CLINICAL SCIENCE OF NUTRITION
Original Article
DOI: 10.62210/ClinSciNutr.2024.95

The effect of immunonutrition support on the prognostic nutritional index in the postoperative period in brain tumors

Müge Akmansu[1], Yasin Korucu[1], Semanur Dabak Gönülal[1]

[1]Department of Radiation Oncology, Gazi University, Ankara, Türkiye

Cite this article as: Akmansu M, Korucu Y, Dabak Gönülal S. The effect of immunonutrition support on the prognostic nutritional index in the postoperative period in brain tumors. *Clin Sci Nutr*. 2024;Early View:1-14.

ABSTRACT

Objective: The prognostic nutritional index (PNI) reflects the immunological response and nutritional status. We evaluated the effect of immunonutrition on PNI in patients with brain tumors receiving chemoradiotherapy and immunonutritional support.

Methods: Demographic, laboratory and clinical data were collected retrospectively from 30 consecutive brain tumor patients who received brain chemoradiotherapy between 2019 and 2022 in our clinic and who were given immunonutrition support during their treatment. The cut-off PNI value before adjuvant therapy was calculated in patients who received immunonutrition support in the postoperative period and compared with the PNI values after adjuvant therapy.

Results: While glioblastoma patients constitute the majority (60%) of all patients diagnosed as pathological, different histopathological brain tumors were also included in the study (meningioma, oligodendroglioma). The mean albümin value before adjuvant treatment was 4.04 g/dL, while the mean albümin value after adjuvant treatment increased to 4.16 g/dL (p=0,057). The optimal cut-off value for PNI was found to be 45.5 by ROC analysis. PNI was calculated as 49.38 ± 6.03 SD before adjuvant treatment and 49.40 ± 6.12 SD after adjuvant treatment (p>0.05).

Retrospective analysis was conducted on over 30 HGG patients who did not receive immunonutritional supplementation containing Arg/gln/HMB (Arginine/glutamine/Beta-Hydroxy Beta-Methylbutyrate). Interestingly, the analysis revealed that the average PNI was 45.15 before adjuvant therapy and decreased to 42.26 after adjuvant therapy, indicating a statistically significant decline in PNI among those without immunonutritional supplementation. This finding suggests a potential beneficial impact of immunonutritional supplementation on PNI.

Conclusions: Immunonutrition support has positive effects on PNI and albumin levels in brain tumor patients who will undergo postoperative radiotherapy/chemoradiotherapy. It can be thought that low PNI, which may be an indicator of hematological and nutritional toxicity predicted by brain chemoradiotherapy, can be prevented by immunonutrition support.

Keywords: prognostic nutritional index, immunonutrition, brain tumors, chemoradiotherapy

INTRODUCTION

High-grade gliomas (HGGs), which are typically classified as WHO Grade III and IV gliomas, represent the most aggressive primary tumors in the brain, characterized by rapid growth and infiltration into the surrounding normal brain tissue.[1] These tumors encompass WHO Grade IV gliomas such as glioblastoma multiforme (GBM) and Grade III gliomas such as anaplastic oligodendroglioma and anaplastic astrocytoma. Symptoms associated with HGGs tend to vary depending on the location and extent of tumor growth. Common symptoms may include headaches, neurological deficits (such as difficulties with speech or motor function), epileptic seizures, sensory impairment, or alterations in behavior.

The treatment approach for high-grade gliomas (HGGs) can vary depending on factors such as the size and

Corresponding author: Semanur Dabak Gönülal
Email: sdabak61@gmail.com

Received: June 24, 2024 Accepted: October 9, 2024
Published: October 17, 2024

location of the tumor, as well as the overall health status of the patient. However, the mainstay of treatment typically involves extensive surgical resection followed by radiotherapy (RT) and concurrent or adjuvant Temozolomide. Nevertheless, the management of HGGs is challenging, and despite receiving optimal treatment at diagnosis, patients often experience progression and recurrences. The median survival for patients with glioblastoma is only 12-14 months, while for patients with anaplastic gliomas, this duration ranges from 2 to 5 years.[2,3]

Positive prognostic factors in patients with high-grade gliomas (HGGs) include young age, high Karnofsky Performance Score (KPS), the presence of specific genetic characteristics (such as the presence of isocitrate dehydrogenase (IDH) mutation, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation), and more extensive surgical resection.[4-8]

Additionally, it is believed that the nutritional status of patients during treatment carries prognostic significance. Nutritional challenges are commonly encountered during and after cancer treatment, leading to risks of weight loss, muscle loss, and malnutrition for patients.[9] A good nutritional status can improve the response to treatment, enhance the quality of life for cancer patients, and extend survival periods. Following cancer treatment, improving nutritional status and strengthening the immune system can reduce the risk of post-treatment complications.[10,11]

Main Points

- In cancer patients, nutritional imbalance and weight loss are commonly observed conditions, attributed to both the disease itself and the treatments administered. Reduced albumin levels are frequently encountered due to various mechanisms associated with cytokine storms, leading to a low PNI score.
- In numerous studies, it has been demonstrated that the Prognostic Nutritional Index (PNI) serves as a reflection of the nutritional status and immune function in cancer patients during the perioperative or postoperative periods. Its prognostic significance has been established, indicating its potential for facilitating early intervention aimed at enhancing overall patient well-being.
- Studies on PNI in GBM patients primarily focus on preoperative assessments, with a relatively limited number of studies conducting postoperative evaluations.
- As far as we know, there is no study directly investigating the impact of immunonutrition on PNI in GBM patients. Immunonutrition aims to enhance immune system activity, distinct from conventional nutritional support.
- In conclusion, the objective of this study is to investigate the association between immunonutrition support and PNI during the postoperative phase in GBM patients, aiming to underscore the significance of both immunonutrition support and PNI.

The Prognostic Nutritional Index (PNI), developed by Buzby and colleagues in 1980, is a screening tool created using various nutritional parameters to assess the risk of nutrition-related complications in patients undergoing surgery.[12] However, in addition to its primary use in assessing the nutritional status and immune system functions of cancer patients, the PNI is also utilized as a measure to predict treatment response and anticipate the risk of post-treatment complications. This makes it valuable in guiding preventive measures tailored to address these risks.

In a meta-analysis of 21 studies examining the relationship between pre-treatment PNI and survival in patients with lung cancer, it was found that patients with low PNI values had worse overall survival rates compared to those with high PNI values.[13]

Different formulas can be used in various studies for PNI assessment, and different parameters can be added or removed. However, the fundamental principle involves the combination of serum albumin level and peripheral lymphocyte count. A commonly used formula for calculating PNI is: PNI = 10 x serum albumin (g/dL) + 0.005 x peripheral lymphocyte count (/mm^3).[14]

PNI can be examined in the perioperative or postoperative period. There are many studies in the literature demonstrating the importance and effectiveness of preoperative PNI.[15-23] However, studies focusing on postoperative PNI are relatively scarce.[19,24-27] Several studies focusing on the prognostic role of postoperative PNI have reported that it predicts prognosis in patients with hepatocellular carcinoma and lung cancer, with high postoperative PNI being associated with a favorable prognosis in these patients.[28-30]

The role of preoperative PNI in predicting prognosis in GBM patients has been investigated in the literature, and similar to other cancer types, preoperative PNI can be considered a prognostic indicator. Low PNI values are generally associated with worse survival rates.[31-36] However, studies investigating the prognostic significance of postoperative PNI in GBM patients are limited.[37] None of theses studies analyse the effect of immune nutrition on PNI during postoperative radiochemotherapy of patients with brain tumor.[38,39]

Immunonutrition refers to the regulation of the immune system activity through the use of special dietary supplements such as arginine, glutamine, branched-

chain amino acids, omega-3 fatty acids, probiotics, and prebiotics.[40] It is important to note here that while nutrition typically aims to provide energy requirements and essential macro and micronutrients to the body, immunonutrition simultaneously aims to enhance the effectiveness of the immune system.[41] While there is no definite information on whether immunonutrition support affects the prognostic nutritional index, the anti-inflammatory effects and positive effects on the immune system of immunonutrition support may contribute to the improvement of prognostic nutritional indexes. The aim of this study is to evaluate the effect of immunonutrition support during adjuvant radiotherapy in patients with high-grade gliomas (HGG) and to assess the value of the prognostic nutritional index (PNI) as a prognostic factor for overall survival (OS). Our hypothesis is that immunonutrition support will increase PNI values during the postoperative chemoradiotherapy period.

MATERIALS AND METHODS

Study population

Gazi University Hospital obtained ethical approval for the study with decision number 720 from the Clinical Research Ethics Committee on October 10, 2022. Gazi University Hospital Ethics Committee waived the requirement for written informed consent due to the retrospective design of the study.

We retrospectively reviewed the database of 30 patients with brain tumors (mostly glioblastoma) diagnosed from December 2019 to September 2022, in Gazi University Hospital. We included patients over the age of 18 who were diagnosed with brain tumor and received immunonutrient support during the postoperative adjuvant treatment process. Exclusion criteria were patients with missing data on preoperative or postoperative laboratory examinations and comorbid autoimmune, inflammatory or hematological disease, which can affect the immune system and nutritional status. The patients used immunonutrition (arginine/glutamine/beta-hydroxy beta-methylbutyrate(HMB)) one sachet twice a day during the radiotherapy treatment.

Data collection

Baseline characteristics including demographics, KPS, body mass index (BMI) data, postoperative laboratory findings (albumin levels and lymphocyte count), pathological diagnoses, tumor grade, tumor size, extent of resection and therapeutic information were collected using an electronic medical record system. High-grade gliomas were defined as WHO Grade III and IV gliomas. The tumor size was defined as the maximum diameter measured on pretreatment MRI. For patients with multiple lesions, tumor size was calculated by summing the long diameter of all enhanced foci. The extent of resection was classified as gross total resection (GTR), subtotal resection (STR) and biopsy according to postoperative MRI and operation notes.

Definition

PNI was calculated using the following formula: 10 × *albumin level (g/dL)* + 0.005 × *lymphocyte count (106/L)*.[14] The postoperative before adjuvant treatment and after adjuvant treatment PNIs were calculated. PNI was calculated both before beginning adjuvant radiochemoterapy or within 1 week from the initiation of treatment and 2 weeks after the ending of adjuvant radiochemotherapy.

In addition, all patients' nutritional risk index parameters (NRI) were also calculated with the same timings as PNIs. Nutritional risk index (NRI) was calculated as follows: NRI = (1.519 × *serum albumin*) (g/L) + 41.7 × (*present weight/ ideal bodyweight*).[42] The patients with NRI score of >100 were considered to be at no nutritional risk, 97.5–100 as at mild risk, 83.5–97.5 at moderate and <83.5 at severe nutritional risk.

Statistical analysis

Data were analyzed with IBM SPSS V23. Conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Paired two-sample t-test was used to compare normally distributed data before and after treatment, and Wilcoxon test was used to compare non-normally distributed data. Independent two-sample t-test was used to compare the normally distributed change values according to the paired groups, and the Mann-Whitney U test was used to compare the nonnormally distributed data. Pearson correlation coefficient was used to analyze the relationship between normally distributed data and Spearman's rho correlation coefficient was used to analyze the relationship between non-normally distributed data. We calculated our own cut-off value for PNI by using ROC analysis. Analysis results were presented as mean ± standard deviation and mean (minimum – maximum) for quantitative data, and as frequency and percentage for categorical data. Significance level was taken as $p<0.050$.

RESULTS

Clinicopathological characteristics and treatment regimens are detailed in Table 1. 30 patients were included in the data analysis. Median age was 58.0 years (range 21–77 years), and the majority of the patients were males (56.7%).The proportion of patients with a KPS score ≥ 70 was 86.7%. In the group of patients with histologic grade 2, 5 of the patients were pathologically diagnosed with astrocytoma, 3 with menengioma, 1 with oligodendroglioma. There

Table 1. Demographic, clinico-pathological featurs and treatment		
	Frequency (n)	Percent (%)
Age (years)		
<60	15	50,0
≥60	15	50,0
Gender		
Male	17	56,7
Female	13	43,3
KPS score		
<70	4	13,3
≥70	26	86,7
Histologic grade (WHO)		
Grade 2	9	31,0
Grade 3	2	6,9
Grade 4	18	62,1
Pathological diagnosis		
Astrocytoma	5	16,7
Atypical Meningioma	3	10,0
Glioblastoma	18	60,0
Oligodendroglioma	3	10,0
Pontin Glioma	1	3,3
Extent of resection		
Biopsy	2	6,7
Gross total	16	53,3
Subtotal	11	36,7
None	1	3,3
Postoperative treatment		
Chemoradiotherapy	21	70,0
Chemotherapy	1	3,3
Radiotherapy	8	26,7
Postoperative dexamethasone		
No	24	80,0
Yes	6	20,0
Postoperative residue		
No	9	30,0
Yes	21	70,0
Immunonutrition support (Arg/Gln/HMB)		
Twice a daily	26	86,7
İntolerance	4	13,3
Before adjuvant therapy NRI group		
No	19	63,3
Mild	4	13,3
Moderate	7	23,3
Severe	0	0
After adjuvant therapy NRI group		
No	23	76,7
Mild	3	10,0
Moderate	3	10,0
Severe	1	3,3
Comorbidity*		
Hypertension	8	44,4
Type II diabetes	7	38,9
Benign Prostatic Hyperplasia	3	16,7
Hypothyroidism	2	11,1
Dyslipidaemia/ Hypercholesterolaemia	2	11,1
Prostate cancer	1	5,6
Cerebrovascular disease	1	5,6
HIV Infection	1	5,6
Glomus tumor	1	5,6

* Multiple response
KPS: Karnofsky performance status
WHO:World Health Organization
Arg/Gln/HMB: Arginine/glutamine/Beta-Hydroxy Beta-Methylbutyrate
NRI:Nutritional risk index
HIV:Human Immunodeficiency virüs

were 2 patients with oligodendroglioma in the grade 3 group. All grade 4 groups were glioblastoma patients, and these patients constituted the majority (60%) of all pathologically diagnosed patients. The most common extent of resection (EOR) was gross total resection (GTR) (53.3%), followed by subtotal resection (STR) (36.7%) and biopsy (6.7%).Adjuvant radiotherapy and chemotherapy was undertaken in 21 patients (70.0%) with the median total dose being 60 Gy. 20% of patients used daily dexamethasone postoperatively.

Eighty-six point seven percent (86.7%) of the patients received immune nutrition support twice daily. The mean albümin value before adjuvant treatment was 4.04 g/dL (3.30 - 4.80), while the mean albümin value after adjuvant treatment increased to 4.16 g/dL (2.90 - 4.80) (Table 2). The mean lymphocyte count before adjuvant treatment was $1.81x10^9$/L (0.90 - 3.10), while the mean lymphocyte count after adjuvant treatment was $1.56x10^9$/L (0.50 - 2.80). There was no statistically significant difference between mean albumin values before and after adjuvant treatment (p=0.057), but a statistically significant difference was found between mean lymphocyte counts (p=0.011) (Table 3). PNI calculated by albumin and lymphocyte parameters was 49.38 ± 6.03 SD before adjuvant treatment and 49.40 ± 6.12 SD after adjuvant treatment. There was no statistically significant difference between the mean PNI values before and after adjuvant treatment (p=0.986). In addition, a statistically significant difference was found between the mean weight before and after adjuvant treatment (p=0.034).

The optimal cut-off value for the PNI was found to be 45.5 using ROC analysis (Table 4). The area under the ROC curve for PNI was 0.99 and the 95% CI was 0.966 - 1, which was statistically significant (p<0.001). Sensitivity of cut-off value was 90.91%, specificity 100%, PVV 100% and NPV 95% (Fig. 1).

According to the cut-off value, patients were classified as low and high PNI. The association of both pre-treatment low-high PNIs and post-treatment low-high PNIs with subgroups was evaluated (Table 5 and 6). All patients with high PNI before treatment had a statistically significant KPS score of 70 and above. Similarly, the majority of patients with post-treatment high PNI consisted of patients with

Table 2. Descriptive statistics of quantitative variables

	Mean ± S. Deviation	Median (min. - maks.)
Age (years)	52,63 ± 17,37	58,00 (21,00 - 77,00)
Height (cm)	168,90 ± 8,58	168,00 (156,00 - 192,00)
Weight (kg) before adjuvant therapy	**72,03 ± 10,72**	**75,00 (50,00 - 95,00)**
Weight (kg) after adjuvant therapy	**71,27 ± 10,67**	**74,00 (50,00 - 90,00)**
BMI (kg/m^2)	25,31 ± 3,68	25,95 (18,40 - 31,30)
KPS	-	80,00 (50,00 - 100,00)
ECOG	-	1,00 (0,00 - 3,00)
Albumin (g/dL) 1 week before adjuvant therapy	**4,04 ± 0,41**	**4,05 (3,30 - 4,80)**
Albumin (g/dL) 2 weeks after adjuvant therapy	**4,16 ± 0,41**	**4,25 (2,90 - 4,80)**
Lymphocyte ($x10^9$/L) 1 week before adjuvant therapy	**1,81 ± 0,63**	**1,70 (0,90 - 3,10)**
Lymphocyte ($x10^9$/L) 2 weeks after adjuvant therapy	**1,56 ± 0,62**	**1,45 (0,50 - 2,80)**
PNI before adjuvant therapy	**49,38 ± 6,03**	**49,00 (38,00 - 62,50)**
PNI after adjuvant therapy	**49,40 ± 6,12**	**49,75 (31,50 - 58,50)**
Postoperative dexamethasone dose (mg)	10,00 ± 4,90	8,00 (4,00 - 16,00)
Preoperative mass size (mm)	49,36 ± 14,68	48,00 (25,00 - 80,00)
NRI before adjuvant therapy	**102,60 ± 6,70**	**102,50 (91,80 - 114,60)**
NRI after adjuvant therapy	**103,81 ± 7,41**	**104,75 (77,40 - 114,60)**

BMI:Body Mass Index
KPS: Karnofsky performance status
ECOG: Eastern Cooperative Oncology Group
PNI:Prognostic nutritional index
NRI:Nutritional risk index

Table 3. Comparison of laboratory and index values before and after adjuvant treatment

	Mean ± S. Deviation	Median (min. - maks.)	Difference (Before - after)		Test statistic	p
			Mean ± S. Deviation	Median (min. - maks.)		
Albumin (g/dL) 1 week before adjuvant therapy	4,04 ± 0,41	4,05 (3,30 - 4,80)	-0,12 ± 0,32	-0,10 (-0,70 - 0,80)	-1,980	0,057*
Albumin (g/dL) 2 weeks after adjuvant therapy	4,16 ± 0,41	4,25 (2,90 - 4,80)				
Lymphocyte (x109/L) 1 week before adjuvant therapy	1,81 ± 0,63	1,70 (0,90 - 3,10)	0,25 ± 0,51	0,30 (-0,80 - 1,40)	2,704	**0,011***
Lymphocyte (x109/L) 2 weeks after adjuvant therapy	1,56 ± 0,62	1,45 (0,50 - 2,80)				
PNI before adjuvant therapy	49,38 ± 6,03	49,00 (38,00 - 62,50)	-0,02 ± 5,10	-0,25 (-11,00 - 13,00)	-0,018	0,986*
PNI after adjuvant therapy	49,40 ± 6,12	49,75 (31,50 - 58,50)				
NRI before adjuvant therapy	102,60 ± 6,70	102,50 (91,80 - 114,60)	-1,21 ± 6,34	-1,50 (-10,70 - 20,70)	-1,436	0,151**
NRI after adjuvant therapy	103,81 ± 7,41	104,75 (77,40 - 114,60)				
Weight (kg) before adjuvant therapy	72,03 ± 10,72	75,00 (50,00 - 95,00)	0,77 ± 1,89	0,00 (-5,00 - 6,00)	2,224	**0,034***
Weight (kg) after adjuvant therapy	71,27 ± 10,67	74,00 (50,00 - 90,00)				

PNI:Prognostic nutritional index
NRI:Nutritional risk index

Table 4. ROC analysis result for PNI value

Cut-off value	AUC (%95 CI)	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≤45,5	0,99 (0,966 - 1)	<0,001	90,91%	100%	1	95%

PPV: Positive predictive value, NPV: Negative predictive value PNI:Prognostic nutritional index

KPS 70 and above. As a result, patients with high post-treatment PNI consisted of patients who had statistically significant high KPS scores, did not use postoperative steroids, and received immunonutrition support.

There was no statistically significant difference between PNI and NRI changes according to age, gender, presence of additional disease, performance status and presence of residuals (p>0.050) (Table 7).

A statistically significant correlation was found between the albumin value 1 week before the adjuvant treatment and the change in PNI, and the increase in the albumin value 1 week before the adjuvant treatment provides a weak increase in the PNI change (r=0.390; p=0.033) (Table 8). A statistically significant correlation was found between the change in Lymphocyte value 2 weeks after adjuvant treatment and the change in PNI, and an increase in lymphocyte value 2 weeks after adjuvant treatment provides a weak decrease in PNI change (r=-0.399; p=0.029). A statistically significant relationship was found between BMI value and NRI change, and an increase in BMI value provides a weak increase in NRI change (r=0.366; p=0.047). A statistically significant relationship was found between the albumin value 1 week before the adjuvant treatment and the change in NRI, and the increase in the albumin value 1 week before the adjuvant treatment provides a moderate increase in the NRI change (r=0.460; p=0.011). There was no statistically significant relationship between the changes in PNI and NRI with other variables (p>0.050).

Table 5. Distribution of categorical variables by pretreatment PNI groups				
	Pretreatment PNI		Test statistic	p
	Low(%)	High(%)		
Age (years)				
<60	5 (50)	10 (50)	0,000	1,000*
≥60	5 (50)	10 (50)		
Gender				
Male	7 (70)	10 (50)	---	0,440**
Female	3 (30)	10 (50)		
Comorbidity				
No	4 (40)	8 (40)	---	1,000**
Yes	6 (60)	12 (60)		
KPS score				
<70	4 (40)	0 (0)	---	**0,008****
≥70	6 (60)	20 (100)		
Histologic grade (WHO)				
Grade 2	3 (30)	6 (31,6)	---	---
Grade 3	1 (10)	1 (5,3)		
Grade 4	6 (60)	12 (63,2)		
Pathological diagnosis				
Astrocytoma	2 (20)	3 (15)	---	---
Atypical Meningioma	1 (10)	2 (10)		
Glioblastoma	6 (60)	12 (60)		
Oligodendroglioma	1 (10)	2 (10)		
Pontin Glioma	0 (0)	1 (5)		
Extent of resection				
Biopsy	2 (20)	0 (0)	---	---
Gross total	5 (50)	11 (55)		
Subtotal	3 (30)	8 (40)		
None	0 (0)	1 (5)		
Postoperative treatment				
Chemoradiotherapy	8 (80)	13 (65)	---	---
Chemotherapy	0 (0)	1 (5)		
Radiotherapy	2 (20)	6 (30)		
Postoperative dexamethasone				
No	6 (60)	18 (90)	---	0,141**
Yes	4 (40)	2 (10)		
Postoperative residue				
No	2 (20)	7 (35)	---	0,675**
Yes	8 (80)	13 (65)		
Immunonutrition support (Arg/Gln/HMB)				
Twice a daily	8 (80)	18 (90)	---	0,584**
İntolerance	2 (20)	2 (10)		

*Yates correction, **Fisher's Exact test, ---: Comparisons were not made due to insufficient
PNI:Prognostic nutritional index
KPS: Karnofsky performance status
WHO:World Health Organization
Arg/Gln/HMB: Arginine/glutamine/Beta-Hydroxy Beta-Methylbutyrate

Table 6. Distributions of categorical variables by posttreatment PNI groups			
	Posttreatment PNI		p
	Low(%)	High(%)	
Age (years)			
<60	3 (37,5)	12 (54,5)	0,682
≥60	5 (62,5)	10 (45,5)	
Gender			
Male	4 (50)	13 (59,1)	0,698
Female	4 (50)	9 (40,9)	
Comorbidity			
No	2 (25)	10 (45,5)	0,419
Yes	6 (75)	12 (54,5)	
KPS score			
<70	3 (37,5)	1 (4,5)	**0,048**
≥70	5 (62,5)	21 (95,5)	
Histologic grade (WHO)			
Grade 2	1 (12,5)	8 (38,1)	---
Grade 3	0 (0)	2 (9,5)	
Grade 4	7 (87,5)	11 (52,4)	
Pathological diagnosis			
Astrocytoma	1 (12,5)	4 (18,2)	---
Atypical Meningioma	0 (0)	3 (13,6)	
Glioblastoma	7 (87,5)	11 (50)	
Oligodendroglioma	0 (0)	3 (13,6)	
Pontin Glioma	0 (0)	1 (4,5)	
Extent of resection			
Biopsy	2 (25)	0 (0)	---
Gross total	3 (37,5)	13 (59,1)	
Subtotal	3 (37,5)	8 (36,4)	
None	0 (0)	1 (4,5)	
Postoperative treatment			
Chemoradiotherapy	8 (100)	13 (59,1)	---
Chemotherapy	0 (0)	1 (4,5)	
Radiotherapy	0 (0)	8 (36,4)	
Postoperative dexamethasone			
No	4 (50)	20 (90,9)	**0,029**
Yes	4 (50)	2 (9,1)	
Postoperative residue			
No	1 (12,5)	8 (36,4)	0,374
Yes	7 (87,5)	14 (63,6)	
Immunonutrition support (Arg/Gln/HMB)			
Twice a daily	5 (62,5)	21 (95,5)	**0,048**
İntolerance	3 (37,5)	1 (4,5)	

*Fisher's Exact test, ---: Comparisons were not made due to insufficient
PNI:Prognostic nutritional index
KPS: Karnofsky performance status
WHO:World Health Organization
Arg/Gln/HMB: Arginine/glutamine/Beta-Hydroxy Beta-Methylbutyrate

Table 7. Comparison of PNI and NRI changes before and after treatment according to categorical variables

	PNI (Before - after)		NRI (Before - after)	
	Mean ± S. Deviation	Median (min. - maks.)	Mean ± S. Deviation	Median (min. - maks.)
Age (years)				
<60	1,23 ± 5,44	-0,50 (-7,00 - 13,00)	0,46 ± 6,95	-1,50 (-10,30 - 20,70)
≥60	-1,27 ± 4,57	0,50 (-11,00 - 4,00)	-2,89 ± 5,39	-1,50 (-10,70 - 4,60)
Test stats.	87,000		90,000	
p	0,305**		0,367**	
Gender				
Male	-0,97 ± 5,64	-1,00 (-11,00 - 13,00)	-1,74 ± 7,55	-1,50 (-10,70 - 20,70)
Female	1,23 ± 4,18	2,00 (-4,00 - 10,00)	-0,52 ± 4,51	0,00 (-7,60 - 6,10)
Test stats.	-1,180		90,500	
p	0,248*		0,408**	
Comorbidity				
No	0,13 ± 4,75	-0,75 (-7,00 - 10,00)	-0,90 ± 4,60	-1,50 (-10,30 - 6,10)
Yes	-0,11 ± 5,45	1,00 (-11,00 - 13,00)	-1,42 ± 7,41	-0,75 (-10,70 - 20,70)
Test stats.	0,122		99,000	
p	0,904*		0,723**	
ECOG				
<1	-0,08 ± 4,29	-0,50 (-7,00 - 10,00)	-1,32 ± 4,08	-1,50 (-10,30 - 6,10)
≥1	0,03 ± 5,77	2,00 (-11,00 - 13,00)	-1,13 ± 7,77	0,00 (-10,70 - 20,70)
Test stats.	-0,056		109,000	
p	0,956*		0,967**	
Postoperative residue				
No	-2,39 ± 4,97	-0,50 (-11,00 - 2,50)	-2,53 ± 4,81	-1,50 (-10,70 - 3,10)
Yes	1,00 ± 4,92	0,00 (-7,00 - 13,00)	-0,65 ± 6,93	-1,50 (-10,30 - 20,70)
Test stats.	-1,724		82,000	
p	0,096*		0,594**	

* Independent two-sample t-test, **Mann Whitney U test
ECOG: Eastern Cooperative Oncology Group
PNI:Prognostic nutritional index
NRI:Nutritional risk index

DISCUSSION

PNI, initially formulated to evaluate the nutritional and immunological statuses of patients undergoing gastrointestinal surgery, stands as a straightforward, cost-effective, and beneficial parameter. Nevertheless, subsequent research has redirected attention towards its application in cancer patients. This shift arises from evidence indicating that elevated PNI levels correlate with improved nutritional status and immune functionality in this demographic. Consequently, heightened PNI values not only facilitate prognostic estimations but also afford opportunities for timely interventions and the formulation of optimal therapeutic strategies. However, it is important to note the process between inflammation and cancer and their relationship with PNI here.

The relationship between inflammation and cancer was first observed by Virchow in 1863, suggesting that the origin of cancer might lie within areas of chronic inflammation. Cytokine storm, characterized by the release of large amounts of cytokines such as IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), is

Table 8. Examination of the relationship between PNI and NRI changes and quantitative data

	PNI		NRI	
	r	p	r**	p
Age (years)	-0,181**	0,337	-0,143	0,451
Height (cm)	-0,105*	0,580	-0,183	0,332
Weight (kg) before adjuvant therapy	0,275*	0,142	0,207	0,273
Weight (kg) after adjuvant therapy	0,222*	0,239	0,192	0,310
BMI (kg/m^2)	0,341*	0,065	0,366	**0,047**
KPS score	-0,148**	0,434	-0,116	0,540
ECOG score	0,071**	0,711	0,028	0,883
Albumin (g/dL) 1 week before adjuvant therapy	0,390*	**0,033**	0,460	**0,011**
Albumin (g/dL) 2 weeks after adjuvant therapy	-0,347*	0,060	-0,198	0,294
Lymphocyte (x10^9/L) 1 week before adjuvant therapy	0,296*	0,112	0,180	0,340
Lymphocyte (x10^9/L) 2 weeks after adjuvant therapy	-0,399*	**0,029**	-0,294	0,115
RT dose (Gy)	-0,224**	0,244	-0,164	0,396
Postoperative dexamethasone dose (mg)	0,559*	0,249	0,525	0,285
Preoperative mass size (mm)	0,005*	0,981	0,009	0,963

* Pearson's correlation coefficient, ** Spearman's rho correlation coefficient
PNI:Prognostic nutritional index
NRI:Nutritional risk index
BMI:Body Mass Index
KPS: Karnofsky performance status
ECOG: Eastern Cooperative Oncology Group
RT:Radiotherapy

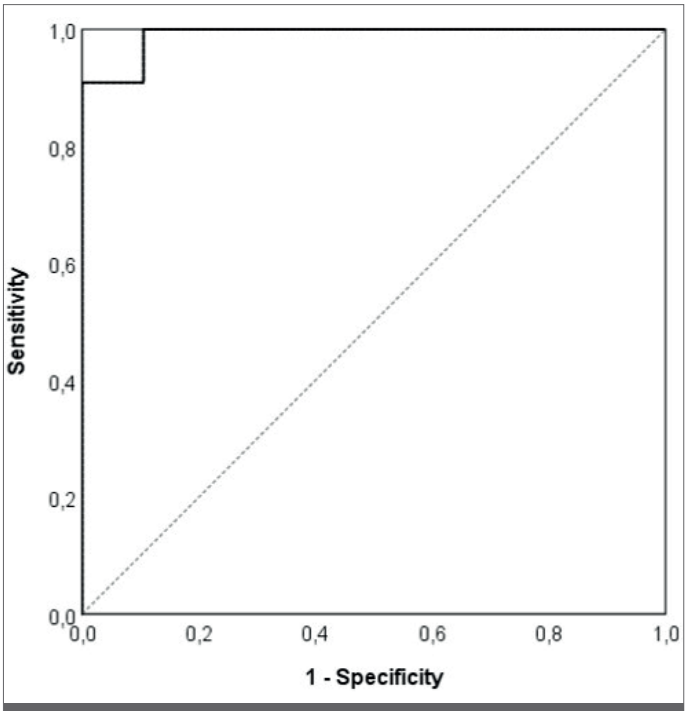

Figure 1. ROC curve of PNI value

associated with the severity of the disease. The role of interleukin-6 (IL-6), particularly elevated during cytokine release, has been investigated in sustaining malignancy in lung cancer patients. Studies have demonstrated that IL-6, through STAT3 signaling, promotes the proliferation and migration of lung cancer cells.[43] In addition, elevated circulating levels of IL-6 in lung cancer patients have been recognized as a predictor of poor survival outcomes.[44] Especially in patients undergoing radiotherapy for head and neck tumors, the release of cytokines such as tumor necrosis factor-alpha and interleukin-6 (IL-6) increases with the impact of the disease, leading to an acute phase response. Additionally, radiotherapy itself increases the release of cytokines that induce cancer cachexia.[45]

In cases of severe cytokine storm, vascular permeability is often increased. This can lead to the leakage of large molecules such as albumin out of the blood vessels, resulting in decreased levels of albumin in the blood plasma. Additionally, the impairment of liver function seen in cytokine storms can lead to a reduction in albumin production, further contributing to the decrease in albumin levels in the blood plasma. This decline in albumin levels can be a significant indicator for managing the patient's

condition and treatment. The importance of using PNI stems from this aspect as well. PNI score evaluates low albumin levels, which are indicative of negative processes such as cytokine storm, hypermetabolic consumption, decreased survival parameters, and even tissue damage in COVID-19 patients.[46]

Recently, there has been a growing focus on investigating the Prognostic Nutritional Index (PNI), particularly in patients with Glioblastoma Multiforme (GBM), to aid in predicting early prognosis and facilitating the formulation of optimal therapeutic decisions. Studies have predominantly centered on the impact of preoperative PNI on overall survival (OS).[31,32,39,47,48] One study suggested that postoperative PNI may better reflect postoperative general conditions than preoperative PNI, and that improving nutritional status just before initiating postoperative adjuvant therapy may help to achieve a favorable outcome.[37]

The aim of our study was to investigate the impact of immunonutritional supplementation during postoperative adjuvant therapy on the PNI in patients with brain tumors. To the best of our knowledge, our study represents the first investigation in this regard. Despite encompassing heterogeneous pathological groups, approximately 70% of our study population consisted of patients with GBM.

In this study, despite the negative effects of intensive chemoradiotherapy (CRT) treatments on PNI parameters, no decrease in PNI was observed; in fact, a minimal increase was noted. However, considering that this change in PNI was not statistically significant, more than 30 HGG patients who did not receive immunonutritional supplementation containing Arg/gln/HMB were retrospectively analyzed. Interestingly, the analysis revealed that the average PNI value was 45.15 before adjuvant therapy and decreased to 42.26 after adjuvant therapy, indicating a statistically significant decrease in PNI among those not receiving immunonutritional supplementation. This finding suggests a potential positive impact of immunonutritional supplementation on PNI.

Previous studies examining the relationship between preoperative serum albumin concentration and the prognosis of GBM have reported that low serum albumin concentration is an independent poor prognostic factor.[49,50] Normally, we wouldn't expect an increase in albumin levels after standard chemoradiotherapy treatment. On the contrary, a decrease is observed following nutritional disturbances associated with treatment side effects. However, in this study, while an increase in the average albumin level was detected, a decrease in albumin values was found in patients who did not receive immunonutritional supplementation.

Studies have documented the suppression of cellular immunity in patients with GBM, where lymphocytes, another component of PNI, play a significant role in cellular immunity.[51,52] Lymphocytes can be affected by hematopoiesis, nutritional status, and anticancer treatments. Postoperative adjuvant chemoradiotherapy (CRT) inhibits lymphocyte differentiation by suppressing the proliferation of hematopoietic progenitor cells, leading to lymphopenia. A previous clinical study reported a close association between treatment-related lymphopenia following surgery and poor prognosis in elderly GBM patients.[53] In our patients, a statistically significant decrease in lymphocyte counts was also observed following treatment. This phenomenon was interpreted as the inhibitory effect of chemotherapy on hematopoiesis.

According to our ROC curve analysis, an optimal PNI cutoff value of 45.5 was identified, with a sensitivity of 90.9% and specificity of 100%. This cutoff value observed in our study was similar to those reported in the literature. This outcome suggests that PNI can serve as both a prognostic and predictive tool.

Additionally, approximately a 1.5% weight loss was observed in this study, which was statistically significant. Besides protein supplementation, exercise support, necessary for converting this protein into muscle, could prevent weight loss in patients. Patients in our clinic received protein supplementation (arg/gln/HMB) but did not receive any specific exercise support. If a specific exercise program had been added to the patients, our results could have been better.

Finally, we calculated the NRI scores to determine the malnutrition groups of the patients. While the group without risk of malnutrition before adjuvant treatment was 63.3%, the group without risk of malnutrition after adjuvant treatment increased to 76.7%. Mild and moderate group patients tend to decrease and they are included in the non-malnutrition group, which may be the success of immune nutrient support despite intensive chemoradiotherapy treatments. Only 1 patient progressed from mild risk to severe risk. He was a patient who received hypofractionated chemoradiotherapy with poor pre-treatment performance status and died a few months after treatment.

Our study has several limitations. First, as this was a non-randomized retrospective study, there was a possibility of unexpected selection bias. In addition, this study was a single-centre study with a small cohort size (n = 30). We think that the statistical results of PNI, albumin and subgroup analyzes were affected due to the small sample size. Secondly, we had insufficient genetic alteration data

including MGMT methylation status, CDKN2A/B deletion, TERT promoter mutation and EGFR amplification status of all the patients, all of which are known to be prognostic factors for gliomas.[54,55] Third, there was a heterogeneous patient population in our study, although the majority consisted of GBM patients. We also did not exclude patients using dexamethasone at the time of data collection, despite its potential confounding effects, because this reflects a real clinical setting. Finally, our study does not include OS and PFS information. Therefore, caution is needed when interpreting our results. We should continue to follow these patients for OS and PFS. Lastly, incorporating conscientious physical therapy and rehabilitation exercises during treatment for these patients may lead to better muscle development and albumin outcomes, potentially enhanced by HMB supplementation.

CONCLUSION

In cancer patients, nutritional imbalance and weight loss are commonly observed conditions, attributed to both the disease itself and the treatments administered. Reduced albumin levels are frequently encountered due to various mechanisms associated with cytokine storms, leading to a low PNI score. According to our study findings, it has been observed that immune nutrient support has a positive effect on PNI and albumin levels in patients with brain tumors undergoing postoperative chemoradiotherapy.

With PNI that can be easily calculated before intensive adjuvant treatments, patients can be risk stratified according to the optimal threshold PNI value, and immune nutrient support can be applied to increase treatment response and compliance in low PNI patients. However, a larger-scale prospective study is needed to determine whether PNI and immune nutrient supplementation will improve the prognosis of GBM patients.

Ethical approval: The study was approved by the Clinical Research Ethics Committee of Gazi University (720 / October 10, 2022).

Informed consent: Written informed consent was obtained from all patients who participated in this study.

Author contributions: Concept – M.A.; Design – M.A., Y.K., S.D.G.; Supervision – M.A., Y.K., S.D.G.; Resources – M.A., Y.K., S.D.G.; Materials – M.A., Y.K., S.D.G.; Data Collection and/or Processing – M.A., Y.K., S.D.G.; Analysis and/ or Interpretation – M.A., Y.K., S.D.G.; Literature Search – M.A., Y.K., S.D.G.; Writing Manuscript – Y.K., S.D.G.; Critical Review – M.A., Y.K., S.D.G.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

REFERENCES

1. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015;17(Suppl 4):iv1-iv62. [Crossref]
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459-466. [Crossref]
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996. [Crossref]
4. Binabaj MM, Bahrami A, ShahidSales S, et al. The prognostic value of MGMT promoter methylation in glioblastoma: A meta-analysis of clinical trials. *J Cell Physiol*. 2018;233:378-386. [Crossref]
5. SongTao Q, Lei Y, Si G, et al. IDH mutations predict longer survival and response to temozolomide in secondary glioblastoma. *Cancer Sci*. 2012;103:269-273. [Crossref]
6. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol*. 2008;9:29-38. [Crossref]
7. Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. *Acta Neurol Scand*. 2010;122:159-167. [Crossref]
8. Kim YS, Kim SH, Cho J, et al. MGMT gene promoter methylation as a potent prognostic factor in glioblastoma treated with temozolomide-based chemoradiotherapy: a single-institution study. *Int J Radiat Oncol Biol Phys*. 2012;84:661-667. [Crossref]
9. Green CJ. Existence, causes and consequences of disease-related malnutrition in the hospital and the community, and clinical and financial benefits of nutritional intervention. *Clinical Nutrition*. 1999;18(Suppl 2):3-28.
10. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. 2015;33:90-99. [Crossref]
11. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med*. 1980;69:491-497. [Crossref]
12. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139:160-167. [Crossref]
13. Wang Z, Wang Y, Zhang X, Zhang T. Pretreatment prognostic nutritional index as a prognostic factor in lung cancer: Review and meta-analysis. *Clin Chim Acta*. 2018;486:303-310. [Crossref]
14. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*. 1984;85:1001-1005.

15. Man Z, Pang Q, Zhou L, et al. Prognostic significance of preoperative prognostic nutritional index in hepatocellular carcinoma: a meta-analysis. *HPB (Oxford)*. 2018;20:888-895. [Crossref]
16. Dai Y, Liu M, Lei L, Lu S. Prognostic significance of preoperative prognostic nutritional index in ovarian cancer: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99:e21840. [Crossref]
17. Sun G, Li Y, Peng Y, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2019;34:681-689. [Crossref]
18. Jeon HG, Choi DK, Sung HH, et al. Preoperative Prognostic Nutritional Index is a Significant Predictor of Survival in Renal Cell Carcinoma Patients Undergoing Nephrectomy. *Ann Surg Oncol*. 2016;23:321-327. [Crossref]
19. Qi Q, Song Q, Cheng Y, Wang N. Prognostic Significance of Preoperative Prognostic Nutritional Index for Overall Survival and Postoperative Complications in Esophageal Cancer Patients. *Cancer Manag Res*. 2021;13:8585-8597. [Crossref]
20. Hirahara N, Tajima Y, Fujii Y, et al. Preoperative Prognostic Nutritional Index Predicts Long-Term Surgical Outcomes in Patients with Esophageal Squamous Cell Carcinoma. *World J Surg*. 2018;42:2199-2208. [Crossref]
21. Sasahara M, Kanda M, Ito S, et al. The Preoperative Prognostic Nutritional Index Predicts Short-Term and Long-Term Outcomes of Patients with Stage II/III Gastric Cancer: Analysis of a Multi-Institution Dataset. *Dig Surg*. 2020;37:135-144. [Crossref]
22. Hofbauer SL, Pantuck AJ, de Martino M, et al. The preoperative prognostic nutritional index is an independent predictor of survival in patients with renal cell carcinoma. *Urol Oncol*. 2015;33:68.e1-7. [Crossref]
23. Liu J, Jiang S, Yang X, Li X, Wang N. The Significant Value of Preoperative Prognostic Nutritional Index for Survival in Pancreatic Cancers: A Meta-analysis. *Pancreas*. 2018;47:793-799. [Crossref]
24. Yang Y, Gao P, Song Y, et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: A meta-analysis. *Eur J Surg Oncol*. 2016;42:1176-1182. [Crossref]
25. Mohri Y, Inoue Y, Tanaka K, Hiro J, Uchida K, Kusunoki M. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. *World J Surg*. 2013;37:2688-2692. [Crossref]
26. Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140:1537-1549. [Crossref]
27. Shibutani M, Maeda K, Nagahara H, et al. The prognostic significance of the postoperative prognostic nutritional index in patients with colorectal cancer. *BMC Cancer*. 2015;15:521. [Crossref]
28. Hayasaka K, Shiono S, Suzuki K, Endoh M, Okada Y. Postoperative prognostic nutritional index as a prognostic factor after non-small cell lung cancer surgery. *Gen Thorac Cardiovasc Surg*. 2020;68:1163-1171. [Crossref]
29. Park S, Ahn HJ, Yang M, Kim JA, Kim JK, Park SJ. The prognostic nutritional index and postoperative complications after curative lung cancer resection: A retrospective cohort study. *J Thorac Cardiovasc Surg*. 2020;160:276-285.e1. [Crossref]
30. Tsukagoshi M, Araki K, Igarashi T, et al. Lower Geriatric Nutritional Risk Index and Prognostic Nutritional Index Predict Postoperative Prognosis in Patients with Hepatocellular Carcinoma. *Nutrients*. 2024;16:940. [Crossref]
31. Xu WZ, Li F, Xu ZK, et al. Preoperative albumin-to-globulin ratio and prognostic nutrition index predict prognosis for glioblastoma. *Onco Targets Ther*. 2017;10:725-733. [Crossref]
32. Zhou XW, Dong H, Yang Y, et al. Significance of the prognostic nutritional index in patients with glioblastoma: A retrospective study. *Clin Neurol Neurosurg*. 2016;151:86-91. [Crossref]
33. Liu M, Wang L. Prognostic significance of preoperative serum albumin, albumin-to-globulin ratio, and prognostic nutritional index for patients with glioma: A meta-analysis. *Medicine (Baltimore)*. 2020;99:e20927. [Crossref]
34. Rigamonti A, Imbesi F, Silvani A, et al. Prognostic nutritional index as a prognostic marker in glioblastoma: Data from a cohort of 282 Italian patients. *J Neurol Sci*. 2019;400:175-179. [Crossref]
35. He Q, Zhao W, Ren Q. The Prognostic Value of the Prognostic Nutritional Index in Operable High-Grade Glioma Patients and the Establishment of a Nomogram. *Front Oncol*. 2022;11:724769. [Crossref]
36. Oyman A, Işık S, Eröz S, et al. The effect of preoperative prognostic nutritional index on outcome in glioblastoma multiforme patients. *J Surg Med*. 2022;6:177-180. [Crossref]
37. Kim YJ, Oh H, Lee SJ, et al. Prognostic significance of the postoperative prognostic nutritional index in patients with glioblastoma: a retrospective study. *BMC Cancer*. 2021;21:942. [Crossref]
38. Garrett C, Becker TM, Lynch D, et al. Comparison of neutrophil to lymphocyte ratio and prognostic nutritional index with other clinical and molecular biomarkers for prediction of glioblastoma multiforme outcome. *PLoS One*. 2021;16:e0252614. [Crossref]
39. Huq S, Khalafallah AM, Botros D, et al. The Prognostic Impact of Nutritional Status on Postoperative Outcomes in Glioblastoma. *World Neurosurg*. 2021;146:e865-e875. [Crossref]
40. Kaźmierczak-Siedlecka K, Daca A, Folwarski M, Makarewicz W, Lebiedzińska A. Immunonutritional support as an important part of multidisciplinary anti-cancer therapy. *Cent Eur J Immunol*. 2020;45:454-460. [Crossref]
41. Çoker A. Immunonutrition. *Turk J Intensive Care*. 2006;4:40-44.
42. Caburet C, Farigon N, Mulliez A, et al. Impact of nutritional status at the outset of assessment on postoperative complications in head and neck cancer. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2020;137:393-398. [Crossref]
43. Yeh HH, Lai WW, Chen HHW, Liu HS, Su WC. Autocrine IL-6-induced Stat3 activation contributes to the pathogenesis of lung adenocarcinoma and malignant pleural effusion. *Oncogene*. 2006;25:4300-4309. [Crossref]

44. Turnquist C, Ryan BM, Horikawa I, Harris BT, Harris CC. Cytokine Storms in Cancer and COVID-19. *Cancer Cell*. 2020;38:598-601. **[Crossref]**
45. Akmansu M, Unsal D, Bora H, Elbeg S. Influence of locoregional radiation treatment on tumor necrosis factor-alpha and interleukin-6 in the serum of patients with head and neck cancer. *Cytokine*. 2005;31:41-45. **[Crossref]**
46. Arslan K, Baş S. The relationship between the prognostic nutritional index and the clinical course of COVID-19: a single-center experience. *Journal of Medicine and Palliative Care*. 2022;3:92-97. **[Crossref]**
47. He ZQ, Ke C, Al-Nahari F, et al. Low preoperative prognostic nutritional index predicts poor survival in patients with newly diagnosed high-grade gliomas. *J Neurooncol*. 2017;132:239-247. **[Crossref]**
48. Ding JD, Yao K, Wang PF, Yan CX. Clinical significance of prognostic nutritional index in patients with glioblastomas. *Medicine (Baltimore)*. 2018;97:e13218. **[Crossref]**
49. Borg N, Guilfoyle MR, Greenberg DC, Watts C, Thomson S. Serum albumin and survival in glioblastoma multiforme. *J Neurooncol*. 2011;105:77-81. **[Crossref]**
50. Liu W, Qdaisat A, Yeung J, et al. The Association Between Common Clinical Characteristics and Postoperative Morbidity and Overall Survival in Patients with Glioblastoma. *Oncologist*. 2019;24:529-536. **[Crossref]**
51. Brooks WH, Netsky MG, Normansell DE, Horwitz DA. Depressed cell-mediated immunity in patients with primary intracranial tumors. Characterization of a humoral immunosuppressive factor. *J Exp Med*. 1972;136:1631-1647. **[Crossref]**
52. Kikuchi K, Neuwelt EA. Presence of immunosuppressive factors in brain-tumor cyst fluid. *J Neurosurg*. 1983;59:790-799. **[Crossref]**
53. Mendez JS, Govindan A, Leong J, Gao F, Huang J, Campian JL. Association between treatment-related lymphopenia and overall survival in elderly patients with newly diagnosed glioblastoma. *J Neurooncol*. 2016;127:329-335. **[Crossref]**
54. Wick W, Meisner C, Hentschel B, et al. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. *Neurology*. 2013;81:1515-1522. **[Crossref]**
55. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. *N Engl J Med*. 2015;372:2499-2508. **[Crossref]**