The Importance of High Mean Platelet Volume in Patients with Gastric Cancer

Mide Kanseri Hastalarında Yüksek Ortalama Trombosit Hacminin Önemi

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ABSTRACT

Objective: The aim of this study was to investigate the use of mean platelet volume (MPV) as a marker in the diagnosis of gastric cancer and the prognostic importance of follow-up after treatment.
Methods: A total of 296 individuals (148 healthy and 148 patients having gastric cancer) between January 2010 and July 2018 were included the study. The possible importance of MPV elevation in diagnosis and prognosis of this cancer type was evaluated.
Results: The mean MPV of the healthy participants was 8.45±0.94 fL, while the mean preoperative MPV value of the patients with gastric cancer was 10.04±0.97 fL (p<0.001). The follow-up of MPV level in the gastric cancer patients revealed a significant change (p<0.001). No crucial difference was observed in MPV level according to tumor characteristics or cancer stage (p>0.05). A significant difference in the MPV level was seen with respect to overall survival, while no significant difference was found for disease free survival (p=0.009 and p=0.353).
Conclusion: High MPV level may be warning when evaluated together with the patient's clinical findings for the prognosis and diagnosis of gastric cancer. It is a noninvasive, simple hematology parameter that requires no additional cost and it may have even greater significance when used with other markers for gastric cancer.

Keywords: Gastric cancer, Mean platelet volume, Cancer survival

Received: 10.07.2020 **Accepted:** 06.15.2021

ÖZET

Amaç: Bu çalışmanın amacı, mide kanseri tanısında bir belirteç olarak ortalama trombosit hacminin (MPV) kullanımını ve tedavi sonrası izlemin prognostik önemini araştırmaktır.
Yöntem: Ocak 2010-Temmuz 2018 tarihleri arasında mide kanseri tanısıyla opere edilen 148 hasta ve 148 sağlıklı birey olmak üzere toplam 296 katılımcı çalışmaya dahil edildi. Bu kanser türünde MPV yüksekliğinin tanı ve prognozdaki olası önemi değerlendirildi.
Bulgular: Sağlıklı katılımcıların ortalama MPV değeri 8.45 ± 0.94 fL, mide kanserli hastaların ameliyat öncesi ortalama MPV değeri 10.04 ± 0.97 fL (p <0.001) idi. Mide kanseri hastalarının takibinde MPV düzeyi anlamlı bir değişiklik gösterdi (p <0.001). Tümör özelliklerine veya kanser evresine göre MPV düzeyinde önemli bir farklılık izlenmedi (p> 0.05). Genel sağkalım açısından MPV düzeyinde anlamlı bir fark görülürken, hastalıksız sağkalım için anlamlı bir fark bulunmadı (p = 0.009 ve p = 0.353).
Sonuç: Mide kanserinin prognozu ve tanısı için hastanın klinik bulguları ile birlikte değerlendirildiğinde yüksek MPV değeri uyarıcı olabilir. Ek maliyet gerektirmeyen noninvaziv, basit bir hematoloji parametresidir ve mide kanseri için diğer belirteçlerle birlikte kullanıldığında daha da büyük öneme sahip olabilir.

Anahtar Sözcükler: Mide kanseri, Ortalama trombosit hacmi, Kanser sağkalımı

Geliş Tarihi: 07.10.2020 **Kabul Tarihi:**15.06.2021

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doi:http://dx.doi.org/10.12996/gmj.2021.121

INTRODUCTION

Globally, gastric cancer is a widespread health problem; despite advances in diagnosis and treatment in recent years, it is the third leading cause of the deaths related to cancer (1).Half of the patients have lymph node metastases at the time ofdiagnosis and in cases of advanced disease; the 5-year survival is in the range of 10% to 15% (2). Although many clinical and laboratory parameters have been studied, early detection of gastric cancer remains a challenge. Studies on the prognosis of gastric cancer have demonstrated the value of factors such as age at diagnosis, nodal involvement, neural invasion, and CA19-9 levels (3).

Some parameters of the inflammatory response that can be observed in a routine hematological examination can be associated with poor outcomes in breast, ovarian, cervical, colorectal, and esophageal cancers. These include assessment of the role of mean platelet volume (MPV) (4). It is a simple and inexpensive laboratory test determined parameter by complete blood count (CBC).High MPV indicates increased platelet turnover and can be elevated due to various factors like hematological diseases, inflammation, and cancer. Platelets play an important and variable role in cancer progression. Therefore, MPV can be potentially used as a parameter in diagnosis and prognosis of many cancers (5-8).

We aimed to investigate whether high MPV has any diagnostic or prognostic value in gastric cancer.

MATERIALS and METHODS

Patients

A total of 148 healthy individuals and 148 patients with the diagnosis of gastric cancer and had undergone surgical treatment between January 2010 and July 2018 were included in the study. Healthy individuals did not have any disease and came for routine control. Gastric cancer patients at all stages were included in the study and the operation was open as a standard. The medical records of the individuals and patients were examined retrospectively. This study was approved by the local ethics committee (Project No: 2018/514/144/9). The medical records of the individuals and patients were examined retrospectively from hospital database. All the surgical specimens were evaluated by a gastrointestinal pathologist. The demographic and clinicopathological variables were evaluated age, gender, tumor size, number of resected and metastatic lymph nodes, type of gastrectomy, tumor stage, differentiation, metastases developed/detected after surgery, postoperative first month follow-up, and length of overall survival (OS) and disease-free survival (DFS). MPV data were evaluated as laboratory parameters. Patients with hematological or renal diseases, hypertension, heart related problems, chronic infections, hepatic impairment, or other types of cancer were excluded from the study.

Blood analysis

Peripheral venous blood (5-7 mL) was drawn into sterile tubes prepared with ethylenediaminetetraacetic acid. Blood samples were obtained between 6 and 7 am to ensure standardization and minimize the impact of hormonal factors. Hematological parameters were analyzed using a Sysmex XE-2100 haematology analyzer (manufactured by Sysmex Corp., Kobe, Japan) within 30 minutes of blood collection.

Statistical analyses

Statistical Package for the Social Sciences 21 (IBM Corp.; Armonk, NY, USA) were used for statistical analyses. Frequencies, percentage, mean, SD, median, andinterquartile range were used for descriptive statistical methods. Indefinite variables with typical distribution were compared through an independent sample t test, and those without normal distribution were assessed using the Mann-Whitney U test. A chi-square test was used to compare categorical variables. Analysis of survival time was performed using the Kaplan-Meier method and the intergroup comparison was evaluated with a log-rank test. Factors affecting survival were assessed using Cox regression analysis. The results were evaluated at a level of significance of $p<0.05$.

RESULTS

A total of 296 individuals were included in the study. There were 2 groups of age- and gender- matched participants: 148 (50%) healthy individuals who came for routine check-up and 148 (50%) gastric cancer patients. No significant difference was found on platelets count in CBC results between two groups. The mean MPV of the healthy participants was 8.45±0.94fL, while the mean preoperative MPV of the individuals with gastric cancer was 10.04±0.97fL ($p<0.001$). The median OS and DFS in gastric cancer patients were 676.50 [684.75] days and 327.00 [261.00] days, respectively. Demographic and clinical parameters according to preoperative median MPV values in gastric cancer patients are summarized in table 1.

The follow-up of MPV level in the gastric cancer patients revealed a significant change. The mean level was 10.04 ± 0.97fL in the preoperative period, 10.59±1.15 fL on the third postoperative day ($p<0.001$), 9.63±1.05 fL during the first postoperative week ($p<0.001$), and 9.96±1.73 fL in the first postoperative month ($p=0.012$) in gastric cancer patients.

The mean MPV level of the surviving gastric cancer patients was 10.09±0.89fL, while that of the patients who died was 9.98±1.08fL ($p=0.484$). Metastasis was detected in 39(26%) patients during follow-up. The mean MPV was 9.95±1.11 for patients with metastasis and 10.08±0.93 patients without metastasis ($p=0.524$). Similarly, no statistically significant difference in MPV level was found using the parameters of tumor size, presence of metastatic lymph node, stage of tumor, or degree of differentiation.

Survival analyses

The analysis of survival in the gastric cancer patients was conducted using the median MPV level and Kaplan-Meier survival curves for OS and DFS. The results are provided in Figure 1a and Figure 1b. A significant difference in the MPV level was seen with respect to OS, while no significant difference was found for DFS ($p=0.009$ and $p=0.353$, respectively, log-rank test). The result of the Cox regression analysis investigating the effect of MPV on OS was significant ($p=0.011$), while it was not significant for DFS ($p=0.389$). The results of the model analysis for OS and DFS are summarized in table 2.

Table 1: Demographic and clinical parameters according to preoperative median MPV values in gastric cancer patients

	n	Decreased MPV (<10.20)	n	Increased MPV (≥10.20)	p
Gender					
Female	72	23 (31.94%)	76	30 (39.47%)	0.340[a]
Male		49 (68.06%)		46 (60.53%)	
Age					
<65 years	72	36 (50.00) %	76	39 (51.32%)	0.873[a]
≥65 years		36 (50.00) %		37 (48.68%)	
Age (years)	72	63.00±11.13	76	64.31±11.95	0.558[b]
Tumor size					
<5 cm	72	25 (34.72%)	76	23 (30.26%)	0.562[a]
≥5 cm		47 (65.28%)		53 (69.74%)	
Resected lymph node		19.50 [13.00]		20.00 [12.75]	0.459[c]
Metastatic lymph node		3.00 [11.00]		3.00 [8.50]	0.929[c]
Gastrectomy type					
Subtotal	72	29 (40.28%)	76	26 (34.21%)	0.445[a]
Total		43 (59.72%)		50 (65.79%)	
Stage					
Stages 1 and 2		29 (40.28%)	76	39 (51.32%)	0.178[a]
Stages 3 and 4		43 (59.72%)		37 (48.68%)	
Differentiation					
Poor	72	37 (51.39%)	76	41 (53.95%)	0.292[a]
Moderate		26 (36.11%)		31 (40.79%)	
Well		9 (12.50%)		4 (5.26%)	
Survival					
Died	72	32 (44.44%)	76	31 (40.79%)	0.653[a]
Survived		40 (55.56%)		45 (59.21%)	
Presence of metastasis	72				
Absent		51 (70.83%)	76	58 (76.32%)	0.449[a]
Present		21 (29.17%)		18 (23.68%)	
1st postoperative month follow-up					
Decreased	72	32 (44.44%)	76	41 (53.94%)	*0.459[a]*
Increased		38 (52.78%)		34 (44.74%)	
Unchanged		2 (2.78%)		1 (1.32%)	
Overall survival (days)	72	627.00 [666.25]	76	698.00 [662.00]	0.211[c]
Disease-free survival (days)	21	325.00 [228.50]	18	441.00 [293.00]	0.091[c]

[a]Chi-square test; [b]Independent sample t test,[c]Mann-Whitney U test. MPV: Mean platelet volume.

Table 2: Cox regression analysis performed for overall survival and disease-free survival

	OS					DFS				
Variables	**β**	**Standard error**	**p**	**Exp (β)**	**95% confidence interval**	**β**	**Standard error**	**p**	**Exp (β)**	**95% confidence interval**
Gender Male or female	-0.354	0.242	0.154	0.708	0.441-1.138	0.924	0.500	0.065	2.518	0.945-6.713
Age (years) <65 or ≥65	0.210	0.233	0.366	1.234	0.782-1.948	0.205	0.434	0.638	1.227	0.524-2.874
Tumor size (cm) <5 or ≥5	0.225	0.247	0.363	1.252	0.772-2.032	-0.142	0.591	0.810	0.867	0.272-2.762
Gastrectomy Subtotal or total	-0.521	0.246	*0.035*	0.594	0.367-0.963	-0.161	0.427	0.706	0.851	0.369-1.966
Differentiation Moderate	-0.478	0.257	0.062	0.620	0.375-1.025	-0.066	0.435	).880	).936	).399-2.195
Well	0.275	0.367	0.454	1.317	0.641-2.706	-0.342	0.763	).654	).710	).159-3.168
Staging Stage1,2 or 3,4	-0.367	0.251	0.144	0.693	0.424-1.134	0.247	).571	).665	).781	).255-2.392
Decreased MPV (<10.20)	-0.037	0.239	0.878	0.964	0.604-1.539					
Increased MPV (≥10.20)						1.083	).462	*).019*	).339	).137-0.837
MPV during follow-up Decreased or did not decrease	0.792	0.273	*0.004*	2.208	1.294-3.770	0.071	0.426	0.867	1.074	0.466-2.477

**OS: Overall Survival, DFS: Disease Free Survival,* MPV: Mean platelet volume

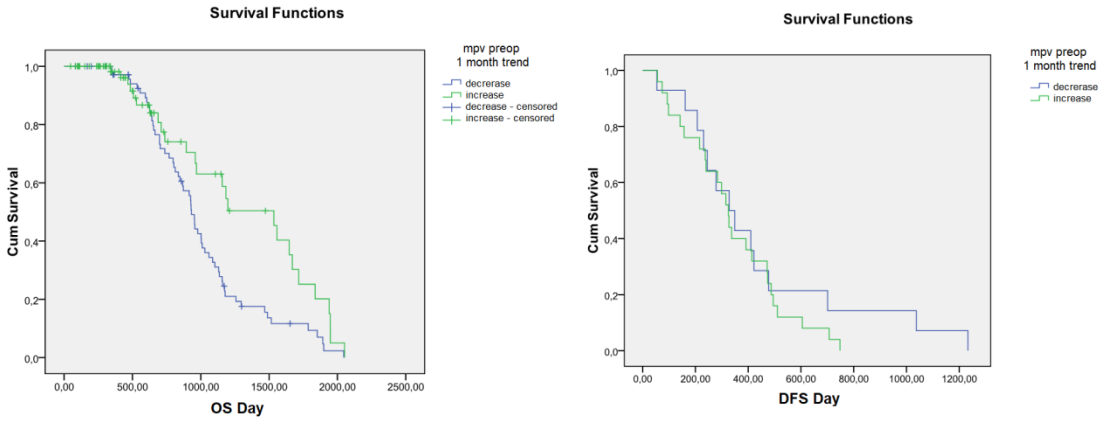

Figure 1: a) Kaplan-Meier curve of mean platelet volume for overall survival.
b) Kaplan-Meier curve of mean platelet volume for disease-free survival.
*DFS: Disease-free survival; MPV: Mean platelet volume; OS: Overall survival.

DISCUSSION

This study analyzed the utility of MPV values in the diagnosis, follow-up, and prognosis of patients with gastric cancer obtained as part of a routine hematological examination that would not require any extra invasive intervention or expenditure.

Experimental and clinical data suggest that the activation of platelets has a positive effect on tumor growth and metastatic spread by adjuvant neoangiogenesis, disruption of the extracellular matrix, and release of bound molecules and variables related to growing (5). In addition to the effect of platelet activation on cancer, a numerical increase seen with other abnormal test results has diagnostic value for an underlying vicious problem (9). This suggests the potential role of platelet-related aspect as a marker for use in cancer diagnosis and in post-treatment follow-up.

An elevated MPV value can be evaluated as a result of systemic inflammatory response, having a crucial status in the progression and development of various cancer types by expediting angiogenesis, proliferation of tumor cells, metastasis of cancer, and the response of cancer cells to treatment (10). In our study, we found higher MPV values in patients with gastric cancer than healthy individuals. The proliferation of megakaryocytes is mediated by numerous cancer-releasing pro-inflammatory cytokines, such as interleukin (IL), IL-1, IL-3 and IL-6 (5).

Research has also demonstrated that larger platelets were more reactive than small ones and that the probability of clustering may lead to thrombosis. An elevated MPV level, which is an indicator of large platelet size, has been reported in patients with myocardial infarction and cerebrovascular embolism (11).

It has been observed that there is a greater proportion of large platelets in cancer patients and may cause an increase in MPV as young, metabolically active platelets enter the circulation (12). Recent findings suggest that MPV may be a valuable marker for the diagnosis of various cancers (13-15). It is a confirmed marker of platelet function and activation that routinely evaluated in hematological analyses. In this study, MPV values were higher in gastric cancer patients at the time of diagnosis than those of healthy individuals. The initial postoperative increase in the MPV level was probably due to the surgery, and that it was decreased below the value measured at the time of diagnosis by the first postoperative month.

There are proven prognostic markers in cancer patients, such as tumor diameter, staging with the TNM classification of malignant tumors, nodal involvement, neural invasion, and tumor markers (16). Several other parameters have also been studied for prognostic significance (16,17). The role of MPV in determining the prognosis of cancer is the subject of several studies and its prognostic value in pancreatic, colorectal and bladder cancers has been demonstrated (18-20). While an increased MPV was associated with a better prognosis in bladder cancer, high MPV value in colorectal and pancreatic adenocarcinomas was associated with a poor prognosis.

Some studies have suggested that MPV has a probable prognostic value in gastric cancer (5,12,21). In these studies, a lower MPV value was shown to be associated with better survival in cases of both resectable and nonresectable gastric cancers. This survival advantage was significant for both OS and DFS. In our study, it was observed that a high MPV value was significantly associated with OS, but not with DFS. Since a high MPV value is a result of systemic inflammatory response in gastric cancer patients, it is expected to decrease after surgery. If the postoperative MPV value does not decrease, it may be associated with a poor prognosis.

Our results suggest that MPV can discriminate patients with gastric cancer from healthy individuals. In addition, changes in MPV value between preoperative and postoperative period may be related to survival. Although the decreasing MPV levels contributed positively to overall survival (OS), no significant difference was shown on DFS. The primary limitation of this retrospective study is that it could not prove whether there was any inflammatory focus other than the tumor that might have an effect on MPV.Also, the results cannot be generalized because this study is single-centered and includes only Turkish participants.Further investigation is needed to validate our results.

In conclusion, although MPV is a non-specific parameter, this non-invasive and inexpensive marker may be useful on the diagnosis and prognosis of gastric cancer. When combined with clinical symptoms, it may raise the suspicion of gastric cancer, and upper gastrointestinal endoscopy can be performed, which is the gold standardfor early detection.

Conflict of interest

No conflict of interest was declared by the authors.

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