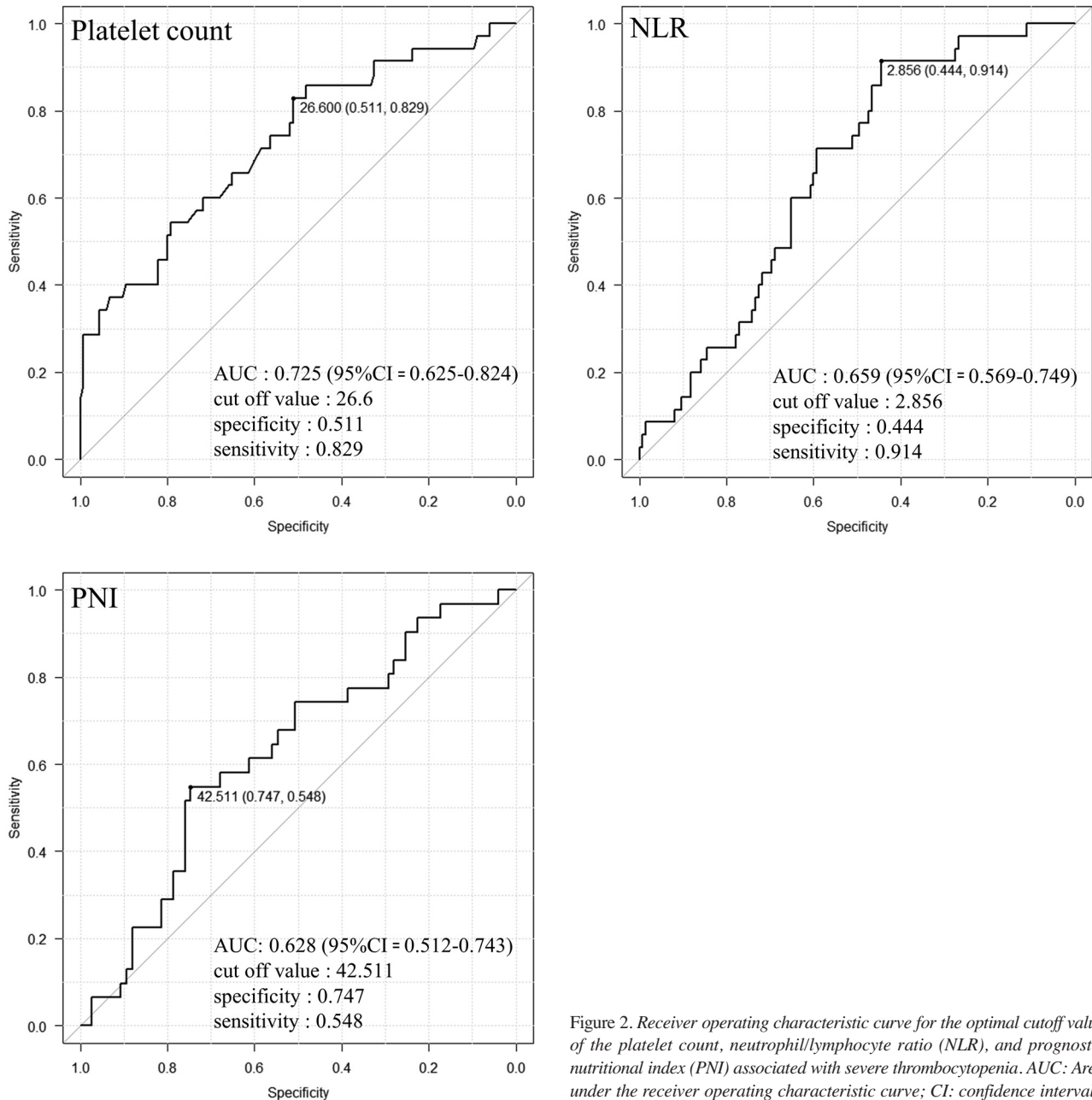


Figure 2. Receiver operating characteristic curve for the optimal cutoff value of the platelet count, neutrophil/lymphocyte ratio (NLR), and prognostic nutritional index (PNI) associated with severe thrombocytopenia. AUC: Area under the receiver operating characteristic curve; CI: confidence interval.

metabolizing enzymes and transporters occurred in patients with systemic inflammation (20–22). In particular, a recent study reported that patients with elevated NLR showed reduced carboplatin clearance and proposed a new formula including NLR (23). Therefore, especially patients with high NLR would receive higher exposure to carboplatin and frequently present with grade 3 or 4 thrombocytopenia.

This study had several limitations. First, as there might be still few hidden confounders and biases due to the retrospective nature of the study wherein it only involves a

single institution and small sample size, validation is necessary for establishing a predictive model for carboplatin-induced thrombocytopenia. Second, as patients who underwent carboplatin plus pemetrexed therapy were examined for carboplatin-induced thrombocytopenia, pemetrexed-induced thrombocytopenia was not ignored. However, as a previous study reported that grade 3 and 4 thrombocytopenia induced by pemetrexed monotherapy was 1.9% (24), the concomitant use of pemetrexed is not likely to affect thrombocytopenia. Third, although dose reduction of carboplatin could avoid the

Table III. Comparison of the incidence of severe thrombocytopenia between patients with below and above the cutoff value of platelet count, NLR and PNI.

Factor	n	Not severe thrombocytopenia	Severe thrombocytopenia	Univariable analysis		Multivariable analysis			Predictive score
				Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	β coefficient	p-Value	
Platelet count $>26.6 \times 10^4/\text{mm}^3$	51	45 (88.2%)	6 (11.8%)	6.14 (2.13-20.6)	<0.001	24.70 (5.75-106.00)	3.2053	<0.001	0
Platelet count $\leq 26.6 \times 10^4/\text{mm}^3$	55	30 (54.5%)	25 (45.5%)						4
NLR ≤ 2.856	32	30 (93.8%)	2 (6.3%)	9.51 (2.13-88.3)	<0.001	15.10 (2.89-78.60)	2.7129	0.0013	0
NLR >2.856	74	45 (60.8%)	29 (39.2%)						3
PNI >42.511	71	56 (78.9%)	15 (21.1%)	3.11 (1.19-8.25)	0.012	6.25 (1.53-25.60)	1.833	0.011	0
PNI ≤ 42.511	35	19 (54.3%)	16 (45.7%)						2

Univariable analysis: Fisher's exact test; Multivariable analysis: multivariable logistic regression analysis. OR: Odds ratio; CI: confidence interval; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index.

Table IV. Univariate analysis of the incidence of severe thrombocytopenia between patients with below and above the cutoff value of predictive score.

Factor	n	Not severe thrombocytopenia	Severe thrombocytopenia	Unadjusted OR (95%CI)	p-Value
Predictive score <7	72	64 (88.9%)	8 (11.1%)	16.1 (5.40-53.6)	<0.001
Predictive score ≥ 7	34	11 (32.4%)	23 (67.6%)		

Fisher's exact test. OR: Odds ratio; CI: confidence interval.

risk of severe thrombocytopenia, at the same time, it might reduce the antitumor effect. As our study could not reveal an optimal carboplatin dose in terms of antitumor effects and adverse effects, further studies are required to obtain a carboplatin dose formula based on NLR and platelet counts.

In conclusion, patients with both a platelet count $\leq 26.6 \times 10^4/\text{mm}^3$ and an NLR >2.856 presented with thrombocytopenia induced by carboplatin plus pemetrexed at a high frequency. Therefore, decreasing the carboplatin dose might need to be considered for these patients. However, further accumulation of data is warranted to establish a predictive model for carboplatin-induced thrombocytopenia.

Conflicts of Interest

Dr. Kaneda reports grants from Eli Lilly. Dr. Kawaguchi reports grants and personal fees from Eli Lilly. All the other Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

MT participated in the design of the study and drafted the manuscript. KT and HK participated in the design of the study and manuscript editing. TK and KN conceived the study, participated in its design and coordination and helped to draft the manuscript. All Authors read and approved the final manuscript.

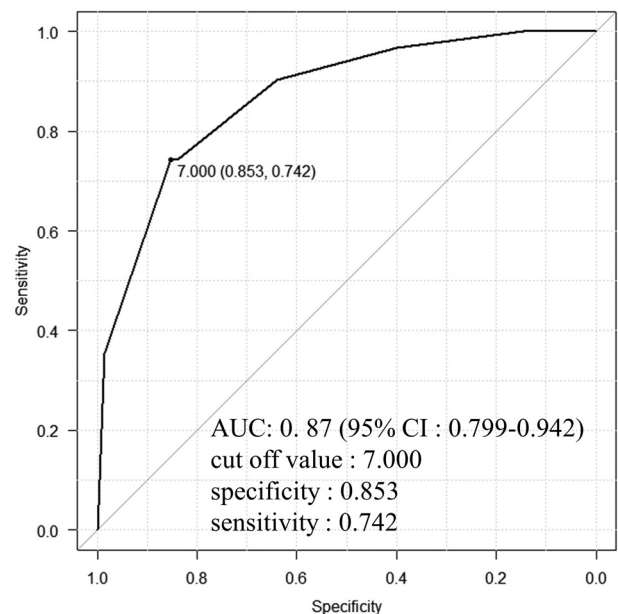


Figure 3. Receiver operating characteristic curve for the optimal cutoff value of the thrombocytopenia predictive score associated with severe thrombocytopenia. AUC: Area under the receiver operating characteristic curve; CI: confidence interval.

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