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The effect of preoperative prognostic nutritional index on outcome in glioblastoma multiforme patients

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Ethics Committee Approval
The Ethics Committee approved the study protocol at the University of Health Sciences, Ümraniye Education and Research Hospital, (Date: 17.06.2021, Number: B.10.1.TKH.4.34.H.GP.0.01/207).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor subtype with a poor prognosis despite various treatments. Some prognostic markers on survival (such as age, Eastern Cooperative Oncology Group Performance Score (ECOG-PS), isocitrated hydrogenase (IDH) status, alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutation status, possibility of extensive surgery) have been defined. Prognostic Nutritional Index (PNI) has been evaluated in various cancers (such as lung, esophagus, and pancreas), and patients with a low PNI score have been associated with a poor prognosis for overall survival (OS). Our study aimed to examine the effectiveness of molecular and demographic characteristics and preoperative PNI score that may affect OS in GBM patients.
Methods: In this retrospective cohort study, GBM diagnosed patients who were 18 years old or older, were included in the study. We measured their pretreatment PNI score and performed multivariate Cox regression analyses of OS in GBM patients.
Results: A total of 107 patients were included in the study. Median age was 58 (range, 32-83) years. 72 patients (67.3%) were male and 35 patients (32.7%) were female. The mean preoperative PNI level was calculated as 50.5. The median overall-survival (mOS) was 19.7 months and the median time to progression (mTTP) was 8.1 months. There was no statistically significant result on overall survival in the univariate analysis of patients with PNI>50.5 (P=0.121). In multivariate analysis, being 70 years or older (P=0.012), IDH-1 wild and ATRX mutant patients (P=0.016), IDH-1 mutant and ATRX wild patients (P=0.037), and TTP 12 months and older (P<0.001) were considered as independent risk factors on overall survival.
Conclusions: In our study, the effect of preoperative PNI score on survival could not be demonstrated. Further studies are needed to elucidate the potential impact of PNI on outcomes in patients with GBM.

Keywords: Glioblastoma multiforme, Prognostic nutritional index, IDH, ATRX, Overall survival

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Introduction

Glioblastoma multiforme (GBM), is the most common primary malignant brain tumor subtype with a poor prognosis despite various treatments. With standard treatments of extensive tumor resection followed by radiotherapy concurrent with temazolamide, the median overall survival (mOS) is around 15 months [1, 2]. Some prognostic markers of survival such as age, ECOG-PS, isocitrated hydrogenase (IDH) mutation, alpha thalassemia/ mental retardation syndrome X-linked (ATRX) mutation status have been defined for the possibility of extensive surgery [3]. While IDH mutation is detected in 90% of secondary GBM, its incidence is rare in primary GBM and the presence of IDH mutation is associated with a good prognosis. Similarly, while ATRX mutation is observed more frequently in secondary GBM, and rare in primary GBM, the prognostic existence of the ATRX mutation is not yet proven [4, 5]. More prognostic markers are needed for the poor survival of the disease. PNI is an indicator that evaluates the patient's nutritional and immune status, calculated with the following formula: 10 x serum albumin (g/dl) + 0.005 x total lymphocyte count (per mm^3). There are studies emphasizing the prognostic importance of preoperative malnutrition and inflammation status on OS in various cancers [6-8]. Although some studies showed preoperative PNI score as an independent risk factor in OS of GBM patients, significant difference was not obtained in other cancers [9-12]. Our study aimed to examine the effectiveness of molecular and demographic characteristics, and preoperative PNI score that may affect OS in GBM patients.

Materials and methods

107 GBM patients diagnosed at University of Health Sciences Umraniye Training and Research Hospital and Marmara University School of Medicine between 2012-2020 were included in the study. The Ethics Committee approved the study protocol at the University of Health Sciences, Ümraniye Education and Research Hospital, (Date: 17.06.2021, Number: B.10.1.TKH.4.34.H.GP.0.01/207). Eligible patients for the study were aged 18 years and older, being diagnosed with histologically/cytologically proven high-grade glioma. Exclusion criteria were presence of secondary primary malignancy, having signs of active infection or chronic liver disease.

Age, gender, ECOG-PS, laboratory values, treatment regimens and survival data of the patients were obtained retrospectively.

Statistical analysis

Categorical variables are presented as number of patients and percentages. The Kaplan-Meier method was used to estimate OS. Log-rank test was used for comparison of the survival functions for each variable. For the assessment of prognostic variables, Cox regression model is used for proportional hazards, calculating the hazard ratio (HR) and confidence intervals of 95%. The selection of variables for Cox model was carried out using the significance obtained from the univariate analysis, considering the significance level of $P \leq 0.10$. All reported *P*-values were two-sided and a *P*-value <0.05 was considered of statistical significance. These analyses were performed using SPSS version 18 (SPSS Inc., Chicago, USA).

Results

A total of 107 patients were included in the study. Median age was 58 (range, 32-83) years. 72 patients (67.3%) were male and 35 (32.7%) were female. There were 74 patients (69.2%) with ECOG-PS of 0-1, and 33 patients (31.8%) with ECOG-PS 2 or above. While diagnosis was made by stereotactic biopsy in 18 patients (16.8%), incomplete surgery was performed in 37 patients (34.6%), and extensive resection was performed in 52 patients (48.6%). 99 patients (92.5%) received adjuvant chemoradiotherapy (radiotherapy + temozolamide), continued with temozolamide, 1 patient (0.9%) received only adjuvant radiotherapy, whereas 7 patients (6.5%) did not receive any treatment postoperatively. From 90 patients (84.1%) examined for IDH-1 mutation, 7 patients (6.5%) were found to be mutant and 83 patients (77.6%) were of wild type. From 84 patients (78.5%) investigated for ATRX mutation, 18 patients (16.8%) were found to be mutant and 66 patients (61.7%) were of wild type (Table 1). The mean serum albumin and lymphocyte level measured preoperatively was 3.9 g/dl and 2100/mm^3, respectively. The mean preoperative PNI level was calculated as 50.5 (Table 2). The median overall-survival (mOS) was 19.7 months and the median time to progression (mTTP) was 8.1 months (Figure 1, 2).

Table 1: Patients characteristic

	n (%)
Gender	
Male	72 (67.3)
Female	35 (32.7)
Age	58 (range, 32-83)
ECOG PS 0	28 (26.2)
1	46 (43)
2	23 (21.5)
3	8 (7.5)
4	2 (1.9)
Surgery; stereotactic biopsy	18 (16.8)
Incomplete resection	37 (34.6)
Maximal resection	52 (48.6)
Adjuvant Treatment	
Crt+temozolamid	99 (92.5)
Radiotherapy	1 (0.9)
No treatment	7 (6.5)
IDH-1 Mutation	90 (84.1)
Mutant	7 (6.5)
Negative	83 (77.6)
ATRX Mutation	84 (78.5)
Mutant	18 (16.8)
Negative	66 (61.7)

Crt: Chemoradiotherapy

Table 2: Patients' serum laboratory parameters

Parameters	Median values
WBC	7800 mm^3
Neutrophil	5250 mm^3
Lymphocyte	2100 mm^3
Thrombocyte	240000 mm^3
Albumin	3.9 g/dl
PNI	50.5

WBC: White Blood Cell

Figure 1: Kaplan-Meier curves in GBM patients. The median overall-survival (mOS) was 19.7 months

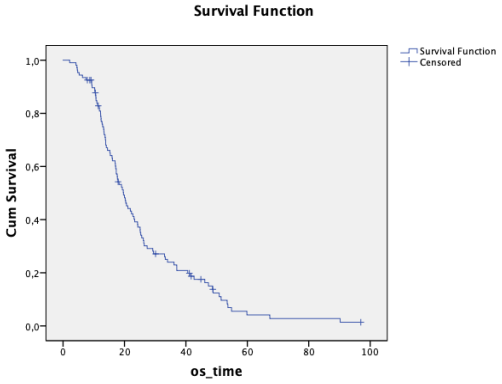
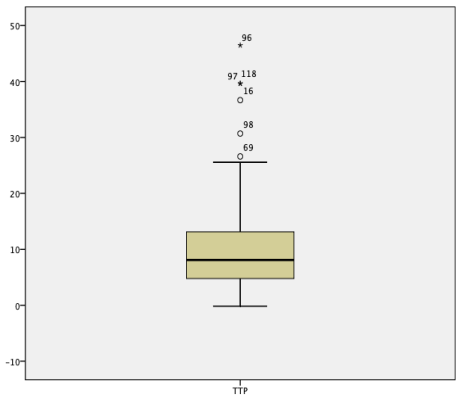


Figure 2: The median time to progression (mTTP) was 8.1 months



In univariate analysis, being 70 years or older, ECOG-PS-2 or above, IDH-1 wild and ATRX mutant patients, IDH-1 mutant and ATRX wild patients, and TTP 12 months and above were found to have significant effect on overall survival (P=0.027, P=0.004, P=0.006, P=0.064 and P<0.001, respectively). In multivariate analysis, being 70 years or older, IDH-1 wild and ATRX mutant patients, IDH-1 mutant and ATRX wild patients and TTP 12 months and older were considered as independent risk factors on overall survival (P=0.012, P=0.016, P=0.037 and P<0.001, respectively) (Table 3). There was no statistically significant result in overall survival in the univariate analysis of patients with PNI >50.5 (P=0.121).

Table 3: Univariate and Multivariate analysis of potential factors associated with OS

		Univariate		Multivariate
	n	OS(months)	*P*-value	*P*-value
Age				
>70	20	20.6 (17.3-23.9)	0.027	0.012
<70	87	12.8 (10.8-14.9)		
Gender				
Female	35	25.1 (18.2-31.9)	0.198	
Male	72	17.7 (14.7-20.6)		
ECOG PS				
0-1	74	21.9 (17.7-26)	0.004	0.330
2-3-4	33	14.4 (9.7-19.1)		
IDH-1 wild, ATRX mutant	15	12.8 (10.2-15.4)	0.006	0.016
IDH-1 mutant, ATRX wild	4	26.1 (0-57)	0.064	0.037
IDH-1 wild, ATRX wild	58	20.4 (18.2-22.5)	0.867	
Time to progression				
More than 12 months	34	34 (21-46.9)	<0.001	<0.001
Less than 12 months	76	15.3 (12.4-18.2)		
PNI				
>50.5	50	23.1 (14.3-31.8)	0.121	
<50.5	49	19.6 (16.8-22.5)		

Discussion

Primary GBMs usually have a poor prognosis. Despite local and systemic treatments (re-resection, re-irradiation, targeted therapy and systemic chemotherapy), the median survival is less than 15 months [1, 13]. It has been stated in various studies that some genetic and molecular markers such as O-6-methylguanine-DNA methyltransferase (MGMT) status, IDH-1, phosphatase and tensin homolog (PTEN), p53, ATRX and telomerase reverse transcriptase gene promoter (TERT) are prognostic factors [13, 14].

However, it is not always possible to assess these molecular and genetic markers. For these reasons, there is a need for prognostic tools of simple, applicable and inexpensive methods that predict which patients will get a better response from the treatment.

The Prognostic Nutritional Index (PNI) is mainly a marker that evaluates the nutritional and immunological status of patients who undergone gastrointestinal surgery, and is calculated by serum lymphocyte and albumin levels [15]. PNI has been evaluated in various cancers (such as lung, esophagus, and pancreas), and patients with a low PNI score have been associated with a poor prognosis for OS [16-18]. There are several studies evaluating the prognostic effect of the PNI score in GBM patients. In a GBM related study by Xu et al. [10], preoperative PNI score (PNI >48) was found to be an independent predictive factor for OS.

In another study, Zhou et al. evaluated the preoperative PNI score in GBM patients and found a prognostic effect on OS in the group with PNI >44.4 [11]. In our study, patients with PNI >50.5 had numerically better OS, however statistical significance could not be proven. In the literature review by Ding et al., statistically significant results were not obtained on OS in the group with PNI >44.4 [19]. Rigamonti et al. [14] emphasized the same results, although the OS results were numerically better in patients with PNI >45.9. Similarly, in the study of He et al. [20], statistical significance was not found, although OS results of PNI >52.55 group were numerically better. This situation may be masked by the fact that the patient population is older than other studies, and other genetic and molecular factors have more negative effects on OS.

Presence of IDH mutation is less frequently detected in primary GBM and is associated with good prognosis [4]. In a meta-analysis of nine studies evaluating IDH mutation status, it was concluded that the presence of IDH mutation was prognostic and correlated with improved survival outcomes [21]. Another molecular marker, ATRX mutation, is seen more frequently in low-grade gliomas and secondary GBM, but is less common in primary GBM patients [22]. The effect of ATRX mutation on survival in GBM patients was investigated in various studies. In the study of Cai et al. [23], better survival results were obtained in ATRX wild and IDH mutant GBM patients. Similarly, in the study of Leeper et al. [24], worse survival results were obtained in ATRX wild, glioma patients. In accordance with the literature, the best survival results were obtained in the IDH mutant and ATRX wild groups, while the worst survival results were obtained in the ATRX mutant and IDH wild groups in our study.

Limitations

Having retrospective design might cause selection bias in the study. Relatively low number of recruited patients and having immunohistochemical ATRX and IDH mutations in 74.8% of the patients, but not in the entire patient population are other limitations. The prognostic effect of other molecular markers could not be evaluated.

The existing data support further investigation on how the patients can be followed closely according to the PNI score, and their nutritional status and survival can be forced for improvements in future.

Conclusion

Despite being an easily calculated, cost-effective indicator and its promising effect on outcomes in earlier studies, PNI could not be shown to have positive impact on overall survival in our study. More studies are needed to assess whether PNI score is prognostic.

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