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Research Article

# The Mean Platelet Volume to Lymphocyte Ratio: A New Prognostic Marker in Resected Gastric Cancer

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## Abstract

**Objectives:** Gastric cancer is the fourth most common cancer. Inflammation is a crucial component of tumor progression. Platelet-to-Lymphocyte Ratio (PLR) is a prognostic indicator in many cancer types. Mean Platelet Volume (MPV) is a parameter that reflects platelet function and activity. In this study, we aimed to investigate the prognostic value of Mean Platelet Volume to Lymphocyte Ratio (MPVLR).

**Methods:** Eighty patients who underwent curative resection between January 2014 and December 2018 were included in the study. Clinicopathological parameters and laboratory analyzes of the patients were obtained from computer records retrospectively. MPVLR cut off value was determined via receiver operating characteristic (ROC) curve analysis (low MPVLR: <4.30/high MPVLR: >4.30). MPVLR and clinicopathological characteristics were analyzed by univariate and multivariate analysis.

**Results:** Median survival (OS) was 24 months, and median disease-free survival (DFS) was 16 months. A significant correlation was found between MPVLR and gender (p=0.036), lymphocyte count (p<0.001), PLR (p<0.001) and adjuvant therapy (p=0.004). Median OS was 15 months in the group with high MPVLR, but median survival was not achieved in the group with low MPVLR (p<0.001). Median DFS was 11 months in the high MPVLR group, and median DFS survival was not achieved in the low MPVLR group (p<0.001). In multivariate analysis for DFS, pathological stage (p=0.019) and MPVLR (p=0.005) were detected as independent prognostic factors, whereas multivariate analysis for OS only MPVLR (p=0.003) was determined as independent prognostic factor.

**Conclusion:** Elevated MPVLR is a poor prognostic factor in patients with gastric cancer undergoing curative resection. Our study showed that MPVLR is a more valuable prognostic factor than PLR.Thus, MPVLR could be a novel biomarker for prognostic estimation.

**Keywords:** Gastric cancer, mean platelet volume to lymphocyte ratio (MPVLR), platelet-to-lymphocyte ratio (PLR), prognostic factor

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Gastric cancer ranks fourth among the most common diseases in the world, while it ranks second among cancer-related deaths.[1, 2] The incidence varies according to geographical regions. More than 50% of new cancer cases occur in developing countries. Gastric cancer is often diagnosed at an advanced stage, and only 25% of patients have a curative resection chance. Clinical staging is performed by endoscopic ultrasound and tomography.[3] Tumor-node-metastasis (TNM) staging is used to predict the treatment plan and oncologic outcomes of the patients.

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However, even in patients with the same stage, the results are different. Therefore, there is a need for new biomarkers that are affordable and easily accessible. New serum prognostic indicators may complement clinical staging and help predict tumor aggression.

Inflammation has a significant role in cancer progression. Continuation of the inflammation process leads to cancer progression, angiogenesis increase and apoptosis inhibition.[4] A systemic inflammatory response is closely correlated with prognosis in many cancer types.[5–7] Circulating inflammatory cells may indicate the status of systemic inflammation and may indirectly reflect the severity and prognosis of cancer.[8, 9] Biomarkers such as neutrophils, lymphocytes, platelets, neutrophil to lymphocyte ratio (NLR) and PLR are indicators of inflammation. PLR is defined as the ratio of platelet count to lymphocyte count. Elevated PLR is associated with poor prognosis in many types of solid cancers.[7, 10] Mean platelet volume is considered an indicator of platelet function and activation. Also, it has been shown to have prognostic effects in many cancer types.[11, 12] There is a hypothesis that platelet diameter may show platelet activation better than platelet count.[13] We planned to use MPV instead of platelets in PLR, which has been shown to be a useful prognostic factor in patients with gastric cancer.[14, 15] Our aim is to investigate the prognostic effect of MPV lymphocyte ratio in patients with curative resected gastric cancer.

## Methods

### Patients

The study included 80 patients diagnosed with gastric cancer between January 2014 and December 2018 and followed by curative resection. Patient data were analyzed retrospectively from electronic records and patient files. We classified patients according to the classification of the American Joint Committee on Cancer (AJJC 7th ed., 2010). Metastatic patients, patients with systemic inflammatory disease, patients with autoimmune disease, and patients with blood disease were excluded from the study.

Hematological parameters were obtained from electronic records before any treatment of patients who underwent surgery. MPV/Lymphocyte Ratio was obtained by dividing MPV by lymphocyte count.

### Statistical Analysis

ROC curve analysis was used to find the value reflecting the highest sensitivity and specificity for MPVLR. The median value was taken for the PLR cutoff value. A chi-square test was used to determine the relationship between MPVLR and clinicopathological characteristics. Prognostic factors were evaluated using univariate and multivariate Cox proportional hazard regression analysis. The factors that were found to be significant in the univariate analysis were included in the multivariate analysis. Kaplan Meier method was used for time-event analysis, including disease-free survival and overall survival. The log-rank test was used to compare time-event end points between patient groups. P<0.05 was accepted as statistically significant. All data were analyzed by SPSS 22 (SPSS Inc., Chicago, IL, USA). Overall survival was defined as the time from diagnosis to death or the last visit. Disease-free survival was defined as the time between diagnosis and the date of relapse or the date of the previous stay.

**Table 1.** Association of the patients' characteristics with the MPVLR

| Characteristics | MPVLR<4.30 | MPVLR>4.30 | p |
|---|---|---|---|
| Age, y | | | |
| <65 | 24 (55.8) | 19 (51.4) | 0.690 |
| >65 | 19 (44.29) | 18 (48.6) | |
| Gender | | | |
| Female | 16 (37.2) | 6 (16.2) | 0.036 |
| Male | 27 (62.8) | 31 (83.8) | |
| Node status | | | |
| N0-1 | 22 (51.2) | 18 (48.6) | 0.823 |
| N2-3 | 21 (48.8) | 19 (51.4) | |
| Depth of invasion | | | |
| T1-2 | 19 (44.2) | 9 (24.3) | 0.063 |
| T3-4 | 24 (55.8) | 28 (75.7) | |
| Stage | | | |
| 1-2 | 23 (53.5) | 16 (43.2) | 0.361 |
| 3 | 20 (46.5) | 21 (56.8) | |
| Grade | | | |
| 1-2 | 20 (46.5) | 11 (29.7) | 0.124 |
| 3 | 23 (53.5) | 26 (70.3) | |
| Lymphocyte count | | | |
| <1400 | 0 (0) | 19 (51.4) | 0.000 |
| >1400 | 43 (100) | 18 (48.6) | |
| Platelet count | | | |
| <350.000 | 34 (79.1) | 28 (75.7) | 0.717 |
| >350.000 | 9 (20.9) | 9 (24.3) | |
| PLR | | | |
| <144 | 36 (83.7) | 7 (18.9) | 0.000 |
| >144 | 7 (16.3) | 30 (81.19) | |
| Adjuvant treatment | | | |
| Yes | 26 (60.5) | 33 (89.2) | 0.004 |
| No | 17 (39.5) | 4 (10.8) | |

MPVLR: Mean platelet volume to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

## Results

### Clinicopathological Characteristics

The clinicopathological characteristics of the patients are summarized in Table 1. 22 (27.5%) patients were female

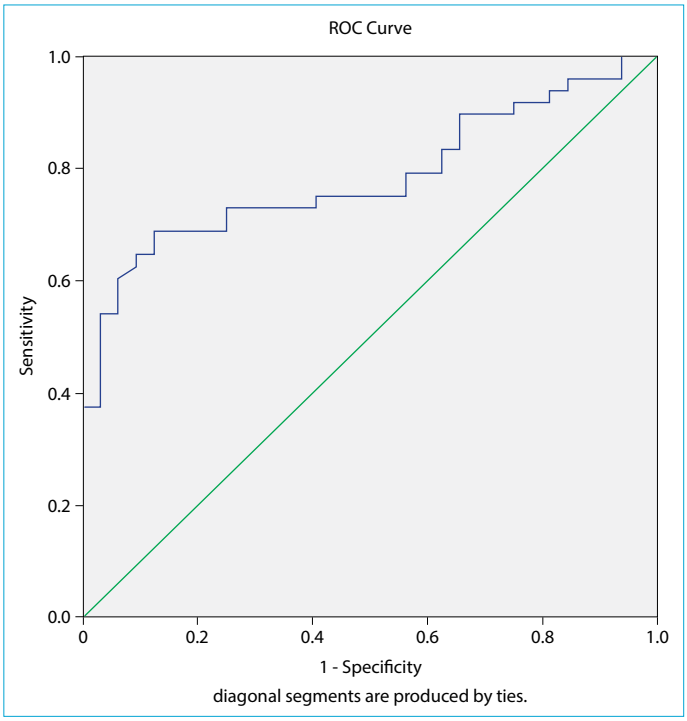


**Figure 1.** ROC curve of MPVLR for survival prediction.

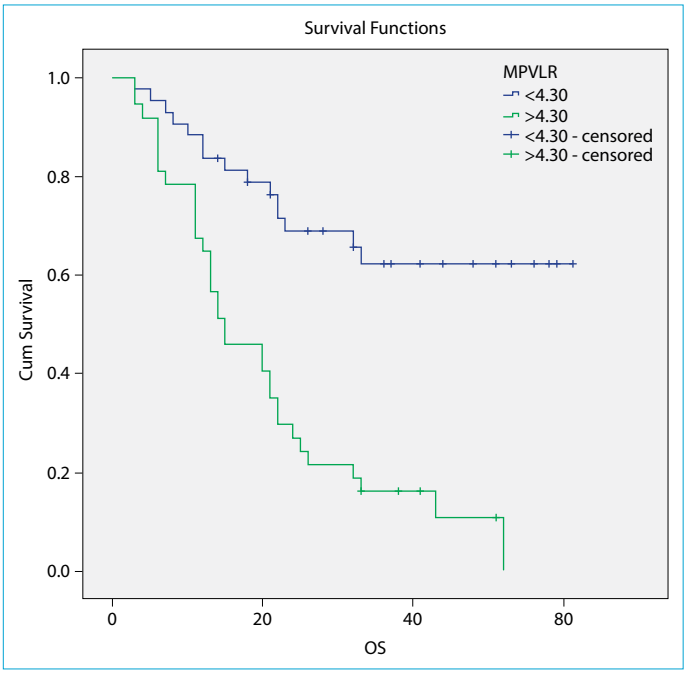


**Figure 2.** Kaplan-Meier survival curves of overall survival according to MPVLR.

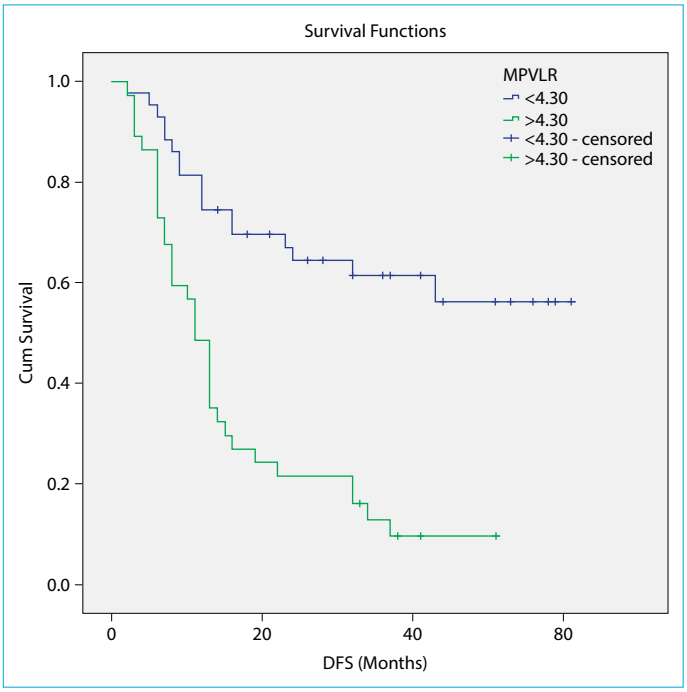


**Figure 3.** Kaplan-Meier survival curves of disease-free survival according to MPVLR.

and 58 (72.5%) patients were male. The median age of the patients was 63 (22-84) years. All patients underwent D2 resection. Recurrence occurred in 50 (62.5%) patients and 48 (60%) patients died. 39 (48.8%) patients were stage 1/2 and 41 (51.3%) patients were stage 3. Twenty-one patients did not receive adjuvant therapy, and 59 patients received five adjuvant 5- fluorouracil-based chemoradiotherapy.

## Relationship Between MPVLR and Clinicopathological Characteristics

The best predicted cut-off value for MPVLR for both OS and DFS was found to be 4.30 by ROC curve analysis (AUC 0.784, p<0.001, sensitivity 68.8%, specificity 87.5%) (Fig. 1). The number of patients with low MPVLR group (MPVLR <4.30) was 43 (53.8%), and the number of patients with high MPVLR group (MPVLR >4.30) was 37 (46.3%). There was a correlation between MPVLR and gender (p=0.038), lymphocyte count (p<0.001), PLR (p<0.001) and adjuvant therapy (p=0.004). However, there was no significant relationship between other clinicopathological characteristics (Table 1).

## Prognostic Factors for OS and DFS

In this study, the median DFS was 16 months. Median OS was 24 months. Median survival was 15 months in patients with high MPVLR, but median survival was not achieved in patients with low MPVLR (p<0.001). OS was significantly shorter in patients with high MPVLR (Fig. 2). While the median DFS was 11 months in patients with MPVLR >4.30, the median DFS was not reached in patients with MPVLR <4.30 (Fig. 3) (p<0.001). Median DFS was significantly worse in patients with high MPVLR than in patients with low MPVLR. In univariate analysis, low lymphocyte count (p<0.001), advanced T (<0.001), N (p<0.001), pathological stage (p<0.001), elevated PLR (p<0.001) were defined as poor prognostic factors for OS (Table 3). Elevated MPVLR

**Table 2.** Univariate and multivariate analyses of factors forthe prediction of progression-free survival

| | HR | 95% CI | p | HR | 95% CI | p |
|---|---|---|---|---|---|---|
| MPVLR | | | | | | |
| <4.30/>4.30 | 3.696 | 2.033-6.718 | 0.000 | 3.467 | 1.449-8.295 | 0.005 |
| Age, y | | | | | | |
| <65/>65 | 0.977 | 0.560-1.706 | 0.935 | | | |
| Gender | | | | | | |
| Female/male | 1.652 | 0.844-3.232 | 0.143 | | | |
| Depth of invasion | | | | | | |
| T1-2/T3-4 | 3.461 | 1.719-6.966 | 0.001 | 1.029 | 0.415-2.548 | 0.951 |
| Adjuvant treatment | | | | | | |
| Yes/No | 2.768 | 1.294-5.922 | 0.009 | 1.202 | 0.542-2.663 | 0.651 |
| Node status | | | | | | |
| N0-1/N2-3 | 2.989 | 1.656-5.394 | 0.000 | 0.617 | 0.143-2.658 | 0.517 |
| Stage | | | | | | |
| Stage1-2/3 | 3.799 | 2.063-6.999 | 0.000 | 1.301 | 0.404-4.186 | 0.019 |
| Lymphocyte count | | | | | | |
| <1.4/>1.4x104/µL | 0.357 | 0.197-0.646 | 0.001 | 0.866 | 0.400-1.836 | 0.712 |
| Platelet count | | | | | | |
| <350.000/>350.000 | 1.568 | 0.830-2.960 | 0.165 | | | |
| MPV(fL) | 1.020 | 0.784-1.327 | 0.886 | | | |
| PLR | | | | | | |
| ≤144/>144 | 2.876 | 1.608-5.142 | 0.000 | 1.178 | 0.525-2.644 | 0.692 |

R: Hazard ratio; 95% CI: 95% confidence interval; PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; MPVLR: Mean platelet volume to lymphocyte ratio.

(p<0.001), low lymphocyte count (p=0.001), advanced T (p=0.001), N (p<0.001), pathological stage (p<0.001), no adjuvant therapy (p=0.009), and PLR (p<0.001) were found to be a poor prognostic factors for DFS (Table 2). Cox regression multivariate analysis showed that only MPVLR (p=0.003) was an independent prognostic factor for OS (Table 3). Multivariate analysis for DFS found pathological stage (p=0.019) and elevated MPVLR (p=0.005) as independent prognostic factors (Table 2).

## Discussion

In the literature, many studies are showing the prognostic effect of PLR in solid tumors. High PLR has been shown to predict poor clinical outcomes in many cancers.[16] MPV is a parameter that indicates platelet activity and function. In this study, we aimed to show the prognostic effect of MPVLR in patients with gastric cancer undergoing curative resection.

In recent years, the importance of inflammatory response in the determination of cancer progression has begun to be defined. Measurement of the systemic inflammatory response is usually performed with circulating cells and acute phase proteins.[17] Inflammation results in neutrophilia, lymphopenia, and thrombocytosis.[18] It has been shown that the elevated systemic inflammatory response is associated with poor outcomes independent of the tumor stage. Especially the number of white blood cells such as lymphocytes, leukocytes, the number of platelets and neutrophil-lymphocyte ratio, platelet lymphocyte ratio, such as the prognostic value of combinations have been shown.[19, 20] Platelets are part of the inflammatory response and thrombocytosis is common in patients with solid tumors.[21] The high platelet count reflects the underlying inflammation. Because it stimulates megakaryocyte proliferation and causes relative thrombocytosis, it is known that platelets interact directly with the tumor cell and include factors that contribute to angiogenesis and invasion of tumor growth.[22] Thrombocytosis is a predictor of poor prognosis in patients with many solid tumors.[23] MPV reflects the diameter of platelets and is associated with platelet production and platelet activation. Large-scale platelets are very active metabolically and enzymatically.[24] Platelet diameter reflects platelet activity better than platelet number.[13] Studies have shown the prognostic significance of MPV in patients with solid tumors.[25, 26]

Lymphocytes play a significant role in immune response and are the essential factors in suppressing cancer progression.[27] It has been shown that the prognosis of solid tumor patients with elevated lymphocyte count is better.[28]

**Table 3.** Univariate and multivariate analyses of factors for the prediction of overall survival

| | Univariable Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| Gender | | | | | | |
| Female/male | 1.075 | 0.610-1.895 | 0.803 | | | |
| Age | | | | | | |
| <65/>65 | 0.167 | 0.814-3.287 | 0.167 | | | |
| MPVLR | | | | | | |
| <4.30/>4.30 | 0.245 | 0.132-0.457 | 0.000 | 3.948 | 1.591-9.796 | 0.003 |
| MPV | 1.031 | 0.788-1.347 | 0.826 | | | |
| Lymphocyte count | | | | | | |
| <1.4/>1.4x104/µL | 0.369 | 0.204-0.668 | 0.001 | 1.063 | 0.493-2.293 | 0.875 |
| Plateletcount | | | | | | |
| <350.000/>350.000 | 1.429 | 0.740-2.760 | 0.288 | | | |
| Node status | | | | | | |
| N0-1/N1-2 | 3.438 | 1.858-6.360 | 0.000 | 0.822 | 0.191-3.548 | 0.793 |
| Depth of invasion | | | | | | |
| T1-2/T3 | 3.982 | 1.913-8.290 | 0.000 | 1.353 | 0.527-3.470 | 0.530 |
| Stage | | | | | | |
| 1-2/3-4 | 4.382 | 2.311-8.300 | 0.000 | 4.254 | 1.107-9.373 | 0.079 |
| Adjuvant treatment | | | | | | |
| Yes/no | 3.117 | 1.391-6.9 | 0.006 | 1.177 | 0.496-2.791 | 0.711 |
| PLR | | | | | | |
| ≤144 />144 | 3.057 | 1.677-5.570 | 0.000 | 1.091 | 0.463-2.567 | 0.842 |

HR: Hazard ratio; 95% CI: 95% confidence interval; PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; MPVLR: Mean platelet volume to lymphocyte ratio.

In a study, MPVLR was found to be significantly higher in patients with diabetic nephropathy compared to patients without diabetic nephropathy.[29] Studies have shown the relationship between inflammation and diabetic nephropathy. Excessive production of inflammatory mediators has been shown to accelerate the development of diabetic nephropathy.[30] In our study, we found that both DFS and overall survival of patients with elevated MPVLR were worse than those with low MPVLR. After multivariate analysis, only MPVLR was an independent prognostic factor. We have found that MPVLR is a more potent prognostic marker than PLR.

These are the limitations of our study. The essential limitation of this study is its retrospective design. Because it was performed in a single-center, the number of patients was low.

In conclusion, our study is the first study investigating the prognostic significance of MPVLR in patients with gastric cancer. High MPV was associated with poor DFS and OS in patients undergoing curative resection for gastric cancer. MPVLR is an independent prognostic factor in patients with gastric cancer. Thus,MPVLR may be used as an inexpensive, easy and feasible prognostic factor in clinical practice in patients with gastric cancer. In light of these findings, prospective studies with more patients are needed.

**Disclosures**

**Ethics Committee Approval:** The ethics committee approved the study of Ankara Diskapi Yildirim Beyazit Training and Research Hospital (Decision date: 04.02.2019 and number: 59/22).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors declare no competing interests.

**Authorship Contributions:** Concept – H.S.; Design – H.S.; Supervision – H.S.; Materials – H.S., S.T., T.E., E.C.; Data collection &/or processing – H.S., S.T.; Analysis and/or interpretation – H.S.; Literature search – H.S., M.A.; Writing – H.S., S.T.; Critical review – H.S., S.T.

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