

Prognostic Value of the Pre-Treatment Prognostic Nutritional Index for Patients with Unresectable Locally-Advanced and Advanced Stage Upper Gastrointestinal Tract Cancer

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Purpose: The prognostic nutritional index (PNI) is used to distinguish immune-nutritional status. Previous studies have shown that it is significantly associated with patient outcomes for various malignancies. This study aimed to evaluate the prognostic impact of PNI in patients with unresectable locally-advanced and advanced stage upper gastrointestinal tract cancer, including esophageal cancer and gastric cancer.

Methods: A retrospective study of 170 unresectable stage III–IV esophageal cancer and gastric cancer patients was conducted from January 2018 to December 2020. In our retrospective analysis, the pretreatment PNI of patients was calculated and analyzed. The Youden index was estimated to select the optimal cut-off value for PNI. Univariate and multivariate flexible parametric proportional hazards models with restricted cubic splines (RCS) were used to identify independent prognostic factors, and the Kaplan–Meier method was used to estimate survival curves.

Results: The median follow-up period was 5 months (ranging from 0.06 to 36.92 months). We determined 52.9 as the cut-off value by using the maximum Youden index. Subsequently, patients in the testing group were classified into high PNI and low PNI groups. Kaplan–Meier curves showed the low PNI group had significantly poorer overall survival (OS) than the high PNI group. Median OS in the low PNI group was 4.43 months compared with 8.23 months in the high PNI group (HR 2.42, 95% CI 1.33–4.40, $p = 0.004$). In the univariate analysis, low PNI, ECOG PS 2, and ECOG PS 3–4 were associated with OS. According to multivariate analysis, low PNI was an independent prognostic factor for OS (HR 2.31, 95% CI 1.24–4.29, $p = 0.008$).

Conclusion: Pretreatment PNI is useful for independent prognosis of unresectable stage III–IV esophageal cancer and gastric cancer in patients.

Keywords: prognostic nutritional index, esophageal cancer, gastric cancer, prognosis

Introduction

According to previous studies, data reveals that malnutrition affects survival in cancer patients because patients with malnutrition or overnutrition tend to have lower immunity.¹ Most cancer patients usually have severe malnutrition, affecting treatment outcomes.^{2,3} They also have a higher incidence of death than patients with good nutritional status.^{2,4,5} Cancer-associated malnutrition is common in cancer patients and differs from starvation-related malnutrition in that it results from a combination of anorexia and metabolic dysregulation caused by the tumor itself or its treatment, leading to cachexia, which occurs in 85% of cancer patients.^{6,7} Patients with such conditions will lose weight, have lower muscle mass, and suffer from impaired immune function. Therefore, cancer-associated malnutrition affects treatment in terms of lower response to cancer treatment and treatment-related adverse events, such as acute febrile neutropenia, and poorer

quality of life after treatment. Patients with upper gastrointestinal tract cancer, ie esophageal cancer and gastric cancer, suffer direct effects of cancer affecting food consumption; absorption causes malnutrition.⁸

Evidence-based medical studies have found that screening cancer patients with malnutrition at the beginning of cancer treatment and implementing nutritional therapy to improve nutritional status significantly resulted in good treatment outcomes.^{9,10} In addition, there are studies on biomarkers related to nutrition and immunity, such as the prognostic nutritional index (PNI), which was a simplified biomarker obtained by calculating the serum albumin and lymphocyte count according to the formula $PNI = 10 \times \text{serum albumin (g/dL)} + (0.005 \times \text{total lymphocyte count})$, to assess immunonutrition in patients in terms of their nutritional status and immune system.^{3,11,12} It was found that PNI had a relationship as an independent prognostic factor for patients with various types of cancer.^{13–15} It was also used for the prognosis of treatment in cancer patients.

For upper gastrointestinal tract cancer, ie esophageal cancer, gastric cancer, there has been a study on using pretreatment-PNI (pre-PNI) as a prognostic factor for poor survival and associated with high incidence of postoperative complications, but it was mainly used to assess the treatment outcome of surgery.^{12,16,17} Patients with low pre-operative PNI levels should be observed more closely after surgery to prevent the occurrence of post-operative complications in the near future. Therefore, the objective of this study was to investigate the ability of pretreatment-PNI as an independent prognostic factor in patients with unresectable locally-advanced stage and advanced stage upper gastrointestinal tract cancer, including esophageal cancer and gastric cancer.

Materials and Methods

Patient Selection and Data Collection

We retrospectively reviewed data from patients with unresectable locally-advanced and advanced stage upper gastrointestinal tract cancer, including esophageal cancer and gastric cancer, who received treatment at the Division of Medical Oncology, Oncology Unit, Buddhasothorn Hospital from January 2018 to December 2020. The definition of unresectable and advanced stage for the decision of palliative treatment was made in the context of a multidisciplinary team discussion and a comprehensive expert review based on the patient's request, comorbid diseases, clinical metastases, distant metastases, M1 nodal metastases, peritoneal disease, T4-tumor airway, aorta, main stem bronchi, and cardiac invasion. The inclusion criteria were as follows: Patients aged over 18 years with a clinical history including baseline patient data, diagnosis data, and data on potential prognostic predictors such as gender, age, weight, height, ECOG performance status (ECOS PS), progression-free interval, date of death, pretreatment white blood cell count, pretreatment protein- albumin, medical records such as chemotherapy and radiation. Patients with incomplete/missing data and those who received cancer treatment from other hospitals were excluded.

We calculated pre-treatment PNI as $10 \times \text{serum albumin (g/dL)} + (0.005 \times \text{total lymphocyte count})$. Pretreatment-PNI was defined as the period covering two weeks before treatment. Dates of death were verified and collected from the database for civil registration in accordance with ID cards recorded by the Bureau of Registration Administration (BORA), Department of Provincial Administration, Thai Ministry of Interior. Only causes of death from cancer were analyzed.

We conducted this retrospective chart review study in compliance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (number BSH-IRB 007/2565), which determined that formal consent was not required.

Statistical Analyses

The Youden index was estimated to select the optimal cut-off value for PNI. The Youden index is calculated as $\max(\text{true positive rate} - \text{false positive rate})$ or equivalently $\max(\text{sensitivity} + \text{specificity} - 1)$. The Youden index is an optimal trade-off between sensitivity and specificity with an equal weight being assigned to sensitivity and specificity. The hazard ratio (HR) with a 95% confidence interval (CI) was used to estimate the prognostic value of PNI on survival. The Kaplan–Meier method was used to estimate the survival rates for different groups, and the differences in the survival curves were tested by log-rank statistics. Potential factors used for univariate and multivariate analyses were PNI, sex,

age, ECOG PS, anemia, BMI, and cancer type. A flexible parametric survival model of univariate and multivariate analyses via the *stpm2* package was used to identify the potential risk factors associated with poor prognosis. The main advantage of this non-rigid parametric survival model, beyond the Cox regression, was its ability to estimate the baseline cumulative hazard function via the use of restricted cubic splines. The correlation between PNI and short-term survival of less than 6 months was assessed by regression analysis.

The analysis focused primarily on PNI, a biomarker of immune nutritional status and systemic inflammation that is associated with malnutrition and clinical cancer staging in both esophageal cancer and gastric cancer, a group of cancers of the upper gastrointestinal tract. In addition, both cancers are treated with chemotherapy at inoperable or advanced stages. Therefore, in analyzing the data of this study, the two cancers were combined.

All statistical tests were two-sided, and p -values <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 16 (StataCorp, TX, USA).

Results

Patient Characteristics

A total of 174 cases were eligible, but 4 cases were excluded because of insufficient data, leaving 170. The patient selection flow chart is displayed in Figure 1. The patients were aged 63 years on average. 126 were male (74.12%), while 44 were female (25.88%). Ninety-four patients were diagnosed with esophageal cancer (55.29%), while seventy-six patients were diagnosed with gastric cancer (44.71%). Ninety-two patients received the best supportive care (54.12%). Seventy-nine patients received cancer-specific treatment (45.88%), ie palliative chemotherapy, radiation, and chemoradiation. The baseline clinical characteristics of 170 patients with unresectable locally-advanced and advanced stage upper gastrointestinal tract cancer are shown in Table 1. The median follow-up period was 5 months (ranging from 0.06 to 36.92 months), and 163 (95.88%) patients had died by the end of the period. The median overall survival (OS) was

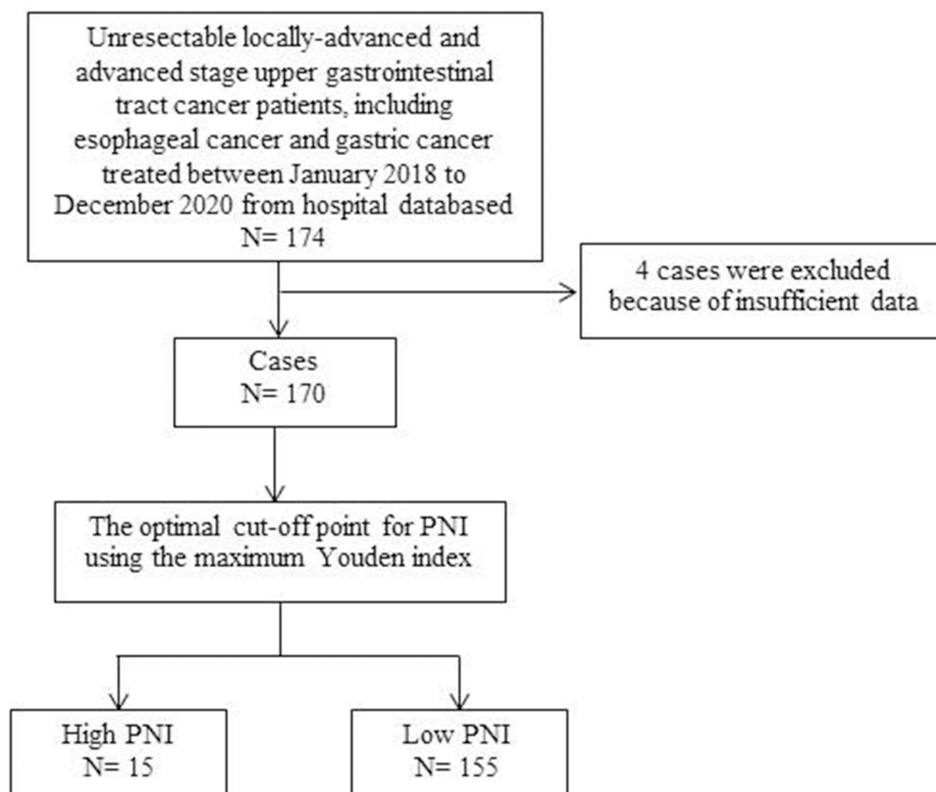


Figure 1 Patient selection flow chart.

Table I Clinical Characteristics of Unresectable Locally-Advanced and Advanced Stage Upper Gastrointestinal Tract Cancer Patients

Variables	Number (%)
Sex	
Male	126(74.12)
Female	44(25.88)
Cancer type	
Esophageal cancer	94(55.29)
Gastric cancer	76(44.71)
Clinical stage	
III	59(34.71)
IV	111(65.29)
ECOG PS	
0	7(4.12)
1	95(55.88)
2	59(34.71)
3	5(2.94)
4	4(2.35)
Cancer treatment	
No (supportive care)	92(54.12)
Palliative chemotherapy	50(29.41)
Radiation	1(0.59)
Chemoradiation	27(15.88)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

4.75 months (95% CI 3.64–5.51). The mean age of the patients was 63.75 ± 0.87 years, mean body mass index (BMI) was 17.87 ± 0.27 , and mean PNI was 41.26 ± 1.22 .

Optimal Cutoff Values for Pretreatment Prognostic Nutritional Index (Pre-PNI)

The optimal cut-off point using the maximum Youden index from the ROC curve of the pre-PNI for predicting death was 52.9, sensitivity of 92.64% and specificity of 42.86%, area under the curve (AUC) = 0.68, 95% CI 0.48–0.88. The ROC curves are presented in Figure 2. According to the optimal cutoff value of pre-PNI, we divided 155 patients with pre-PNI <52.9 into the low PNI group and 15 patients with pre-PNI ≥ 52.9 into the high PNI group, after which we compared survival between the two groups. Low PNI (pre-PNI <52.9) was significantly associated with poorer OS. Median OS in low PNI group was 4.43 months (95% CI 3.38–5.28) compared with 8.23 months (95% CI 2.62–28.23) in the high PNI group (HR 2.42, 95% CI 1.33–4.40, $P = 0.004$) (Figure 3).

Correlation Between Pre-PNI Variable and Clinical Characteristics Potential Variables and Survival

In the univariate analysis, low PNI, ECOG PS 2, and ECOG PS 3–4 were associated with OS. Low PNI, age > 60 years, ECOG PS 2, ECOG PS 3–4, and gastric cancer were significantly related to prognosis by multivariate exploratory data analysis (Table 2).

Prognostic Impact of Pre-PNI

Low PNI, age > 60 years, ECOG PS 2, ECOG PS 3–4, and gastric cancer that were statistically significant in the multivariate exploratory data analysis were included in the multivariate flexible parametric proportional hazards

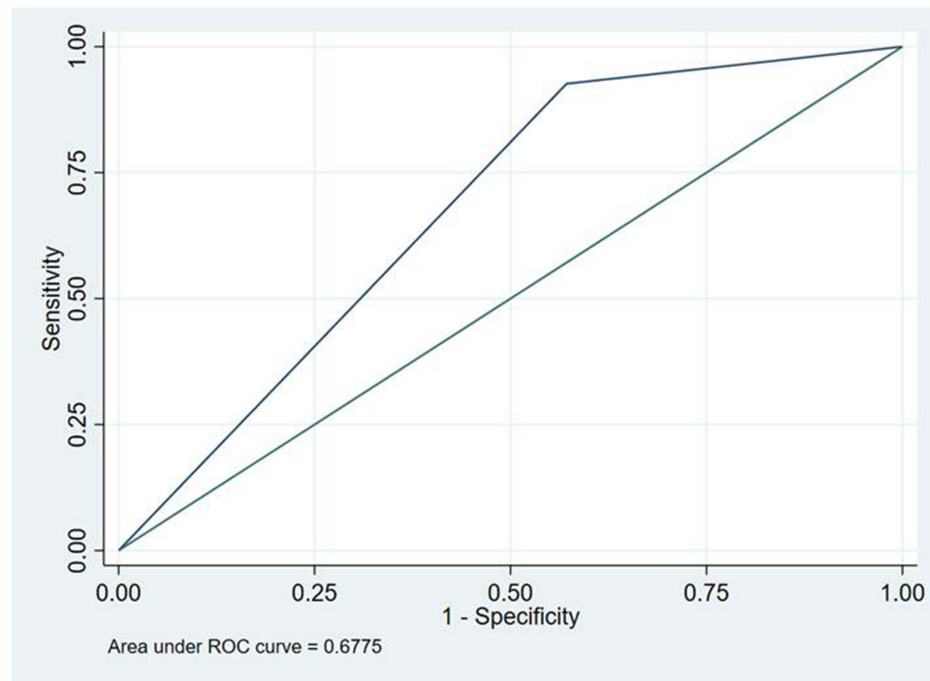


Figure 2 Receiver operating characteristic curve of the cut-off value for PNI.

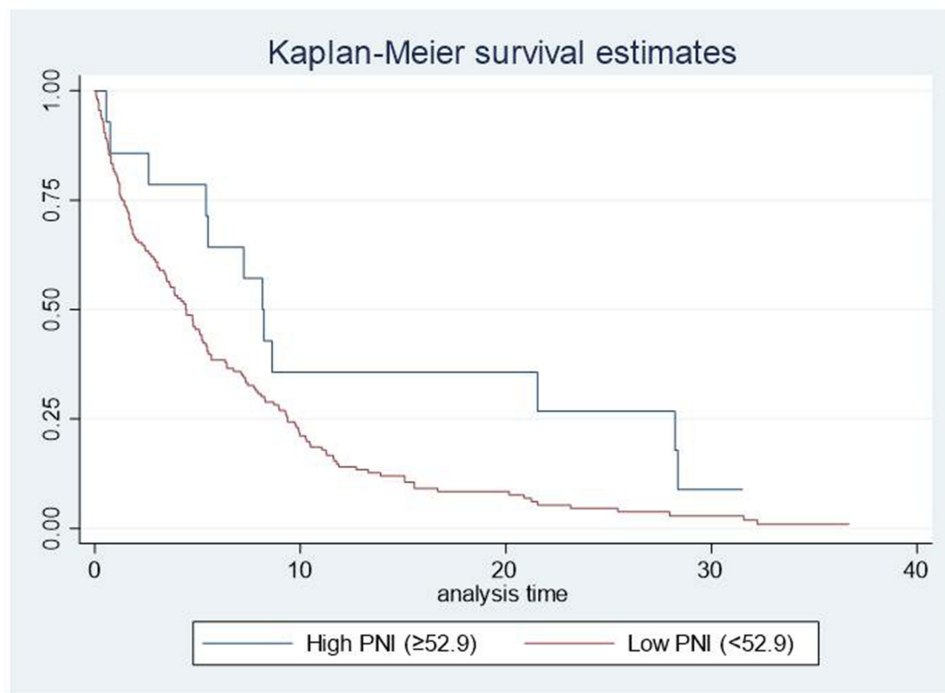


Figure 3 Kaplan-Meier survival curve of the overall survival between high PNI and low PNI groups.

Table 2 Results of Univariate and Multivariate Flexible Parametric Proportional Hazards Model with Restricted Cubic Splines (RCS) of Potential Variables for Overall Survival of Unresectable Locally-Advanced and Advanced Stage Upper Gastrointestinal Tract Cancer Patients

Variables	Univariate Analyses			Multivariate Analyses		
	uHR	95% CI	p-value	mHR	95% CI	p-value
PNI						
High (≥ 52.9)	1	(Omitted)		1	(Omitted)	
Low (< 52.9)	2.42	1.33–4.40	0.004	2.18	1.14–4.14	0.018
Sex						
Female	1	(Omitted)		1	(Omitted)	
Male	1.20	0.84–1.70	0.318	1.47	0.98–2.22	0.064
Age (in years)						
≤ 60	1	(Omitted)		1	(Omitted)	
> 60	1.03	0.75–1.41	0.858	0.66	0.47–0.94	0.021
ECOG PS						
0–1	1	(Omitted)		1	(Omitted)	
2	1.95	1.40–2.72	< 0.001	2.22	1.54–3.21	< 0.001
3–4	2.14	1.08–4.26	0.030	3.01	1.40–6.46	0.005
Hemoglobin, g/dL						
≤ 11	1	(Omitted)		1	(Omitted)	
< 11	1.19	0.86–1.64	0.286	0.88	0.62–1.24	0.465
BMI						
> 25	1	(Omitted)		1	(Omitted)	
18.5–25	1.42	0.57–3.54	0.456	1.66	0.64–4.33	0.300
< 18.5	1.54	0.62–3.79	0.348	1.60	0.60–4.20	0.345
Cancer type						
Esophageal cancer	1	(Omitted)		1	(Omitted)	
Gastric cancer	1.19	0.87–1.62	0.281	1.46	1.03–2.08	0.032

Note: A p-value of < 0.05 was considered statistically significant.

model with restricted cubic splines (RCS) analysis to explore the impact of low PNI when adjusting other prognostic factors.

Multivariate analysis identified low PNI as a strong independent prognostic factor in patients with unresectable locally-advanced and advanced stage upper gastrointestinal tract cancer (HR 2.31, 95% CI 1.24–4.29, $P = 0.008$) (Table 3).

Discussion

In this study, we detected a relationship between pre-PNI, age > 60 years, ECOG PS 2, ECOG PS 3–4, gastric cancer, and survival outcomes of unresectable locally-advanced stage and advanced stage upper gastrointestinal tract cancer. The optimal cut-off value was 52.9 for PNI, corresponding to the maximum Youden index. According to the cut-off point, it was found that the patients with low pre-PNI (< 52.9) were related to poorer survival outcomes when compared with the group with high pre-PNI (HR 2.42, 95% CI 1.33–4.40, $p = 0.004$) and according to the analysis by multivariate flexible parametric proportional hazards model with restricted cubic splines (RCS) analysis. The main advantage of this non-rigid parametric survival model, beyond the Cox regression, was its ability to estimate the baseline cumulative hazard function via the use of restricted cubic splines. The PNI was identified as an independent prognostic factor for OS (HR 2.31, 95% CI 1.24–4.29, $p = 0.008$). Thus, pre-PNI could be used as a marker to identify patients with unresectable locally-

Table 3 Results of Multivariate Analyses of Prognostic Factors for Overall Survival of Unresectable Locally-Advanced and Advanced Stage Upper Gastrointestinal Tract Cancer Patients

Variables	Multivariate Flexible Parametric Proportional-Hazards Model with Restricted Cubic Splines (RCS)		
	mHR	95% CI	p-value
PNI High (≥ 52.9) Low (< 52.9)	1 2.31	(Omitted) 1.24–4.29	0.008*
Age (in years) < 60 > 60	1 0.70	(Omitted) 0.49–0.99	0.043
ECOG PS 0–1 2 3–4	1 2.06 2.05	(Omitted) 1.44–2.95 1.02–4.11	0.000 0.042
Cancer type Esophageal cancer Gastric cancer	1 1.26	(Omitted) 0.92–1.73	0.143

Note: *Statistically significant p-values when adjusted by age, ECOG PS and cancer type.

advanced stage and advanced stage upper gastrointestinal tract cancer who are likely to have poorer clinical survival outcomes. PNI was calculated by the primary laboratory, which is based on serum albumin level in peripheral blood and total lymphocyte count to determine patients' nutritional status and immune response system. Therefore, it is a simplified and economical biomarker that can be used generally.

The prevalence of malnutrition in cancer patients was found at up to 70% and is usually related to higher mortality.¹⁸ Mechanisms of malnutrition related to poorer survival outcomes were not clear but were described in various forms. For example, 1) malnutrition caused immune suppression, resulting in a favorable microenvironment for tumor recurrence and leading to cancer recurrence, and 2) malnutrition might cause lower tolerance with treatment, resulting in lower treatment malnutrition screening and remedy to reduce mortality and significantly improve the prognosis of cancer patients.^{19–21}

PNI is a simplified biomarker that reflects the immune-nutritional status and systemic inflammation in the body, which is beyond merely the nutrition status assessment of patients. Because immune status was also correlated with tumor formation and recurrence, it was used as a prognostic factor of nutritional status and the treatment outcomes or illnesses in various types of cancer, eg lung, gastrointestinal, breast, and gynecologic cancers.^{22–26} What is more, it was also used to study other diseases, eg chronic kidney disease, COVID-2019, heart failure, and critically ill patients.^{27–30} In addition, PNI also contains a comprehensive scoring system called the controlling nutritional status (CONUT) score, which is a screening tool to identify undernourished patients in the hospitalized population.³¹ The score is derived from the values of serum albumin, total cholesterol, and lymphocyte counts. Albumin represents the protein reserves, total cholesterol represents caloric depletion, and lymphocyte count represents immune defense. There is a theory of knowledge for using it as a prognostic factor similar to PNI, which may need to be studied further.

The prominence of this study is that it is the first to use PNI to assess the prognosis of patients with unresectable locally-advanced stage (stage III) and advanced stage upper gastrointestinal tract cancer (stage IV). This is significant because there is still limited data concerning the use of PNI as an independent prognostic factor in stage III/IV patients. Several previous studies mostly found that PNI could be used as an independent prognostic factor in patients with upper gastrointestinal tract cancer, both esophageal cancer and stomach cancer, during the stages that surgery was still possible

(stage I–III), ie pre-operative or post-operative setting. Also, the cut-off point of PNI in each particular study was different. However, according to the data by meta-analysis, it was found that low PNI could be a useful predictor reflecting the incidence of complications after surgery and prognosis.^{23,32} In this study, analyzes of both esophageal cancer and gastric cancer were included in the same analysis because both cancers are most commonly affected by malnutrition among upper gastrointestinal tract cancers. In addition, chemotherapy was mainly used in patients with inoperable stage and advanced stage. Therefore, the role of PNI as a prognostic factor reflecting immune nutrition status and systemic inflammation is of interest. Therefore, this is the first study to demonstrate that low PNI could be used as an independent prognostic factor for non-operative treatment stage III/IV upper gastrointestinal tract cancer. In clinical applications, PNI can be used to assess a patient's prognosis and provide a simple indirect assessment of nutritional status. It will also be interesting to further investigate whether improving nutrition in patients up to an elevated PNI can contribute to longer survival. However, this study had limitations. First, it was a retrospective study conducted at a single institution. The second limitation of the study is the small sample size. Therefore, further study is required external validation with a larger number of patients to confirm the results of this study.

In conclusion, our study demonstrated that low PNI values are useful factors for predicting the prognosis as an independent prognostic factor of stage III–IV upper gastrointestinal tract cancer patients. However, more studies are required to verify and support these conclusions.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We conducted this retrospective chart review study in compliance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board, which determined that formal consent was not required because it was a retrospective chart review study based on data obtained from databases in which patients cannot be identified.

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Disclosure

The authors have no conflicts of interest to declare.

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