Prognostic Value of Mean Platelet Volume in Glioblastoma Multiforme

Glioblastoma Multiforme'de Ortalama Platelet Hacminin Prognostik Değeri

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ABSTRACT

Objectives: Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor. Despite optimal treatment (maximal surgical resection, adjuvant radiotherapy and chemotherapy), the prognosis is very poor. Beside known prognostic factors, there is no method at the time of diagnosis to predict recurrence. We aimed to identify mean platelet volume (MPV) as an indicator of prognosis in GBM.
Methods: One hundred and seven patients who were diagnosed with GBM histopathologically, admitted to the medical oncology clinic were included. MPV values were recorded for all patients at diagnosis. Kaplan-Meier method and Cox regression were used to evaluate the prognostic impact of MPV.
Results: Kaplan-Meier survival curves showed that patients belonging to the high-MPV group had a worse median OS (14 month versus 20 month, P=0.004). MPV was an independent prognostic factor in GBM.
Conclusions: MPV is a cheap, easily accessible and reproducible test that can be used prognostically in GBM patients before treatment.

Key Words: Glioblastoma multiforme, platelet, prognosis

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ÖZET

Amaç: Glioblastoma multiforme (GBM) en sık görülen primer malign beyin tümörüdür. Optimal tedaviye rağmen (maksimal cerrahi rezeksiyon, adjuvan radyoterapi ve kemoterapi) prognoz oldukça kötüdür. Bilinen prognostik faktörlerin yanı sıra, tanı anında nüksü öngörmek için herhangi bir yöntem yoktur. Bu çalışmada GBM'de ortalama trombosit hacmininin (MPV) prognoz ile ilişkisini değerlendirmeyi amaçladık.
Yöntem: Histopatolojik olarak GBM tanısı alan ve medikal onkoloji kliniğine başvuran 107 hasta çalışmaya dahil edildi. Hastaların tanı anındaki MPV değerleri kaydedildi. MPV'nin prognostik etkisini değerlendirmek için Kaplan-Meier yöntemi ve Cox regresyonu kullanıldı.
Bulgular: Kaplan-Meier sağkalım eğrileri, yüksek MPV grubuna ait hastaların daha kısa sağkalıma sahip olduğunu gösterdi (14 ay vs 20 ay , P = 0.004).MPV, GBM'de bağımsız bir prognostik faktördür.
Sonuç: GBM hastalarında, tedavi öncesi MPV değerleri prognostik olarak kullanılabilecek ucuz, kolay erişilebilir ve tekrarlanabilir bir testtir.

Anahtar Sözcükler: Glioblastoma multiforme, platelet, prognoz

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor (1). Although optimal treatment strategies, the prognosis is quite poor; five-year survival rate is approximately 5%. Total surgical resection followed by concurrent chemoradiotherapy and adjuvant chemotherapy constitute the optimal treatment strategy. Age, performance status, optimal surgical treatment, isocitrate dehydrogenase-1 mutation (IDH-1) and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status are prognostic factors (2,3). However, there is no method to predict recurrence at time of diagnosis.

In addition to their roles in hemostasis, platelets are also involved in inflammation and cancer. Cancer activated platelets contribute to the progression of tumorigenesis, angiogenesis and the development of metastasis (4). High platelet levels have been shown to be associated with poor prognosis in many cancers.(5-7).Mean platelet volume (MPV) is a measure of platelet size and a good indicator of platelet activity. Studies found that changes in MPV values are associated with prognosis in many cancers (8-10). To our knowledge there are no studies that evaluate the role of MPV values as a prognostic factor in GBM. In this study we aimed to investigate MPV values as a prognostic factor in GBM.

MATERIALS and METHODS

Study population and exclusion criteria

The study included 107 patients who were diagnosed with GBM histopathologically, admitted to the medical oncology department of Gazi University Medical Faculty Hospital between April 2015 and January 2017. Subtotal or total resection or biopsy was used for histopathologic diagnosis. Patients who previously received any treatment for GBM, have any disease or taken any drug that would change MPV values, who were under 18 years, and had other malignancies were excluded. Ethics committee approval was received for this study from the ethics committee of Gazi University Faculty of Medicine (Date: 16 March 2018, Approval Number: 24074710-13).

Data collection

Patients data were recorded by retrospectively screening of patient files and hospital information system. Hemoglobin, leukocyte (WBC), lymphocyte, neutrophil, platelet, MPV, red blood cell distrubition width (RDW), neutrophil-lymphocyte rate (NLR) values at the diagnosis were recorded. Overall survival (OS) was calculated from the date of diagnosis to date of death. For patients who were still alive at the time of analyze, it was defined as the duration from the date of diagnosis until March 2018.

Statistical analysis

Histogram and Shapiro-Wilk's tests were used to analyze the variables. Frequency, mean ± standard error, median (range) or median (IQR) values were given according to the variables distribution characteristics. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off value of MPV to identify sensitivity and specificity for the OS prediction. Comparisons of categorical variables between groups were made using Student's t-tests or Mann-Whitney U tests according to distribution characteristics in comparison of Chi-Square and continuous variables. Cox proportional hazards model was used to evaluate the effect of the variables on the survival. Hazard ratios (HRs) estimated using Cox analysis were reported as relative risks with their corresponding 95% confidence intervals (CIs). Survival curves were obtained using the Kaplan-Meier method and compared by the log-rank test. Statistical significance level was accepted as $p < 0.05$ for all analyses. Statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL).

RESULTS

The study were included 107 cases. The mean age was 53,1 (range 26-76) years. There were 71 males (66,4%) and 36 females (33,6%). Numbers of patients were diagnosed by biopsy, subtotal resection and total resection were 9 (8,4%) , 87 (81,3%) and 11 (10,3%) respectively.

A ROC curve for OS prediction was plotted to verify the optimal cut-off value for MPV, which was 7.27 fL (Figure 1). MPV predicts cancer prognosis with a sensitivity of 71.6% and a specificity of 69.7% (AUC = 0.678; 95% CI: 0.565–0.790 ; p = 0.003). Patients were divided into 2 groups: patients with MPV ≤ 7.27 fL as group 1 and patients with MPV > 7.27 fL as group 2. There were 45 (42.1%) patients with MPV ≤ 7.27 fL and 62 (57,9%) patients with MPV > 7.27 fL. Demographic, clinical and laboratory data of groups are shown in Table 1.

Table 1. Comparison of demographic, clinical and laboratory data of groups

	MPV ≤ 7.27 *(n=45)*	**MPV > 7.27 *(n=62)***	***P value***
Female/male	15/30	21/41	0.561
Age (years)	52.66±1.89	53.45±1.36	0.788
Family history n (%)	2(4.4)	4(6.5)	0.501
Hemoglobin (g/dL)	13.38±0.20	13.20±0.19	0.539
Platelet ($\times10^9$/L)	291.44±12.28	258.93±9.42	*0.035
WBC ($\times10^9$/L)	8.71±0.49	9.69±0.48	0.109
Neutrophil ($\times10^9$/L)	6.04±0.43	6.88±0.46	0.139
Lymphocyte ($\times10^9$/L)	2.21±0.42	1.94±0.90	0.698
RDW	14.75±0.30	16.87±0.90	0.092
PLR	162.05(125.2)	134.07(81.8)	*0.045
NLR	3.29(2.17)	3.11(3.11)	0.830
RPR	0.048(0.02)	0.059(0.03)	*0.006

* indicates that there was a statistically significant difference. Parameters were expressed as n (%), mean (SE) or median (IQR). MPV = mean platelet volume; WBC = white blood cell count; RDW = red cell distribution wide; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; RPR = red cell distribution width-to-platelet ratio.

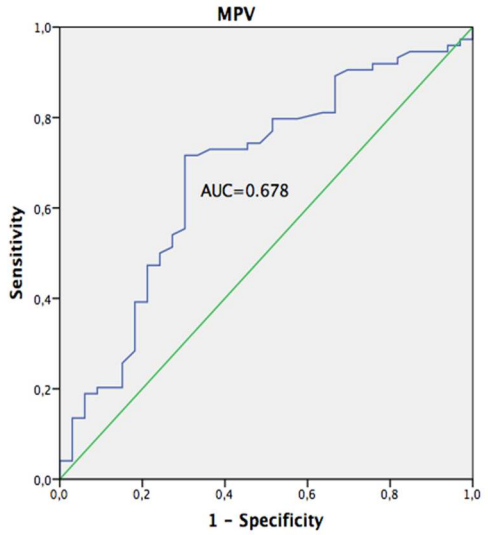

Figure 1. Optimized cut-off value was determined for MPV using standard ROC curve analysis

The median follow-up time of the patients was 20.72 months (range 1-196) and 93 (86.9 %) patients died. Platelet, PLR and RPR are different between groups (p=0.035; p=0.045; p=0.006), but there was no significant difference in the univariate analysis of overall survival (p=0.806; p=0.954; p=0.483). When the effect of the variables on the survival was determined by the cox proportional hazards model, MPV was an independent prognostic factor in patients with GBM (HR: 2.146; 95% CI: 1.311-3.432; p =0.002) (Table 2). Kaplan-Meier survival analysis was performed to calculate overall survival due to MPV levels. Kaplan-Meier survival curves showed that patients belonging to the high-MPV group had a worse median OS (14 month versus 20 month; P=0.004; Figure 2)

Table 2. Results of the univariate analysis of overall survival in patients with glioblastoma multiforme

	Hazard Ratio	95% CI	*P value*
Platelet	1	0.996-1.003	0.806
MPV (fl) (≤ 7.27 versus > 7.27)	2.146	1.311-3.432	0.002
PLR	1	0.997-1.003	0.954
RPR	0.55	0.000-180.55	0.483

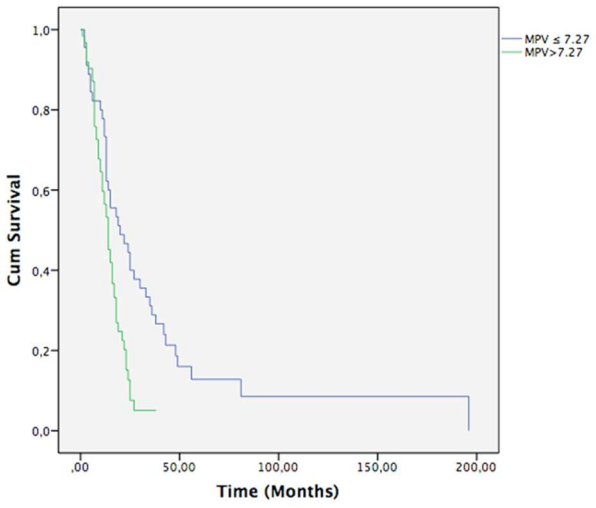

Figure 2. Kaplan-Meier analysis curve for overall survival regarding baseline MPV

DISCUSSION

The prediction of the prognosis of the GBM is an important role in follow-up and treatment. It is suggested that MPV is a useful marker for determining prognosis in many cancers. This study showed that MPV elevation is associated with poor prognosis in GBM. To our knowledge, this is the first study that evaluates MPV in GBM.

GBM is the most common and most fatal primary brain tumor. Despite new treatment modalities, overall survival is not satisfactory in GBM. Concurrent chemoradiotherapy and adjuvant chemotherapy is the standart treatment after diagnosis. Although median age at dignosis is approximately 65, median age was 53 in our study. The majority of the patients were males in accordance with the literature.

Beside known prognostic factors, there is no easily accessible method for predicting prognosis of the GBM. MPV is a measure of platelet size and a good indicator of platelet activity (11). Platelets with large volumes are metabolically more active. high values can be indicative of aggressive disease progression. Previous studies have shown that pretreatment high MPV levels associated with short survival in colon, breast and pancreas cancer (12-14). But this relationship in GBM have not been evaluated before. Similar to these reports, we found that pre-treatment high MPV levels correlated with short survival in GBM.

Platelets play an active role in angiogenesis and metastasis as well as in hemostasis and thrombosis. Although they have antiangiogenic factors, proangiogenic factors predominate on the tumor microenviroment (15). Vascular Endothelial Growth Factor (VEGF), which is one of the proangiogenic factors, is also very important for GBM which is a vascular tumor (8). VEGF, one of the angiogenic markers, is not detected in low grade astrocytomas, but is found in high grade gliomas, especially in necrotic regions (16). Platelets of patients with GBM are more prone to VEGF secretion and patients with high VEGF levels are reported to have worse prognosis (17). A study by Brockmann and et al. [18] found that preoperative high platelets counts were related with short survival in GBM. Though, in Boonyawan and et al. (19) found that GBM patients with high platelet counts after chemoradiotherapy had short survival. Unlike the literature, no significant prognostic contribution of platelet level was found in our study. Although the number of platelets is not high, a high level of MPV indicating platelet activation may be indicative of short survival.

Despite unknown mechanisms underlying the association between MPV levels and prognosis in GBM, MPV may provide early information on clinical outcome in GBM at the time of diagnosis. Patients with high pretreatment MPV levels may be followed more closely and may be treated more intensely.

CONCLUSION

MPV is a cheap, easily accessible and reproducible test,that can be used prognostically in GBM patients before treatment. However, the underlying mechanisms of MPV and prognosis relationship in GBM patients need to be elucidated.

Conflict of interest

No conflict of interest was declared by the authors.

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