

Role of the Prognostic Nutritional Index in Patients With Soft-tissue Sarcoma

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Abstract. *Background:* This study aimed to determine whether the prognostic nutritional index (PNI) can predict the prognosis in patients with soft-tissue sarcoma (STS) before treatment and to examine whether there is an association between PNI values and clinical characteristics. *Patients and Methods:* The data on 100 patients with primary STS were retrospectively reviewed. The cohort included 55 men and 45 women, with a mean age of 64 years. The mean follow-up duration was 41.7 months. *Results:* The median PNI was 51.35. The PNI was significantly inversely associated with tumor size, tumor grade, and age. We found that the PNI was a significant prognostic marker for disease-specific and event-free survival using univariate and multivariate analyses. Patients with a low PNI had poorer disease-specific and event-free survival than those with a high PNI. *Conclusion:* These results suggest that the PNI can be used as a prognostic marker in patients with STS.

Soft-tissue sarcoma (STS) is a rare, heterogeneous group of tumors (1). The incidence of STS is fewer than six per 100,000 cancer cases, which represents 1-2% cases of all cancer in adults (1). Despite recent advances in the diagnosis and treatment of STS, patients who develop metastasis have high mortality rates. Therefore, many studies have attempted to define different factors for predicting the prognosis of patients with STS. Older age and deep, trunkal, high-grade, and large size of STS have been reported to be prognostic factors that are linked to poor prognosis (2-4). In addition, systemic inflammation has been associated with poor

prognosis. In terms of STS, elevated levels of C-reactive protein and interleukin-6, hypoalbuminemia, and anemia have been correlated with poor oncological outcomes (5-9). In addition to the systemic inflammation status, nutrition and immune status play important roles in the prognosis of patients with several types of cancer (10-14).

The prognostic nutritional index (PNI), calculated using the serum albumin level and total lymphocyte count, is an effective indicator for assessing nutritional and immunological conditions. Initially described by Onodera *et al.* (15), it has been validated as an independent prognostic factor in several types of cancer, including renal cell cancer (10), pancreatic cancer (11), colorectal cancer (12), esophageal carcinoma (13), and hepatocellular carcinoma (14). However, it is unclear whether the PNI is useful in predicting the prognosis of patients with STS.

Therefore, this study aimed to determine whether the PNI can predict the prognosis in patients with STS before treatment and examine whether there is an association between PNI values and clinical characteristics.

Patients and Methods

Patient characteristics. Between February 2002 and April 2019, 100 patients with primary STS were retrospectively reviewed. Patients with recurrent disease and those who were referred for additional resection after a previous unplanned excision were excluded from this study. The study cohort included 55 men and 45 women, with a mean age of 64 years (range=12-88 years) at the time of diagnosis. The mean follow-up duration was 41.7 months (range=0.6-208 months). Histological diagnosis and tumor grade were determined using the French Federation of Cancer Centers Sarcoma Group grading system (15). The PNI values were calculated from preoperative laboratory parameters using the formula $10 \times \text{serum albumin level (g/dl)} + 0.005 \times \text{lymphocyte count (n}/\mu\text{l)}$ in the peripheral blood (16). Serum albumin levels and lymphocyte counts were measured before the initial treatment in all patients.

Clinicopathological analysis was performed relating the PNI to various factors, including age, sex, and tumor grade, size, and depth.

The primary study aim was to examine the prognostic factors associated with patient survival, including the PNI, using univariate and multivariate analyses. The following factors were studied: age (≥ 66 vs.

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Key Words: Prognostic nutritional index, soft tissue sarcoma, survival.

Table I. The relationship between the prognostic nutritional index (PNI) and clinicopathological characteristics.

Variable		N	Average PNI	p-Value
Age	<64 Years	42	51.65	0.33
	≥64 Years	58	50.42	
Gender	Male	55	51.25	0.58
	Female	45	50.56	
Tumor depth	Superficial	12	52.02	0.52
	Deep	88	50.79	
Tumor size	<10 cm	49	52.79	0.0003
	>10 cm	51	49.16	
Tumor grade	Low	33	52.96	0.020
	High	67	49.89	

Table II. Spearman's correlation between the prognostic nutritional index (PNI) and tumor size and age as continuous variables.

Variable	Spearman rho	p-Value
Tumor size	-0.271	0.006
Age	-0.242	0.015

<66 years), sex, tumor grade (1 vs. 2 and 3), tumor size (>10 cm vs. <10 cm), tumor depth, and PNI. The secondary aim was to examine the prognostic factors associated with oncological outcomes. Written informed consent was obtained from the patients. This study was approved by the Institutional Review Board at our hospital (no. 1310).

Statistical analysis. The statistical associations of the clinicopathological factors were evaluated using the Mann-Whitney U-test for quantitative data and the chi-square test for qualitative data. Disease-specific survival (DSS) was defined as the time from the initial surgery to the date of death from sarcoma. Event-free survival (EFS) was defined as the time from surgery to disease recurrence/metastasis. DSS and EFS curves were constructed using the Kaplan-Meier method, and the log-rank test was used to compare survival and oncological events. Univariate and multivariate analyses were performed using the Cox proportional hazards model. The variables included in the multivariate analysis were significant factors identified in univariate analysis. A value of $p < 0.05$ was considered significant in all statistical analyses.

Results

A total of 100 patients were included in this study. The tumors were classified histologically as follows: 60 Liposarcomas (28 well-differentiated, 16 de-differentiated, six myxoid, and one pleomorphic), 15 myxofibrosarcomas, nine undifferentiated pleomorphic sarcomas and rhabdomyosarcomas, four malignant peripheral nerve sheath tumors and synovial sarcomas, and eight tumors of other histological types. The histological diagnoses and tumor grades were determined using the French Federation of Cancer Centers Sarcoma

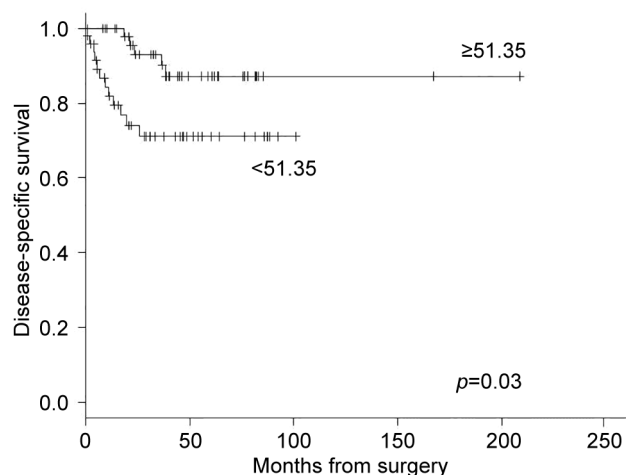


Figure 1. Kaplan-Meier curve showing the disease-specific survival for 100 patients with soft-tissue sarcoma according to prognostic nutritional index (PNI) using a cut-off of 51.35.

Group grading system (15). A total of 33 patients had grade 1 sarcomas, and 67 patients had grade 2 or 3 sarcomas. The mean tumor size at diagnosis was 11.8 cm (range=1-38 cm). The tumor depth was superficial and deep in 12 and 88 patients, respectively. Primary tumor resection was performed in all patients. A total of 23 patients received radiotherapy, and 33 patients received chemotherapy.

The median preoperative albumin level was 4.2 g/l (range=2.5-5.0 g/l), and the median lymphocyte count was 1640 cells/ μ l (range=380-3,560 cells/ μ l) considering the whole patient cohort. The median PNI value was 51.35 (mean=50.94, range=31.2-65.75). The relationships between clinicopathological characteristics and PNI are shown in Table I. Tumor grade and size were significantly inversely associated with the PNI. Spearman's rank test showed that PNI values were weakly correlated with tumor diameter and age (Table II).

At the final follow-up, 82 (82%) patients were alive, 16 (16%) patients had died of the disease, and 2 (2%) patients had died of other causes. The DSS at 5 years was 78.5% [95% confidence interval (CI)=67.8-86%].

When patients were divided into two groups according to the median PNI value (51.35), those with a low PNI had poorer DSS than those with a high PNI (Figure 1). The 5-year DSS rate was 71.1% (95% CI=54.4-82.6%) in patients with a low PNI, whereas that in patients with a high PNI was 87.2% (95% CI=71.7-94.5%) ($p=0.03$). Univariate analysis of all possible prognostic factors confirmed the predictive value of age ($p=0.046$), histological grade ($p=0.003$), and the PNI ($p=0.003$). Histological grade and the PNI were considered to be of prognostic significance in multivariate analysis (Table III).

Table III. The prognostic factors for disease-specific survival (DSS) in 100 patients with soft-tissue sarcoma.

Variable	Subgroup	N	Univariate analysis		Multivariate analysis	
			5-Y DSS	p-Value	HR (95% CI)	p-Value
Age	<66 Years	45	89.4%	0.046	1	0.057
	≥66 Years	55	70.2%			
Gender	Male	55	75.8%	0.45		
	Female	45	83.8%			
Tumor depth	Superficial	12	91.7%	0.36		
	Deep	88	77.5%			
Tumor size	<10 cm	49	85.9%	0.19		
	>10 cm	51	72.7%			
Tumor grade	Low	33	96.4%	0.003	1	0.04
	High	67	68.1%			
PNI	≥51.35	51	85.4%	0.03	0.9112 (1.001-1.007)	0.009
	<51.35	49	71.1%			

CI: Confidence interval; HR: hazard risk; PNI: prognostic nutritional index, 5-Y: 5-year.

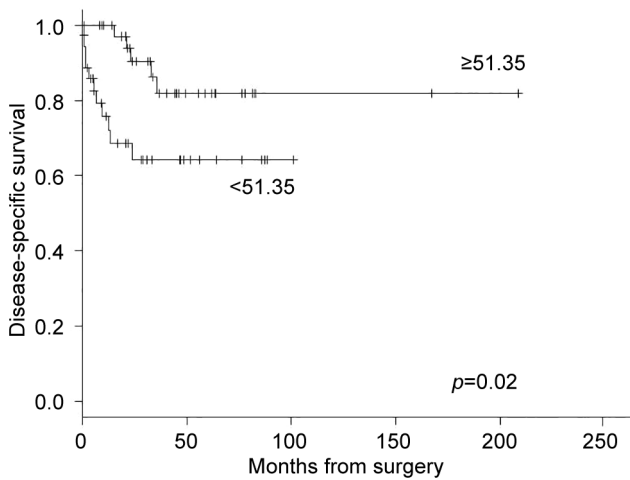


Figure 2. Kaplan-Meier curve showing the disease-specific survival for 74 patients with soft-tissue sarcoma, after exclusion of those with well-differentiated liposarcoma, according to prognostic nutritional index (PNI) using a cut-off of 51.35.

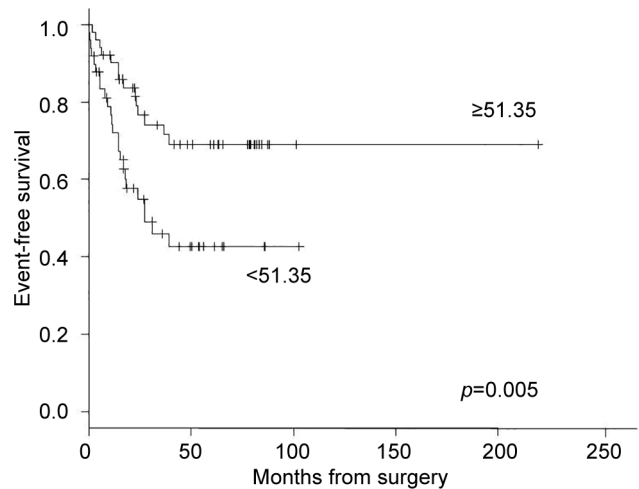


Figure 3. Kaplan-Meier curve showing the event-free survival for 100 patients with soft-tissue sarcoma according to prognostic nutritional index (PNI) using a cut-off of 51.35.

Next, we excluded 26 patients with well-differentiated liposarcoma from our cohort due to their excellent prognosis and examined the relationship between PNI and survival in the remaining 74 patients. The median PNI value was 51.35 (mean=50.37, range=31.2-65.75) in 74 patients. Patients with a low PNI had poorer DSS than those with a high PNI ($p=0.02$). The 5-year DSS rate was 64.3% (95% CI=44.3-78.7%) for patients with a low PNI, while that for those with a high PNI was 81.9% (95% CI=61.3-92.1%) (Figure 2). Univariate analysis of all possible prognostic factors confirmed the prognostic significance of tumor size ($p=0.045$), age ($p=0.02$), and the PNI ($p=0.02$) (Table IV).

Considering the whole cohort, recurrence and metastasis were observed in 15 (15%) and 30 (30%) patients, respectively. The EFS rate was 60.4% (95% CI=48.5-70.4%). Patients with a low PNI had a poorer EFS than those with a high PNI (Figure 3). The 5-year EFS rate was 42.7% (95% CI=27.0-57.6%) in patients with a low PNI, while that in those with a high PNI was 71.5% (95% CI=55.8-82.5%).

Univariate and multivariate analyses showed that a low PNI and high histological grade were independent predictors of recurrence/metastasis (Table V).

Next, we excluded 26 patients with well-differentiated liposarcoma and examined the relationship between the PNI

Table IV. The prognostic factors for disease-specific survival (DSS) in patients with soft-tissue sarcoma after exclusion of 26 with well-differentiated liposarcoma (n=74).

Variable	Subgroup	N	Univariate analysis		Multivariate analysis	
			5-Y DSS	p-Value	HR (95% CI)	p-Value
Age	<66 Years	35	89.2%	0.02	1	0.046
	≥66 Years	39	60.3%			
Gender	Male	38	68.6%	0.46	1.046 (1.001-1.093)	0.046
	Female	36	79.1%			
Tumor depth	Superficial	8	91.7%	0.36	1	0.13
	Deep	66	77.5%			
Tumor size	<10 cm	42	83.7%	0.045	1.059 (0.9842-1.139)	0.13
	>10 cm	32	56.5%			
Tumor grade	Low	7	100%	0.19	1	0.051
	High	67	70.8%			
PNI	≥51.35	38	81.9%	0.02	0.9241 (0.8536-1.000)	0.051
	<51.35	36	64.3%			

CI: Confidence interval; HR: hazard risk; PNI: prognostic nutritional index, 5-Y: 5-year.

and events. Patients with a low PNI had a poorer EFS than those with a high PNI ($p=0.02$). The 5-year EFS rate was 39.8% (95% CI=21.4-57.7%) in patients with low PNI, while that in those with a high PNI was 58.6% (95% CI=38.4-74.2%) (Figure 4). Univariate analysis of all possible prognostic factors confirmed the prognostic ability of tumor histology ($p=0.03$), age ($p=0.03$), and the PNI ($p=0.02$). The PNI remained a significant factor in multivariate analysis (Table VI).

Discussion

Onodera *et al.* developed the PNI as an index to screen for the feasibility of surgery for gastrointestinal cancer (15). It is useful as an index not only for perioperative complications but also for prognosis prediction. It has been validated as an independent prognostic factor in several types of cancer (10-15). In this study, using univariate and multivariate analyses, we found that the PNI was a significant prognostic marker for DSS and EFS in 100 patients with STS. When we excluded 26 patients with well-differentiated liposarcoma, the PNI significantly predicted EFS ($p=0.008$) in multivariate analysis, although the PNI showed marginal significance for DSS ($p=0.051$). These results suggest that PNI is a prognostic marker in patients with STS.

The PNI reflects not only the nutritional and immune status but also the inflammatory status of patients (7, 17, 18). A low PNI is caused by a low albumin level and/or lymphocyte count. Serum albumin is an important indicator of inflammatory reaction and nutritional status (3, 19). Several studies have previously demonstrated that high levels of the cytokine interleukin-6 contribute to the development of hypoalbuminemia and elevated C-reactive protein level (8, 20).

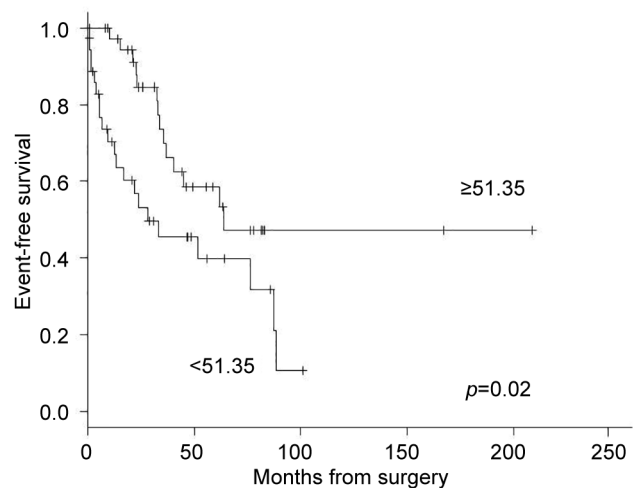


Figure 4. Kaplan-Meier curve showing the event-free survival for 74 patients with soft-tissue sarcoma, after exclusion of those with well-differentiated liposarcoma, according to prognostic nutritional index (PNI) using a cut-off of 51.35.

The combination of hypoalbuminemia and an elevated C-reactive protein level, which are used in the Glasgow prognostic score or the high-sensitivity modified Glasgow prognostic score, has been shown to provide additional prognostic information in patients with STS (2, 5, 6). Lymphocytes, the other element considered in the PNI, are the most important type of peripheral blood cells and work against the proliferation, migration, and invasion by cancer cells (21). Therefore, in the case of lymphocytopenia, the cellular immune system cannot function properly and an appropriate inflammatory reaction cannot be

Table V. The prognostic factors for event-free survival (EFS) in 100 patients.

Variable	Subgroup	N	Univariate analysis		Multivariate analysis	
			5-Y DSS	p-Value	HR (95% CI)	p-Value
Age	<66 Years	45	69.5%	0.1		
	≥66 Years	55	49.0%			
Gender	Male	55	54.5%	0.66		
	Female	45	62.3%			
Tumor depth	Superficial	12	91.7%	0.36		
	Deep	88	77.5%			
Tumor size	<10 cm	49	59.4%	0.59		
	>10 cm	51	56.3%			
Tumor grade	Low	33	89.3%	<0.0001	1	<0.001
	High	67	41.0%			
PNI	≥51.35	51	71.5%	0.005	0.9204 (0.8706-0.9729)	0.001
	<51.35	49	42.7%			

CI: Confidence interval; HR: hazard risk; PNI: prognostic nutritional index, 5-Y: 5-year.

Table VI. The prognostic factors for event-free survival (EFS) in patients with soft-tissue sarcoma after exclusion of 26 with well-differentiated liposarcoma (n=74).

Variable	Subgroup	N	Univariate analysis		Multivariate analysis	
			5-Y DSS	p-Value	HR (95% CI)	p-Value
Age	<66 Years	35	58.7%	0.03	1	0.36
	≥66 Years	39	42.1%			
Gender	Male	38	45.1%	0.41	1.012 (0.9864-1.038)	
	Female	36	55.3%			
Tumor depth	Superficial	8	44.3%	0.09		
	Deep	66	87.5%			
Tumor size	<10 cm	42	65.0%	0.07		
	>10 cm	32	30.7%			
Tumor grade	Low	7	100%	0.03	1	0.99
	High	67	45.5%			
PNI	≥51.35	38	58.6%	0.02	0.9253 (0.8732-0.9805)	0.008
	<51.35	36	39.8%			

CI: Confidence interval; HR: hazard risk; PNI: prognostic nutritional index, 5-Y: 5-year.

established. Therefore, the PNI is an index that reflects chronic inflammation, the immune system, and nutritional status and has prognostic significance in cancer patients. In this study, tumor size and grade were associated with PNI. Therefore, a low PNI may be indicative of the action of an aggressive tumor in patients with STS. Recently, the PNI was shown to be an independent prognostic factor for progression-free survival in patients with metastatic breast cancer who were treated with eribulin (22). Eribulin is also administered to patients with STS, and future studies should be conducted to investigate possible markers of survival.

This study has some limitations. There is no 'normal' value established for PNI, and it may be difficult to confirm its

validity in different cohorts. The cutoff value used for predicting survival ranges from 40 to 52.8 in several types of cancer (10-15, 22-33), a range which includes that of the present study (51.35). However, several other markers, such as the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for predicting DSS in patients with STS, have standard levels because of the nature of their calculation methods (2, 34). Systemic inflammatory diseases such as collagen disease were not considered, although all patients underwent initial screening, including computed tomography of the chest and routine blood examinations before their treatment. The retrospective design of this study is another limitation. However, we believe that the PNI could be a useful prognostic marker in patients with STS.

Conflicts of Interest

There were no conflicts of interest in this study.

Authors' Contributions

Tomoki Nakamura and Yumi Matsuyama conceived the study, collected and analyzed the data and wrote the article. Keisuke Yoshida, Koichi Nakamura and Tomohito Hagi analyzed and interpreted the clinical data. Akihiro Sudo and Kunihito Asanuma interpreted the clinical data, and reviewed the article.

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