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Research Article

Mean Platelet Volume to Lymphocyte Ratio: A New Biomarker Predicting Response in Patients with Solid Tumors Treated with Nivolumab

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ABSTRACT

Introduction: Although immune checkpoint inhibitors (ICIs) are widely used in cancer treatment, identifying factors that predict treatment response remains a challenge in clinical practice. There is a need for biomarkers to identify patients who may not benefit from these treatments. It is crucial to identify a simple and cost-effective biomarker that can be easily incorporated into clinical practice. This study aims to investigate the mean platelet volume to lymphocyte ratio (MPVLR), as measured by a hemogram test, and median overall survival (mOS) in patients with cancer treated with nivolumab. **Methods:** A total of 131 adult patients with metastatic cancer, including malignant melanoma (MM), renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), and head and neck cancer (HNC), were included in this study. Baseline demographics, ECOG (Eastern Cooperative Oncology Group) performance status, tumor type, and blood count parameters were recorded. Univariate and multivariate analyses were conducted to evaluate potential risk factors. **Results:** The median age of the patients was 59.87 ± 11.97 years, and the median follow-up period was 20.20 months (IQR, 12.80–27.60). RCC (43.5%) and MM (25.9%) were the most common diagnoses. Patients with ECOG scores of 0–1 had a longer mOS than those with scores of 2–3 (mOS: 20.60 months [95% CI, 14.94–25.29] vs. 5.24 months [95% CI, 0–16.42], $p < 0.001$). Additionally, patients with lactate dehydrogenase (LDH) levels within the normal range had a longer mOS than those with high LDH levels (mOS: 24.54 months [95% CI, 14.13–34.96] vs. 13.10 months [95% CI, 4.49–21.72], $p = 0.038$). Patients with low MPVLR also had a longer mOS than those with high MPVLR (mOS: 33.70 months [95% CI, 25.99–41.42] vs. 11.07 months [95% CI, 6.89–15.24], $p < 0.001$). In the multivariate Cox regression analysis, high MPVLR, ECOG score of 2–3, and high LDH level were associated with shorter mOS ($p < 0.001$, $p = 0.001$, and $p = 0.046$, respectively). **Conclusion:** This study demonstrates that MPVLR could serve as a novel biomarker for predicting response to nivolumab treatment. Incorporating MPVLR into clinical practice may aid in identifying patients who are less likely to benefit from the treatment.

Keywords: immunotherapy, nivolumab, biomarker, mean platelet volume to lymphocyte ratio

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and have become a standard component of therapy in various cancer types, improving survival and long-term treatment response.[1–4] They have shown effective results, including a cure, in chemotherapy-resistant cancers such as metastatic malignant melanoma (MM) and renal cell carcinoma (RCC).[5,6] However, when we look at the objective response rates, they are approximately 13% in head and neck cancers (HNCs), 25% in RCC, 20% in non–small cell lung cancer (NSCLC), and 27% for MM in the second and later lines of treatment.[3,4,7,8] It is crucial to identify factors that predict

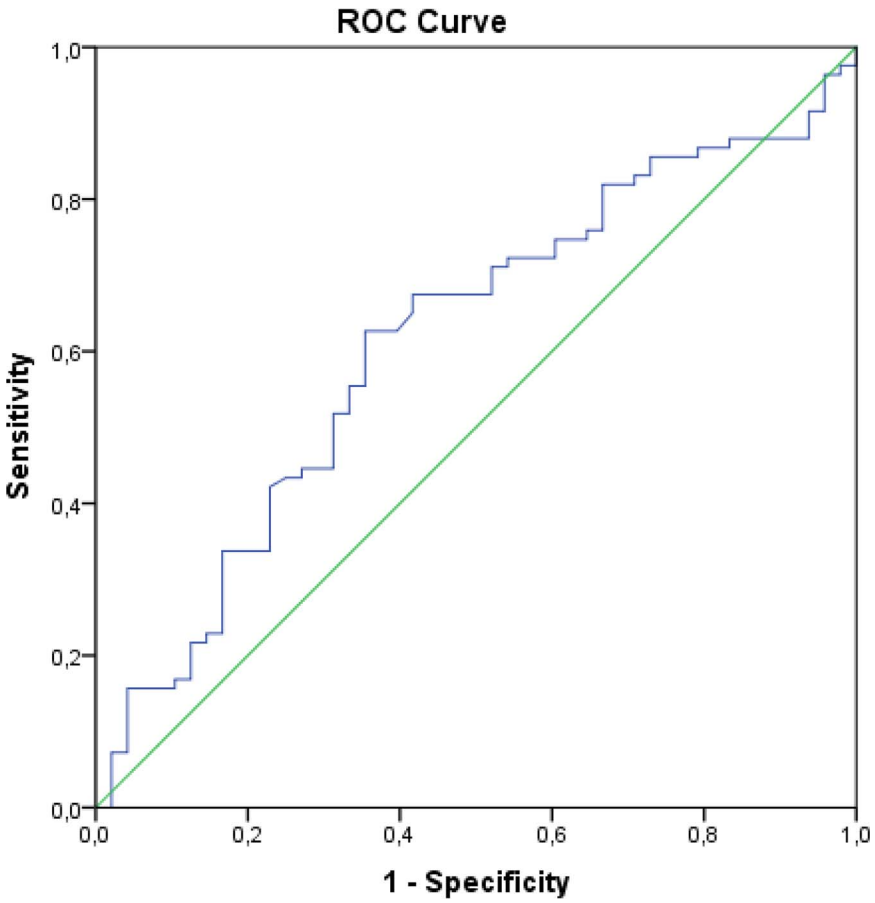

Figure 1. ROC analysis for mean platelet volume to lymphocyte ratio. The AUC value of MPVLR to predict survival was 0.61 (0.51–0.71 and $p = 0.032$). The ideal MPVLR was determined as 6.06905. AUC: area under the ROC curve; MPVLR: mean platelet volume to lymphocyte ratio; ROC: Receiver Operating Characteristic.

treatment response and avoid administering ICIs to patients who are unlikely to respond favorably.

Tumor-associated inflammation has been recognized as a prognostic factor and plays a significant role in both tumor development and patient outcomes.[9,10] Several studies have highlighted the prognostic value of parameters such as pan-immune-inflammation value (PIV) and neutrophil to lymphocyte ratio (NLR) in patients treated with ICIs.[11,12]

Platelets, as essential blood cells involved in inflammation, have been shown to affect prognosis in specific cancers, including NSCLC and cervical cancer.[13,14] Mean platelet volume (MPV) serves as a marker of platelet activation and function, as well as an indicator of platelet diameter.[15] MPV is associated with inflammation, making it a potential marker for response to ICIs. Because MPV is routinely measured and represents a simple and cost-effective test, it holds promise as a biomarker. Previous studies have demonstrated elevated MPV levels in hepatocellular carcinoma, ovarian cancer, colon cancer, and lung cancer.[16] Moreover, a study has shown the prognostic significance of the MPV to lymphocyte ratio (MPVLR) in solid tumors.[17] Studies examining the relationship between lymphocyte count and ICIs have shown that lymphopenia is associated with a poor response to treatment.[18]

To the best of our knowledge, a study examining the relationship between MPVLR and response to ICIs has not been conducted, and in our study, we aimed to examine the effect of MPVLR on median overall survival (mOS) in patients receiving nivolumab.

METHODS

The study was approved by the ethics committee of Istinye University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived.

Data Collection

This retrospective cohort study included 131 patients with stage 4 MM, RCC, NSCLC, or HNC who received nivolumab treatment at Hacettepe University Cancer Institute between May 2015 and July 2022. Patients enrolled in clinical trials were excluded from the study.

Only patients who received nivolumab treatment under reimbursement conditions in the country were included. Patients who received concurrent radiotherapy or had immunologic, rheumatologic, or hematologic conditions were excluded. PD-L1, tumor mutation burden (TMB), and microsatellite instability (MSI) were not routinely assessed for nivolumab treatment in the patient group included in this study; hence, they were not included in the analysis.

All patients who had baseline measurements and at least one follow-up cross-sectional imaging examination with contrast after the first dose of immunotherapy were included. Patients who continued treatment at another center or had imaging performed at a different facility were excluded. Baseline patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, baseline lactate dehydrogenase (LDH) levels (normal: ≤ 247 U/L, high: > 247 U/L), neutrophil levels (normal: 2100–8900/μL, high: > 8900/μL), thrombocyte levels (normal: 173,000–390,000 μL, high > 390,000 μL), NLR, and MPVLR were recorded, along with survival data.

Follow-up imaging, typically conducted at 3-month intervals after treatment initiation, was evaluated according to the iRECIST criteria for response assessment.[19] The median progression-free survival (mPFS) was determined as the time from randomization to progression or death. OS was determined as the time between the initiation of nivolumab treatment and the time of death or the last follow-up.

Statistical Analysis

An NLR cutoff of 5, recommended for a robust relation with prognosis in immunotherapy-treated patients, was used.[20] Receiver Operating Characteristic (ROC) analysis was performed to determine the MPVLR cutoff value. The AUC (area under the ROC curve) value of MPVLR to predict survival was 0.61 (0.51–0.71 and $p = 0.032$); ROC analysis is shown in Figure 1. The ideal MPVLR was determined as 6.06905. Patients with an MPVLR of 6.06905 and below were defined as low, and those with an MPVLR above 6.06905 were defined as high.

Baseline characteristics were presented as percentages, medians, and IQRs as appropriate. Survival analysis was conducted by using the Kaplan-Meier method and Cox regression analyses. Hazard ratios with 95% CIs were reported. SPSS (Statistical Package for Social Sciences) version 26 was used for the analyses, with *p*-values below 0.05 considered statistically significant.

RESULTS

A total of 131 patients were included in the study. The median age was 59.87 ± 11.97 years, and the median follow-up was 20.20 months (IQR, 12.80–27.60); 64.9% of the patients were male, and 37.4% were older than 65 years. Before treatment, 81.7% of the patients had an ECOG score of 0 or 1. Of the patients, 25.9% were diagnosed with MM, 43.5% with RCC, 16% with NSCLC, and 14.5% had HNC. Fifty-five percent of the patients had lung metastases, and 25.4% had liver metastases. Approximately 53.4% of patients had a high MPVLR, 28% had NLR scores above 5, and 30.6% had high LDH levels. The baseline characteristics of patients are shown in Table 1.

Table 1. Baseline clinical and laboratory features of patients

Parameter	*n* (%)
Age, y	
< 65	82 (62.6)
≥ 65	49 (37.4)
Sex	
Female	46 (35.1)
Male	85 (64.9)
ECOG score	
0–1	107 (81.7)
2–3	24 (18.3)
Diagnosis	
Melanoma	34 (25.9)
RCC	57 (43.5)
NSCLC	21 (16.0)
HNC	19 (14.5)
Liver metastasis	
Present	32 (25.4)
Absent	99 (75.6)
Lung metastasis	
Present	72 (55.0)
Absent	59 (45.0)
Immunotherapy plus chemotherapy	
Present	25 (19.1)
Absent	106 (80.9)
Line of treatment	
1–2	61 (46.6)
> 2	70 (53.5)
Neutrophil to lymphocyte ratio	
< 5	94 (71.8)
≥ 5	37 (28.2)
Lactate dehydrogenase level, U/L[a]	
Normal	84 (69.4)
> Upper limit of normal	37 (30.6)
Mean platelet volume to lymphocyte ratio	
≤ 6.06905	61 (46.6)
> 6.06905	70 (53.4)

[a]Lactate dehydrogenase levels are missing for 10 patients.
ECOG: Eastern Cooperative Oncology Group; HNC: head and neck cancer; NSCLC: non–small cell lung cancer; RCC: renal cell carcinoma.

The mOS was longer in the group with low MPVLR than in the group with high MPVLR (mOS: 33.70 months [95% CI, 25.99–41.42] vs. 11.07 months [95% CI, 6.89–15.24], respectively; $p < 0.001$). The relationship between MPVLR and OS is shown in Figure 2. In MM, the mOS was longer in the group with low MPVLR than in the group with high MPVLR (mOS: not reached vs. 11.20 months [95% CI, 7.99–14.40], respectively; $p = 0.001$). In NSCLC, the mOS was longer in the group with low MPVLR than in the group with high MPVLR (mOS: 25.16 months [95% CI, 8.93–41.39] vs. 3.02 months [95% CI, 0–7.95], respectively; $p = 0.016$). In

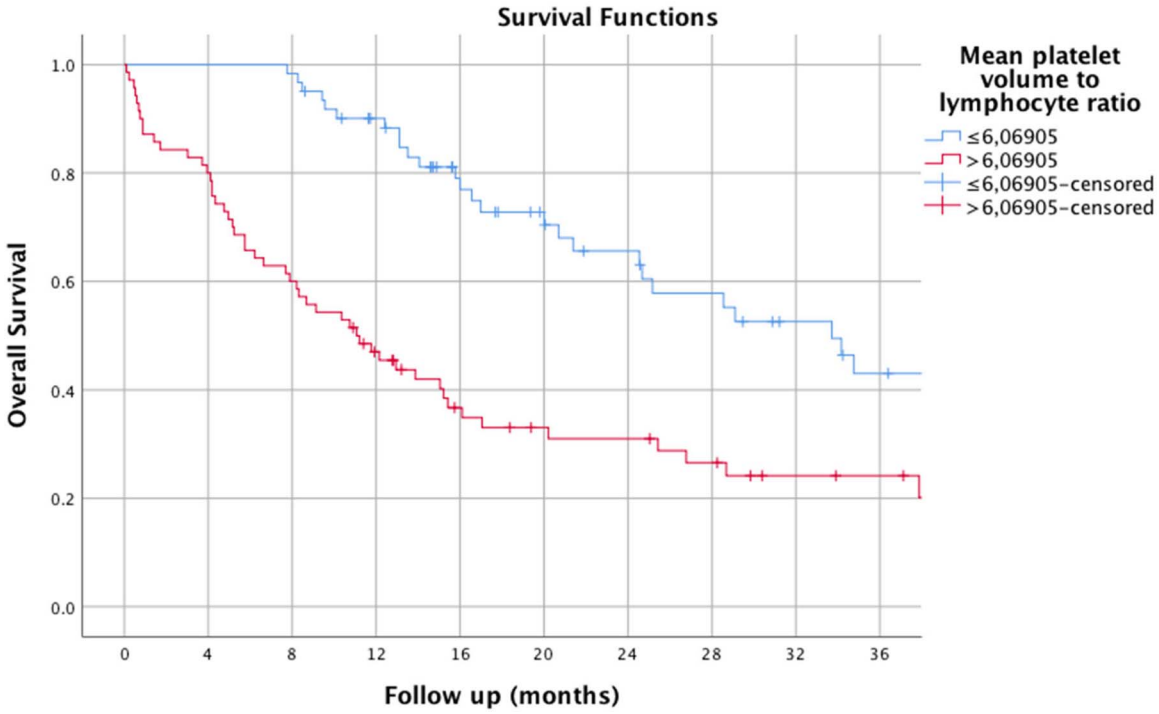

Figure 2. Comparison of overall survival according to mean platelet volume to lymphocyte ratio (overall survival time is significantly shorter in patients with MPVLR > 6.0695). MPVLR: mean platelet volume to lymphocyte ratio.

RCC, the mOS was numerically longer in the group with low MPVLR than in the group with high MPVLR (mOS: 28.55 months [95% CI, 10.82–46.27] vs. 8.84 months [95% CI: 0–33.43], respectively; $p = 0.187$). In HNC, the mOS was numerically longer in the group with low MPVLR than in the group with high MPVLR (mOS: 18.80 months [95% CI, 0–71.61] vs. 3.03 months [95% CI, 6.20–18.11], respectively; $p = 0.199$).

The mOS was longer in the group with low NLR than in the group with high NLR (mOS: 24.54 months [95% CI, 19.19–29.88] vs. 7.68 months [95% CI, 4.04–11.32], respectively; $p = 0.015$). Patients with ECOG scores of 0–1 had a longer mOS than patients with ECOG scores of 2–3 (mOS: 20.60 months [95% CI, 14.94–25.29] vs. 5.24 months [95% CI, 0–16.42], respectively; $p < 0.001$). Patients with LDH levels within the normal range had a longer mOS than patients with high LDH levels (mOS: 24.54 months [95% CI, 14.13–34.96] vs. 13.10 months [95% CI, 4.49–21.72], respectively; $p = 0.038$). No correlation was found between other clinical features (age, sex, diagnosis, site of metastasis, line of treatment, with or without chemotherapy) and mOS (Table 2). In multivariate Cox regression analysis, high MPVLR, ECOG score 2–3, and high LDH level were associated with shorter mOS time ($p < 0.001$, $p = 0.001$, and $p = 0.046$, respectively). The univariate and multivariate analysis results of the factors that were found to be associated with survival in Kaplan-Meier analysis are shown in Table 3.

The mPFS was longer in the group with low MPVLR than in the group with high MPVLR (mPFS: 13.04 months [95% CI, 9.29–16.79] vs. 4.30 months [95% CI, 2.11–6.49], respectively; $p < 0.001$) (Fig. 3).

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate the relationship between MPVLR and mOS

Table 2. Baseline clinical features that were not found to be associated with survival

	***n* (%)**	***p*-value**
Age, y		
< 65	82 (62.6)	0.469
≥ 65	49 (37.4)	
Sex		
Female	46 (35.1)	0.996
Male	85 (64.9)	
Diagnosis		
Melanoma	34 (25.9)	0.342
RCC	57 (43.5)	
NSCLC	21 (16.0)	
HNC	19 (14.5)	
Liver metastasis		
Present	32 (25.4)	0.417
Absent	99 (75.6)	
Lung metastasis		
Present	72 (55.0)	0.106
Absent	59 (45.0)	
Immunotherapy plus chemotherapy		
Present	25 (19.1)	0.244
Absent	106 (80.9)	

HNC: head and neck cancer; NSCLC: non–small cell lung cancer; RCC: renal cell carcinoma.

Table 3. Univariate and multivariate analysis of factors associated with overall survival

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	**95% CI**	***p***	**Hazard Ratio**	**95% CI**	***p***
NLR (< 5 vs. ≥ 5)	1.773	1.112–2.827	0.016	1.182	0.703–1.987	0.529
LDH level, U/L (normal vs. > ULN)	1.620	1.023–2.566	0.040	1.603	1.008–2.549	0.046
ECOG score (0–1 vs. 2–3)	2.850	1.689–4.810	< 0.001	2.504	1.448–4.329	0.001
MPVLR (≤ 6.06905 vs. > 6.06905)	2.557	1.633–4.004	< 0.001	2.414	1.519–3.836	< 0.001

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MPVLR: mean platelet volume to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; ULN: upper limit of normal.

in patients with cancer treated with nivolumab. Our findings suggest that patients with high MPVLR have shorter mOS and mPFS, highlighting the importance of close monitoring and attention to disease progression in these individuals.

Whereas the development of ICIs in cancer treatment has progressed rapidly, the identification of factors predicting treatment response has lagged behind. Whereas some patients experience excellent responses, including long-term survival and potential cure, others have rapid disease progression.[21,22] Tissue-based biomarkers such as PD-L1 level, TMB, and MSI have been investigated to identify patients who would benefit from ICIs, but there is also a need for more cost-effective blood-based parameters.[23–25] Several studies have explored blood-based and clinical factors, including parameters like NLR, platelet to lymphocyte ratio (PLR), and PIV score, to predict treatment response.[12,26–29] The development of blood-based prognostic factors, such as MPVLR, which is a simple and inexpensive test, would be particularly beneficial in resource-limited settings where access to immunotherapy is more challenging.

Elevated MPV value is encountered more frequently in cancer patients compared to healthy individuals and has been associated with vascular invasion.[30] Studies have shown that patients with low MPV levels in metastatic colorectal cancer have better response to treatments that include bevacizumab.[31] High MPV levels have been associated with poor response to chemotherapy in gastric cancer and anti-EGFR treatment in NSCLC.[32,33] Lymphocytes play a crucial role in the mechanism of action of ICIs, and recent studies have demonstrated a relationship between lymphocyte count and prognosis in patients treated with ICIs.[34] Whereas NLR and PLR have been shown to predict

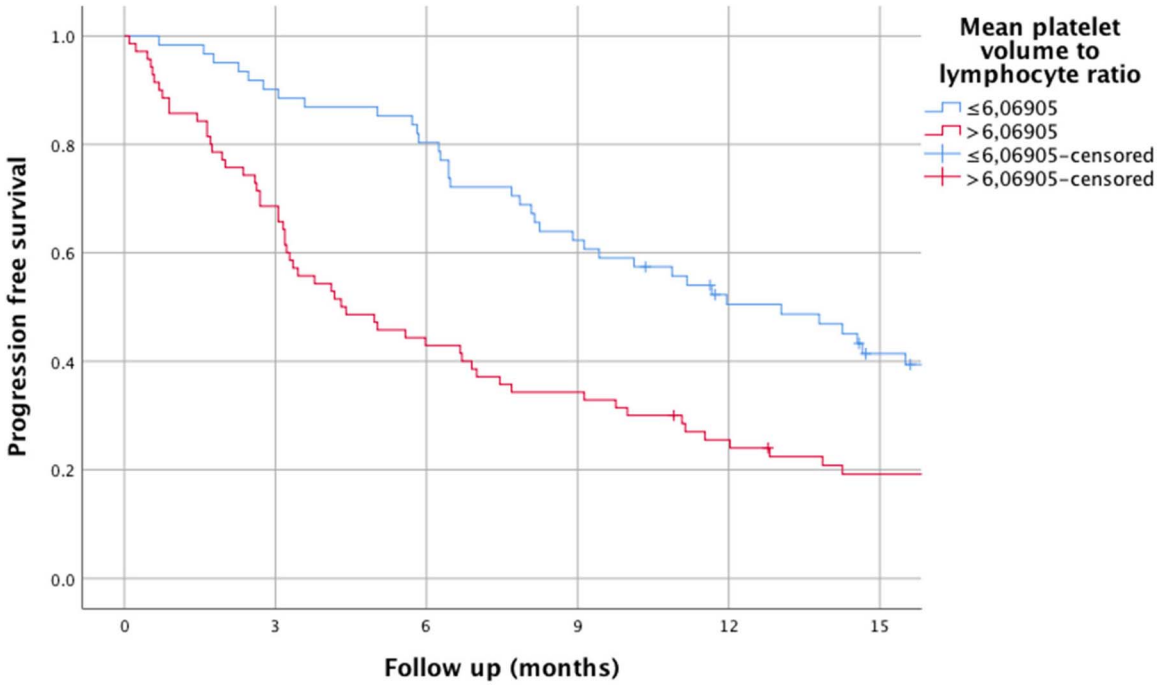

Figure 3. Comparison of progression-free survival according to MPVLR (progression-free survival time is significantly shorter in patients with MPVLR > 6.0695). MPVLR: mean platelet volume to lymphocyte ratio.

response to immunotherapy, the relationship between MPVLR and response has not been explored.[26,35] In our study, MPVLR predicted treatment response in the general group; when we evaluated four cancer types separately, it was found to be statistically significant in MM and NSCLC, and numerically longer in RCC and HNC. Also in our study, we found that MPVLR is a stronger predictor of OS than NLR.

Previous studies, including ours, have demonstrated that patients with high LDH levels and ECOG scores of 2–3 derive less benefit from immunotherapy.[36,37] Elevated LDH levels may indicate a higher disease burden, while a higher ECOG score may reflect disease-related critical illness or comorbidities that compromise overall health.

This study has several limitations, including its retrospective nature and the heterogeneity of the patient population. Subgroup analyses were limited owing to the small number of patients in specific subgroups. Therefore, randomized controlled prospective studies are warranted to further investigate this topic. Nonetheless, our study is significant as the first to establish the prognostic importance of MPVLR, a blood-based parameter, and if supported by future research, it could become a valuable biomarker in clinical practice.

CONCLUSION

In conclusion, our study demonstrates significantly lower OS in patients with higher baseline NLR values, elevated LDH levels, poorer ECOG status, and increased MPVLR. This study highlights the prognostic significance of MPVLR as a blood-based parameter and suggests its potential use as a biomarker in clinical practice.

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