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Impact of Prognostic Nutritional Index on Survival in Recurrent High-Grade Glial Tumors Treated with Systemic Treatment

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Abstract

Background: Primary brain tumors are relatively rare malignancy, with high-grade gliomas (glioblastoma multiforme and anaplastic gliomas) are the most common types . We aimed to evaluate the prognostic value of Prognostic Nutritional Index (PNI), which is calculated by lymphocyte count and albumin, in recurrent high-grade glioma patients treated with systemic treatment.

Methods: Data of 92 patients with recurrent high-grade glioma who received systemic treatment and followed in our clinic between 2012-2018 was retrospectively collected and analyzed. PNI was calculated as: [(10 × serum albumin (g/dL)) + (0.005 × total lymphocyte count)]. Patients were categorized according to the median PNI value. We investigated the prognostic role of PNI groups, and survival outcomes.

Results: Median value of PNI was 46.02, and median follow-up duration was 9 months (1-68 months). Median overall survival (OS) was 8.1 months (95%CI: 6.04-10.3). Median OS was significantly longer in patients with PNI> 46.02 compared to patients with PNI ≤ 46.02 (13.9 months (95%CI: 9.8-18.1), and 6.07 months (95%CI: 4.3-7.7), p=0.01, respectively). In multivariate analysis, PNI was found to be an independent prognostic factor for OS [HR:0.54(95%CI:0.3-0.97), p=0.03)].

Conclusion: In our study, the PNI was found to be an independent prognostic biomarker in patients with recurrent high-grade gliomas, but further prospective trials are necessary to validate its prognostic role.

Introduction

Primary brain tumors are relatively rare malignancy, with high-grade gliomas [glioblastoma multiforme (GBM) and anaplastic gliomas] are the most common types[1]. Maximum tumor resection followed temozolomide based adjuvant chemoradiotherapy is the current standard of care. Despite this treatments survival benefit, vast majority of patients relapse in the follow up period[2]. After recurrence patients have a poor prognosis with a median overall survival (OS) of 9 to 10 months, and treatment options are limited[3]. However, responses to treatment and survival rates differ among patients, and many molecular pathological and clinical features have been reported as prognostic factors for survival[4]. Besides this, inflammation and coagulation biomarkers have also been used as prognostic markers in gliomas[5,6].

Many studies have reported that nutritional status and inflammation are associated with survival in patients with solid tumors[7,8]. Various inflammation-based prognostic indices have been defined, and the prognostic nutritional index is one of them. The prognostic nutritional index (PNI) is calculated by using albumin and lymphocyte count (the formula: [10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm3)]. PNI was shown to be related to clinical outcomes in patients with malignancy, and lower PNI value to be a biomarker for poor prognosis[9-13]. Similarly, nutritional status and inflammation could reflect survival outcomes in high-grade gliomas[5]. Serum albumin level has been found to be an independent prognostic factor for survival, and lower albumin levels correlated with poor prognosis in

patients with GBM[14-16]. Recent studies also showed the PNI to be an independent prognostic factor for survival in GBM[17-21]. While the effect of preoperative PNI was studied in GBM, recurrent glioblastoma patients have not been included in these studies. Therefore, there is not enough data showing the association between PNI and survival outcomes in recurrent high-grade glioma patients.

In current study, we aim to investigate the prognostic value of PNI in recurrent high-grade glioma patients.

Patients And Methods

Patients

We retrospectively evaluated the data from a total of 92 recurrent high-grade glioma patients treated with systemic treatment between 2012 and 2018 in Marmara University Medical Oncology Outpatient Clinic. Inclusion criteria were histologically/cytologically diagnosis of high-grade glioma, having recurrent disease after current standard of care, treated with systemic treatment (bevacizumab alone or with irinotecan) and having complete medical records. We recorded the demographic, clinicopathologic features, and laboratory results of these patients from a database of medical oncology outpatient clinics.

Prognostic Nutriotional Index (PNI)

PNI was calculated using lymphocyte count and albumin levels obtained from routine blood analysis done just before the first day of systemic treatment. PNI was calculated as follows: [(10 × serum albumin (g/dL)) + (0.005 × total lymphocyte count)]. Patients were categorized according to the median PNI value which was 46.02 in our patient group. Patients were classified into two groups: Low PNI: PNI: ≤ 46.02 and High PNI: PNI> 46.02, respectively.

Inflammatory-Based Indices

Neutrophil, lymphocyte, and platelet count obtained from routine blood analysis results done just before the first day of systemic treatment were used to calculate inflammatory-based indices. Systemic inflammation index (SII), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated as follows: SII= Neutrophil counts x (platelet counts / lymphocyte counts), NLR= Neutrophil count / lymphocyte count, and PLR= Platelet count / lymphocyte count.

Statistical Analysis

Overall survival time (OS) was defined as the time from start of systemic treatment until death with any reason or last visit. Survival analysis was performed with Kaplan-Meier method. Comparison of demographic features between PNI groups was carried out using Pearson $\chi 2$ test. Prognostic factors were compared using log-rank test in univariate analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were also calculated. All p values were 2-sided in the tests, and p values of <0.05 were considered statistically significant. Multivariate analysis was carried out using Cox proportional hazards

model to assess the effect of prognostic factors on overall survival. SPSS 22 program was used for statistical analysis.

Results

Demographic and Clinicopathologic Characteristics of Patients

Twenty-seven of 92 patients were female (29%) and median age was 51 (range 19-78 years). Demographic and clinical characteristics of patients were outlined in **Table 1**. Median value of PNI was 46.02 (min 24-max 62.3). Baseline demographics and clinicopathologic findings were statistically similar between the PNI groups, except for age distribution. Median age was 46 (range 18-74 years) in high PNI (> 46.02) group, and 53.5 (range 17-77) in low PNI (≤ 46.02) group (p=0.03).

Survival Outcomes

Median follow-up duration was 9 months (range 1-68 months). During the follow-up period, 70 (76%) out of 92 patients have died. For all cohort, median OS was 8.1 months (95%CI: 6.04-10.3) **(Figure 1)**. Twelve-months and 24 months OS rates were 40% and 20%, respectively. Median OS was significantly longer in high PNI compared to low PNI group. Median OS for high PNI group was 13.9 months (95%CI: 9.8-18.1), and 6.07 months (95%CI: 4.3-7.7) in low PNI **(p=0.01, Figure 2)**. Survival outcomes according to PNI are given in **Table 2**.

Univariate and multivariate analysis results are summarized in **Table 3**. In multivariate analysis, ECOG PS (HR: 3.4), gender (HR: 2.7), isocitrate dehydrogenase-1 (IDH-1) status (HR: 0.2), ATRX status (HR: 3.3), and PNI (HR: 0.54) were found to be independent prognostic factors for overall survival. However, SII (HR: 1.5), PLR (HR: 1.0), and NLR (HR: 1.5) were not significant independent predictors of better survival **(Figure 3A-C)**.

Discussion

In our study, we reported that PNI score was an independent prognostic factor for survival in recurrent high-grade gliomas,and showed that patient with high PNI had better OS. Prognostic nutritional index (PNI) is an inflammation-based prognostic scoring system calculated by using two inflammatory markers, lymphocyte count and albumin. PNI has been originally used to assess the prognostic significance of nutritional and immunological status in malnourished cancer patients undergoing gastrointestinal surgery, and then it has been indicated as an independent and useful prognostic model for predicting survival in various tumors such as colorectal and genitourinary cancer[9,22–24]. Significance of preoperative PNI in patients with glioblastoma has been reported in the current literature. Zhou et al. showed that a PNI > 44.4 was an independent prognostic factor for better survival in patients with glioblastoma [HR: 0.47 (95%CI:0.23–0.97), p = 0.04)][17]. Xu et al. revealed that PNI was an independent prognostic factor for survival [HR: 0.75 (95%CI:0.37–0.98), p = 0.03)] in their study, and low PNI value was significantly related with poor survival in patients who received adjuvant chemoradiotherapy[18]. Two other

retrospective studies have been confirmed PNI as an independent prognostic factor for survival in newly diagnosed glioblastoma[19–20]. Conversely, Rigamonti et al. didn't find any association between PNI and OS in their series of glioblastoma patients [HR = 0.79 (95%CI:0.61–1.03), p = 0.07][21]. Studies about the clinical significance of PNI in patients with high-grade glioma are summarized in **Table-4**.

Recurrent high-grade gliomas generally have a poor prognosis. Despite local and systemic treatment options such as re-resection, re-irradiation, stereotactic radiosurgery, targeted therapy, and different chemotherapeutic agents, median overall survival is less than 12 months[25–27]. Several clinical and molecular prognostic biomarkers have been reported in different retrospective trials, which included patients with recurrence disease[28]. We found ECOG PS (HR: 3.4), gender (HR: 2.7), IDH status (HR: 0.2), ATRX status (HR: 3.3), and PNI (HR: 0.54) as independent prognostic markers for OS in our retrospective trial. Liau et al. shown that female sex associated with better survival in patients with recurrent GBM treated with bevacizumab [HR 2.1, 95%CI (1.24–3.93), p = 0.007][29]. In another study, Tian et al. demonstrated that female patients with newly diagnosed GBM have a higher cancer-specific survival compared to male patients [HR 0.89, 95%CI (0.84–0.95), p < 0.001][30]. IDH-1 mutation has been proven to be a prognostic factor in patients with high-grade glioma and was associated with better OS in a meta-analysis[31]. Chaurasia et al. indicated that wild type ATRX was significantly associated with better survival in their study which included a total of 163 GBM patients who underwent surgery[32]. Also, another study has shown that the ATRX mutation was related to poor survival in grade II glioma patients[33]. On the other hand, many other molecular and genetic markers such as MGMT methylation status, 1p/19 g deletion, PDGF, PTEN, EGFR, p53, and TERT have been identified as prognostic factors in high-grade glioma[34]. But, these molecular and genetic markers are limited used in many lower-middle-income countries due to the high economic cost. PNI is a more reliable, objective, simple, useful, and cheaper prognostic scoring model for recurrent high-grade gliomas to select the patients who underwent aggressive treatment strategies, and this was the rationale for our study. In the current study, we established that a high PNI value was associated with better survival in recurrent high-grade gliomas [HR = 0.54, (95% CI 0.30–0.97), p = 0.03]. Unlike other studies, our cohort consisted of recurrence high-grade glioma patients. To best of our knowledge, this is the first study to assess the prognostic value of PNI in recurrent high-grade gliomas.

Several studies have been reported preoperative NLR, SII, and PLR as independent prognostic factors for predicting survival in patients with newly diagnosed GBM[35–38]. But, we did not find an association between inflammatory-based indexes and survival outcomes in recurrent high-grade gliomas (HR for SII, PLR, and NLR: 1.08, 1.0, and 1.5, respectively). There is no previous study evaluating the association between these inflammation-based indices and survival in recurrent high-grade gliomas. We might conclude that the prognostic value of PNI is superior to other inflammation-based indexes for survival in patients with recurrent high-grade gliomas.

Our study has many limitations. First, this was a retrospective analysis with relatively small sample size, which may have caused some selection bias. Secondly, we were able to make PNI group-specific analysis

according to only IDH1 and ATRX mutational status. Other genetic markers such as MGMT methylation status and 1p/19q co-deletion status could not be evaluated, because of the absence of data.

Conclusion

In conclusion, our study showed that low PNI correlates with poor overall survival in patients with recurrent high-grade glioma. Since our study was retrospective and included relatively low number of patients, larger prospective trials are needed in order to confirm this conclusion. Moreover, we suggest that PNI could be used as a cheap, easy, repeatable and accessible prognostic marker in routine clinical practice.

Declarations

Consent of Publication

Written informed consent was obtained from the patients for publication of this original research. A copy of the written consent is available for review by the Editor-in-Chief of this journal."

Ethics Approval and Consent To Participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethics/institutional review board approval of research Faculty of Medicine, Marmara University, Istanbul, Turkey. Number: 09.2018.410 Date: 01.06.2018

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Availability of Data and Material

All the data supporting our findings is contained within the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper

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Tables

Table 1: Baseline clinicopathological characteristics of the patients

	Findings	All Patients n=92 (%)
Age, years (min-max)		51 (19-78)
Age groups (years)	<45	28 (30)
	≥45	64 (70)
Gender	Female	27 (29)
	Male	65 (71)
ECOG PS	0-1	66 (72)
	2-4	26 (28)
Surgery	Gros total resection	40 (43)
	Subtotal resection	31 (34)
	Stereotactic Biopsy	21 (23)
Pathology	Glioblastoma Multiforme	64 (70)
	Anaplastik glioma (WHO grade 3)	28 (30)
IDH-1 status (n=72) (%)	Mutant	12 (17)
	Wild	60 (83)
ATRX status (n=72) (%)	Mutant	16 (22)
	Wild	56 (78)
Systemic treatment	Bevacizumab	37 (40)
	Bevacizumab with irinotecan	55 (60)
White Blood Count (□/L) (Median)		8900 (min 3100- max 17800)
Neutrophile Count (□/L) (Median)		6600 (min 1700- max 15400)
Lymphocyte Count (□/L) (Median)		1300 (min 600-max 1700)
Platelete Count x10^3 (□/L) (Median)		235 (min 33-max 505)
Albumine (g/dL) (Median)		3.9 (min 2.4-max 5.1)
Neutrophil-lymphocyte Ratio (NLR)(Median)		4.4 (min 1.1-max 25.6)
Platelet-lymphocyte Ratio (PLR) (Median)		173.6 (min 41.9-440.9)
Systemic Inflammation Index (SII) (Median		1142 (min 90.7- max 5755)
Prognostic nutrional index (PNI) (Median)		46.02 (min 24-max 62.3)

Table 2: Clinical outcomes according to PNI

Characterestic		All patients n=92	PNI ≤ 46.02 n=46	PNI > 46.02 n=46	p
Status n (%)	Exitus	70 (76)	38 (83)	32(70)	0.1
	Alive	22 (24)	8(17)	14 (30)	
Overall Survivial	Median (months) (95%CI)	8.1 (6.04-10.3)	6.07 (4.3-7.7)	13.9 (9.8-18.1)	0.01
	1 years (%)	40	22	57	
	2 years (%)	20	13	27	

Table 3: Cox-regression model of overall survival (OS) in High-Grade Glial Tumors

			Univariate Analysis				Multivariate Analysis			
		Median OS (Months)	HR	95%CI		p	HR	95%CI		p
				Lower	Upper			Lower	Upper	
Age	≤ 45	10.4	1.4	0.82	2.46	0.2				
	> 45	7.3								
ECOG PS	0-1	12.3	2.39	1.42	3.92	**0.01**	3.46	1.64	7.32	**0.002**
	2-4	4.2								
Gender	Female	11.8	1.72	1.00	2.93	**0.04**	2.74	1.32	5.68	**0.004**
	Male	7.3								
Surgery	Gross total resection	13.9	0.51	0.3	0.84	**0.008**				
	Subtotal/biopsy	7.2								
Pathology	GBM	7.9	0.78	0.45	1.34	0.3				
	Anaplastic Glioma	9.3								
IDH-1 status	Mutant	25.6	0.36	0.14	0.93	**0.02**	0.26	0.10	0.67	**0.001**
	Wild	8.1								
ATRX status	Mutant	3.7	3.3	1.6	6.8	**0.001**	3.30	1.53	7.14	**0.004**
	Wild	13.9								
NLR	≤ 4.4	14.3	1.5	0.94	2.56	0.08				
	> 4.4	7.7								
PLR	≤ 173.6	8.7	1.00	0.99	1.03	0.45				
	> 173.6	9.6								
SII	> 1142	9.6	1.08	0.67	1.75	0.73				
	≤ 1142	7.9								
PNI	> 46.02	13.9	0.56	0.35	0.90	**0.01**	0.54	0.30	0.97	**0.03**
	≤ 46.02	6.07								

Table 4: Review of current literature investigating the clinical significance of the prognostic nutritional index (PNI) in patients with high-grade gliomas

	Design	Patients	PNI (cut-off)	Result
Zhou XW et al.[17]	Retrospective Preoperative prognostic value of PNI	All patients GBM (n=84)	44.4	PNI<44.4 vs PNI≥44.4 mOS: 270 vs 375 days [HR: 0.47 (95%CI:0.23-0.97), p=0.04)]
Zhe Xu et al.[18]	Retrospective Preoperative prognostic value of PNI	All patients GBM (n=166)	48	PNI ≤ 48 vs PNI >48 mOS:not reported 1 year survival: 63% (sensitivity 0.834, specificity 0.429, 95%CI 0.523–0.739; *p=0.045*) [HR: 0.75 (95%CI:0.37-0.98), p=0.03)]
Ding JD et al.[19]	Retrospective Preoperative prognostic value of PNI	All patients GBM (n=300)	44	PNI <44 vs PNI ≥44 mOS: 9.8 vs 13.8 months [HR = 0.56, (95% CI 0.38–0.80), p = 0.002]
Z.Q. He et al.[20]	Retrospective Preoperative prognostic value of PNI	52.1% patients GBM 47.9% patients AG (n=188)	55.55	PNI<55.55 vs PNI≥ 55.55 mOS: 13.57 vs. 33.23 [HR = 0.57, (95% CI 0.44–0.75), $p < 0.001$]
Rigamonti A et al.[21]	Retrospective Preoperative prognostic value of PNI	All patients GBM (n=282)	45.9	PNI<45.9 vs PNI≥ 45.9 mOS: 11.3 vs 13 months [HR=0.79 (95%CI:0.61–1.03), p=0.07]
Current study	Retrospective Prognostic value of PNI in recurrent disease	70% patients GBM 30% patients AG (n=92)	46.02	PNI ≤ 46.02 vs PNI> 46.02 mOS: 6.07 vs. 13.9 months [HR = 0.54, (95% CI 0.30–0.97), p = 0.03]

GBM: Glioblastome Multiforme (WHO Grade 4), AG: Anaplastic Glioma (WHO Grade 3)

Figures

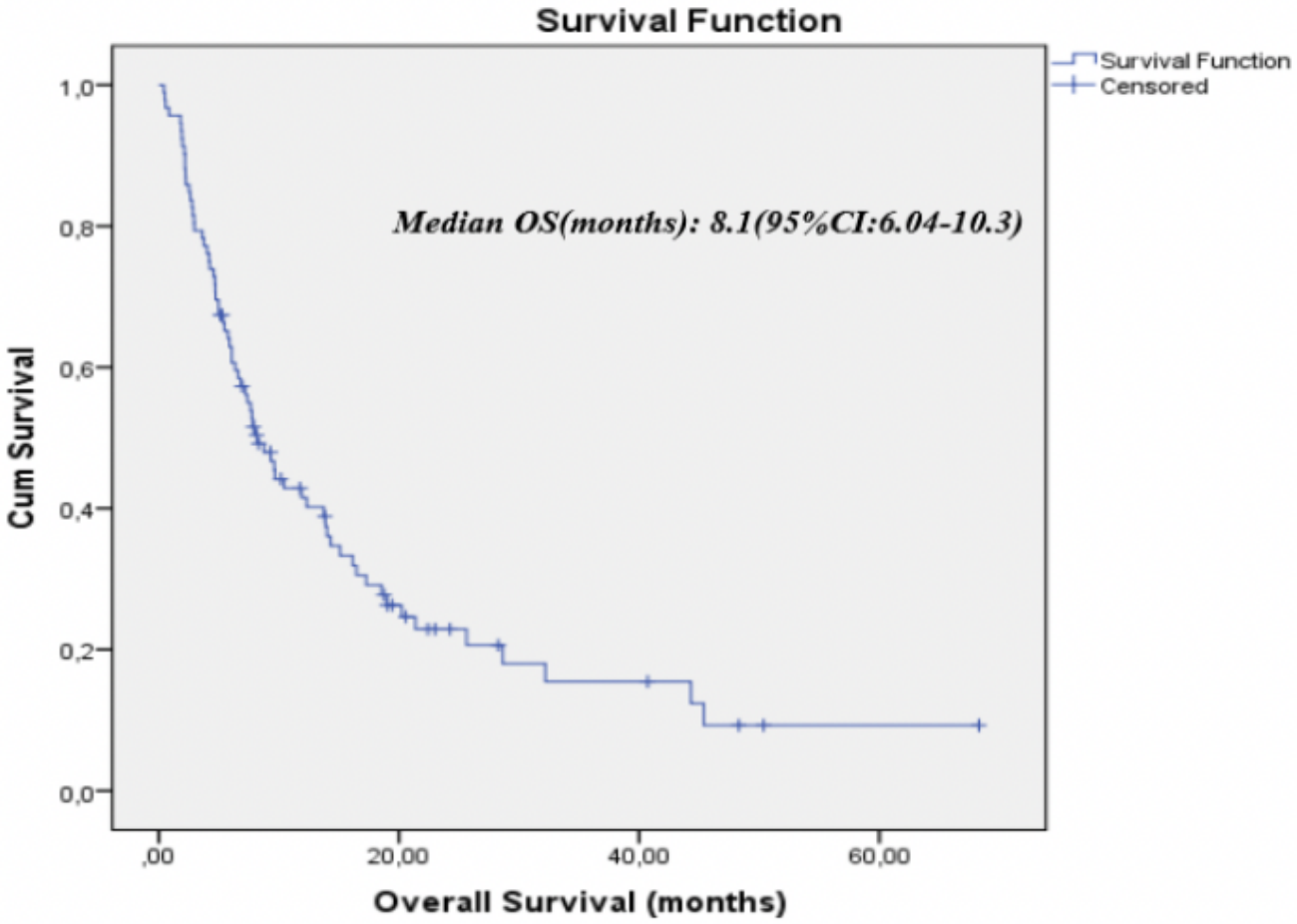


Figure 1

Overall Survival Graphic of All Cohort by Kaplan Meier

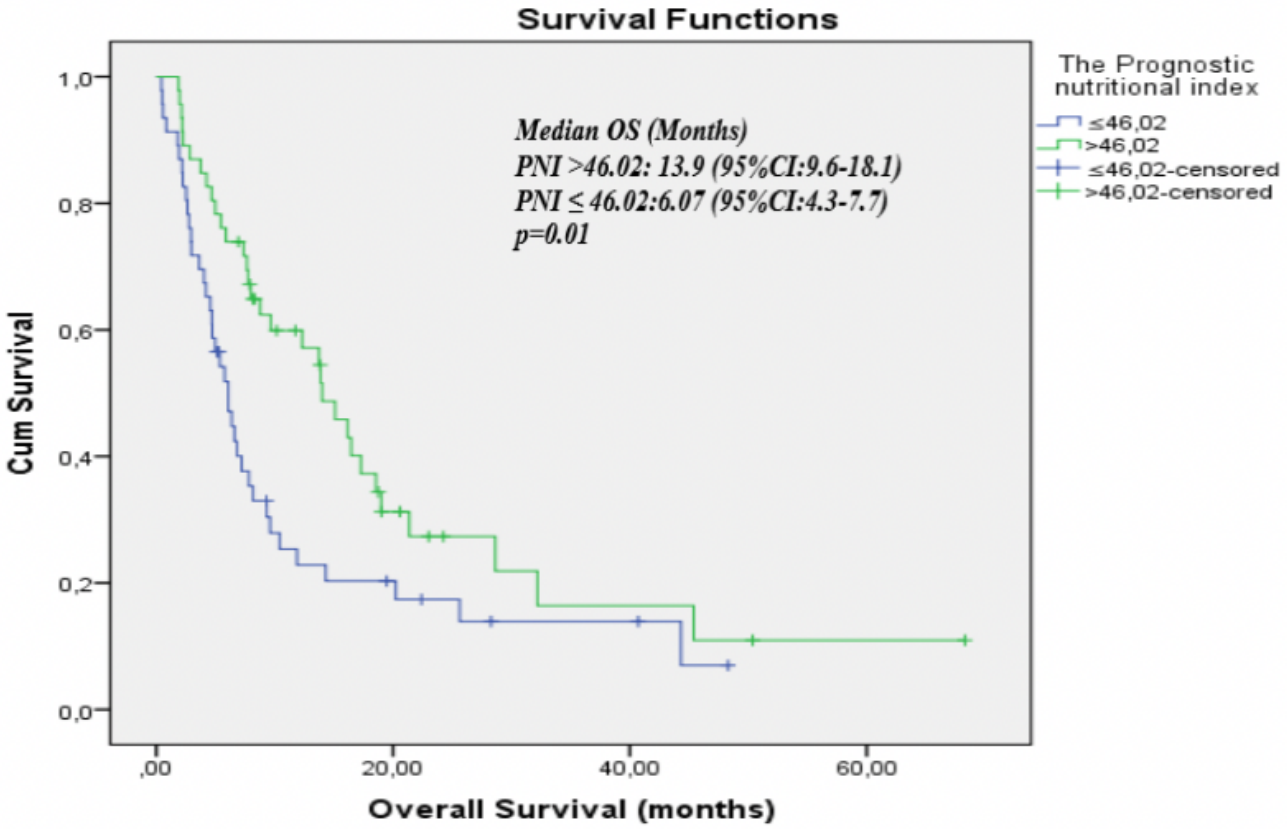


Figure 2

Overall survival graphic according to PNI groups by Kaplan-Meier

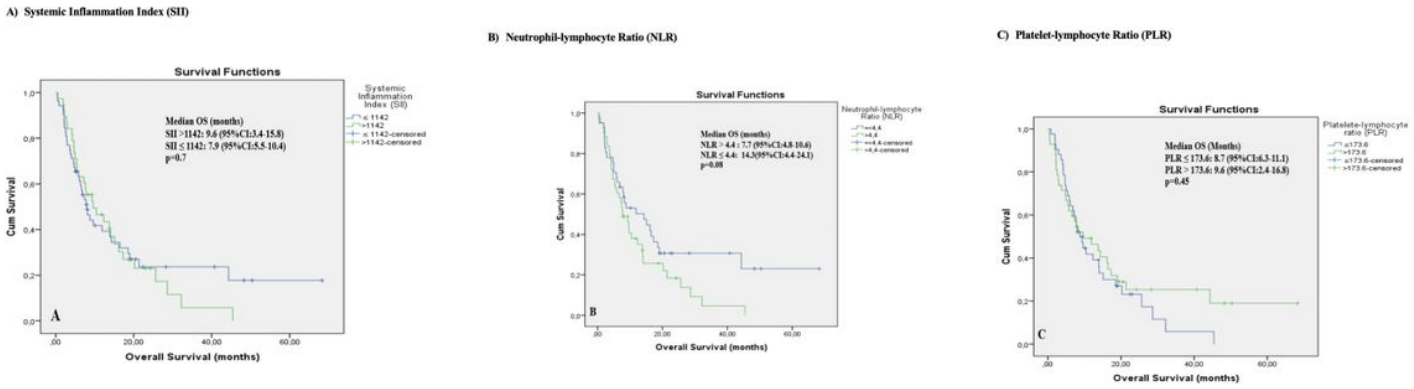


Figure 3

Overall survival graphic according to Inflammation Based Indices by Kaplan-Meier