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Prognostic impact of the mean platelet volume/platelet count ratio in terms of survival in advanced non-small cell lung cancer

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ABSTRACT

Background: Mean platelet volume (MPV) is a platelet volume index. Classically, MPV was recognized as a hallmark of platelet activation. Recent studies have revealed that the MPV and MPV/platelet count (PC) ratio can predict long-term mortality in patients with ischemic cardio-vascular disease. In addition, these indices were correlated with the pathophysiological characteristics of patients with various disorders, including malignant tumors.
Patients and methods: We retrospectively analyzed various hematological indices of patients with advanced non-small cell lung cancer (NSCLC). The aim of this study was to evaluate the contribution of platelet volume indices to survival in these patients.
Results: A total of 268 patients were enrolled in the study. The median age of the patients was 68 years (range: 31–87 years). We compared various hematological indices between the NSCLC group and an age- and sex-matched comparator group. MPV was significantly decreased in the NSCLC group compared to the comparator group. In contrast, the PC was significantly increased in the NSCLC group. Consequently, the MPV/PC ratio was also decreased in the NSCLC group (0.397 vs. 0.501). In receiver operating characteristics (ROC) curve analysis, the MPV/PC ratio was associated with a sensitivity of 62.3% and a specificity of 74.6% at a cutoff value of 0.408730 (area under the curve [AUC], 0.72492)]. Univariate analysis revealed that overall survival (OS) was significantly shorter in the group with a low MPV/PC ratio than in the other group (median survival time [MST]: 10.3 months vs. 14.5 months, log-rank, $P = 0.0245$). Multivariate analysis confirmed that a low MPV/PC ratio was an independent unfavorable predictive factor for OS (hazard ratio [HR]: 1.668, 95% confidence interval [CI]: 1.235–2.271, $P = 0.0008$).
Conclusion: These data clearly demonstrate that the MPV/PC ratio was closely associated with survival in patients with advanced NSCLC.

1. Introduction

Mean platelet volume (MPV) is a platelet volume index [1]. Classically, MPV was recognized as a hallmark of platelet activation. Larger platelets are more reactive than smaller ones as they can more easily release chemical mediators in response to endogenous or exogenous stimuli [2]. Therefore, MPV was considered to be closely correlated with various thromboembolic disorders. Recent studies revealed that the MPV and MPV/platelet count (PC) ratio can predict long-term mortality in patients with ischemic cardio-vascular disease [3,4]. In addition, these indices were also associated with the pathophysiological characteristics of various disorders, including malignant tumors [5–8]. The prognostic impact of PC in patients with non-small cell lung cancer (NSCLC) has been extensively discussed [9–11]. Thrombocytosis was recognized as an unfavorable predictive factor for overall survival (OS). However, there has been no direct analysis of the survival impact of platelet indices in patients with NSCLC. In this study, we retrospectively analyzed patients with advanced NSCLC. The aim of this study was to evaluate the contribution of platelet volume indices to survival in advanced NSCLC patients. In this report, we clearly demonstrated the survival impact of the MPV/PC ratio in patients with advanced NSCLC.

2. Patients and methods

2.1. Data collection

The medical records of all patients with NSCLC who had undergone medical examination and received treatment from January 2002 to December 2012 at Kansai Medical University Takii Hospital

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Table 1
Patient characteristics.

Characteristics	Total patients (n = 268)	MVP/PC ratio ≤ 0.48730 (n = 166)	MVP/PC ratio > 0.408730 (n = 102)	P-value
Age, years				0.1231
Median (range)	68 (31–87)	67 (32–85)	69 (31–87)	
Sex				0.4142
Female	76 (28.4)	50 (30.1)	26 (25.5)	
Male	192 (71.6)	116 (69.9)	76 (74.5)	
ECOG PS				0.7774
0–2	210 (78.4)	131 (78.9)	79 (77.5)	
3 or 4	58 (21.6)	35 (21.1)	23 (22.5)	
Smoking history				0.6054
Never smoked	74 (27.6)	44 (26.5)	30 (29.4)	
Past or current smoker	194 (72.4)	122 (73.5)	72 (70.6)	
Histological diagnosis				0.2380[a]
Squamous cell carcinoma	63 (23.5)	43 (25.9)	20 (19.6)	
Adenocarcinoma	195 (72.8)	116 (69.9)	79 (77.5)	
Others	10 (3.7)	7 (4.2)	3 (2.9)	
Initial clinical stage				0.3496
IIIB	15 (5.6)	11 (6.6)	4 (3.9)	
IV	253 (94.4)	155 (93.4)	98 (96.1)	
Systemic chemotherapy				0.2353
None	41 (15.3)	22 (13.3)	19 (18.6)	
≥1 regimen	227 (84.7)	144 (86.7)	83 (81.4)	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; MPV/PC ratio, MPV/platelet count ratio. Percentage is represented in parentheses.
[a] Squamous vs. non-squamous.

(Moriguchi-City, Japan) were retrospectively reviewed. Patients were included in this study if they had advanced NSCLC (stage IIIB or IV), regardless of whether they had been treated with systemic chemotherapy. The clinical disease stage was assigned on the basis of the seventh edition of the TNM Classification for Lung Cancer [12,13]. Data on sex, age, smoking history, clinical stage, histological typing of cancer, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and OS were obtained retrospectively from the patients' medical records. Patients who underwent thoracic radiation treatment with curative intent were excluded from the study, as were patients with large cell neuroendocrine carcinoma. The age- and sex-matched comparator group was randomly selected from among patients with chronic obstructive pulmonary disease (COPD) or bronchial asthma who had undergone medical examination in our hospital during the aforementioned period. The case–control ratio was defined as 2:1. Patients with a history of malignant tumor were excluded from the comparator group. Patients with levels of C-reactive protein (CRP) higher than the institutional normal upper limit were also excluded from the comparator group, as were patients with an active infection or inflammation. Laboratory data, including the complete blood count (CBC), were obtained from medical records. The results preceding the initial histological or cytological diagnosis of NSCLC were considered.

This retrospective study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board (the clinical research board of Kansai Medical University Takii Hospital, institutional ID: 24-33, UMIN–CTR: UMIN000010287).

2.2. Biochemical analysis of blood samples

CBC and various platelet volume indices were measured using ethylenediaminetetraacetic acid (EDTA)-treated blood. An automated blood cell counter was used for these analyses (Sysmex XE-2100, Kobe, Japan). The CRP concentration was measured using an automatic analyzer (Beckman Coulter AU5400, Miami, FL).

2.3. Statistical analysis

Statistically significant differences between the groups were compared using the chi-square or Student's t test. Receiver operating characteristics (ROC) curve analysis was used to estimate an optimal cutoff value for the MPV/PC ratio. OS was defined as the time from initial diagnosis to the time of death from any cause or the date the patient was last known to be alive. Univariate and multivariate analyses of OS were performed using the Kaplan–Meier product-limit method with the log-rank test and the Cox proportional hazards model, respectively. The 95% confidence interval (CI) for the survival rate was calculated using Greenwood's method. To calculate the 95% CI of the median survival time (MST), the Brookmeyer and Crowley method was used. All statistical analyses were conducted using the JMP (version 9.0.2) software program for Windows (SAS Institute Inc, Cary, NC). All statistical tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

A total of 268 patients with NSCLC were enrolled in this study. The characteristics of these 268 patients are summarized in Table 1. All the patients were Asian (Japanese, Korean, or Chinese), their median age was 68 years (range: 31–87 years), and they included 76 women and 192 men. One hundred and ninety-four patients had a history of smoking whereas the remaining 74 patients had never smoked. The numbers of patients with squamous cell carcinoma, adenocarcinoma, and other carcinomas were 63, 195, and 10, respectively. The ECOG PS was 0–2 in 210 patients and 3–4 in 58 patients. Fifteen patients had stage IIIb disease, whereas 253 patients had stage IV disease. Two hundred and twenty-seven

patients had received at least 1 regimen of systemic chemotherapy, whereas 41 patients had received best supportive care alone. Specifically, a history of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment was reported in 107 patients, whereas the remaining 161 patients had not received EGFR-TKI treatment.

3.2. Comparison of hematological indices between NSCLC patients and the control group

To evaluate the hematological indices of patients with NSCLC, a comparator group of 134 age- and sex-matched patients was randomly selected from among patients with COPD or bronchial asthma. The data from the 2 groups are summarized in Table 2. There were no significant differences in age and sex between the 2 groups. The MPV, platelet distribution width (PDW), and platelet large cell ratio (P-LCR) were significantly lower in the patients with NSCLC than in the comparator group. In contrast, the PC, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), white blood cell count WBC), and CRP level were significantly elevated in the patients with NSCLC than in the comparator group. Red blood cell distribution width (RDW) did not differ significantly between the groups. Interestingly, the MPV/PC ratio was also significantly decreased in the patients with NSCLC. We calculated the cutoff value for the MPV/PC ratio using ROC curve analysis. A cutoff value of 0.408730 was found to be an identifier value for patients with advanced NSCLC, with a sensitivity of 74.6% and specificity of 74.6% (area under the curve [AUC], 0.72492).

3.3. Comparisons according to the MPV/PC ratio

We divided the patients with NSCLC into 2 groups according to the cutoff value for the MPV/PC ratio of 0.408730. The characteristics of the 2 groups are summarized in Table 1. There were no significant differences in age, sex, PS, clinical stage, smoking history, or histological typing proportions between the 2 groups. We also reanalyzed the MPV, PC, and MPV/PC ratio in 3 groups: NSCLC patients with a low MPV/PC ratio; those with a high MPV/PC ratio; and the comparator group (Fig. 1). MPV was significantly decreased in the NSCLC patients with low MPV/PC ratio compared to the comparator group (9.31 ± 0.61 vs. 10.16 ± 0.82, $P < 0.0001$, Fig. 1A). However, there was no significant difference in MPV values between the NSCLC patients with a high MPV/PC ratio and the comparator group (10.00 ± 0.87 vs. 10.16 ± 0.82, $P = 0.2191$). In contrast, the PC was significantly increased in NSCLC patients with a low MPV/PC ratio compared to the comparator group (32.1 ± 7.1 vs. 21.7 ± 5.5, $P < 0.0001$, Fig. 1B). However, the PC was also slightly decreased in NSCLC patients with a low MPV/PC ratio compared to the comparator group (19.7 ± 3.8 vs. 21.7 ± 5.5, $P = 0.0013$). These findings suggest that NSCLC patients with a high MPV/PC ratio and the comparator group share similar characteristics in terms of volume and number of platelets. However, the NSCLC patients with a low MPV/PC ratio were an independent group, not only from the comparator group but also from the group with a

Table 2
Patient characteristics.

Characteristics	NSCLC patients ($n = 268$)	Comparator group ($n = 134$)	P value
Age, years			0.8445
Median (range)	68 (31–87)	68 (33–85)	
Sex			1.0000
Female	76	38	
Male	192	96	
Smoking history			0.0101*
Never smoked	74	54	
Past or current smoker	194	80	
PC, $10^4/\mu L$	27.2 ± 8.7	21.7 ± 5.5	<0.0001*
MPV, fl	9.59 ± 0.80	10.16 ± 0.82	<0.0001*
PDW, fl	10.74 ± 1.53	11.70 ± 1.67	<0.0001*
P-LCR, %	21.42 ± 6.45	25.86 ± 6.62	<0.0001*
MPV/PC ratio, fl $10^{-4}\mu L^{-1}$	0.397 ± 0.160	0.501 ± 0.144	<0.0001*
MCV, fl	91.8 ± 5.4	93.1 ± 4.3	0.0139*
MCHC, g/dL	32.9 ± 0.9	33.2 ± 1.0	0.0034*
RDW, fl	45.4 ± 4.5	45.1 ± 4.5	0.5817
WBC, $10^2/\mu L$	85.6 ± 41.9	64.8 ± 19.7	<0.0001*
CRP, mg/dL	2.761 ± 4.296	0.088 ± 0.069	<0.0001*

Data are presented as mean ± standard deviation. NSCLC, non-small cell lung cancer; PC, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; P-LCR, platelet large cell ratio; MPV/PC ratio, MPV/platelet count ratio; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cell; CRP, C-reactive protein.

* $P < 0.05$.

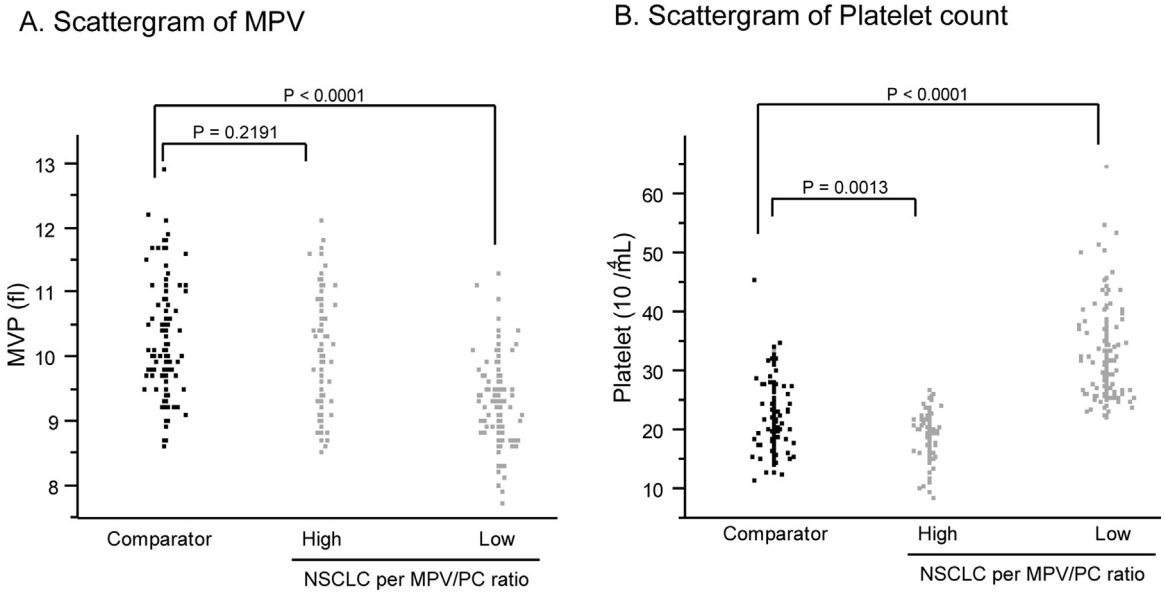

Fig. 1. Dot plot analyses of the mean platelet volume (MPV) and platelet count (PC). Dot plot analyses of the MPV (A) and PC (B) in the different groups of NSCLC patients and the control group.

Table 3
Univariate analysis of overall survival.

Variable	MST (months)	*P* value
MPV/PC ratio, low vs. high	10.3 vs. 14.5	0.0245*
Female vs. male	15.8 vs. 9.6	0.0018*
Never-smoker vs. smoker	16.3 vs. 10.3	0.0028*
Age, <70 years vs. ≥75 years	11.8 vs. 10.0	0.5922
ECOG PS 0/1/2 vs. 3/4	13.4 vs. 3.8	<0.0001*
Non-sq vs. sq	12.5 vs. 8.6	0.0003*
Stage IIIb vs. IV	17.8 vs. 10.6	0.2390

MST, median survival time; PS, performance status; Sq, squamous cell carcinoma; MPV/PC ratio, MPV/platelet count ratio; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
* $P < 0.05$.

Table 4
Multivariate analysis of overall survival.

Covariate	HR	95% CI	*P* value
MPV/PC ratio, low vs. high	1.668	1.235–2.271	0.0008*
Female vs. male	0.505	0.331–0.759	0.0009*
Never-smoker vs. smoker	1.018	0.673–1.522	0.9325
Age, <75 years vs. ≥75 years	0.853	0.611–1.214	0.3697
PS 0/1/2 vs. 3/4	0.305	0.215–0.449	<0.0001*
Non-Sq vs. Sq	0.578	0.411–0.824	0.0027*
Stage IIIB vs. IV	0.536	0.271–0.954	0.0330*

MST, median survival time; PS, performance status; Sq, squamous cell carcinoma; G, grade; ns, not significant.
* $P < 0.05$.

high MPV/PC ratio, with respect to the kinetics of the circulating platelets.

3.4. Univariate analyses for OS

We conducted a series of survival analyses on June 1, 2013. At that time, 203 patients had died, 46 patients were lost to follow-up, and 19 patients were still alive. Consequently, the censoring rate was estimated at 24.3%. In univariate analyses, OS was significantly increased in patients who were women ($P = 0.0018$); those had never smoked ($P = 0.0028$); those with a PS of 0, 1, or 2 ($P < 0.0001$); and those with non-squamous cell carcinoma ($P = 0.0003$). However, clinical stage ($P = 0.2390$) and patient age ($P = 0.5922$) were not statistically significant (Table 3). We also analyzed the contribution of the MPV/PC ratio to OS. The MSTs were 10.3 months (95% CI: 7.7–13.1) and 14.5 months (95% CI: 10.0–18.6) for patients with low and high MPV/PC ratios, respectively (Fig. 2). The 1-year survival rates were 43.8% (95% CI: 35.9–51.7) and 55.8% (95% CI: 44.5–66.1) for those with low and high MPV/PC ratios, respectively. In univariate analysis, OS was significantly decreased in the patients with a low MPV/PC ratio ($P = 0.0245$). We subsequently conducted a multivariate analysis to evaluate the independent survival impact of the covariates.

3.5. Multivariate analysis for OS

Multivariate analysis clearly revealed that a low MPV/PC ratio was an independent unfavorable prognostic factor for OS (hazard ratio [HR], 1.668, 95% CI: 1.235–2.271, $P = 0.0008$). In contrast, being female ($P = 0.0009$); having a PS of 0, 1, or 2 ($P < 0.0001$); having non–squamous cell carcinoma ($P = 0.0027$); and having stage IIIb disease ($P = 0.0330$) were independent favorable prognostic factors (Table 4). Being younger than 70 years ($P = 0.3697$) was however not a significant factor. In contrast to the results of univariate analysis, no significant difference in OS was observed between patients with and without a history of smoking ($P = 0.9325$). These results suggest the presence of a confounding factor that that affects the impact of a smoking history.

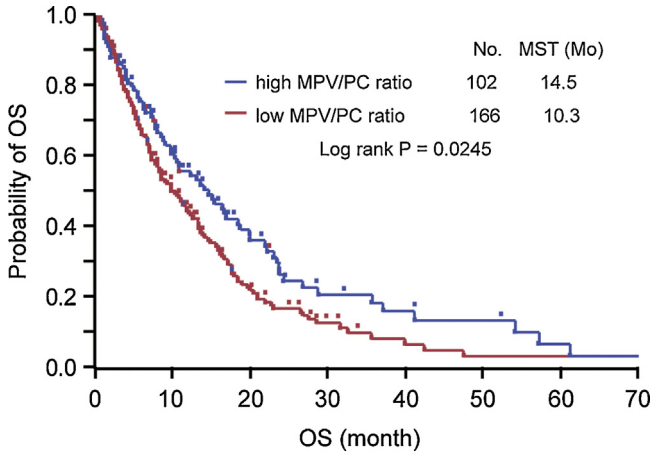

Fig. 2. Kaplan–Meier curves for overall survival (OS) of the patients according to the MPV/PC ratio. The median survival times (MSTs) for the group with a low MPV/PC ratio and the group with a high MPV/PC ratio were 10.3 and 14.5 months, respectively (log-rank, $P = 0.0245$).

4. Discussion

At present, evaluation of the MPV is attracting a great deal of interest. Several reports have shown that an elevation of MPV is closely associated with the severity and prognosis of cerebro- and cardio-vascular disorders [3,4,14,15]. Khode et al. showed that MPV was significantly higher in patients with acute myocardial infarction than in healthy controls [16]. Furthermore, the MPV/PC ratio was preferentially proposed as a predictor of long-term mortality after non-ST elevation myocardial infarction [3]. In addition to ischemic cardiovascular disorders, the elevation of MPV has also been reported in malignant tumors. Osada et al. showed that the MPV was higher in patients with gastric cancer than in control patients [7]. They also demonstrated upregulation of P-selectin, a well-known marker of platelet activation, on the surface of platelets in the gastric cancer patients. Furthermore, Cho et al. demonstrated that the MPV and MPV/PC ratio were elevated in patients with hepatocellular carcinoma (HCC) [6]. However, counterevidence has also been reported. Mutlu et al. analyzed the MPV in patients with various cancers at the time of diagnosis and at the time of any thrombotic event [17]. They did not detect MPV elevation at the time of diagnosis. Moreover, they found a significant reduction in MPV values at the time of thrombotic events compared to those at diagnosis. In addition, Aksoy et al. revealed that the MPV was significantly decreased in various cancer patients with metastasis to the bone marrow compared to control patients [18]. These findings strongly support our own. We revealed a significant reduction in the MPV and MPV/PC ratio in patients with advanced NSCLC. This is the first report presenting a reduction in the MPV and MPV/PC ratio in patients with NSCLC. We found one previous report assessing platelet indices for patients with lung cancer [19]. However, they did not show significant reduction in the MPV values in the patients with lung cancer. It is possible that they could not demonstrate differences in platelet indices between patients with lung cancer and healthy controls because their study population was smaller and heterogeneous.

However, this phenomenon in NSCLC is contradictory to that seen in gastric cancer and HCC [5–8]. One possible explanation could be that the circulating platelet count is restricted by thrombopoiesis in the bone marrow and is therefore inversely correlated to MPV [1,20]. Strict physiological controls play an important role in the maintenance of homeostasis. As the lung is a vital organ, an advanced tumor derived from it could easily evoke a status

of chronic inflammation due to various complications, including obstructive pneumonia and malignant serositis, leading to an upregulation of various proinflammatory cytokines such as TNF-α, IL-1, and IL-6 [21–23]. These cytokines induce acceleration of thrombopoiesis in the bone marrow, leading to an elevation in the circulating platelet count [24,25]. In addition, lung cancer cell-derived micro-particles bearing P-selectin and tissue factor also accelerate the activation of platelets, resulting in disseminated micro-thrombosis [26]. As larger platelets are more reactive in response to stimuli, selective consumption of larger platelets might occur. Consequently, the MPV of circulating platelets would be decreased. Micro- and macro-thromboembolic events are one of the major complications for patients with advanced NSCLC and can be fatal [27–29]. Therefore, this may be a possible explanation for the poor prognosis of patients with a low MPV/PC ratio.

The MPV and PC were also significant prognostic factors for OS in univariate analyses ($P = -0.0270$ and $P = 0.0124$, respectively). However, multivariate analysis did not indicate the superiority of them against the MPV/PC ratio when considered independently (HR of a low MPV/PC ratio: 1.668 [$P = 0.0008$], HR of a low MPV: 1.381 [$P = 0.0121$], and HR of a high PC: 1.380 [$P = 0.0114$]). Therefore, we concluded that the MPV/PC ratio was a more reliable and accurate biomarker than the MPV or PC alone.

Despite the retrospective nature and small size of the present study, our results clearly demonstrated that a low MPV/PC ratio at initial diagnosis was an independent unfavorable prognostic factor for patients with advanced NSCLC. Further investigation should clarify the etiology by which the amount and volume of circulating platelets modulate mortality in patients with NSCLC.

Conflict of interest

The authors have declared no conflict of interest.

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