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Research Article

Impact of Prognostic Nutritional Index on Long-Term Outcomes in Patients with Gastric Cancer: Izmir Oncology Group (IZOG) Study

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Abstract

Objectives: We aimed to investigate the effect of the Prognostic Nutritional Index (PNI) and other well-known prognostic factors in gastric cancer (GC) patients based on pathological parameters and to analyze its predictive value for gastric cancer survival.

Methods: The PNI was calculated by using serum albumin and total lymphocyte count on the time diagnosis. Associations between PNI and clinical, demografic and histopathological parameters were analyzed.

Results: Data of 364 patients with GC were evaluated retrospectively. The median OS was 27 months (95%CI, 20.3 to 33.6)) in the high prognostic nutrition index and 14 months (95%CI, 11.5 to 16.4) in the low prognostic nutrition index (p<0.0001). In the multivariate Cox regression model, prognostic nutrition index (B=0.410, 95% CI=1.023 to 2.221 p=0.038), lymphovascular invasion (B=.907, 95% CI=1.398 to 4.390 p=0.002), stage (B=0.842 95% CI=1.349 to 3.992 p=0.002) and lymph node metastasis (B=-.896, 95% CI=1.199 to 4.908 p=0.014) were statistically significant predictors for OS.

Conclusion: The PNI, a simple, well-validated, and cost-effective biomarker is an independent prognostic factor for OS in patients with GC. Our results can emphasize prognostic benefit from careful nutritional support during diagnosis and treatment for patients with poor nutritional parameters.

Keywords: Prognostic nutrition index, gastric cancer, survival

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Gastric cancer (GC) is one of the most comon cancer worldwide.[1] Patients with gastric cancer were usually diagnosed at advanced or metastatic stage and only a limited number of them have a chance of potential surgical resection. However, the prognosis of gastric cancer patients is poor even after undergoing complete surgical resection. Both systemic recurrence and local recurrence rate is very high after surgery alone.[2] It remains at around 5% five year survival for stage 4 despite aggressive therapies in cases with GC.[3-5]

Many prognostic factors affect the survival of patients with GC include advanced stage, lymph node involvement and

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lymphovascular invasion.[6] Most of these factors cannot be altered by physicians. Besides this, various nutritional status and inflammation related biomarkers have been considered crucial for predicting cancer survival, such as prognostic nutritional index (PNI).[7-9] This index, calculated using total lymphocyte count in peripheral blood and serum albumin levels, is an effective indicator for assessing nutritional and immunological conditions of cancer patients.[7] Malnutrition and inflammation plays a important role in tumor development, as well as perioperative morbidity, resistance to chemotherapy. progression and metastasis.[10,11]

Various studies demonstrated that there was association between PNI and survival in various cancer, including lung, colorectal, endometrial, breast cancer, malignant melanoma and other many cancer types.[9,12-17] PNI has also been studied in gastric cancer. In fact, Onedera et al first evaluated the PNI in gastrointestinal surgery.[7] This study showed that the PNI is a significant predictor of postoperative complications. Also there are some other studies which support these findings.[18,19] In addition, association between survival and PNI have been demonstrated in GC. Kazuhiro et al. investigated 548 patients with gastric cancer who underwent gastrectomy and a low PNI was an independent predictor for poor OS independent of the tumor stage.[20] Similarly, low PNI is found to be an independent predictor of poor OS in another studies.[10,15,18,20-22] Besides, the PNI predicts pathological node positivity with a high specificity in patients with a clinical diagnosis of advanced GC.[23] On the other hand, there are also negative studies. Although Katsunobu et al. found preoperative PNI as a prognostic indicator for stage 1 and 2 gastric cancer, they did not find a relationship with postoperative morbidity.[13] In addition, Yang et al. found that a low PNI was not significantly associated with poor OS in patients with stage 4 GC.[19] As a result of these evidences, the importance of perioperative nutritional support to prolong survival in patients with low PNI was emphasized.[24]

The results for PNI are conflicting. In addition, PNI was evaluated in either operable early stage gastric cancer or patients with advanced stage were included in the studies. The aim of our study is to investigate the effect of PNI, which is calculated at the time of diagnosis in a large sample size of patients with GC based on clinical and pathological parameters, on survival.

Methods

Patient Selection

The medical records of patients with GC who were admitted to the medical oncology clinic of Izmir Katip Celebi University Ataturk Training and Research Hospital between 2005 and 2020 were retrospectively reviewed. The clinical and histopathological characteristics of all patients, including sex, age, pathological lymph node status, status of lymph node dissection, TNM staging, pathological differentiation, lymphovascular invasion, perineural invasion were collected. The levels of PNI was recorded during diagnosis. Patients with chronic inflammatory or autoimmune disease, steroid treatment, active infection (high fever, classical symptoms, and signs of the infection) and bleeding were excluded from the study. The local Institutional Review Board approved the study.

Assessment of PNI

Assessment of Onodera's PNI, albumin and TLC were measured preoperatively and Onodera's PNI was calculated as $10\times$Alb (g/dl)$+0.005\times$TLC (per mm^3).[7] Cut-off levels of PNI was determined according to receiver operating characteristic (ROC) curve analysis.

Evaluation of Histopathological Characteristic Changes

The TNM staging was performed according to the American Joint Committee on Cancer (AJCC 2018) classification.[5] The nodal dissections were performed according with the principles of the Japanese Gastric Cancer Association6. Clinicopathological traits were coded as binary variables including histological grade (well/moderate vs poorly differentiated), pathological T stage (pT1/2 vs pT3/4)), pathological N stage (pN0 vs pN1/2/3) and pathological TNM stage (stage1/2/3 vs stage 4). The surgical lymph node resections were categorized into underwent D1-plus lymph-node dissection vs D2/D3 lymphadenectomy.

Treatment Endpoints

Overall survival (OS) which was calculated from the date of pathological diagnosis to the date of death or the final follow-up visit.

Statistical Analysis

The Kaplan–Meier method was performed to estimate survival outcomes and groups were compared by the log-rank test. Cox proportional hazards models were fit to determine the association between PNI with survival outcomes after adjustment for patient and disease characteristics. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor and all statistical tests were carried out two-sided and a P value ≤ 0.05 was considered statistically significant. All tests were two-tailed. All statistical analyses were made using the Statistical Package of Social Science (SPSS) version 16.0 software (Chicago, IL).

Results

The characteristics of the 364 patients included in the study are reported in Table 1. Of the 364 patients, 251 were men and 113 were women and their median age was 61 years (range 17-88). According to TNM staging, 33 patients had T1, 24 patients has T2, 95 patients had T3, and 79 patients had T4 tumor. The majority of the patients underwent D1-plus lymphadenectomy (34.9 %) and had a N3 lymph node metastasis (22.3 %). Thirty-nine (39.6 %) of the patients presented AJCC stage 4 disease. At the time of the final follow-up 260 (76.4 %) of the all patients died. Eighty-six (23.6 %) of the patients presented no evidence of progression during the last evaluation (Table 1).

Table 1. Clinical characteristics of the patients with gastric cancer

Characteristics of the patients	n (%)
Age (years), median (range)	61 (17-88)
Sex , Male/Female	251/113 (69/31)
Grade	
well	33 (9.1)
modarate	92 (25.3)
poor	123 (33.8)
Lymphovascular invasion	
Yes	134 (36.8)
No	72 (19.8)
Perineural invasion	
Yes	125 (34.3)
No	74 (20.3)
Tumor invasion depth	
T1	33 (9.1)
T2	24 (6.6)
T3	95 (26.1)
T4	79 (21.7)
Lymph node involvement	
N0	60 (16,5)
N1	38 (10,4)
N2	53 (14,6)
N3	81 (22,3)
Dissection type	
D1	127 (34.9)
D2	92 (25.3)
D3	9 (2.5)
Pathological TNM staging	
1	34 (9.3)
2	38 (10.4)
3	148 (40.7)
4	144 (39.6)
Disease status at last follow-up	123 (33,9)
No evidence of disease	86 (23.6)
Evidence of disease	18 (4.3)
Dead	260 (71,4)
Median PNI (range)	46.8 (23.6-65.9)

PNI: prognostic nutritional index.

The cut-off value of 46 for prognostic nutrition index determined by ROC analysis predicted survival with 63.5% sensitivity and 56.4% specificity (p=0.0001, AUC=0.644) (Fig. 1). The median OS was 27 months (95%CI, 20.3 to 33.6) in the high prognostic nutrition index and 14 months (95%CI, 11.5 to 16.4) in the low prognostic nutrition index (p=0.0001) (Fig. 2). PNI values were significantly correlated with age (p<0.001), tumor invasion depth (p=0.027), lymph

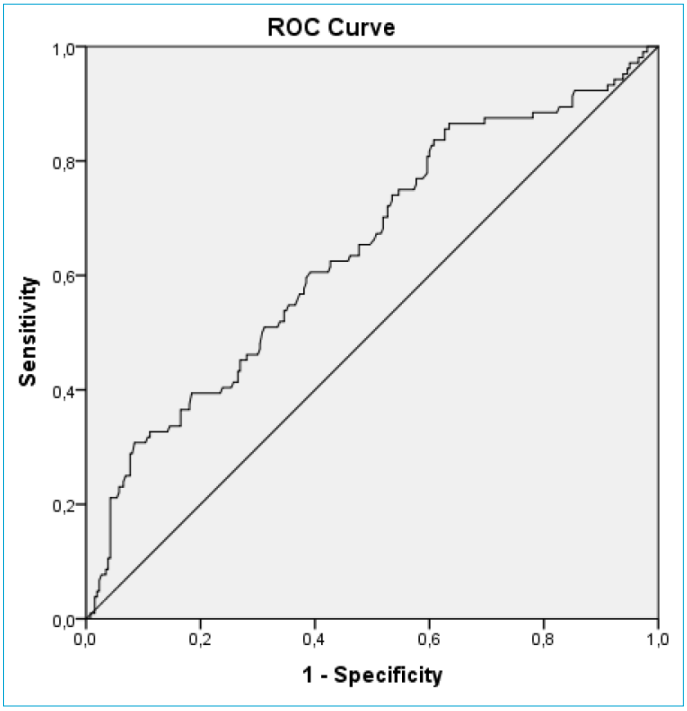

Figure 1. 1 Prediction of death by ROC analysis for PNI. The best cut-off value for the prediction of survival was 46 for AUC = 0.644 (95 % CI 0.580–0.708).

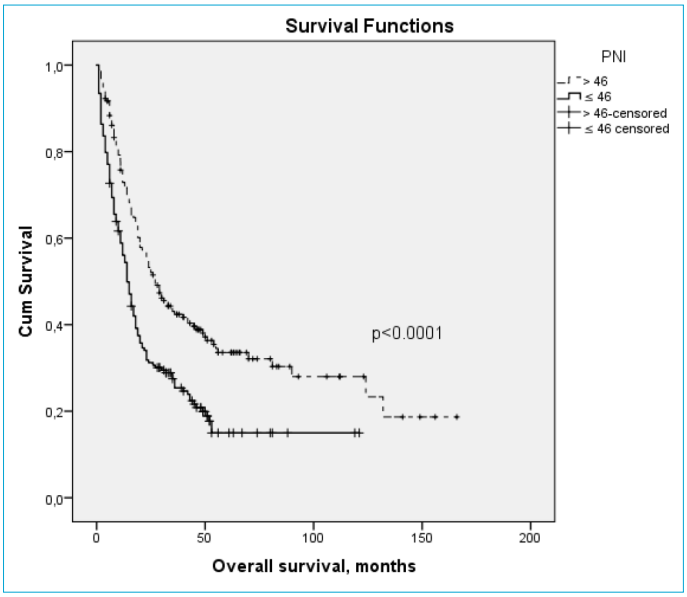

Figure 2. Kaplan-Meier curves for overall survival according to PNI.

node metastasis (p=0.015) and stage (p<0.001).

Patients were grouped as stage I-III or IV disease. There was a statistically significant difference between the groups in terms of OS [stage I-III (42 months) vs. stage IV patients (8 months), log rank p=0.0001]. We also demonstrated that the median OS of the patients with gastric cancer who had positive lymph nodes was shorter than those with negative lymph nodes (29 months vs not reached, p<0.001). The presence of LVI indicated that the patients with LVI had a poorer survival outcome than those without LVI (median OS, 24 months vs not reached, p<0.0001). Smilarly, univariate analysis showed that the D1 nodal dissection (p=0.049), perineural invasion (p<0.0001), aged 60 or above (p=0.004) and poorly differentiated tumor grade (p=0.044) were associated with worse OS.

In the multivariate analysis, we included PNI, age, stage, tumor invasion depth, lymph node involvement, disection type and histological differentiation type in the Cox regression model to identify independent prognostic factors for GC. The results showed that prognostic nutrition index (B=0.410, 95% CI=1.023 to 2.221 p=0.038), lymphovascular invasion (B=.907, 95% CI=1.398 to 4.390 p=0.002), stage (B=0.842 95% CI=1.349 to 3.992 p=0.002), and lymph node metastasis (B=-.896, 95% CI=1.199 to 4.908 p=0.014) were statistically significant predictors for OS (Table 2).

Discussion

In our study, we investigated the prognostic signifcance of the PNI in 364 patients with gastric cancer. We found that low PNI patients had a significantly shorter survival than high PNI patients. We showed that stage, lymph node metastasis, lymphovascular invasion and PNI were independent predicting factors for OS in multivariate analyses.

Plasma albumin is produced by hepatocytes and regulated by proinflammatory cytokines, including oxidative stress, inteleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α). Plasma albümin which negatively affects catabolic metabolism plays an important regulatory role in body fluid distribution substrate transport and acid–base physiology between the intravascular and extravascular space.[25] It also has been widely used as an indicator of nutritional status and/or hepatic function.[26] It is known that circulating lymphocytes play an important immunological role in various carcinomas and it's level is associated with the survival.[27,28] Therefore, since PNI is a combination of lymphocyte and serum albumin, the association between PNI and survival is easy to understand in patients with GC.

The PNI is a simple and objective indicator initially recommended by Onodera et al to estimate the risk of perioperative complications such as delayed tissue repair, anastomotic leakage and the length of postoperative hospital stay in patients undergoing gastrointestinal surgery.[7] Recently, a growing amount of evidence also suggests that the PNI at diagnosis could be a favorable prognostic factor and a more reliable evaluation tool for the physiological status of cancer patients.[8,9,29]

The associations between PNI values and the clinicopathological characteristics of 364 gastric cancer patients was firstly analyzed in our study. We demonstrated that PNI values were significantly associated with age, tumor invasion depth, lymph node metastasis and stage. Similarly, Hirahara et al. found a significant relationship between PNI and invasion depth, lymph node metastasis, age and stage.[22]

In our analysis, the PNI cut-off value is 46 and this outcome indicated to accurately predict survival. Firstly, this value was set at 45 by Onedera because resection and anastomosis of the gastrointestinal tract can be safely performed

Table 2. Univariate analysis of factors associated with overall survival and Cox proportional hazards regression model of clinical factors predicting overall survival in patients with gastric cancer

	Log Rank (Mantel Cox)		Cox-proportional Hazard	
	Chi-square	p	B (%95CI)	p
PNI (low vs. high)	20.360	**<0.001**	0.410 (1.023-2.221)	**0.038**
Age (60> vs. ≤60)	8.442	**0.004**	-0.359 (0.465-1.048)	0.083
Lymphovascular invasion (Yes vs. No)	19.360	**<0.001**	0.907 (1.398-4.390)	**0.002**
Perineural invasion (Yes vs. No)	12.510	**<0.001**	0.388 (0.878-2.473)	0.142
Grade (well-modarete vs. poor)	4.050	**0.004**	-0.139 (0.530-1.430)	0.583
Dissection type (D1 vs. D2-3)	3.87	**0.049**	0.397 (.0997-2.216)	0.051
Tumor invasion depth (T1-2 vs. T3-4)	27.500	**<0.001**	0.443 (0.740-3.281)	0.243
Lymph node involvement (NOvs.N1-3)	81.615	**<0.001**	0.886 (1.119-4.908)	**0.014**
Stage (1-3 vs. 4)	175.906	**<0.001**	0.842 (1.349-3.992)	**0.002**

PNI: Prognostic nutrition index.

when PNI values are >45.87. Kosuga et al. set the optimal cut-off value of PNI for predicting nodal metastasis at 46 according to the ROC analysis.[23] Hirahara et al. aimed to evaluate the prognostic significance of the PNI, as well as to determine an optimal cutoff value, which can better predict OS in patients with gastric cancer. ROC analysis was performed and an optimal cutoff value for the preoperative PNI was set at 44.3 based on OS and Cancer specific survival.[22] Our cutoff value was consistent with other results.

Lymphovascular invasion (LVI), a pathological finding defined by the infiltration of tumor cells into the lymphatic and/or vascular vessel wall or the presence of tumor embolism with a cavity lined with endothelium, is considered an important pathway for the spread of tumor cells.[30] LVI has been reported to be the strongest risk factor for lymph node metastasis in patients with GC.[31] Some studies reported that the presence of LVI was significantly associated with poor survival outcome, regardless of lymph node metastasis or tumor stage.[31,32] Despite few studies suggesting that the presence of LVI has no effect on the prognostic outcome of node-positive patients or patients with early-stage gastric cancer, the presence of LVI is generally known as a negative risk factor for survival in studies.[33,34] There was a lower OS in the patients with LVI as compared to the patients without LVI in our study. LVI was also identified as an independent prognostic factor of survival outcomes in multivariate analysis.

The optimal treatment of GC is surgical resection with lymph node dissection (LND). D1 dissection intent to clear the lymph nodes with the highest risk of involvement and thus all perigastric and right gastric artery lymph nodes are removed. In a D2 dissection, all D1 lymph nodes plus lymph nodes along the common hepatic, splenic artery, coeliac axis and are removed.[35] Paraaortic and hepatoduodenal lymph nodes dissection are named D3 disection35. While D2 lymph node dissection is considered a standard surgical procedure for resectable gastric cancer in Japan and Korea, the necessity of D2 dissection is still a matter of debate due to postoperative morbidity and mortality in Western countries.[36] In the Dutch gastric cancer group trial, 711 patients who underwent gastric resection with curative intent were randomized to undergo either a D1 or D2 LND. There was no difference between groups for OS.[36] The British Cooperative trial conducted also failed to evidence a survival benefit for D2 over D1 lymph node dissection.[37] In our study, patients with D2/D3 lymph node dissection found to have a prolonged survival in univariate analysis but this was not significant in multivariate analysis.

Pathological nodal stage (N) is based on the the number of involved lymph nodes which is better predictor for outcome than the location of involved lymph nodes.[38] In the eighth TNM staging system, cut offs for definition of N parameter have been changed: One to 2 involved metastatic nodes are classified as pN1, 3 to 6 involved metastatic nodes are classified as pN2, and those with 7 or more involved metastatic nodes are classified as pN338. In GC patients who will have curative resection, one of the most important prognostic indicator is the presence or absence of lymph node metastasis.[39] Kim et al. to identify the clinicopathological characteristics of lymph node-negative gastric carcinoma, and also to evaluate outcome indicators in the lymph node-negative patients.[40] They found that lymph node-negative patients have a favorable outcome attributable and curability is one of the most reliable predictors of long-term survival.[40] The relationship between the number of lymph nodes examined and the outcome in patients with node-negative gastric cancer was evaluated by bruno et al.[41] The outcomes of node negative cases were similar to early gastric cancer.[41] We found that gastric cancer patients after curative resection with positive lymph nodes (N1-3) had much shorter median OS than those with negative lymph nodes in accordance with the literature.

The prevalence of advanced stage cancer is reported as 35%.[42,43] In our study, the prevalence rate for stage 4 and 3 disease was found as 39.6% and 40.7% respectively. Despite these major advances in our understanding of the biology of cancer, the 5-year survival rate was 5.4% in stage IV gastric cancer and survival rates decreases inversely with disease stage.[42,43] In the present study, overall survival was significantly longer with stage 1-3 patients than with stage 4 patients ($p<0.001$). Despite studies reporting that non-stage 4 cancer patients with low PNI levels generally have a worse prognosis and a higher rate of postoperative complications, survival data are limited in all stage patients.[44] Our results promote the hypothesis that a low PNI value is declarative of chronic inflammation and malnutrition in patients with more aggressive or advanced cancers.

The limitations of this study are the retrospective study design, the absence of randomization, and the exclusion of patients' body mass indexes. The PNI value can be more valuable if it can be correlated with Body composition values using the tanita device that makes Body Composition Analyzer.

In conclusion, the PNI, a simple, well-validated, and cost-effective biomarker is an independent prognostic factor for OS in patients with GC. Our results can emphasize prognostic benefit from careful nutritional support during diagnosis and treatment for patients with poor nutritional parameters.

Disclosures

Ethics Committee Approval: İzmir Katip Celebi University 19.12.2018 decision no: 436.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authorship Contributions: Concept – Y.Y., B.D.; Design – Y.Y., B.D.; Supervision – Y.Y., B.D.; Materials – Y.Y., A.S., O.O., A.A.; Data collection &/or processing – U.O., S.S., M.E.K., U.V., T.S., B.B.K.; Analysis and/or interpretation – Y.Y., B.D.; Literature search – Y.Y., Z.G., S.U., Y.K.; Writing – Y.Y., B.D.; Critical review – Y.Y., B.D., A.A.

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