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Nutritional Risk Index (NRI) predicts the clinical outcomes of patients with gastric cancer who received immune checkpoint inhibitors (PD-1/PD-L1)

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Abstract

Numerous studies have consistently indicated a connection between the clinical results of individuals who receive immunotherapy and their nutritional condition. This study aims to evaluate the predictive capacity of the Nutritional Risk Index (NRI) in gastric cancer patients who are undergoing treatment with immune checkpoint inhibitors (ICIs). This study included a total of 146 individuals diagnosed with gastric cancer and received a combination of chemotherapy and immunotherapy using PD-1/PD-L1 inhibitors. The threshold was established by utilizing the receiver operating characteristic (ROC) curve. To analyze the clinical and pathological characteristics of the 2 groups, we performed Chi-square test or Fisher exact test. Univariate and multivariate analyses were performed to assess the factors influencing progression-free survival (PFS) and overall survival (OS) rates. Additionally, we developed nomograms to accurately predict the probability of 1- year and 3-year survival in these patients. According to the threshold, there were 38 (26.0%) patients in the low NRI category and 108 (74.0%) patients in the high NRI category. In the high NRI group, the median survival PFS was 32.50 months, while it was 11.77 months in the low NRI group. Likewise, the average survival OS in the 2 categories was 18.57 months compared to an indefinite duration. Individuals classified in the low NRI category encountered reduced PFS and OS, with a hazard ratio (HR) of 2.015 and 2.093 respectively, along with corresponding *P*-values of .009 and .006. The analysis of multiple variables showed that the number of platelets and TNM stage were separate factors that predicted both PFS and OS. Additionally, NRI was further recognized as a separate predictive factor for overall survival. The analysis of a specific subgroup revealed that individuals in the low NRI category experienced worse PFS and OS, especially within the group receiving ICIs. The C-index and the respective 95% CI of the nomograms to forecast the likelihood of PFS and OS survival were 0.646 (0.583–0.709) and 0.693 (0.635–0.751). NRI has the capability to forecast the clinical results of individuals who were diagnosed with gastric cancer and have received ICIs. This makes it a feasible biomarker for identifying patients who could benefit from ICIs.

Abbreviations: ADHF = acute decompensated heart failure, ALB = albumin, B = basophil, BMI = body mass index, CONUT = controlling nutritional status, CPS = Combined positive score, E = eosinophils, GPS = Glasgow prognostic score, Hb = Hemoglobin, Hct = hematocrit, HR = hazard ratio, ICIs = immune checkpoint inhibitors, L = lymphocyte, M = monocyte, N = neutrophils, NLR = neutrophil to lymphocyte ratio, NRI = Nutritional Risk Index, OS = overall survival, P = platelet, PALB = prealbumin, PFS = progression-free survival, PLR = platelet to lymphocyte ratio, R = red blood cell, ROC = receiver operating characteristic, SII = systemic immune-inflammation index, TP = total protein, W = white blood cell.

Keywords: clinical outcomes, gastric cancer, immune checkpoint inhibitors, Nutritional Risk Index, PD-1/PD-L1

1. Introduction

Although there has been a decline in the occurrence and death rates of gastric cancer in the past few decades, it continues to be widespread in Asian nations primarily because of factors like the increase in population.[1]Gastric cancer, ranked fifth in terms of prevalence and third in terms of cancer-related mortality

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the ethics committee of Harbin Medical University Cancer Hospital (Number: 2019-57-IIT). Due to the retrospective character of this study, the Ethics Committee of Harbin Medical University Cancer Hospital decided to waive informed consent.

All methods were carried out in accordance with relevant guidelines and regulations.

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globally, continues to be a significant health issue.[2]Significant advancements have been made in the field of gastric cancer with the introduction of clinical trials focused on immunotherapy. ICIs have gained recognition for their potential efficacy in treating gastric cancer.[3–5] Even in patients with recurrent and metastatic gastric cancer, the application of ICIs can still obtain promising curative effects and clinical outcomes.[6,7] As early as 2017, pembrolizumab was given the green light by the FDA for the treatment of gastric cancer.[8] Presently, frequently utilized indicators for immunotherapy encompass the manifestation of PD-1/PD-L1, microsatellite instability (MSI), and tumor mutational burden (TMB).[9,10] However, studies have discovered that some gastric cancer patients who are PD-1/PD-L1 negative or have low TMB can still benefit from ICIs.[11–13] Therefore, there is a need to identify simple and reliable biomarkers that can accurately determine the sensitivity of gastric cancer patients to ICIs.

Due to the unique anatomical structure, individuals diagnosed with gastric cancer are more susceptible to malnutrition.[14] Previous investigations have demonstrated a significant correlation between nutritional status and cancer prognosis. Patients who experience malnutrition tend more metastasis and shorter survival, especially those with gastric cancer.[15–17] Consequently, the clinical outcomes of cancer patients have been shown to be directly influenced by validated blood parameters such as albumin (ALB) and nutritional indexes like the prognostic nutritional index (PNI), the prognosis of individuals diagnosed with gastric cancer can be predicted using these biomarkers, which are commonly utilized.[18] Recent studies have also explored the link between nutritional status and ICIs, revealing that cancer patients with malnutrition have worse long-term prognoses after ICIs. One study by Kurosaki et al focused on 107 advanced gastric cancer patients who were treated with nivolumab. The researchers specifically examined the relationship between the Glasgow prognostic score (GPS) and the clinical outcomes of these patients. The findings demonstrated a significant association between higher GPS scores and shorter OS. Hence, GPS was recognized as a reliable indicator for forecasting the results of individuals with gastric cancer who are receiving nivolumab therapy.[19] Chen and his colleagues carried out an additional investigation, analyzing the clinical and pathologic information of 146 individuals with gastric cancer. Their aim was to explore the potential of controlling nutritional status (CONUT) in ICIs. Their findings indicated that individuals in the high CONUT score category experienced a reduction in both progression-free survival (PFS) and OS.[20] Furthermore, markers of inflammation, like the ratio of neutrophils to lymphocytes (NLR), ratio of platelets to lymphocytes (PLR), and

Table 1

The clinical information of all patients.

		Low NRI	High NRI	
n	**Level**	**38**	**108**	***P***
Sex (%)	Male	25 (65.8)	77 (71.3)	.525
	Female	13 (34.2)	31 (28.7)	
Age (%)	<60	20 (52.6)	55 (50.9)	.856
	≥60	18 (47.4)	53 (49.1)	
BMI (%)	<21.55 (kg/m^2)	30 (78.9)	43 (39.8)	<.001
	≥21.55 (kg/m^2)	8 (21.1)	65 (60.2)	
Surgery (%)	Yes	19 (50.0)	67 (62.0)	.195
	No	19 (50.0)	41 (38.0)	
Primary tumor site (%)	Upper 1/3	6 (15.8)	15 (13.9)	.213
	Middle 1/3	16 (42.1)	29 (26.9)	
	Low 1/3	15 (39.5)	54 (50.0)	
	Whole	1 (2.6)	10 (9.3)	
Borrmann type (%)	Borrmann I	0 (0.0)	3 (2.8)	.228
	Borrmann II	3 (7.9)	3 (2.8)	
	Borrmann III	15 (39.5)	52 (48.1)	
	Borrmann IV	1 (2.6)	9 (8.3)	
	Unknown	19 (50.0)	41 (38.0)	
Tumor size (%)	<50 mm	13 (34.2)	28 (25.9)	.496
	≥50 mm	9 (23.7)	23 (21.3)	
	Unknown	16 (42.1)	57 (52.8)	
Differentiation (%)	Poor	23 (60.5)	72 (66.7)	.201
	Moderately + Well	10 (26.3)	31 (28.7)	
	Unknown	5 (13.2)	5 (4.6)	
TNM stage (%)	I	0 (0.0)	10 (9.3)	.222
	II	3 (7.9)	11 (10.2)	
	III	10 (26.3)	29 (26.9)	
	IV	25 (65.8)	58 (53.7)	
Lauren type (%)	Intestinal	8 (21.1)	25 (23.1)	.341
	Diffuse	5 (13.2)	16 (14.8)	
	Mixed	3 (7.9)	20 (18.5)	
	Unknown	22 (57.9)	47 (43.5)	
PD-1 (%)	Negative	15 (39.5)	50 (46.3)	.474
	Positive	3 (7.9)	13 (12.0)	
	Unknown	20 (52.6)	45 (41.7)	
PD-L1 (%)	Negative	13 (34.2)	29 (26.9)	.09
	Positive	5 (13.2)	34 (31.5)	
	Unknown	20 (52.6)	45 (41.7)	
Treatment (%)	ICIs	24 (63.2)	65 (60.2)	.747
	Chemotherapy	14 (36.8)	43 (39.8)	

Abbreviation: BMI = body mass index, ICIs = immune checkpoint inhibitors, NRI = Nutritional Risk Index.

Table 2

The blood parameters of all patients.

		Low NRI	High NRI	
n	Level	38	108	*P*
TP (%)	<68.70 (g/L)	30 (78.9)	42 (38.9)	<0.001
	≥68.70 (g/L)	8 (21.1)	66 (61.1)	
ALB (%)	<38.95 (g/L)	35 (92.1)	38 (35.2)	<0.001
	≥38.95 (g/L)	3 (7.9)	70 (64.8)	
PALB (%)	<200 (mg/L)	30 (78.9)	42 (38.9)	<0.001
	≥200 (mg/L)	8 (21.1)	66 (61.1)	
R (%)	<4.34 (10^{12}/L)	28 (73.7)	44 (40.7)	<0.001
	≥4.34 (10^{12}/L)	10 (26.3)	64 (59.3)	
W (%)	<6.44 (10^9/L)	20 (52.6)	53 (49.1)	0.706
	≥6.44 (10^9/L)	18 (47.4)	55 (50.9)	
N (%)	<3.82 (10^9/L)	17 (44.7)	56 (51.9)	0.451
	≥3.82 (10^9/L)	21 (55.3)	52 (48.1)	
L (%)	<1.70 (10^9/L)	24 (63.2)	49 (45.4)	0.059
	≥1.70 (10^9/L)	14 (36.8)	59 (54.6)	
M (%)	<0.48 (10^9/L)	18 (47.4)	54 (50.0)	0.78
	≥0.48 (10^9/L)	20 (52.6)	54 (50.0)	
E (%)	<0.09 (10^9/L)	19 (50.0)	48 (44.4)	0.554
	≥0.09 (10^9/L)	19 (50.0)	60 (55.6)	
B (%)	<0.02 (10^9/L)	11 (28.9)	23 (21.3)	0.337
	≥0.02 (10^9/L)	27 (71.1)	85 (78.7)	
Hb (%)	<112.5 (g/L)	30 (78.9)	43 (39.8)	<0.001
	≥112.5 (g/L)	8 (21.1)	65 (60.2)	
Hct (%)	<38.1 (L/L)	30 (78.9)	42 (38.9)	<0.001
	≥38.1 (L/L)	8 (21.1)	66 (61.1)	
P (%)	<232.0 (10^9/L)	19 (50.0)	53 (49.1)	0.922
	≥232.0 (10^9/L)	19 (50.0)	55 (50.9)	

ALB = albumin, B = basophils, E = eosinophils, Hb = hemoglobin, Hct = hematocrit, L = lymphocytes, M = monocytes, N = neutrophils, P = platelet count, PALB = prealbumin, R = red blood cell count, TP = total protein, W = white blood cell count.

systemic immune-inflammation index (SII), have shown predictive significance among gastric cancer patients undergoing ICIs treatment.[21,22]In conclusion, there is a need for further research to explore the utilization of nutritional and inflammatory biomarkers in patients with gastric cancer undergoing treatment with ICIs.

To predict the nutritional risk of hospitalized patients, a Nutritional Risk Index (NRI) was developed, which took into account the levels of ALB and the fluctuations in body weight.[23] In later investigations, NRI demonstrated its capability to forecast the outlook of different types of tumors, such as esophageal carcinoma, stomach cancer, and oral malignancy.[24–27] Rey-Ferro et al first applied NRI to gastric cancer in 1997 and found that NRI was associated with postoperative mortality of gastric cancer patients.[28] Nevertheless, the prognostic capability of NRI in individuals with gastric cancer receiving ICIs remains uncertain.

This study aims to investigate the prognostic value of NRI in individuals diagnosed with gastric cancer who have undergone ICIs treatment. To accomplish this, we collected a grand total of 146 individuals diagnosed with stomach cancer from our establishment and performed an examination on the utilization of NRI in patients treated with ICIs. Additionally, a subgroup analysis was performed, and a nomogram was created to confirm the predictive capability of NRI in individuals diagnosed with gastric cancer.

2. Materials and methods

2.1. Patients

A total of 146 patients diagnosed with gastric cancer from August 2016 to December 2020 were treated with ICIs or chemotherapy in this study. The patient information was examined following the guidelines of the Helsinki Declaration and its subsequent amendments. To be eligible for patient selection, the following criteria were applied: all patients underwent an invasive gastroscope examination and received a pathological diagnosis; all patients were treated with either ICIs or chemotherapy; and all patients were not experiencing acute inflammation. The study excluded patients who had insufficient clinical data. Both clinical and pathological information were collected using an extensive electronic medical records system. As this study was conducted retrospectively, the Ethics Committee of Harbin Medical University Cancer Hospital exempted the requirement for informed consent (Ethics approval number: 2019-22-IIT).

2.2. Follow-up and data collection

PFS and OS were assessed through routine telephone follow-up. PFS was defined as the duration from the initial day of surgery, administration of ICIs, or initiation of chemotherapy to the date when disease progression was observed. Various imaging tests, such as X-rays of the chest and abdomen or enhanced computed tomography, were employed to detect any indications of disease progression. If there was no indication of advancement, the determination of PFS was made by considering either the date of death or the most recent follow-up. The OS was from the initial day of ICIs, surgical procedures, or chemotherapy to demise or the most recent follow-up.

2.3. Nutritional Risk Index (NRI)

NRI = 1.519 × albumin (g/L) + 41.7 × personal weight/ideal weight. Ideal weight for male = height – 100 – [(Height – 150)/4]; female = Height – 100 – [(Height – 150)/2.5]. Cutoff point for NRI was determined by receiver operating characteristic (ROC) curve. Based on their NRI values, all participants

Table 3

The univariate and multivariate analysis for PFS.

	PFS			
	Univariate analysis		Multivariate analysis	
Parameters	**Hazard ratio (95%CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Sex (male vs female)	1.099 (0.645–1.872)	.729		
Age (<60 vs ≥60)	0.914 (0.554–1.506)	.724		
BMI (<21.55 vs ≥21.55)	0.865 (0.526–1.424)	.569		
TP (<68.70 g/L vs ≥68.70 g/L)	0.842 (0.511–1.386)	.498		
ALB (<38.95 g/L vs ≥38.95 g/L)	0.803 (0.487–1.324)	.39		
R (<4.34 10^{12}/L vs ≥4.34 10^{12}/L)	1.166 (0.708–1.922)	.547		
W (<6.44 10^9/L vs ≥6.44 10^9/L)	0.876 (0.531–1.445)	.604		
N (<3.82 10^9/L vs ≥3.82 10^9/L)	1.014 (0.616–1.670)	.956		
L (<1.70 10^9/L vs ≥1.70 10^9/L)	0.631 (0.380–1.074)	.075		
M (<0.48 10^9/L vs ≥0.48 10^9/L)	0.891 (0.540–1.472)	.653		
E (<0.09 10^9/L vs ≥0.09 10^9/L)	0.995 (0.604–1.640)	.984		
B (<0.02 10^9/L vs ≥0.02 10^9/L)	1.558 (0.828–2.931)	.169		
Hb (<112.5 g/L vs ≥112.5 g/L)	1.105 (0.672–1.819)	.694		
Hct (<38.1 L/L vs ≥38.1 L/L)	1.314 (0.796–2.170)	.286		
P (<232.0 10^9/L vs ≥232.0 10^9/L)	0.583 (0.350–0.973)	.039	0.455 (0.263–0.787)	.005
NRI (<94.17 vs ≥94.17)	2.015 (0.187–3.421)	.009	1.457 (0.814–2.609)	.205
Radical resection (R0 vs non-R0)	2.501 (1.478–4.231)	.001	1.899 (0.783–4.605)	.156
Surgery (yes vs no)	2.069 (1.242–3.446)	.005	1.605 (0.416–6.190)	.492
Primary tumor site (Low 1/3 vs Others*)	0.944 (0.573–1.555)	.822		
Borrmann type (I + II vs III + IV + Unknown)	0.448 (0.264–0.761)	.003	0.643 (0.229–1.809)	.403
Tumor size (<50 mm vs ≥50 mm + Unknown)	1.131 (0.847–1.511)	.405		
Differentiation (Poor vs Others)	0.895 (0.578–1.386)	.619		
TNM stage (I + II vs III + IV)	5.531 (1.731–17.674)	.004	4.143 (1.228–13.974)	.022
Lauren type (Intestinal vs Others)	1.415 (1.125–1.781)	.003	1.042 (0.727–1.495)	.821
PD-1 (Negative + Unknown vs Positive)	1.602 (1.205–2.129)	.001	2.226 (0.517–9.572)	.282
PD-L1 (Negative + Unknown vs Positive)	1.747 (1.257–2.430)	.001	1.217 (0.532–2.784)	.642
Treatment (ICIs vs Chemotherapy)	0.356 (0.197–0.642)	.001	0585 (0.288–1.192)	.14

ALB = albumin, B = basophils, BMI = body mass index, E = eosinophils, Hb = hemoglobin, Hct = hematocrit, L = lymphocytes, M = monocytes, N = neutrophils, NRI = Nutritional Risk Index, P = platelet count, R = red blood cell count, TP = total protein, W = white blood cell count.

*Others of primary tumor site was upper 1/3 + middle 1/3 + whole; others of differentiation were moderately + well + unknown; others of lauren type was diffuse + mixed + unknown.

were divided into 2 groups: the low-value group (NRI < 94.06) and the high-value group (NRI ≥ 94.06).

2.4. Statistical analysis

For the statistical analysis in this research, we employed R 4.1.3 (Vienna, Austria) as our chosen tool. Statistical differences were determined by considering *P* values <0.05 on both sides. To assess differences between the 2 groups, we employed either the Chi-square test or Fisher exact test. We utilized the Kaplan–Meier to ascertain the rate of survival and employed the Log-rank test for comparing disparities in survival duration. We assessed the comparative risks by utilizing hazard ratio (HR) and a 95% CI. To examine the independent predictors for PFS and OS, we developed a Cox proportional hazards regression model. In addition, a nomogram was created to estimate the likelihood of surviving for 1 and 3 years in terms of both PFS and OS.

3. Results

3.1. Patient characteristics

According to the ROC curve, 38 patients (26.0%) were classified into the low NRI group and 108 patients (74.0%) into the high NRI group. The median age of all patients was 59 years, with 102 males (69.9%) and 44 females (30.1%). Of these patients, 86 (58.9%) received both surgery and adjuvant therapy, while 60 (41.1%) received adjuvant therapy only. When divided by median body mass index (BMI), correlation analysis showed that the low NRI group had a significantly lower BMI than the high NRI group ($P < .001$) (Table 1).

3.2. Nutritional and hematological parameters

In this study, we collected pretreatment nutritional and hematological measurements from participants to analyze their relationship with NRI, using either the Chi-square test or Fisher exact test. Participants were divided into low- and high-value groups based on the median values for total protein (TP), albumin (ALB), prealbumin (PALB), red blood cells (R), white blood cells (W), neutrophils (N), lymphocytes (L), monocytes (M), eosinophils (E), basophils (B), hemoglobin (Hb), hematocrit (Hct), and platelets (P), across 146 cases. Detailed results are presented in Table 2. Significant correlations were found between NRI and TP ($P < .001$), PALB ($P < .001$), R ($P < .001$), Hb ($P < .001$), and Hct ($P < .001$). Additionally, Fisher exact test showed that the low NRI group had significantly lower ALB levels ($P < .001$) compared to the high NRI group.

3.3. Univariate and multivariate Cox hazard analysis for PFS and OS

Data analysis revealed significant associations between PFS and OS with several factors: PALB ($P = .013$ and 0.006), platelets ($P = .039$ and 0.036), NRI ($P = .009$ and 0.006), radical resection ($P = .001$ and $P < .001$), surgery ($P = .005$ and 0.006), Borrmann type ($P = .003$ and 0.003), TNM stage ($P = .004$ and 0.001), Lauren type ($P = .003$ and 0.002), PD-1 ($P = .001$ and $P < .001$), PD-L1 ($P = .001$ and $P < .001$), and treatment ($P = .001$ and $P < .001$). Multivariate analysis further identified platelets ($P = .005$ and 0.007), and TNM stage ($P = .022$ and 0.015) as independent prognostic factors for both PFS and OS, with NRI ($P = .048$) also emerging as an

Table 4

The univariate and multivariate analysis for OS.

	OS			
	Univariate analysis		Multivariate analysis	
Parameters	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex (male vs female)	1.084 (0.636–1.846)	.768		
Age (<60 vs ≥60)	0.878 (0.533–1.446)	.61		
BMI (<21.55 vs ≥21.55)	0.871 (0.529–1.434)	.588		
TP (<68.70 g/L vs ≥68.70 g/L)	0.789 (0.478–1.299)	.351		
ALB (<38.95 g/L vs ≥38.95 g/L)	0.776 (0.471–1.280)	.32		
R (<4.34 10^{12}/L vs ≥4.34 10^{12}/L)	1.073 (0.651–1.767)	.783		
W (<6.44 10^9/L vs ≥6.44 10^9/L)	0.895 (0.542–1.477)	.664		
N (<3.82 10^9/L vs ≥3.82 10^9/L)	1.094 (0.664–1.803)	.725		
L (<1.70 10^9/L vs ≥1.70 10^9/L)	0.649 (0.392–1.076)	.094		
M (<0.48 10^9/L vs ≥0.48 10^9/L)	0.903 (0.547–1.492)	.691		
E (<0.09 10^9/L vs ≥0.09 10^9/L)	0.931 (0.565–1.534)	.78		
B (<0.02 10^9/L vs ≥0.02 10^9/L)	1.373 (0.731–2.580)	.324		
Hb (<112.5 g/L vs ≥112.5 g/L)	1.051 (0.639–1.730)	.844		
Hct (<38.1 L/L vs ≥38.1 L/L)	1.200 (0.727–1.979)	.475		
P (<232.0 10^9/L vs ≥232.0 10^9/L)	0.579 (0.347–0.966)	.036	0.477 (0.278–0.817)	.007
NRI (<94.17 vs ≥94.17)	2.093 (1.231–3.560)	.006	1.778 (1.006–3.144)	.048
Radical resection (R0 vs non-R0)	2.800 (1.631–4.807)	<.001	2.128 (0.912–4.967)	.081
Surgery (yes vs no)	2.093 (1.242–3.526)	.006	1.148 (0.279–4.713)	.848
Primary tumor site (low 1/3 vs others*)	0.985 (0.598–1.622)	.952		
Borrmann type (I + II vs III + IV + unknown)	0.445 (0.259–0.765)	.003	0.657 (0.236–1.830)	.422
Tumor size (<50 mm vs ≥50 mm + unknown)	1.140 (0.853–1.523)	.377		
Differentiation (poor vs others)	0.856 (0.553–1.327)	.488		
TNM stage (I + II vs III + IV)	6.605 (2.060–21.181)	.001	4.487 (1.341–15.018)	.015
Lauren type (Intestinal vs Others)	1.426 (1.133–1.796)	.002	1.111 (0.781–1.581)	.557
PD-1 (negative + unknown vs positive)	1.694 (1.272–2.256)	<.001	2.288 (0.517–10.113)	.275
PD-L1 (negative + unknown vs positive)	1.863 (1.336–2.597)	<.001	1.150 (0.512–2.586	.735
Treatment (ICIs vs chemotherapy)	0.325 (0.179–0.590)	<.001	0.616 (0.295–1.287)	.197

ALB = albumin, B = basophils, BMI = body mass index, E = eosinophils, Hb = hemoglobin, Hct = hematocrit, L = lymphocytes, M = monocytes, N = neutrophils, NRI = Nutritional Risk Index, P = platelet count, R = red blood cell count, TP = total protein, W = white blood cell count.

*Others of primary tumor site was upper 1/3 + middle 1/3 + whole; others of differentiation were moderately + well + unknown; others of lauren type was diffuse + mixed + unknown.

independent predictor for OS. Detailed findings are presented in Tables 3 and 4.

3.4. Survival for NRI

The median PFS and OS for all patients were 13.92 months and 25.02 months, respectively. In the low NRI group, the median PFS was 11.77 months, compared to 32.50 months in the high NRI group, while the median OS was 18.57 months versus an indefinite duration. Consequently, patients in the low NRI group exhibited significantly shorter PFS and OS (HR = 2.015, $P = .009$ for PFS and HR = 2.093, $P = .006$ for OS) (Fig. 1A and B).

3.5. Survival for treatment

To evaluate the predictive value of NRI in gastric cancer patients treated with ICIs, we included 89 patients (61.0%) in the ICIs group and 57 patients (39.0%) in the chemotherapy group. Correlation analysis revealed significant associations between treatment and several variables, including W ($P = .027$), N ($P = .011$), M ($P = .007$), surgery ($P < .001$), radical resection ($P < .001$), Lauren type ($P < .001$), and tumor size ($P = .046$). Further analysis using Fisher exact test showed significant correlations between therapy type and Borrmann type ($P < .001$), TNM stage ($P < .001$), PD-1 ($P < .001$), and PD-L1 ($P < .001$). Detailed results are presented in Table 5. In the ICIs group, the median PFS and OS were 20.60 months and 30.27 months, respectively, while these durations were not reached in the chemotherapy group. This study found that ICIs treatment was associated with shorter PFS (HR = 0.356, $P = .001$) and OS (HR = 0.325, $P < .001$) compared to the control (Fig. 2A and B).

To fulfill the objectives of this research, we examined the role of NRI in patients receiving ICIs and chemotherapy, with a particular emphasis on those treated with ICIs. In the ICIs group, 24 patients (27.0%) were classified in the low NRI category, while 65 patients (73.0%) were in the high NRI category. The low NRI group had median PFS and OS of 9.67 and 18.37 months, respectively, compared to 21.77 and 37.23 months in the high NRI group. Patients in the low NRI group demonstrated significantly shorter PFS and OS than those in the high NRI group (HR = 1.631, $P = .120$ for PFS and HR = 2.186, $P = .016$ for OS) (Fig. 3A and B). This highlights a marked reduction in both PFS and OS for the low NRI group. In the chemotherapy group, 14 patients (24.6%) were in the low NRI group, while 43 patients (75.4%) were in the high NRI group. Median PFS was not reached in either the low or high NRI groups, and median OS was 33.07 months in both groups. Fig. 4A and B indicate that patients in the high NRI group had longer PFS and OS than those in the low NRI group (HR = 2.864, $P = .047$ for PFS and HR = 2.568, $P = .075$ for OS).

3.6. Survival for platelet count

In the multivariate analysis, platelet count was identified as an independent predictor of outcomes for individuals with stomach cancer. To further validate the prognostic potential of NRI, we assessed NRI levels in patients with different platelet counts. Based on the median platelet value, 72 patients (49.3%) were assigned to the low platelet group, and 74 patients (50.7%) to the high platelet group. In the low platelet group, median

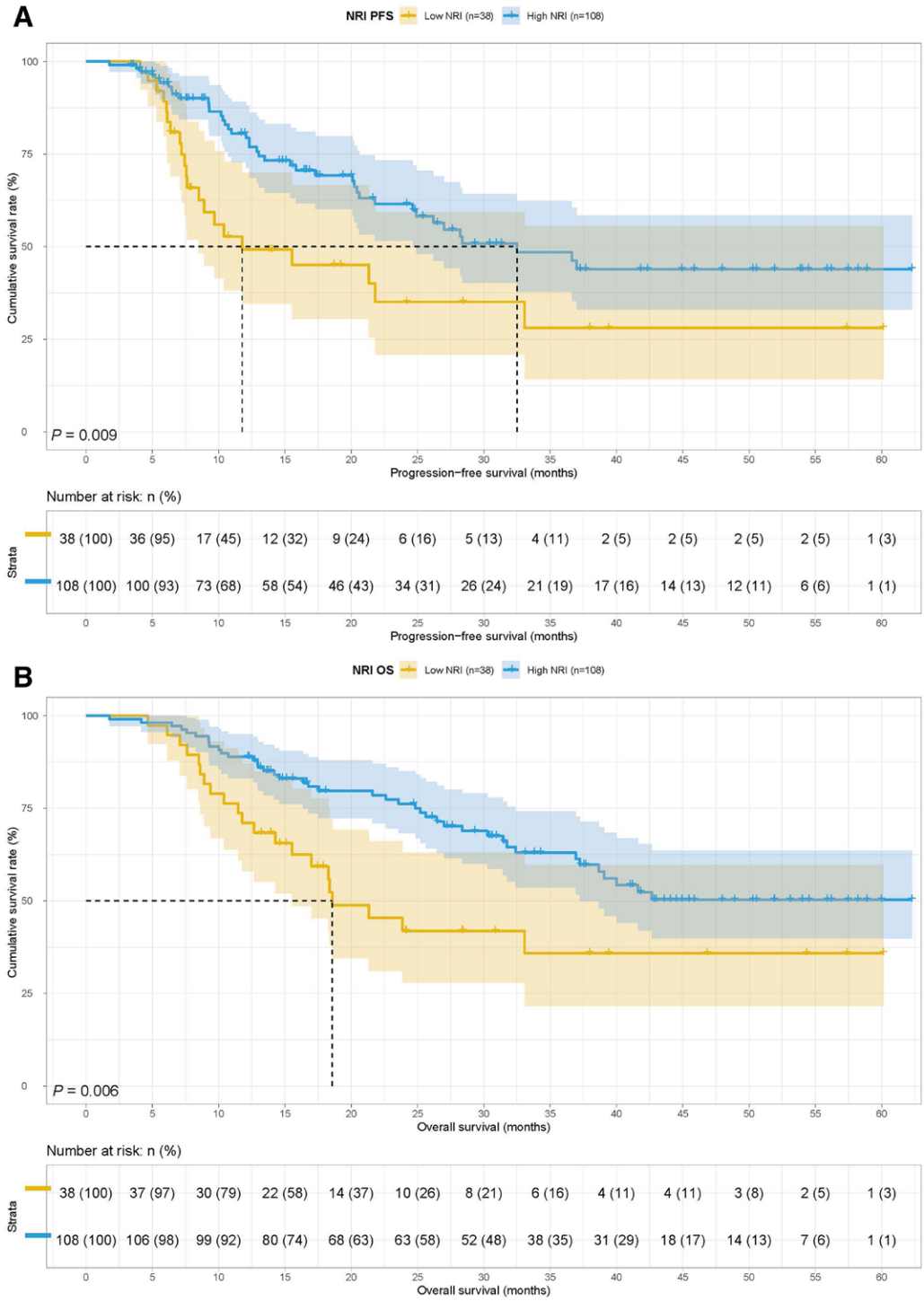

Figure 1. Nutritional Risk Index related survival curve of (A) PFS and (B) OS in all patients. OS = overall survival, PFS = progression-free survival.

PFS and OS were 21.77 and 37.23 months, respectively, while median survival was not reached in the high platelet group. Notably, patients in the low platelet group showed shorter PFS and OS compared to those in the high platelet group (HR = 0.583, $P = .039$ for PFS and HR = 0.579, $P = .036$ for OS) (Fig. 5A and B).

Among patients with low platelet counts, 19 (26.4%) were in the low NRI category, and 53 (73.6%) were in the high NRI category. The low NRI group had a median PFS of 15.53 months, while the high NRI group had a longer PFS of 26.20 months. Similarly, the low NRI group had a median OS of 18.57 months, compared to a significantly longer OS of 39.07 months in the high NRI group. Patients in the low NRI category showed reduced PFS and OS compared to those in the high NRI category (HR = 1.680, $P = .139$ for PFS and HR = 2.010, $P = .049$ for OS) (Fig. 6A and B). In the group with elevated platelet counts, there were 19 patients (25.7%) in the low NRI category and 55 patients (74.3%) in the high NRI category. The low NRI group had median PFS and OS durations of 11.77 and 33.07 months, respectively, while the high NRI group did not reach the median survival for either PFS or OS. The low NRI group had significantly shorter PFS (HR = 2.732, $P = .019$) and OS (HR = 2.367, $P = .042$) than the high NRI group (Fig. 7A and B).

Table 5

The clinical information of all patients analyzed by treatment.

		ICIs	Chemotherapy	
n	Level	89	57	*P*
Age (%)	<60	47 (52.8)	28 (49.1)	.664
	≥60	42 (47.2)	29 (50.9)	
BMI (%)	<21.55 (Kg/m^2)	40 (44.9)	33 (57.9)	.127
	≥21.55 (Kg/m^2)	49 (55.1)	24 (42.1)	
TP (%)	<68.70 (g/L)	44 (49.4)	28 (49.1)	0.97
	≥68.70 (g/L)	45 (50.6)	29 (50.9)	
ALB (%)	<38.95 (g/L)	46 (51.7)	27 (47.4)	0.611
	≥38.95 (g/L)	43 (48.3)	30 (52.6)	
PALB (%)	<200 (mg/L)	49 (55.1)	23 (40.40	0.083
	≥200 (mg/L)	40 (44.9)	34 (59.6)	
W (%)	<6.44 (10^9/L)	38 (42.7)	35 (61.4)	0.027
	≥6.44 (10^9/L)	51 (57.3)	22 (38.6)	
N (%)	<3.82 (10^9/L)	37 (41.6)	36 (63.2)	0.011
	≥3.82 (10^9/L)	52 (58.4)	21 (36.8)	
L (%)	<1.70 (10^9/L)	44 (49.4)	29 (50.9)	0.865
	≥1.70 (10^9/L)	45 (50.6)	28 (49.1)	
M (%)	<0.48 (10^9/L)	36 (40.4)	36 (63.2)	0.007
	≥0.48 (10^9/L)	53 (59.6)	21 (36.8)	
E (%)	<0.09 (10^9/L)	44 (49.4)	23 (40.4)	0.282
	≥0.09 (10^9/L)	45 (50.6)	34 (59.6)	
B (%)	<0.02 (10^9/L)	18 (20.2)	16 (28.1)	0.274
	≥0.02 (10^9/L)	71 (79.8)	41 (71.9)	
R (%)	<4.34 (10^{12}/L)	40 (44.9)	32 (56.1)	0.187
	≥4.34 (10^{12}/L)	49 (55.1)	25 (43.9)	
Hb (%)	<112.5 (g/L)	43 (48.3)	30 (52.6)	0.611
	≥112.5 (g/L)	46 (51.7)	27 (47.4)	
Hct (%)	<38.1 (L/L)	40 (44.9)	32 (56.1)	0.187
	≥38.1 (L/L)	49 (55.1)	25 (43.9)	
P (%)	<232.0 (10^9/L)	45 (50.6)	27 (47.4)	0.707
	≥232.0 (10^9/L)	44 (49.4)	30 (52.6)	
Surgery (%)	Yes	38 (42.7)	48 (84.2)	<0.001
	No	51 (57.3)	9 (15.8)	
Radical resection (%)	R0	23 (25.8)	42 (73.7)	<0.001
	non-R0	66 (74.2)	15 (26.3)	
Borrmann type (%)	Borrmann I	2 (2.2)	1 (1.8)	<0.001
	Borrmann II	4 (4.5)	2 (3.5)	
	Borrmann III	23 (25.8)	44 (77.2)	
	Borrmann IV	9 (10.1)	1 (1.8)	
	Unknown	51 (57.3)	9 (15.8)	
Tumor size (%)	<50 (mm)	19 (21.3)	22 (38.6)	0.046
	≥50 (mm)	19 (21.3)	13 (22.8)	
	Unknown	51 (57.3)	22 (38.6)	
TNM stage (%)	I	3 (3.4)	7 (12.3)	<0.001
	II	5 (5.6)	9 (15.8)	
	III	15 (16.9)	24 (42.1)	
	IV	66 (74.2)	17 (29.8)	
Lauren type (%)	Intestinal	14 (15.7)	19 (33.3)	<0.001
	Diffuse	8 (9.0)	13 (22.8)	
	Mixed	8 (9.0)	15 (26.3)	
	Unknown	59 (66.3)	10 (17.5)	
PD-1 (%)	Negative	18 (20.2)	47 (82.5)	<0.001
	Positive	6 (6.7)	10 (17.5)	
	Unknown	65 (73.0)	0 (0.0)	
PD-L1 (%)	Negative	8 (9.0)	34 (59.6)	<0.001
	Positive	16 (18.0)	23 (40.4)	
	Unknown	65 (73.0)	0 (0.0)	

ALB = albumin, B = basophils, BMI = body mass index, E = eosinophils, Hb = hemoglobin, Hct = hematocrit, L = lymphocytes, M = monocytes, N = neutrophils, P = platelet count, PALB = prealbumin, R = red blood cell count, TP = total protein, W = white blood cell count.

3.7. Construction of nomograms to predict PFS and OS

Multivariate analysis in this study identified both platelet count (P) and TNM stage as independent prognostic factors for PFS. Additionally, P, TNM stage, and NRI were recognized as independent predictors of overall survival (OS). Based on these findings, a nomogram was developed (Fig. 8A and B) to estimate 1- and 3-year PFS and OS. The C-index for the nomogram's predictive accuracy was 0.646 (95% CI: 0.583–0.709) for PFS and 0.693 (95% CI: 0.635–0.751) for OS.

4. Discussion

Several clinical trials have validated the significance of ICIs in managing the disease and extending the lifespan of

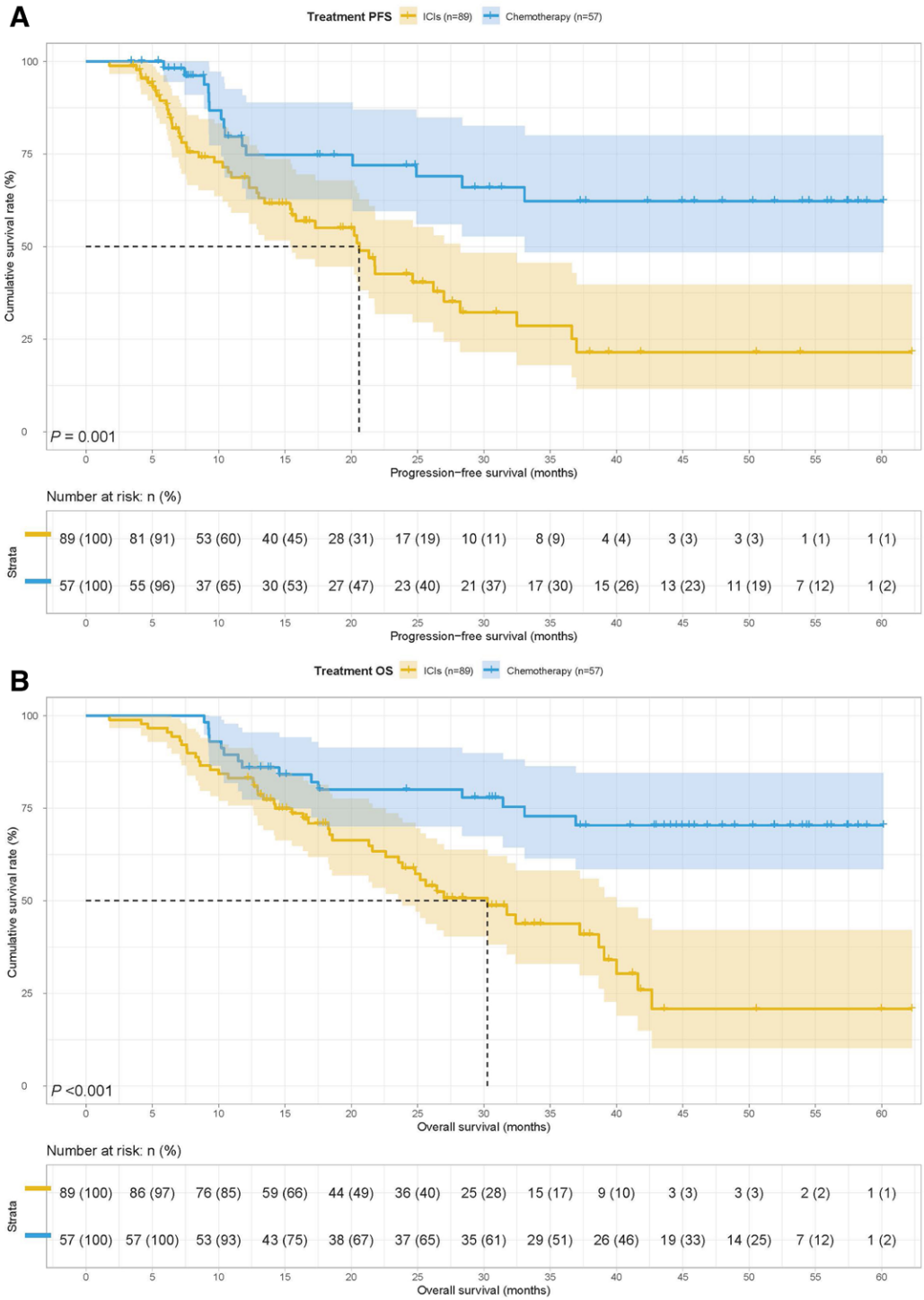

Figure 2. Treatment (ICIs vs chemotherapy) related survival curve of (A) PFS and (B) OS in all patients. ICIs = immune checkpoint inhibitors, OS = overall survival, PFS = progression-free survival.

individuals diagnosed with stomach cancer. However, currently available biomarkers like the PD-1/PD-L1 and its associated combined positive score are insufficient to encompass all gastric cancer patients.[29–32] Therefore, a further search for more immunotherapy-related biomarkers is needed to establish a more complete prediction system. At the same time, continuous studies have been conducted to explore the prognostic value of inflammatory and nutritional indicators in individuals with gastric cancer who are receiving immunotherapy. In this investigation, we established a group of individuals with gastric cancer who received ICIs to explore the correlation between the NRI and the clinical outcomes of these individuals.

NRI serves as a biomarker indicating the fluctuation in patients' body weight throughout the illness, making it a reliable indicator for forecasting nutritional condition. In subsequent studies, researchers began to study the predictive effect of NRI on various disease-related risks. Cho et al collected the body weight and albumin of 5625 patients with acute decompensated heart failure and analyzed their 1-year mortality by NRI in 2018.The study revealed a significant association between low NRI values and higher 1-year mortality rates, establishing NRI

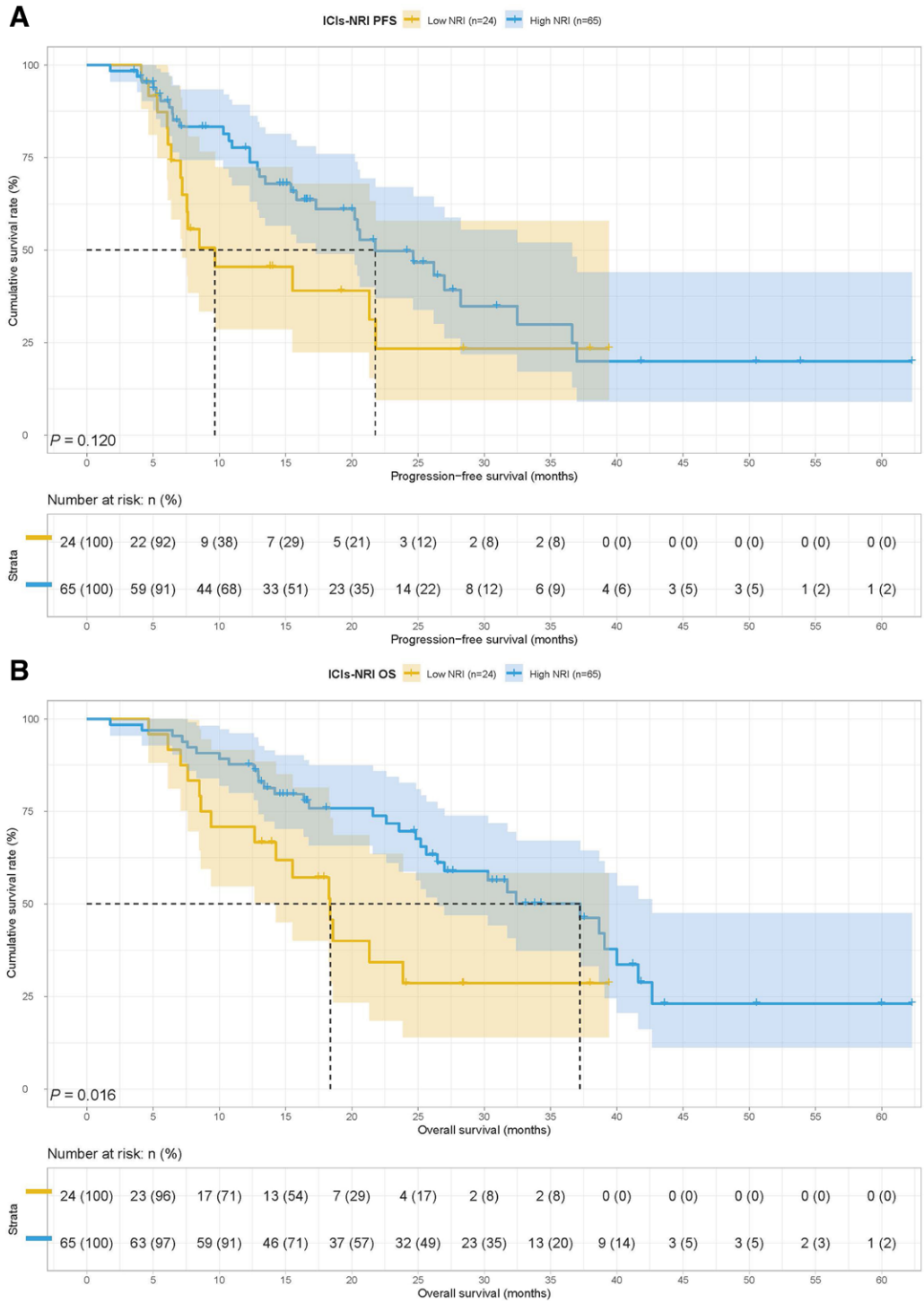

Figure 3. Nutritional Risk Index related survival curve of (A) PFS and (B) OS in the ICI group. ICIs = immune checkpoint inhibitors, OS = overall survival, PFS = progression-free survival.

as an independent predictive factor for 1-year mortality in acute decompensated heart failure patients.[33] Liu et al Examined the utilization of NRI in individuals afflicted by COVID-19. 141 individuals diagnosed with COVID-19 were included in their analysis. The findings indicated that patients with low NRI experienced a longer duration of hospital stay, higher medical costs, decreased appetite, more severe disease manifestations, and greater weight change compared to normal patients.[34] Numerous studies have additionally shown a notable correlation between NRI and the medical results among individuals with cancer. Lin et al and Chen et al investigated the prognostic potential of NRI in breast carcinoma. A cohort of 1347 individuals diagnosed with breast cancer who underwent either mastectomy or lumpectomy was gathered, along with another group of 785 breast cancer patients who received neoadjuvant chemotherapy. Investigated the effect of NRI on breast patients in their study by univariate and multivariate survival analysis. Finally, they both found that low NRI value significantly related to shorter OS in breast cancer.[35,36] Cancer cachexia status often appears in the terminal stage of cancer, a multicenter and prospective study by Xie et al examined the prognostic value of NRI in individuals diagnosed with cancer cachexia and

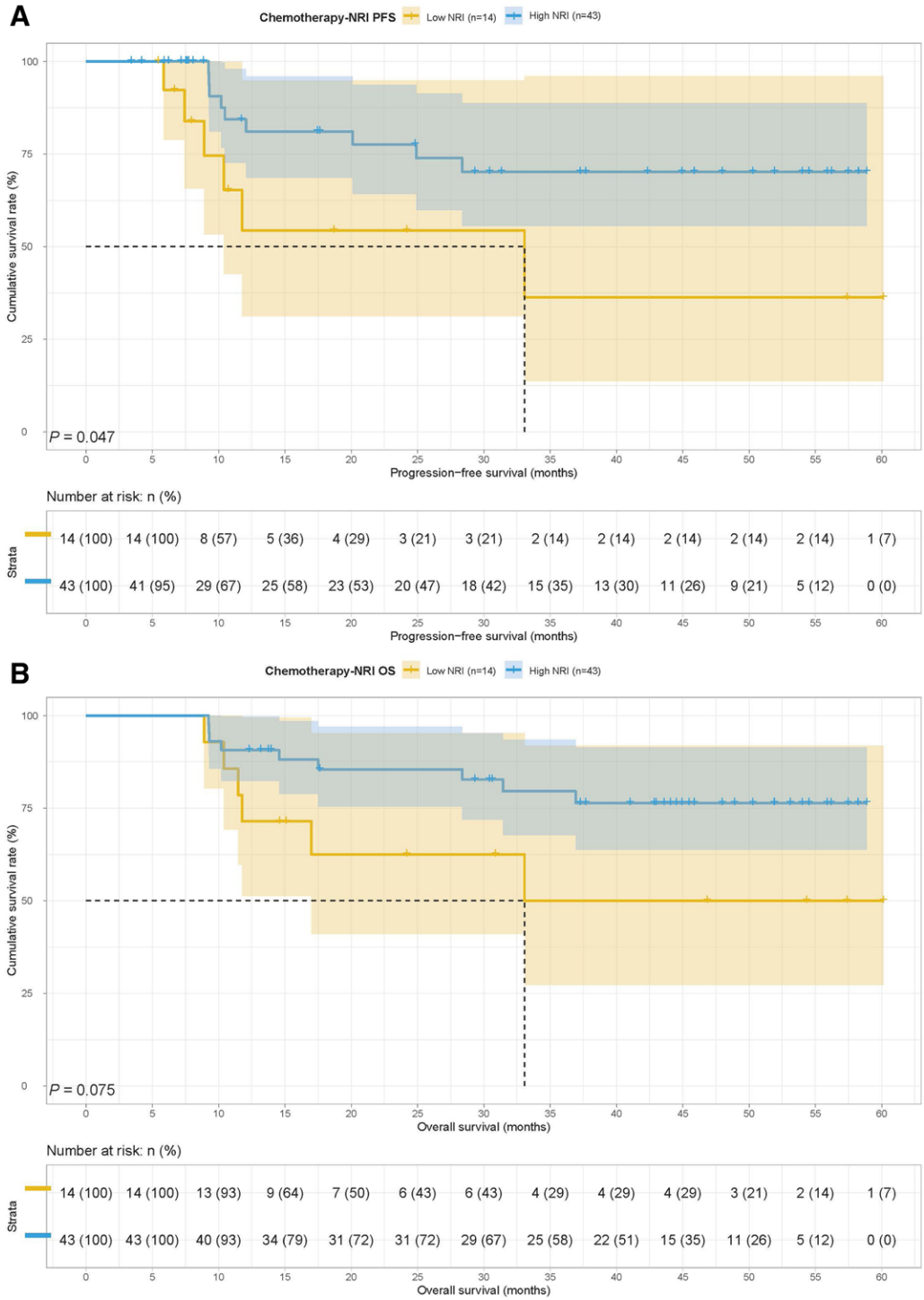

Figure 4. Nutritional Risk Index related survival curve of (A) PFS and (B) OS in the chemotherapy group. OS = overall survival, PFS = progression-free survival.

discovered that a decreased NRI independently predicted the presence of cancer cachexia.[37] Additionally, numerous studies have analyzed the usage of NRI in cases of gastric cancer. Ma et al. collected 175 gastric and esophageal cancer patients and found that NRI and the change in NRI after treatment held significant prognostic value for OS.[38] Seo et al and Sun et al additionally, comparable findings were discovered, indicating that individuals with a decreased NRI experienced reduced survival duration and unfavorable treatment outcomes.[39,40] In conclusion, NRI was found to be an accurate predictive biomarker for prognosis in various cancers.

The focus of this research was to investigate the predictive capacity of NRI in patients with gastric cancer who were treated with ICIs. The results suggested that individuals classified as having a low NRI experienced worse PFS and OS in both the immunotherapy and chemotherapy treatment groups, particularly in the immunotherapy group. Additionally, we conducted subgroup analyses to assess the application of NRI in gastric cancer. The outcomes demonstrated that patients with low NRI levels experienced shorter PFS and OS across all subgroups. Through multivariate analysis, we identified platelet count and TNM stage as independent prognostic factors for both PFS and

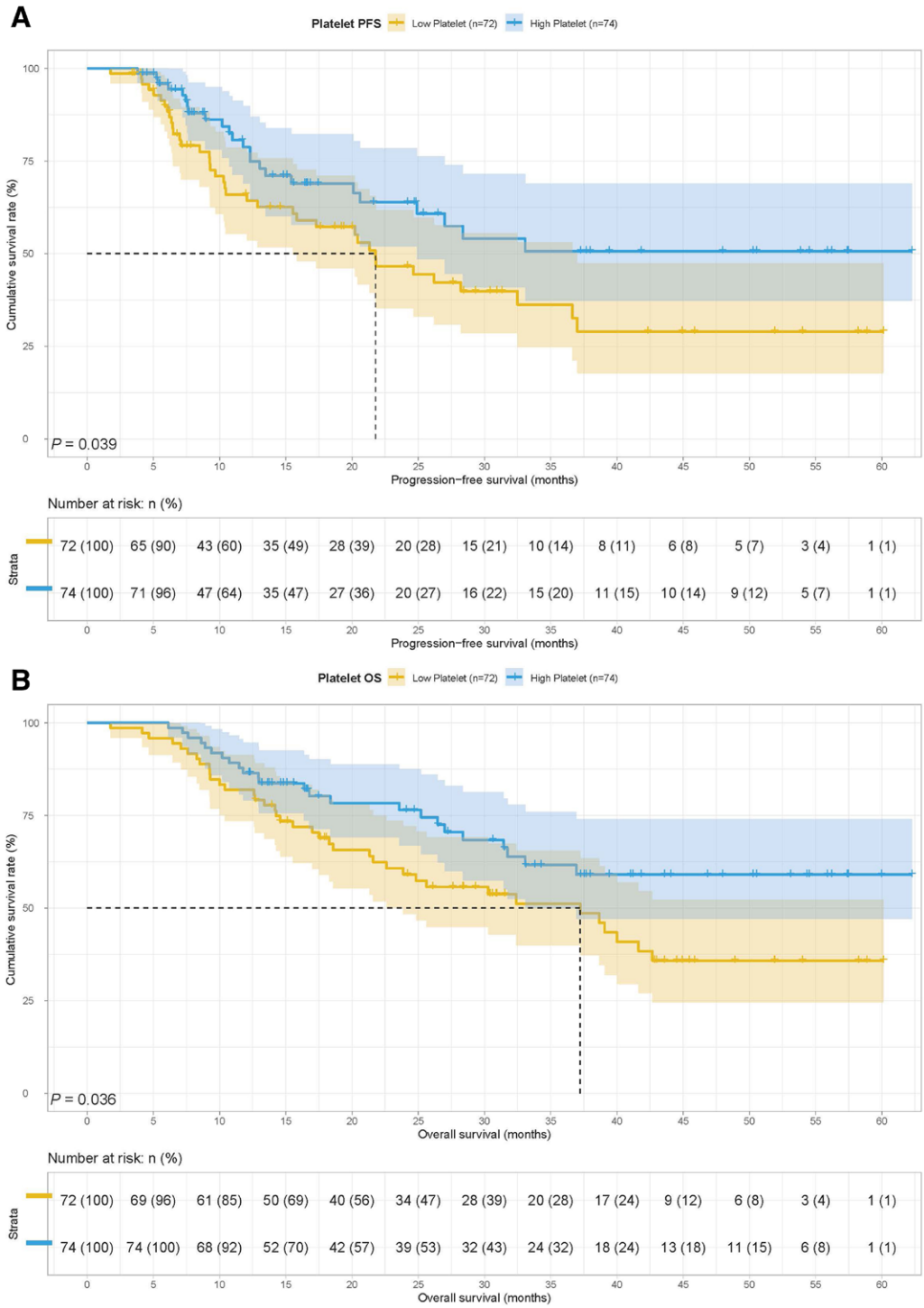

Figure 5. Platelet related survival curve of (A) PFS and (B) OS in all patients. OS = overall survival, PFS = progression-free survival.

OS. Moreover, NRI also emerged as an autonomous predictor for OS.

In survival analysis, we explored the survival difference between gastric cancer patients undergoing different treatments (ICIs vs chemotherapy) and found patients in the ICIs group experienced shorter PFS and OS compared to chemotherapy. To explore the causes of this result, we conducted a correlation analysis of the factors affecting treatment. The results showed that treatment was related to extensive blood parameters and clinical pathology status. In previous studies, it was found that ICIs was strongly associated with nonsurgical treatments and advanced TNM stages, both of which were identified as important independent prognostic factors for patients.[41,42] Currently, ICIs are specifically advised for individuals with advancing stomach cancer who have not shown improvement with traditional treatment. This is the primary cause for the reduced PFS and OS in gastric cancer patients undergoing ICIs.

The precise mechanisms by which NRI forecasts the clinical results of stomach cancer are still not understood. NRI contains albumin and body weight, which have close associations with the prognosis of patients afflicted with gastric cancer.[43–45] Albumin serves as an indicator of both the nutritional condition

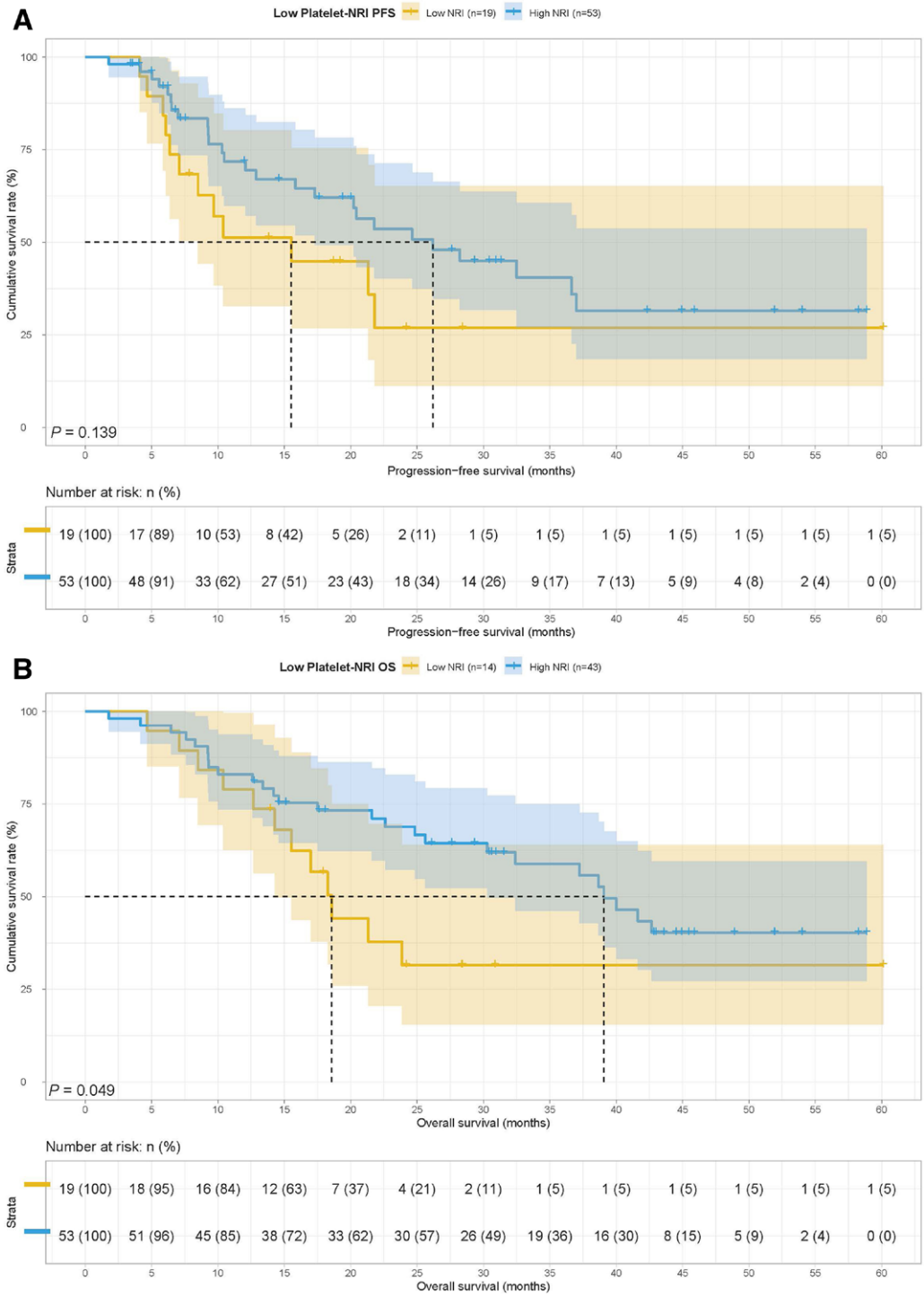

Figure 6. Nutritional Risk Index related survival curve of (A) PFS and (B) OS in the low platelet group. OS = overall survival, PFS = progression-free survival.

and the overall inflammatory state in patients, as evidenced by its correlation with systemic inflammation.[46] The liver can be affected by inflammatory factors, which can hinder the production of albumin by the liver.[47,48] To some degree, the decreased serum albumin level indicates the limited hepatic functional reserve of individuals, resulting in reduced treatment tolerance and decreased survival time.[49] The nutritional status of individuals diagnosed with gastric cancer is also indicated by their body weight, which is also linked to their tolerance for surgery or chemotherapy.[50] Several studies have shown that the weight of the body was a separate predictive factor for people who have been diagnosed with stomach cancer. Likewise, the validated association between BMI and clinical outcomes in patients who underwent ICIs has been further affirmed.[51,52] The antitumor activity of ICIs depends on normal immune function. The loss of albumin and body weight affected normal immune function, thus affecting the therapeutic effect of ICIs.[53] Therefore, NRI can predict the efficacy of ICIs.

Finally, some unavoidable limitations existed in this study. First, potential information bias inevitably appeared in single-center retrospective studies, prospective clinical trials would be important to overcome information bias. Second, patients in this study used different kinds of ICIs, and the effect of different ICIs on patients was not considered. Third, NRI reflects

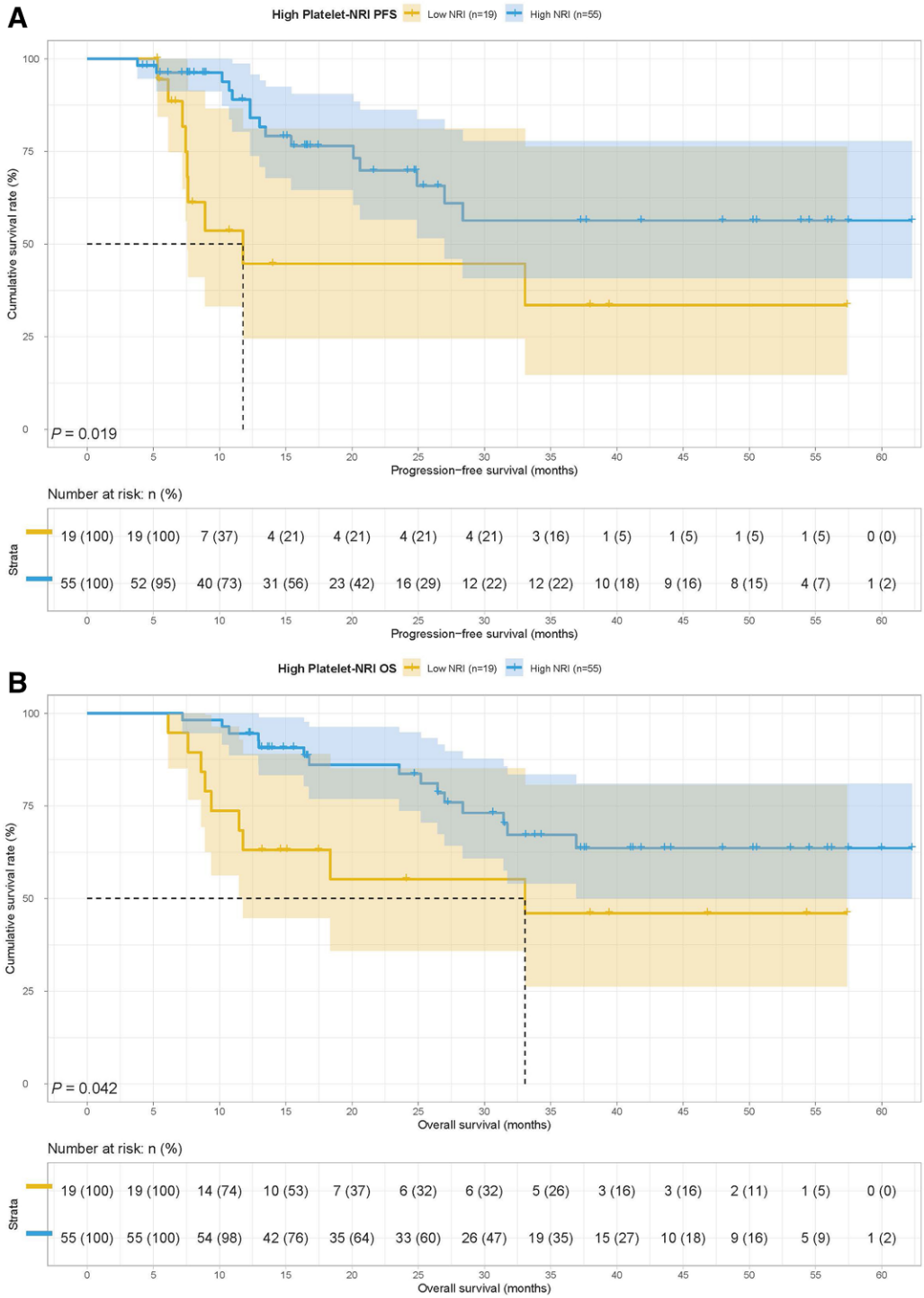

Figure 7. Nutritional Risk Index related survival curve of (A) PFS and (B) OS in the high platelet group. OS = overall survival, PFS = progression-free survival.

the nutritional status of the patient and can be combined with inflammatory markers such as C-reactive protein and lymphocytes to fully evaluate the status of patients. Furthermore, the findings of this study should be validated through larger sample sizes and randomized controlled trials.

5. Conclusion

Patients categorized in the low NRI group demonstrated inferior PFS and OS in all analyses. NRI, being a dependable indicator, showcased its capability in forecasting the medical results of individuals with stomach cancer who received ICIs. As a result, NRI has the capacity to function as a valuable indicator for ICIs, assisting in the identification of patients who would gain from this therapy.

Author contributions

Data curation: Qi Huang.
Funding acquisition: Wei Zhang.
Investigation: Qi Huang.
Methodology: Zhidong Yin.

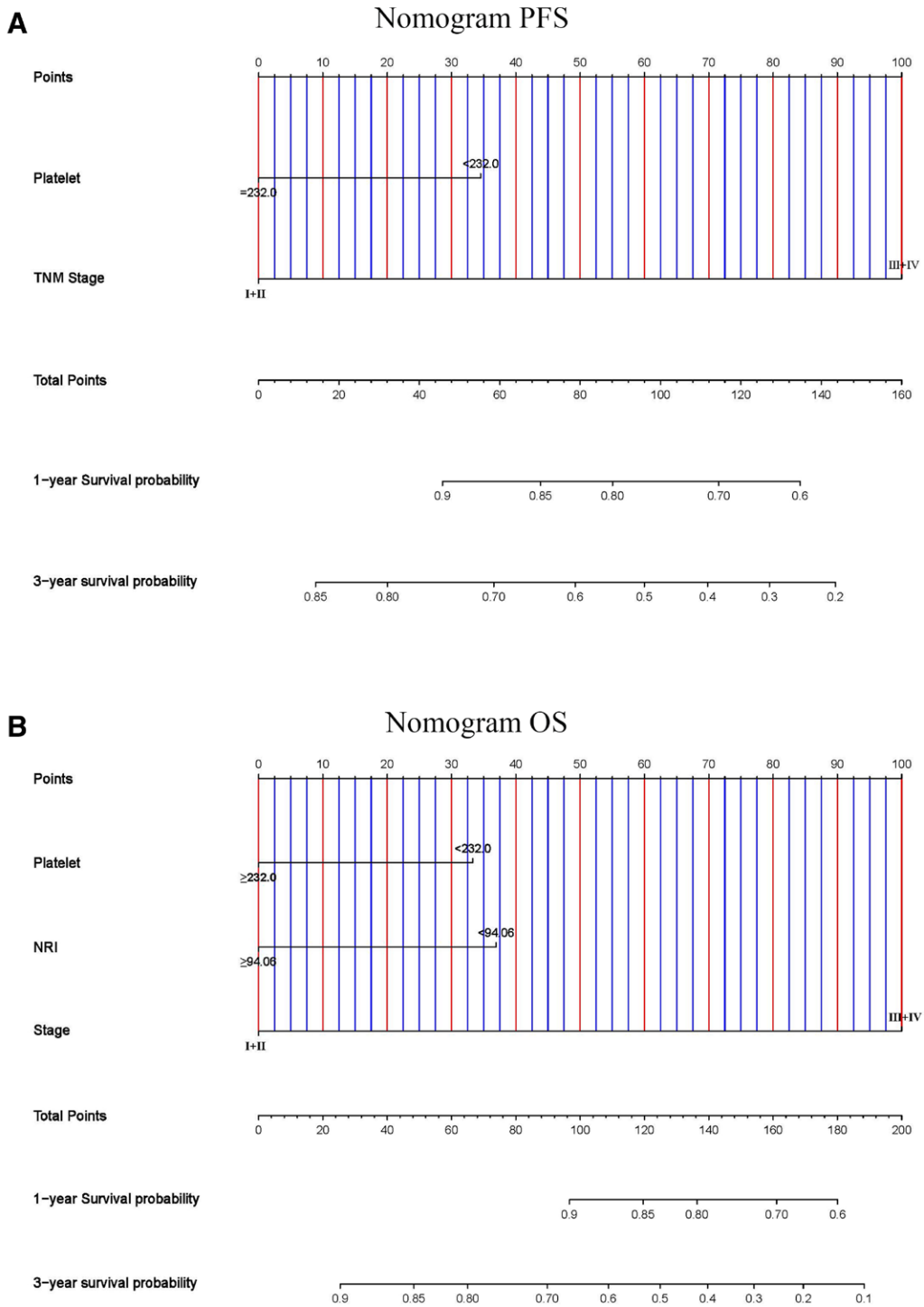

Figure 8. Nomogram for predicting 1- and 3-year survival probability of (A) PFS and (B) OS. OS = overall survival, PFS = progression-free survival.

Project administration: Wei Zhang.
Resources: Wei Zhang.
Supervision: Zhidong Yin.
Writing – original draft: Yuehua Xu, Limin Zhang.
Writing – review & editing: Yuehua Xu, Limin Zhang.

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