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Research Article

Preoperative Prognostic Nutritional Index is a Strong Predictor of Survival in Patients with Localized Soft Tissue Sarcoma

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Abstract

Objectives: Prognostic nutritional index (PNI) is an inflammation-based score which was found to be predictive of survival for different types of cancer. Aim of present study is to investigate the association between PNI and survival outcomes in patients with soft tissue sarcoma (STS) operated with curative intent.

Methods: We retrospectively collected data of 86 patients with localized STS. Preoperative PNI was calculated with the following formula:10×serum albumin (g/dL)+0.005×total lymphocyte count (per mm^3). Patients were classified into 2 groups based on median PNI value.

Results: Median age was 52.5 (18-86) years. There were 49 male and 37 female patients. Most common histology was liposarcoma (26.7%). Our cohort mainly included stage 3 (69.8%) and grade 3 (66.3%) tumors. Radiotherapy and chemotherapy were applied to 69.8% and 48.8% of patients, respectively. Median value of PNI was 48.2 (25.5-68.0). Median follow-up duration was 25 months (3-120). Median overall survival (OS) was 84.6 months (95% CI, 72.0-97.3). Median OS of patients with high PNI (≥48.2) was significantly longer than patients with low PNI (<48.2), being 99.6 months(95% CI, 83.6-115.6) and 64.5 months(95% CI, 50.3-78.7), respectively(p=0.02). Multivariate analysis determined PNI as an independent prognostic indicator for OS [HR: 2.96, (95% CI 1.11–7.87), p=0.02] along with age.

Conclusion: Our findings suggest that PNI predicts OS independently in patients with STS. Therefore, PNI is a valuable prognostic tool in preoperative setting.

Keywords: Prognosis, prognostic nutritional index (PNI), survival, soft tissue sarcoma (STS)

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Soft tissue sarcomas (STSs) are rare tumors of connective tissue that account for only 1% of all adulthood cancers.[1] Despite providing better local control rates with multimodal therapies that combine extensive surgical resections with radiotherapy/chemotherapy, the risk of developing recurrence or metastasis is still high particularly for high-grade tumors. Overall, one-fourth of patients will develop metastatic disease following treatment of prima-

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ry tumor; however the frequency increases up to 40-50% for the patients with high-risk STSs (>5 cm in size, higher grade, deep tumors).[2,3] Furthermore, these uncommon tumors still have poor prognosis with an estimated 5-year overall survival rate of 65% according to the statistics from the Surveillance, Epidemiology, and End Results Program (SEER).[4] Thus, there is a growing interest in discovering novel biomarkers to more accurately predict survival which may help to stratify patients for further treatments and improve clinical outcomes.

Systemic inflammation has received much attention over the last years regarding its pivotal role in development and progression of cancer.[5] Various inflammation-based indices were found to be associated with dismal prognosis in patients with STS.[6-10] The prognostic nutritional index (PNI) is one of the indices that reflects inflammation and has a simple formula combining serum albumin concentration and peripheral blood lymphocyte count.[11]

So far, numerous studies have revealed the prognostic significance of PNI in different type of tumors.[12-16] However, there seems to be insufficient data about prognostic role of PNI in STS. Only one study has reported PNI as a predictor of wound complications for STS.[17] Therefore, in this study, we aimed to investigate the association between PNI and survival outcomes in STS patients operated with curative intent.

Methods

Study Design and Patient Selection

We retrospectively reviewed medical records of patients diagnosed and treated with STS between May 2000 and August 2020. Inclusion criteria were as follows: Biopsy-proven diagnosis with STS; patients who underwent surgical resection of a primary tumor without metastasis; available laboratory results before surgery; complete clinical data; a minimum follow-up of 3 months. Certain subtypes treated with individual approaches such as Kaposi sarcoma, gastrointestinal stromal tumor, solitary fibrous tumor, dermatofibrosarcoma protuberans, hemangioendothelioma were excluded from the study. Patients who had been treated with neoadjuvant chemotherapy or radiotherapy were also excluded. Furthermore, cases with active infection or fever at the time of surgery or history of any chronic inflammatory disease were excluded.

Data Collection

Demographic, clinicopathologic and treatment-related data were obtained retrospectively from medical records. In this context, age at diagnosis, gender, tumor histology, size, grade, localization, stage, surgical margins, use of postoperative chemotherapy and/or radiotherapy were noted. Each patient's tumor was staged according to the 8th edition (2017) of American Joint Committee on Cancer (AJCC) classification.[18] Tumors were graded and reported according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system.[19] Dates of recurrence if occurred and dates of death or last visit were also recorded. Ethical approval for this study was obtained from Ethics Committee of our institute (Date of approval: 14 September 2020, Protocol Code: 09.2020.981).

Prognostic Nutritional Index (PNI)

Routine preoperative blood examination was used to calculate PNI for each patient. PNI was defined by the following formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm3). The optimum cut-off point could not be determined using a receiver operating characteristic (ROC) curve possibly due to the insufficient number of patients. Therefore, we categorized the patients into 2 groups; with low PNI and high PNI based on median PNI value.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and group percentages. Chi-square test was used to determine differences between PNI groups regarding demographic and clinicopathologic features. Kaplan-Meier method was carried out for construction of survival curves. Comparison of survival times was done using log-rank test. Disease-free survival (DFS) was defined as the interval from surgery until relapse of disease, death or last visit. Overall survival (OS) was defined as the interval from diagnosis until death from any reason or last visit. Univariate and multivariate analyses were conducted using the Cox proportional hazard model to evaluate factors that predict OS. Confidence interval (CI) was selected as 95% and a two-sided p value of less than 0.05 was set for statistically significance.

Results

Patient Characteristics

A total of 86 patients were included in our study. There were 49 male (57%) and 37 female (43%) patients with a median age of 52.5 (range 18-86) years. Most common tumor histology was liposarcoma (26.7%), followed by undifferentiated pleomorphic sarcoma (17.4%), myxofibrosarcoma (13.9%), synovial sarcoma (11.6%), sarcomas not otherwise specified (11.6%), leiomyosarcoma (7.0%), malignant peripheral nerve sheath tumor (4.7%) and fibrosarcoma (3.5%). Myxoinflammatory fibroblastic sarcoma, clear cell

sarcoma and angiosarcoma were the least frequent subtypes with one patient for each (1.2%). Lower extremities were the most common localizations for primary tumor (68.6%). Grade 3 tumors (66.3%) were observed more than low-grade tumors (31.4%). Median tumor size was 10.25 cm (range 2.9-26 cm), and precisely half of the patients had a tumor of larger than 10 cm. Most patients had stage 3 disease (69.8%). Tumor margins were negative in 84.9% of the patients. Postoperative radiotherapy and chemotherapy were applied to 69.8% and 48.8% of the patients, respectively. Baseline characteristics of all study population were presented in Table 1.

The association between PNI and Clinicopathologic Characteristics

Median value of PNI in our cohort was 48.2 (range 25.5-68.0). Therefore, we classified patients into 2 groups according to this cut-off point: low PNI (<48.2) and high PNI (≥48.2) including 45 and 41 patients, respectively. The relationship between PNI and clinicopathologic characteristics was outlined in Table 2. There was no statistically significant difference between groups in terms of baseline demographic and clinicopathologic features except the number of deaths (p=0.01).

Survival Analysis

During a median follow-up of 25 months (range 3-120 months), 34 (39.5%) patients had recurrent disease and 23 (26.7%) patients died. For all cohort, median DFS and OS were 65.4 months (95% CI, 52.2-78.6) and 84.6 months (95% CI, 72.0-97.3), respectively.

Incidence of recurrent disease was similar in low PNI (18 of 45 patients, 39.9%) and high PNI (16 of 41, 39.0%) groups (p=0.92). Regarding DFS, there was no statistically significant difference between groups (p=0.98). Median DFS was 59.0 months (95% CI, 43.3-74.6) and 64.0 months (95% CI, 44.7-83.2) in low and high PNI groups, respectively.

The number of deaths in low PNI group (17 of 45, 37.7%) was significantly higher than that in high PNI group (6 of 41, 14.6%) (p=0.01). Median OS of patients with high PNI was significantly longer than patients with low PNI, being 99.6 months (95% CI, 83.6-115.6) and 64.5 months (95% CI, 50.3-78.7), respectively (p=0.02). Survival curves according to PNI were shown in Figure 1 and 2.

In univariate analysis, PNI was significantly associated with OS (p=0.02), as well as age (p=0.005), tumor grade (p=0.03) and tumor size (p=0.03). When these factors were furthermore analyzed in a multivariate analysis, age (p=0.03) and PNI (p=0.02) remained independent prognostic indicators for OS. Univariate and multivariate analyses of factors for predicting overall survival were summarized in Table 3.

Table 1. Baseline characteristics of study population

Findings	All patients n=86 (%)
Median age (years)	52.5 (18-86)
Sex	
Male	49 (57.0)
Female	37 (43.0)
Surgical margins	
R0	73 (84.9)
R1	9 (10.5)
R2	4 (4.7)
Histology	
Liposarcoma	23 (26.7)
Leiomyosarcoma	6 (7.0)
Myxofibrosarcoma	12 (13.9)
Fibrosarcoma	3 (3.5)
Myxoinflammatory fibroblastic sarcoma	1 (1.2)
UPS	15 (17.4)
Synovial sarcoma	10 (11.6)
Clear cell sarcoma	1 (1.2)
Angiosarcoma	1 (1.2)
Malignant peripheral nerve sheath tumor	4 (4.7)
Sarcomas not otherwise specified	10 (11.6)
Tumor grade	
1	7 (8.1)
2	20 (23.3)
3	57 (66.3)
Unknown	2 (2.3)
Tumor size	
≤10 cm	43 (50.0)
>10 cm	43 (50.0)
Tumor localization	
Upper extremity	18 (20.9)
Lower extremity	59 (68.6)
Others (abdominal/pulmonary/retroperitoneum)	9 (10.5)
AJCC stage	
1	9 (10.5)
2	11 (12.8)
3	60 (69.8)
Unknown	6 (7.0)
Radiotherapy	
Yes	60 (69.8)
No	26 (30.2)
Chemotherapy	
Yes	42 (48.8)
No	44 (51.2)
Recurrence	
Yes	34 (39.5)
No	52 (60.5)
Exitus	
Yes	23 (26.7)
No	63 (73.3)

PNI: Prognostic Nutritional Index; UPS: undifferentiated pleomorphic sarcoma; AJCC: American Joint Committee on Cancer.

Table 2. Relationship between PNI and clinicopathologic characteristics

Variables	All patients (n=86)	PNI<48.2 (n=45)	PNI≥48.2 (n=41)	p
Age (years)				
≤52	43 (50.0)	20 (44.4)	23 (56.1)	0.28
>52	43 (50.0)	25 (55.6)	18 (43.9)	
Sex				
Male	49 (57.0)	28 (62.2)	21 (51.2)	0.30
Female	37 (43.0)	17 (37.8)	20 (48.8)	
Surgical margins				
R0	73 (84.9)	36 (80.0)	37 (90.2)	0.18
R1-2	13 (15.1)	9 (20.0)	4 (9.8)	
Histology				
Liposarcoma	23 (26.7)	14 (31.1)	9 (22.0)	0.83
Leiomyosarcoma	6 (7.0)	3 (6.7)	3 (7.3)	
Fibrosarcoma/myxofibrosarcoma	15 (17.4)	9 (20.0)	6 (14.6)	
UPS	15 (17.4)	8 (17.8)	7 (17.1)	
Synovial sarcoma	10 (11.6)	4 (8.9)	6 (14.6)	
Others	17 (19.9)	7 (15.5)	10 (24.4)	
Tumor grade				
1-2	27 (31.4)	11 (24.5)	16 (39.0)	0.14
3	57 (66.3)	33 (73.3)	24 (58.6)	
Unknown	2 (2.3)	1 (2.2)	1 (2.4)	
Tumor size				
≤10 cm	43 (50.0)	21 (46.7)	22 (53.7)	0.38
>10 cm	43 (50.0)	24 (53.3)	19 (46.3)	
Tumor localization				
Extremity	77 (89.5)	39 (86.7)	38 (92.7)	0.17
Others	9 (10.5)	6 (13.3)	3 (7.3)	
AJCC stage				
1-2	20 (23.3)	9 (20.0)	11 (26.8)	0.51
3	60 (69.8)	33 (73.3)	27 (65.9)	
Unknown	6 (7.0)	3 (6.7)	3 (7.3)	
Radiotherapy				
Yes	60 (69.8)	35 (77.8)	25 (61.0)	0.09
No	26 (30.2)	10 (22.2)	16 (39.0)	
Chemotherapy				
Yes	42 (48.8)	22 (48.9)	20 (48.8)	0.99
No	44 (51.2)	23 (51.1)	21 (51.2)	
Recurrence				
Yes	34 (39.5)	18 (40.0)	16 (39.0)	0.92
No	52 (60.5)	27 (60.0)	25 (61.0)	
Exitus				
Yes	23 (26.7)	17 (37.8)	6 (14.6)	0.01
No	63 (73.3)	28 (62.2)	35 (85.4)	

PNI: Prognostic Nutritional Index; UPS: undifferentiated pleomorphic sarcoma; AJCC: American Joint Committee on Cancer.

Discussion

STSs are a diverse group of tumors including more than 50 subtypes with remarkable heterogeneity in clinical behavior and outcomes as well as treatment efficacy.[1] This clinical challenge in STS treatment has led an increasing number of studies evaluating various prognostic factors and novel biomarkers in order to make personalized treatment decisions. In the present study, we aimed to demonstrate the impact of PNI on survival outcomes in patients with operable STS, and PNI was found to be an independent prognostic indicator of survival. To the best of our knowledge, this is the first study that investigates the prognostic role of PNI in this group of patients.

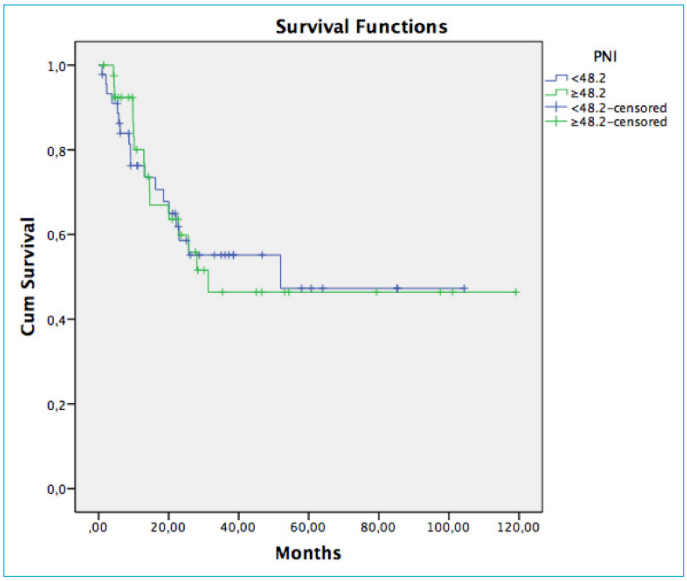

Figure 1. Kaplan-Meier curve showing disease-free survival stratified by Prognostic nutritional index (PNI).

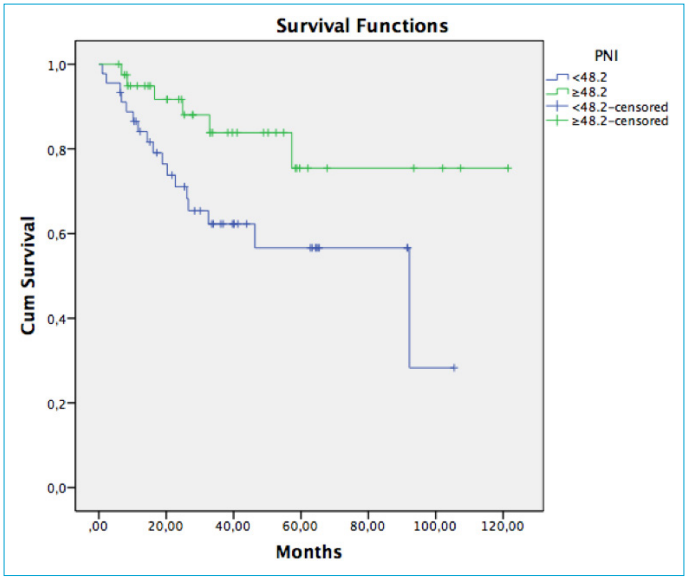

Figure 2. Kaplan-Meier curve showing overall survival stratified by Prognostic nutritional index (PNI).

Accumulating amount of evidence has proved the close relation between systemic inflammation and neoplastic transformation.[20] It is well defined that tumor microenvironment consists of inflammatory cells and mediators as crucial elements. Furthermore, it is estimated that about 25% of neoplasms are triggered by chronic inflammation on the basis of persistent infections or prolonged contribution of inflammatory cells and mediators.[21] Previous studies have also focused on the association between inflammatory state and development of malnutrition in cancer.[22]

Numerous prognostic indices based on inflammation have been defined and furthermore investigated in STS. Neutrophil/lymphocyte ratio (NLR),[9] Glasgow Prognostic Score (GPS),[8,9] Aarhus Composite Biomarker Score (ACBS),[9] C-reactive protein/Albumin ratio (CAR)[7,8] and fibrinogen/albumin ratio (FAR)[10] were found to be independently associated with survival outcomes.

PNI is one of those inflammation-based scores with a basic formula including serum albumin level and lymphocyte count. Therefore, PNI reflects inflammatory and nutritional status at the same time. It was first described by Onodera et al. to assess the operative risk of malnourished patients with gastrointestinal cancers.[11] In the following years, the prognostic value of PNI was evaluated in various tumor types and there found to be a strong relation between PNI and survival outcomes.[12-16] In our study, PNI was an independent prognostic indicator for OS in patients with non-metastatic STS operated with curative intent (HR: 2.96, (95% CI 1.11–7.87), p=0.02), and this data is consistent with the results of previous studies in other tumor types. Patients with high PNI had significantly longer OS. Older age was the other independent predictor of poor survival. To date, PNI was evaluated only in one study including 44 patients treated with surgery and pre- or postoperative radiotherapy for STS, and the primary objective was the success of PNI in predicting wound complications.[17] The authors concluded that PNI was a strong predictor of wound complications following surgery and radiotherapy for STS.

The underlying mechanism for "higher PNI-better clinical outcome" is very understandable when examining previous data on PNI components. Serum albumin level is a good reflector of nutritional status of patients with cancer since malnutrition and weight loss may cause hypoalbuminemia. Inflammation also suppresses albumin synthesis. It is well known that various proinflammatory cytokines such as interleukin-6, interleukin-1 and TNF-a are released during systemic inflammatory response to the tumor and lead to a significant catabolic state.[23,24] Many studies found out that higher albumin levels were associated with better survival.[25] Lymphocytes play a crucial role in cellular immunity and tumor-associated inflammation which goes hand in hand with neoplastic transformation.[26] Lymphopenia was found to be related with poor survival in numerous cancers.[27] Taken all together, two basic and cheap laboratory indices create a promising prognostic index which may be used in several cancer types.

Depending upon our findings, we strongly believe that PNI is a valuable prognostic tool which may be used in preoperative setting of STS. While this prognostic index shows a great success to predict the biological behavior of tumors independently, it has also advantages such as being practical, reliable, and cheap.

Table 3. Univariate and multivariate analyses of factors for predicting overall survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age (years)				
≤52	Reference	0.005	Reference	0.03
>52	3.86 (1.51-9.82)		2.88 (1.07-7.77)	
Sex				
Female	Reference	0.12	Reference	0.43
Male	2.08 (0.81-5.32)		1.51 (0.53-4.27)	
PNI				
≥48.2	Reference	0.02	Reference	0.02
<48.2	2.85 (1.12-7.25)		2.96 (1.11-7.87)	
Surgical margins				
R0	Reference	0.77		
R1-2	1.17 (0.39-3.46)			
Histology				
Liposarcoma	Reference	0.08	Reference	0.06
Leiomyosarcoma	0.65 (0.07-5.57)		0.69 (0.07-6.13)	
Fibrosarcoma/myxofibrosarcoma	0.99 (0.23-4.16)		0.85 (0.19-3.79)	
UPS	3.45 (1.04-11.40)		3.07 (0.87-10.76)	
Synovial sarcoma	0.00 (0.00-)		0.00 (0.00-)	
Others	4.18 (1.26-13.87)		5.08 (1.44-17.92)	
Tumor grade				
1-2	Reference	0.03	Reference	0.47
3	3.80 (1.12-12.82)		1.66 (0.41-6.71)	
Tumor size				
≤10 cm	Reference	0.03	Reference	0.10
>10 cm	2.65 (1.08-6.45)		2.19 (0.85-5.60)	
Tumor localization				
Extremity	Reference	0.86		
Others	1.13 (0.26-4.85)			
AJCC stage				
1-2	Reference	0.21		
3	2.93 (0.85-10.10)			
Unknown	3.13 (0.63-15.56)			
Chemotherapy				
No	Reference	0.59		
Yes	0.80 (0.35-1.82)			
Radiotherapy				
No	Reference	0.20		
Yes	0.57 (0.25-1.34)			

HR: Hazard ratio; CI: Confidence interval; PNI: Prognostic Nutritional Index; UPS: undifferentiated pleomorphic sarcoma; AJCC: American Joint Committee on Cancer.

We are clearly aware that our research has some limitations which may have influenced the results obtained. The first is the retrospective design including relatively small number of patients which may cause a selection bias. The second is, since there has been no previously defined cut-off scores for PNI in the literature, we classified patients into two groups according to median value and performed statistical analyses based on these two groups. The third is the heterogeneity of the patients with a broad range of histologic sub-types.

Conclusion

In conclusion, the present study demonstrated that high PNI correlated with favorable survival in patients with localized STS operated with curative intent. Besides being a potentially effective biomarker for assessment of survival, preoperative PNI is also an easy, cheap, attainable and reliable tool. Therefore, PNI may be routinely assessed in preoperative setting of STS patients. We suggest that patients with a low PNI value should be evaluated carefully

for further treatments in clinical practice. However, future prospective and large-scale studies are needed to verify our results.

Disclosures

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of Marmara University (Date of approval:14 September 2020, Protocol Code: 09.2020.981).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – T.A.T., O.A.; Design – T.A.T., S.I.; Supervision – P.F.Y., F.D., B.E., H.K.T., Z.O., O.E.; Materials – T.A.T., N.D., T.B., R.A.; Data collection &/or processing – T.A.T., N.S., O.S.; Analysis and/or interpretation – T.A.T., O.A., N.D.; Literature search- T.A.T., A.Y., A.C.; Writing – T.A.T.; Critical review – T.A.T., P.F.Y., F.D., B.E., H.K.T., Z.O., O.E.

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