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The prealbumin-CD19$^+$ index predicts surgical survival in patients with GC

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Abstract

Objective This study aimed to establish a prealbumin (PALB)-CD19$^+$ index that combines nutritional and immune statuses to comprehensively evaluate the prognosis of GC patients undergoing surgery.

Methods A total of 389 patients who were diagnosed with GC and who underwent surgical procedures at our institution between January 2016 and December 2020 were included in this study. Among them, 97 patients underwent subtotal gastrectomy, 271 underwent total gastrectomy, and 21 underwent palliative resection. The PALB-CD19$^+$ index was developed using Cox regression analysis and regression coefficients, and LASSO regression analysis was employed to eliminate multicollinearity. Receiver operating characteristic (ROC) curves were used to calculate optimal cut-off values, and the prognostic value of different indices was compared using the area under the curve (AUC). Cox regression analysis was further utilized to identify independent prognostic factors. Survival analysis was conducted to explore differences in progression-free survival (PFS) and overall survival (OS) among patient groups. Finally, the prognostic significance of relevant factors was validated using a nomogram.

Results This study included 389 patients, 276 males and 113 females, with a mean age of 59.10 ± 10.19 years. Cox analysis identified PALB and CD19$^+$ as significant factors influencing survival, forming the basis for the PALB-CD19$^+$ index. The cut-off values for PALB and CD19$^+$ were determined to be 230.50 mg/L and 15.40%, respectively. Cox regression analysis confirmed that the PALB-CD19$^+$ index was an independent prognostic factor for both PFS and OS. Survival analysis demonstrated that patients with a lower PALB-CD19$^+$ index had significantly shorter PFS and OS (χ^2 = 45.54, $P < 0.001$; $\chi^2 = 47.69$, $P < 0.001$). Subgroup analysis across different TNM stages further validated the prognostic value of the PALB-CD19$^+$ index (all $P < 0.05$). Nomograms incorporating the PALB-CD19$^+$ index showed high accuracy, with concordance indices (C-index) in the training and validation cohorts approaching or exceeding 0.8.

Conclusions The PALB-CD19$^+$ index exhibits potential prognostic value in predicting surgical outcomes in GC patients. Its ability to integrate nutritional and immune parameters may provide clinicians with a novel and comprehensive tool for identifying high-risk patients and guiding personalized treatment strategies.

Keywords GC, Prealbumin, CD19$^+$ B cell, Gastric surgery, Clinical outcomes

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Introduction

GC (GC) ranks as the fifth most diagnosed cancer worldwide and the third leading cause of cancer-related death, accounting for over one million new cases and approximately 770,000 deaths annually [1]. The disease exhibits significant geographical disparities, with the highest incidence rates observed in East Asia, particularly in China, Japan, and South Korea [2]. In contrast, incidence rates are lower in North America and Western Europe but have been increasing in certain populations due to changing risk factor exposure [3]. Despite advancements in comprehensive treatment strategies, including surgery, chemotherapy, targeted therapy, and immunotherapy, as well as notable progress in minimally invasive surgery and novel drug development [4–6], the overall prognosis for GC patients remains poor, particularly in those with advanced stages of the disease [7]. For many GC patients, the risk of postoperative recurrence remains high, underscoring the importance of regular follow-up and precise interventions [8].

Accurate and convenient prognostic biomarkers are essential for the effective postoperative management of patients with GC [9]. Recent studies have demonstrated that nutritional status plays a critical role in disease progression and survival, particularly in cancers of the digestive system [10–13]. Several nutritional indicators, such as prealbumin, have been shown to be significantly correlated with patient prognosis [14–17]. Moreover, immune status is pivotal in the control and treatment of GC. The effectiveness of immune function directly influences patient responses to immunotherapy, and its unique antitumour mechanisms depend on a well-functioning immune system [18–20].

The interplay between nutritional and immune status in GC patients is particularly noteworthy. Malnutrition can impair immune function, leading to lymphocyte depletion and a reduced ability to combat tumours, whereas diminished immune activity may exacerbate malnutrition, creating a vicious cycle [21]. Therefore, a comprehensive assessment of both immune and nutritional status may provide a more complete perspective for predicting postoperative outcomes.

Peripheral lymphocyte subset analysis is an effective method for evaluating the quantity and activity of various lymphocyte subsets, such as T cells and B cells, and provides a direct reflection of the immune system's status and functionality [22]. Previous studies have highlighted the significant application value of this method in cancer research [23, 24]. However, tools that integrate immune and nutritional factors for prognostic evaluation in postoperative GC patients are lacking.

Therefore, the present study hypothesizes that integrating immune and nutritional parameters into a single index (the PALB-CD19$^+$ index) can more accurately predict postoperative progression-free survival (PFS) and overall survival (OS) in GC patients. To test this hypothesis, this study combined peripheral lymphocyte subset analysis with biochemical parameter testing to identify the most prognostically significant immune and nutritional factors. Using these factors, a novel immune–nutritional composite index was developed and evaluated through Cox regression models to systematically assess its prognostic capability in postoperative GC patients. These findings provide a new theoretical basis and clinical tool for stratified management and precise interventions for GC patients following surgery.

Materials and methods

Patients

We enrolled 389 patients diagnosed with GC who underwent surgical procedures at our institution between January 2016 and December 2020. Among them, 97 patients underwent subtotal gastrectomy, 21 patients underwent palliative resection, and the remaining patients underwent total gastrectomy. The inclusion criteria for this study were as follows: (1) a diagnosis of gastric adenocarcinoma confirmed through gastric endoscopic pathological examination, (2) age 18 years or older, (3) peripheral blood lymphocyte detection performed via flow cytometry the day before surgery, (4) no history of other malignancies, (5) absence of chronic inflammatory or consumptive diseases, and (6) availability of complete clinical and pathological data. The exclusion criteria were (1) loss to follow-up, (2) abandonment of treatment for any reason, (3) severe organ dysfunction, (4) active infections, (5) autoimmune diseases, and (6) any conditions that could interfere with the evaluation of immune or nutritional status (Fig. 1). This study was based on the Helsinki Declaration and its amendments and was conducted under the supervision of the Ethics Committee of Harbin Medical University Cancer Hospital (Ethics Number: 2019-57-IIT).

Flow cytometry

All patients included in this study underwent lymphocyte subset analysis. On the morning of the testing day, peripheral venous blood samples (100 μL) were collected from fasted subjects. TBNK reagent (Becton, Dickinson and Company) was added according to the manufacturer's instructions, followed by vortexing and incubation at room temperature (20–25 °C) in the dark for 30 min. Subsequently, 2 mL of red blood cell lysis solution was added, and the samples were incubated at room temperature (20–25 °C) for 15 min to lyse the red blood cells. After centrifugation, the supernatant was discarded, and the cells were resuspended in 500 μL of PBS. Finally, the samples were analysed using a BD FACSCanto II flow cytometer with BD FACSCanto™ clinical software v2.4,

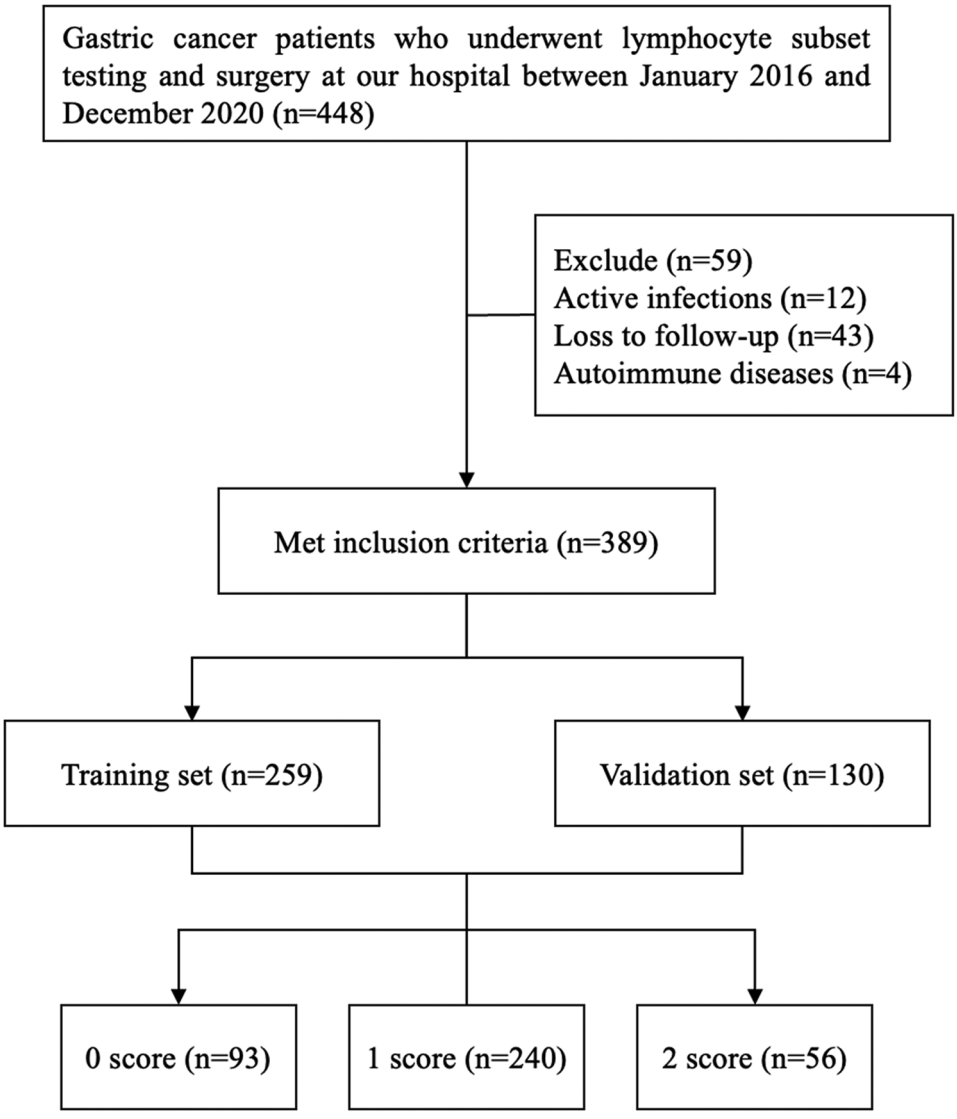

Fig. 1 Flow chart of patient selection in this study

which automatically detected and calculated the percentages of lymphocyte subsets (Fig. 2).

Data collection

The pathological data of the patients were retrieved from the medical records system. Progression-free survival (PFS) and overall survival (OS) were assessed through regular telephone follow-ups conducted every three months. The follow-up duration varied depending on the patient's survival status, with the final follow-up completed in December 2023. PFS indicated the period from treatment initiation to disease progression, death, or the latest follow-up appointment. Disease progression was confirmed by imaging or pathological assessments. OS referred to the duration from treatment commencement to either death or the last follow-up visit.

Establishment of combined indices related to lymphocyte subsets

Patients were randomly assigned to a training set ($n = 259$) or a validation set ($n = 130$) using a random number table method. Correlation analysis revealed no significant differences in any of the factors between the two groups (all $P > 0.05$). Additional details can be found in Supplementary Tables 1 and 2.

To determine the most significant factors that influence survival, we conducted a preliminary analysis of the blood parameters of patients in the training set. The results revealed significant correlations ($P < 0.05$) between patient OS and several factors. In addition, LASSO analysis revealed multicollinearity among albumin, red blood cells, haemoglobin, and $CD3^+CD16^+CD56^+$ (Fig. 3). After multivariate Cox analysis of the remaining indicators was conducted, prealbumin (PALB) and $CD19^+$ were

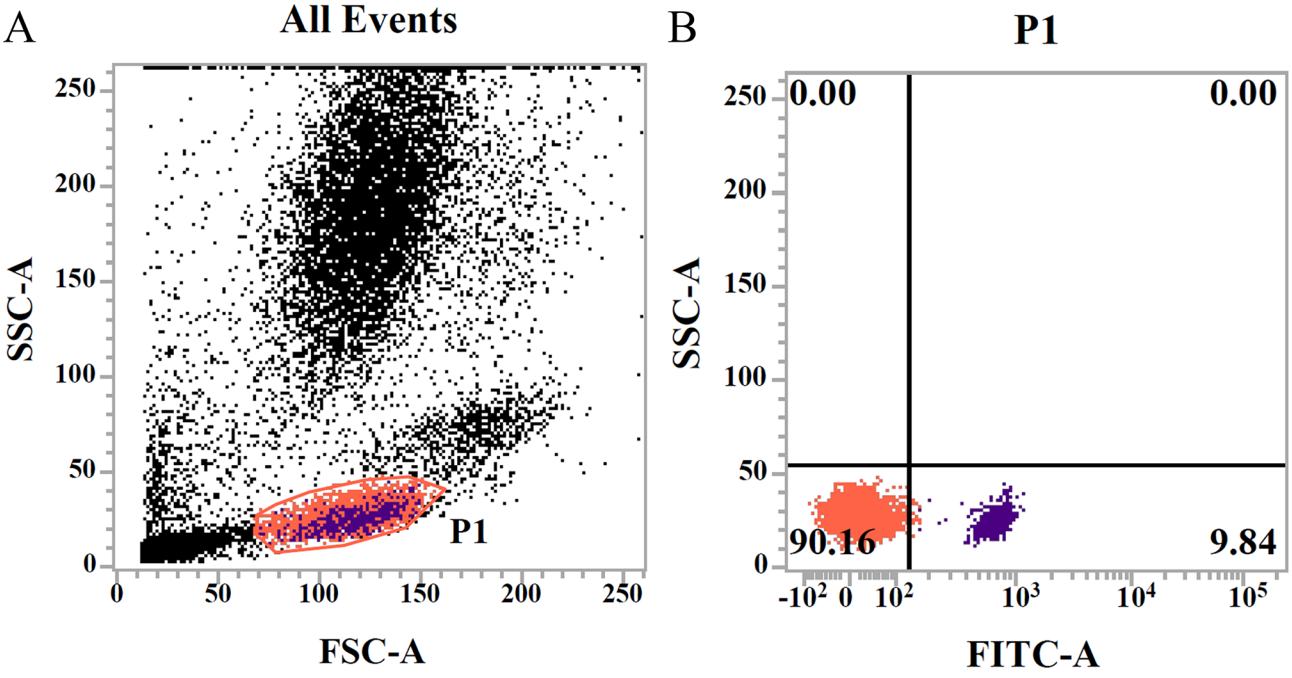

Fig. 2 Flow cytometry analysis of lymphocyte subsets. (**A**) Gating of lymphocyte populations (P1) based on forwards scatter (FSC-A) and side scatter (SSC-A) properties. (**B**) FITC marker expression analysis of the gated lymphocyte population (P1), which revealed 90.16% FITC-negative and 9.84% FITC-positive cells

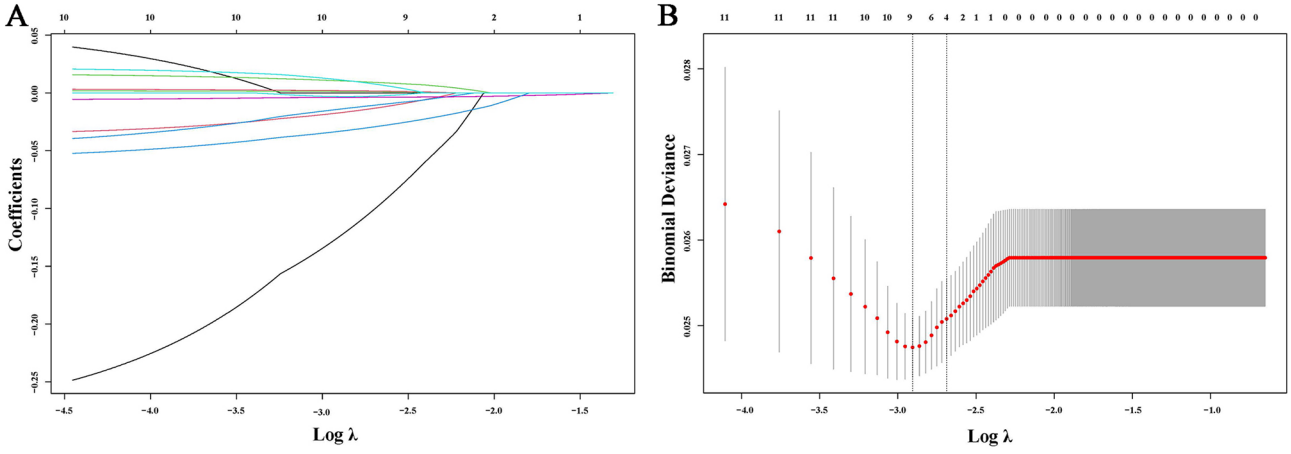

Fig. 3 LASSO regression analysis. (**A**) Lasso analysis of blood parameters; (**B**) determination of the best λ value

identified as independent prognostic markers for OS (Table 1).

The AUC values for PALB and $CD19^+$ were 0.645 (95% CI: 0.553–0.692) and 0.665 (95% CI: 0.572–0.738), respectively. The cut-off values for PALB and $CD19^+$ were 230.50 mg/L and 15.40%, respectively (Fig. 4). Patients were grouped based on these values, with those with lower levels of PALB and $CD19^+$ assigned a score of 0 and those with higher levels assigned a score of 1. Ultimately, all patients were categorized into 0-score, 1-score, and 2-score groups.

Statistical analysis

Categorical variables are expressed as numbers and percentages (n, %) and were compared using the chi-square test or Fisher's exact test. The normality of continuous variables was assessed via the Kolmogorov–Smirnov test. Continuous variables that followed a normal distribution are presented as the means ± standard deviations (SDs) and were analysed via t tests or one-way analysis of variance (ANOVA). Nonnormally distributed variables are expressed as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney U test. All statistical analyses were performed using R 4.3.1

Table 1 Univariate and multivariate Cox survival analysis

Items	HR (95%CI)	*P*	HR (95%CI)	*P*
ALT (U/L)	0.947(0.908–0.989)	0.013	0.990(0.965–1.016)	0.454
AST (U/L)	0.932(0.879–0.989)	0.021	0.997(0.973–1.042)	0.680
γ-GGT (U/L)	0.989(0.972–1.006)	0.195		
LDH (U/L)	1.003(0.979–1.027)	0.818		
TBIL (μmol/L)	0.989(0.977–1.001)	0.071		
DBIL (μmol/L)	0.964(0.923–0.996)	0.001	0.948(0.807–1.115)	0.520
IDBIL (μmol/L)	0.956(0.919–0.994)	0.024	0.977(0.898–1.064)	0.595
TP (g/L)	0.934(0.835–1.045)	0.233		
ALB (g/L)	0.935(0.883–0.990)	0.022		
GLOB (g/L)	0.983(0.933–1.036)	0.523		
PALB (mg/L)	0.994(0.992–0.997)	< 0.001	0.975(0.952–0.997)	< 0.001
BUN (mmol/L)	0.973(0.896–1.058)	0.522		
CREA (μmol/L)	1.001(0.996–1.005)	0.746		
UA (μmol/L)	0.999(0.996–1.001)	0.315		
ALP (U/L)	1.002(0.999–1.004)	0.164		
Glu (mmol/L)	1.023(0.872-1.200)	0.778		
WBC (10^9/L)	0.990(0.903–1.086)	0.833		
NEU (10^9/L)	1.042(0.955–1.138)	0.353		
LYM (10^9/L)	0.684(0.513–0.911)	0.009	0.778(0.567–1.067)	0.120
MON (10^9/L)	1.225(0.469–3.201)	0.678		
RBC (10^9/L)	0.700(0.515–0.952)	0.023		
HGB (10^9/L)	0.700(0.515–0.952)	0.023		
HCT (10^9/L)	0.975(0.948–1.004)	0.092		
PLT (10^9/L)	1.001(0.999–1.004)	0.350		
$CD3^+$ (%)	1.003(1.000-1.006)	0.028	1.004(1.001–1.008)	0.075
$CD4^+$ (%)	0.998(0.976–1.021)	0.885		
$CD8^+$ (%)	1.028(1.004–1.052)	0.023	1.019(0.994–1.046)	0.137
$CD3^+CD4^+CD8^+$ (%)	0.913(0.720–1.158)	0.454		
$CD19^+$ (%)	0.933(0.892–0.977)	0.003	0.948(0.904–0.995)	0.030
$CD3^-CD16^+CD56^+$ (%)	0.994(0.973–1.015)	0.549		
$CD3^+CD16^+CD56^+$ (%)	1.032(1.002–1.063)	0.035		

HR: hazard ratio; CI: confidence interval; ALT: alanine transaminase; AST: aspartate aminotransferase; γ-GGT: γ-glutamyl transferase; LDH: lactate dehydrogenase; TBIL: total bilirubin; DBIL: direct bilirubin; IDBIL: indirect bilirubin; TP: total protein; ALB: albumin; GLOB: globulin; PALB: prealbumin; BUN: blood urea nitrogen; CREA: creatinine; UA: uric acid; ALP: alkaline phosphatase; Glu: glucose; WBC: white blood cell; NEU: neutrophil; LYM: lymphocyte; MON: monocyte; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; PLT: Platelet

(https://www.r-project.org), with significance set at a two-tailed $P < 0.05$. Receiver operating characteristic (ROC) curves were employed to determine optimal cut-off values. Survival differences were analysed via Kaplan–Meier (K–M) curves and log-rank tests. Univariate and multivariate Cox survival analyses were conducted to identify prognostic factors, with LASSO regression employed to address potential multicollinearity. Finally, nomograms were constructed to predict patient survival probabilities.

Results

Patient characteristics

This study included a total of 389 patients, 276 males and 113 females, with a mean age of 59.10 (10.19) years and a mean BMI of 22.98 (3.22) kg/m^2. The PALB-$CD19^+$ index was distributed among the patients as follows: 93 individuals scored 0 points, 240 scored 1 point, and 56 scored 2 points. The PALB-$CD19^+$ index was associated with age, BMI, radical resection, primary tumour site, positive lymph node (LNP) status, tumour size, differentiation, TNM stage, and CA724 levels (all $P < 0.05$), as indicated in Table 2.

Cox survival analysis

Univariate analysis revealed that age, BMI, the PALB-$CD19^+$ index, radical resection, Borrmann type, LNP, tumour size, and TNM stage were correlated with PFS and OS (all $P < 0.05$). Furthermore, age, the PALB-$CD19^+$ index, Borrmann type, and TNM stage were determined to be independent prognostic factors for both PFS and OS (all $P < 0.05$), as depicted in Tables 3 and 4.

Post-hoc power analysis for cox regression

A post hoc power analysis was performed to evaluate the statistical power of the Cox regression analysis in this study. Using G*Power software, the analysis was based on an HR of 0.300, a total sample size of 389, an event rate of 36.2%, and a significance level (α) of 0.05. The achieved statistical power was calculated to be 89%, demonstrating that the study had sufficient sensitivity to detect significant differences in survival outcomes at this hazard ratio.

Survival analysis for the PALB-$CD19^+$ index

The training set included 61 individuals with a PALB-$CD19^+$ index of 0, 163 with a score of 1, and 35 with a score of 2. For patients with a score of 0, the median PFS and OS were 39.68 months and 45.52 months, respectively. In contrast, the median PFS and OS for patients with scores of 1 and 2 were not reached. Patients with a lower PALB-$CD19^+$ index had worse PFS and OS ($\chi^2 = 45.54$, $P < 0.001$ and $\chi^2 = 47.69$, $P < 0.001$) (Fig. 5A, B). Similarly, the validation set included 32 individuals with a PALB-$CD19^+$ index of 0, 77 with a score of 1, and 21 with a score of 2. Patients with a score of 0 had a median PFS of 52.39 months and a median OS of 53.21 months. In comparison, neither the median PFS nor the OS were reached for patients with scores of 1 or 2. The PALB-$CD19^+$ index was also found to be associated with PFS and OS ($\chi^2 = 16.76$, $P < 0.001$ and $\chi^2 = 18.11$, $P < 0.001$) (Fig. 5C, D).

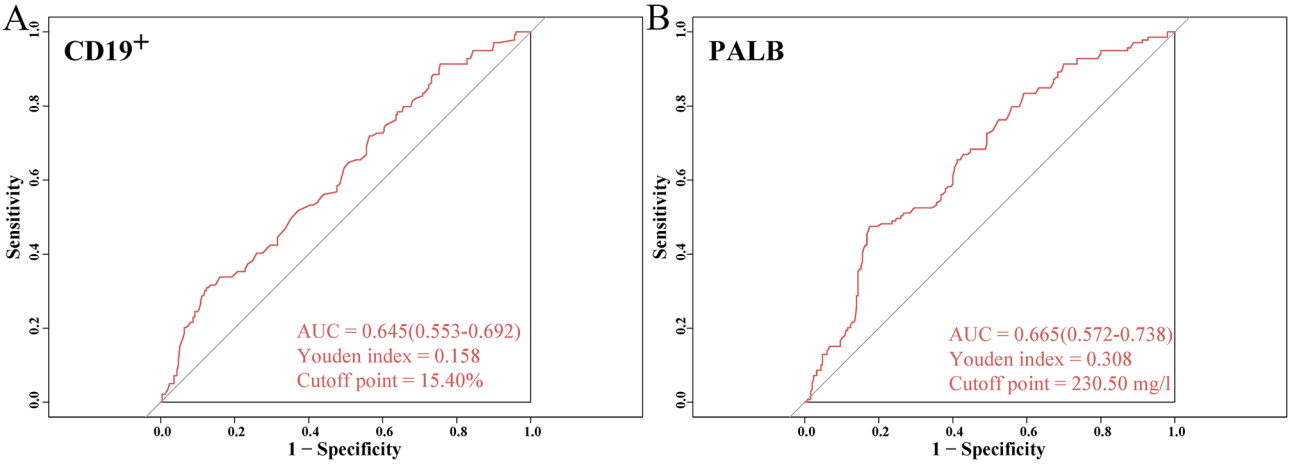

Fig. 4 Calculation of the optimal cut-off value for the ROC curve. (**A**) ROC curve of CD19+; (**B**) ROC curve of PALB

The training set consisted of 161 patients with TNM stages I + II, including 24 with a PALB-CD19$^+$ index of 0, 110 with a score of 1, and 27 with a score of 2. The median PFS and OS were not reached in any of the three groups of patients. Patients with a lower PALB-CD19$^+$ index had significantly worse PFS and OS (χ^2 = 6.068, P = 0.019 and χ^2 = 6.303, P = 0.017) (Fig. 6A, B). Similarly, the validation set consisted of 91 patients with TNM stages I + II, including 17 with a PALB-CD19$^+$ index of 0, 58 with a score of 1, and 16 with a score of 2. The median PFS and OS were also not reached in any of the three groups of patients. Patients with a lower PALB-CD19$^+$ index also had worse PFS and OS durations (χ^2 = 3.418, P = 0.045 and χ^2 = 3.592, P = 0.049) (Fig. 6C, D).

Moreover, the training set consisted of 98 patients in TNM stages III + IV, including 37 with a PALB-CD19$^+$ index of 0, 53 with a score of 1, and 27 with a score of 2. The median PFS durations for patients in with scores of 0, 1, and 2 were 23.17 months, 40.35 months, and not reached, respectively. The median OS durations for these groups were 22.37 months, 43.56 months, and not reached, respectively. Patients with different PALB-CD19$^+$ indices exhibited significant differences in PFS and OS (χ^2 = 17.609, P < 0.001 and χ^2 = 19.353, P < 0.001) (Fig. 7A, B). The validation set consisted of a total of 39 patients in TNM stages III + IV, including 15 with a PALB-CD19$^+$ index of 0, 19 with a score of 1, and 5 with a score of 2. For patients with scores of 0, 1, and 2, the median PFS durations were 18.94 months, 39.88 months, and not reached, respectively, whereas the median OS durations were 19.29 months, 42.22 months, and not reached, respectively. PFS and OS remained associated with the PALB-CD19$^+$ index (χ^2 = 6.890, P = 0.025 and χ^2 = 8.260, P = 0.012) (Fig. 7C, D).

Comparison of the prognostic value of the PALB-CD19$^+$ index with those of classic prognostic markers

To further explore the prognostic value of the PALB-CD19$^+$ index, we calculated and analysed the AUCs of various classical nutritional and inflammatory prognostic markers, with the calculation formulas provided in Supplementary Table 3. The results revealed that the AUC of the PALB-CD19$^+$ index was 0.704 (0.599–0.815), which was the highest among all prognostic markers, further demonstrating its strong prognostic predictive ability (Table 5).

Nomograms for the PALB-CD19$^+$ index

Global Schoenfeld tests revealed that all independent prognostic factors conformed to the proportional hazard assumption (Fig. 8A, B). In the training set, we constructed nomograms including the PALB-CD19$^+$ index based on independent prognostic factors (Fig. 8C, D). The respective C-indices and 95% CI95% CIs were 0.808 (0.694–0.901) for PFS and 0.815 (0.733–0.897) for OS. We explored the accuracy of the nomograms using the validation set. The C-indices and 95% CIs for PFS and OS in the validation set were 0.796 (0.651–0.865) and 0.801 (0.644–0.859), respectively. The calibration curves plotted with data from the validation set illustrated the strong predictive accuracy of the nomograms (Fig. 8E, F).

Discussion

Due to its unique anatomical structure, GCs have a more significant impact on patients' nutritional status than other cancers do. Malnutrition, in turn, compromises immune function, thereby influencing prognosis in multiple ways. This study established a novel prognostic indicator, the PALB-CD19$^+$ index, by integrating nutritional and immune status, enabling the accurate prediction of prognosis in GC patients undergoing surgery. The PALB-CD19$^+$ index effectively identifies high-risk patients for

Table 2 Patients' characteristic

	0-score	1-score	2-score	*P* value
Items	***n*** **= 93**	***n*** **= 240**	***n*** **= 56**	
Age (years), mean (SD)	63.77(10.58)	57.34(10.81)	55.21(9.36)	< 0.001
Sex (%)				0.477
Male	68(73.1)	172(71.1)	36(64.3)	
Female	25(26.9)	68(28.3)	20(35.7)	
BMI (Kg/m^2), mean (SD)	21.69(3.77)	23.02(3.28)	25.14(3.73)	0.001
Radical resection (%)				< 0.001
Yes	77(82.8)	229(95.4)	56(100)	
No	16(17.2)	11(4.6)	0(0.0)	
Primary tumor site (%)				< 0.001
Upper 1/3	7(7.5)	6(2.5)	2(3.6)	
Middle 1/3	4(4.3)	46(19.2)	11(19.6)	
Low 1/3	62(66.7)	169(70.4)	41(73.2)	
Whole	20(21.5)	19(7.9)	2(3.6)	
Borrmann type (%)				0.193
I	4(4.3)	25(10.4)	17(30.4)	
II	25(26.9)	76(31.7)	15(26.8)	
III	56(60.2)	123(51.2)	23(41.1)	
IV	8(8.6)	16(6.7)	1(1.8)	
LNP (%)				0.013
Yes	54(58.1)	103(42.9)	20(35.7)	
No	39(41.9)	137(57.1)	36(64.3)	
Tumor size (%)				< 0.001
< 20 mm	4(4.3)	20(8.3)	22(39.3)	
20–50 mm	23(24.7)	122(50.8)	17(30.4)	
> 50 mm	66(71.0)	98(40.8)	17(30.4)	
Differentiation (%)				< 0.001
Poor	34(26.6)	81(33.8)	19(33.9)	
Moderately	50(53.8)	125(52.1)	17(30.4)	
Well	3(3.2)	17(7.1)	17(30.4)	
Unknown	6(6.5)	17(7.1)	3(5.4)	
Lauren type (%)				0.730
Intestinal	49(52.7)	115(47.9)	33(58.9)	
Diffuse	13(14.0)	45(18.8)	6(10.7)	
Mixed	25(26.9)	66(27.5)	14(25.0)	
Unknown	6(6.5)	14(5.8)	3(5.4)	
TNM stage (%)				< 0.001
I	15(16.1)	112(46.7)	31(55.4)	
II	26(28.0)	56(23.3)	12(21.4)	
III	39(41.9)	65(27.1)	12(21.4)	
IV	13(14.0)	7(2.9)	1(1.8)	
CEA (%)				0.136
< 1.97 ng/mL	38(40.9)	126(52.5)	30(53.6)	
≥ 1.97 ng/mL	55(59.1)	114(47.5)	26(46.4)	
CA199 (%)				0.521
< 10.19 U/L	41(44.1)	117(48.8)	30(53.6)	
≥ 10.19 U/L	52(55.9)	123(51.2)	26(46.4)	
CA724 (%)				< 0.001
< 2.17 U/L	30(32.3)	125(52.1)	39(69.6)	
≥ 2.17 U/L	63(67.7)	115(47.9)	17(30.4)	
CA125II (%)				0.303

Table 2 (continued)

	0-score	1-score	2-score	*P* value
Items	***n*** **= 93**	***n*** **= 240**	***n*** **= 56**	
< 10.21 U/L	41(44.1)	118(49.2)	32(57.1)	
≥ 10.21 U/L	52(55.9)	122(50.8)	24(42.9)	

PALB: prealbumin; BMI: body mass index; LNP: Lymph node positive; CEA: carcinoembryonic antigen; CA199: carbohydrate antigen 199; CA724: carbohydrate antigen 724; CA125II: carbohydrate antigen 125II

Table 3 Univariate and Multivariate analysis for PFS

	PFS			
	Univariate analysis		**Multivariate analysis**	
Parameters	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1.036(1.017–1.055)	< 0.001	1.020(1.000-1.040)	0.046
Sex				
Male	Ref			
Female	0.883(0.606–1.286)	0.516		
BMI	0.926(0.879–0.976)	0.004	0.997(0.945–1.051)	0.903
PALB-CD19^{+} index				
0-score	Ref		Ref	
1-score	0.339(0.241–0.478)	< 0.001	0.588(0.398–0.867)	0.007
2-score	0.114(0.041–0.264)	< 0.001	0.326(0.133–0.801)	0.015
Radical resection				
Yes	Ref		Ref	
No	4.850(3.040–7.738)	< 0.001	1.481(0.695–3.158)	0.309
Primary tumor site				
Upper 1/3	Ref			
Middle 1/3	0.643(0.234–1.771)	0.393		
Low 1/3	0.953(0.387–2.344)	0.916		
Whole	2.518(0.966–6.566)	0.059		
Borrmann type				
I	Ref		Ref	
II	9.129(2.202–17.849)	0.002	3.156(0.674–14.782)	0.145
III	11.524(2.831–19.902)	0.001	3.431(0.750-15.705)	0.112
IV	40.414(9.419–53.405)	< 0.001	7.801(1.72-38.701)	0.012
LNP				
Yes	Ref		Ref	
No	3.130(2.195–4.463)	< 0.001	1.053(0.562–1.970)	0.873
Tumor size				
< 20 mm	Ref		Ref	
20–50 mm	2.650(1.049–6.693)	0.039	1.717(0.605–4.870)	0.310
> 50 mm	6.180(2.509–15.220)	< 0.001	1.050(0.703–1.568)	0.811
TNM stage				
I	Ref		Ref	
II	3.912(2.104–7.273)	< 0.001	2.927(1.435–5.973)	0.003
III	10.883(6.229–19.014)	< 0.001	7.424(3.152–17.485)	< 0.001
IV	48.905(24.504–97.601)	< 0.001	16.557(5.921–46.302)	< 0.001

PFS: progression-free survival; HR: hazard radio; CI: confidence interval; BMI: body mass index; LNP: lymph node positive

timely intervention, offering a new reference for the individualized treatment of GC.

Nutritional status has a profound effect on cancer patients. In 2022, Qian and colleagues analysed multiple nutritional biomarkers, including the prognostic nutritional index (PNI), in 661 patients. They reported that several indicators, particularly the PNI, could predict patient prognosis [25]. Similarly, Zhang et al. conducted a study analysing various nutritional markers in elderly cancer patients. After an in-depth analysis of 1494 patients, they not only identified prevalent malnutrition among elderly cancer patients but also confirmed the significant potential of nutritional indices akin to the PNI in this population [26]. Bullock and colleagues

Table 4 Univariate and Multivariate analysis for OS

	OS			
	Univariate analysis		**Multivariate analysis**	
Parameters	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1.037(1.018–1.056)	< 0.001	1.021(1.001–1.041)	0.037
Sex				
Male	Ref			
Female	0.875(0.601–1.275)	0.488		
BMI	0.930(0.883–0.980)	0.007	0.998(0.947–1.052)	0.938
PALB-CD19$^+$ index				
0-score	Ref		Ref	
1-score	0.328(0.232–0.462)	< 0.001	0.555(0.377–0.817)	0.003
2-score	0.108(0.047–0.250)	< 0.001	0.300(0.122–0.738)	0.009
Radical resection				
Yes	Ref		Ref	
No	5.054(3.167–8.066)	< 0.001	1.838(0.899–3.759)	0.095
Primary tumor site				
Upper 1/3	Ref			
Middle 1/3	0.626(0.227–1.723)	0.365		
Low 1/3	0.956(0.389–2.352)	0.956		
Whole	2.482(0.952–6.474)	0.063		
Borrmann type				
I	Ref		Ref	
II	9.004(2.172–37.328)	0.002	3.151(0.673–14.748)	0.145
III	11.449(2.813–45.598)	0.001	3.307(0.722–15.152)	0.124
IV	39.365(9.173–68.924)	< 0.001	7.895(1.587–39.280)	0.012
LNP				
Yes	Ref		Ref	
No	3.033(2.127–4.324)	< 0.001	1.071(0.573–2.002)	0.830
Tumor size				
< 20 mm	Ref		Ref	
20–50 mm	2.632(1.042–6.648)	0.041	1.609(0.571–4.532)	0.368
> 50 mm	6.222(2.526–15.326)	< 0.001	1.150(0.668–1.486)	0.985
TNM stage				
I	Ref		Ref	
II	3.877(2.085–7.209)	< 0.001	2.965(1.460–6.023)	0.003
III	10.448(5.984–18.243)	< 0.001	7.824(3.324–18.417)	< 0.001
IV	41.804(21.114–82.765)	< 0.001	12.427(4.601–33.562)	< 0.001

PFS: progression-free survival; HR: hazard radio; CI: confidence interval; BMI: body mass index; LNP: lymph node positive

further corroborated this viewpoint through a meta-analysis focused on elderly cancer patients [27]. Like our study, PALB was typically not used in isolation but rather in combination with other indicators, such as the controlling nutritional status (CONUT), fibrinogen-to-prealbumin ratio, and C-reactive protein and PALB ratio (CRP/PALB), to establish biomarkers. Chen and Sun conducted a study in 2022 focusing on GC patients receiving immunotherapy. They analysed the CONUT score in 146 patients and reported that it was significantly correlated with prognosis [28]. Ying collected and analysed the prognostic value of the fibrinogen-to-prealbumin ratio in up to 2917 colorectal cancer patients, revealing its significant application potential [29]. Additionally, PALB is often combined with the C-reactive protein level. Lu et al. studied 419 GC patients who underwent C-reactive protein testing and analysed the difference in prognostic value when C-reactive protein was combined with multiple indicators. Ultimately, they reported that the CRP/PALB ratio had greater predictive value than the use of a single indicator [30]. Peripheral lymphocyte subsets have also been widely researched for their application in GC. In 2022, Sun and colleagues analysed the predictive ability of lymphocyte subsets in surgically treated GC patients. They not only reported that various lymphocyte subsets were correlated with prognosis but also unexpectedly discovered that B cells had greater prognostic value [31].

We identified CD19$^+$ and PALB as the most significant blood parameters influencing patient prognosis.

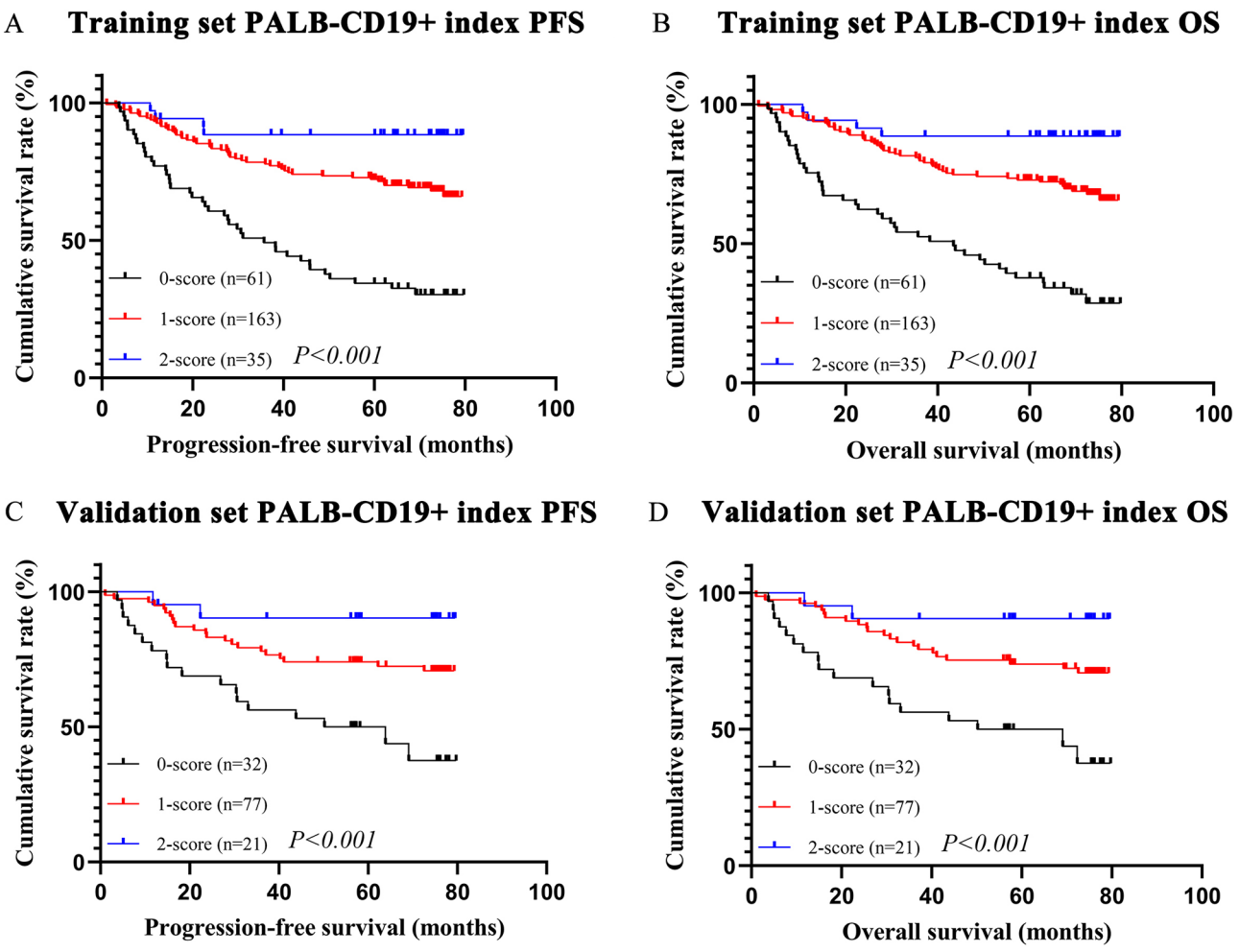

Fig. 5 Survival analysis of the PALB-CD19 + index. (**A**) Survival analysis of the PALB-CD19 + index for PFS in the training set; (**B**) survival analysis of the PALB-CD19 + index for OS in the training set; (**C**) survival analysis of the PALB-CD19 + index for PFS in the validation set; (**D**) survival analysis of the PALB-CD19 + index for PFS in the validation set

Therefore, we combined them to establish a new PALB-CD19$^+$ index and stratified the patients accordingly. Survival analysis revealed that the PALB-CD19$^+$ index was significantly associated with both PFS and OS in all patients in both the training and validation sets. Furthermore, the PALB-CD19$^+$ index demonstrated greater prognostic value across different TNM stages. Notably, the PALB-CD19$^+$ index has the greatest prognostic value among various classical inflammatory and nutritional prognostic markers. In this study, the PALB-CD19$^+$ index was also identified as an independent prognostic factor, alongside age, Borrmann type, and TNM staging. Additionally, nomograms incorporating the PALB-CD19$^+$ index showed high accuracy.

In previous studies, age and TNM staging have been widely recognized as important factors influencing the prognosis of various cancers, while the Borrmann classification distinguishes the degree of malignancy based on tumour morphology and is also significantly associated with patient prognosis [32, 33]. In this study, the PALB-CD19 + index was identified as an independent prognostic factor, along with age, Borrmann classification, and TNM staging, further demonstrating its strong prognostic value and potential for clinical application. The specific mechanisms by which the PALB-CD19$^+$ index predicts prognosis remain unclear but may involve the following aspects. CD19$^+$ B cells are essential components of lymphocytes and play crucial roles in antitumour immunity [34]. When the body detects tumour antigens, activated B cells differentiate into plasma cells, which produce large quantities of antibodies [35, 36]. Moreover, antibodies can activate the complement system, further enhancing the immune response [37]. Additionally, B cells contribute to antitumour immunity by directly participating in cellular immune responses [38]. Activated B cells can interact with T cells to recognize and attack tumour cells [39]. Furthermore, B cells can secrete various cytokines, such as interferons and tumour

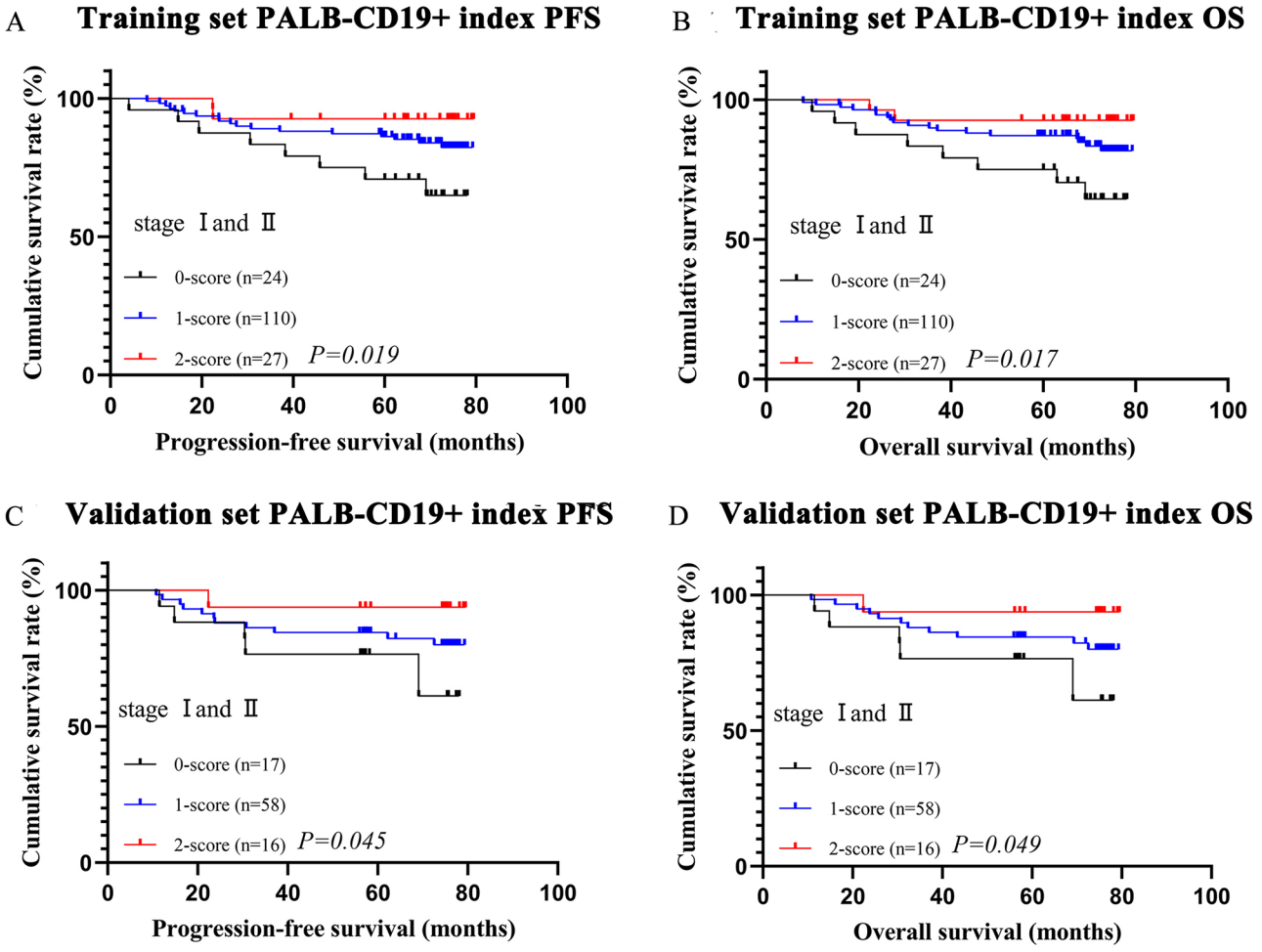

Fig. 6 Survival analysis of PALB-CD19 + index patients with TNM stages I+II. (**A**) Survival analysis of the PALB-CD19 + index for PFS in the training set; (B) survival analysis of the PALB-CD19 + index for OS in the training set; (**C**) survival analysis of the PALB-CD19 + index for PFS in the validation set; (**D**) survival analysis of the PALB-CD19 + index for PFS in the validation set

necrosis factor, to regulate and enhance cellular immune responses, which promotes the apoptosis and clearance of tumour cells [40]. Consequently, B cells are significantly associated with the prognosis of cancer patients [41]. Plasma proteins are closely related to nutritional status because their synthesis and degradation are influenced by nutrient intake [42]. The major plasma proteins included albumin, prealbumin, and globulins, all of which have been extensively studied and confirmed to be associated with the prognosis of cancer patients [43–46]. In this study, the predictive value of prealbumin surpassed that of albumin, which could be attributed to several reasons. Compared with albumin, prealbumin has a shorter half-life, approximately 2–3 days, making it more sensitive to recent changes in nutritional status [47]. This heightened sensitivity allows prealbumin to indicate nutritional deficiencies in patients at an earlier stage [48]. Additionally, prealbumin is synthesized primarily in the liver, and its concentration is influenced by both liver function and nutritional status [49]. In contrast, albumin is more susceptible to the effects of inflammation, making it a less sensitive marker of nutritional status [50–52]. Therefore, prealbumin more accurately reflects the patient's liver function status, thereby better assessing the patient's overall health condition [53].

In this study, the newly developed PALB-CD19^{+} index, which consists of PALB and CD19^{+}, demonstrated remarkably high prognostic value. Its predictive ability not only exceeds that of individual markers but also significantly outperforms a range of classical inflammatory and nutritional prognostic markers widely used in GC. This performance is a result of the close relationship between nutritional status and immune function [54]. Both cellular and humoral immunity rely on relatively normal nutritional status in patients [55]. The relatively short half-life of PALB enables it to more sensitively and rapidly reflect patients' nutritional status [47]. B cells, on the other hand, contribute to both cellular and humoral

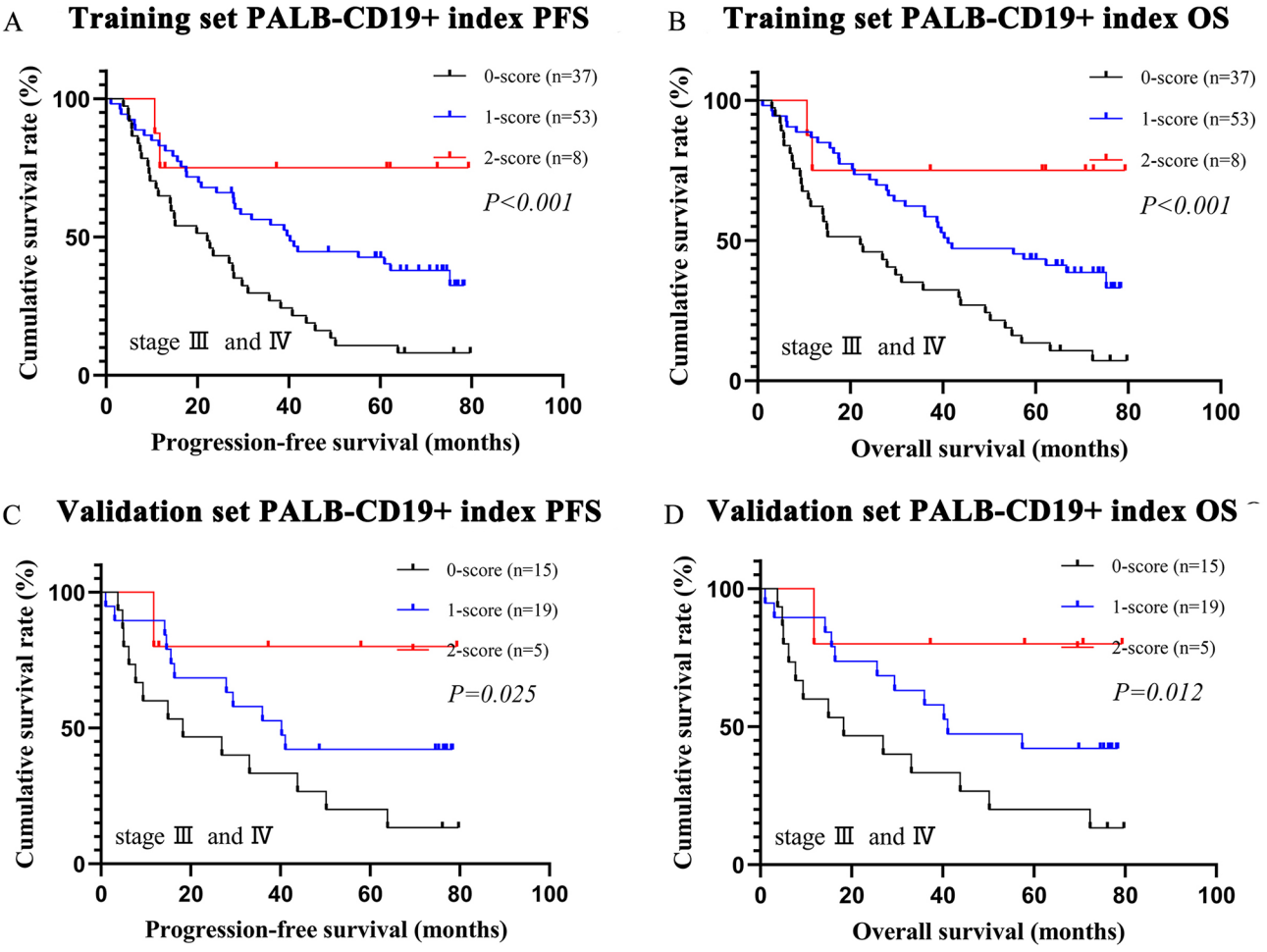

Fig. 7 Survival analysis of PALB-CD19 + index patients with TNM stages III + IV. (**A**) Survival analysis of the PALB-CD19 + index for PFS in the training set; (**B**) survival analysis of the PALB-CD19 + index for OS in the training set; (**C**) survival analysis of the PALB-CD19 + index for PFS in the validation set; (**D**) survival analysis of the PALB-CD19 + index for PFS in the validation set

Table 5 Comparison of prognostic value of classic prognostic markers

Items	AUC	95%CI
NLR	0.632	0.557–0.697
PLR	0.584	0.526–0.673
LMR	0.575	0.499–0.638
NRI	0.681	0.572–0.761
GNRI	0.683	0.574–0.766
PNI	0.678	0.611–0.749
SII	0.567	0.498–0.637
SIRI	0.641	0.591–0.771
ALI	0.649	0.582–0.738
PALB	0.665	0.572–0.738
CD19+	0.645	0.553–0.692
PALB-CD19 + index	0.704	0.599–0.815

NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; PNI: Prognostic Nutritional Index; NRI: Nutritional Risk Index; GNRI: Geriatric Nutritional Risk Index; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; ALI: Advanced Lung Cancer Inflammation Index; PALB: prealbumin

immunity through multiple functions, allowing them to more accurately reflect patients' immune status [39, 40]. Therefore, combining these two indices improves their prognostic value. The introduction of the PALB-CD19$^+$ index not only further expands the clinical application of lymphocyte subset detection technology but also provides clinicians with a new, more accurate method to identify patients who are at high risk for metastasis and recurrence, which is highly important.

This study highlights the potential of the PALB-CD19$^+$ index as a robust and innovative prognostic marker for GC patients, bridging the interplay between nutritional status and immune function. Its ability to outperform traditional markers underscores the importance of integrated biomarkers that capture the dynamic interactions of the tumour microenvironment and systemic health. Future advancements in this area could focus on expanding the clinical applications of the PALB-CD19$^+$ index, including its role in guiding personalized treatment strategies and monitoring therapeutic responses.

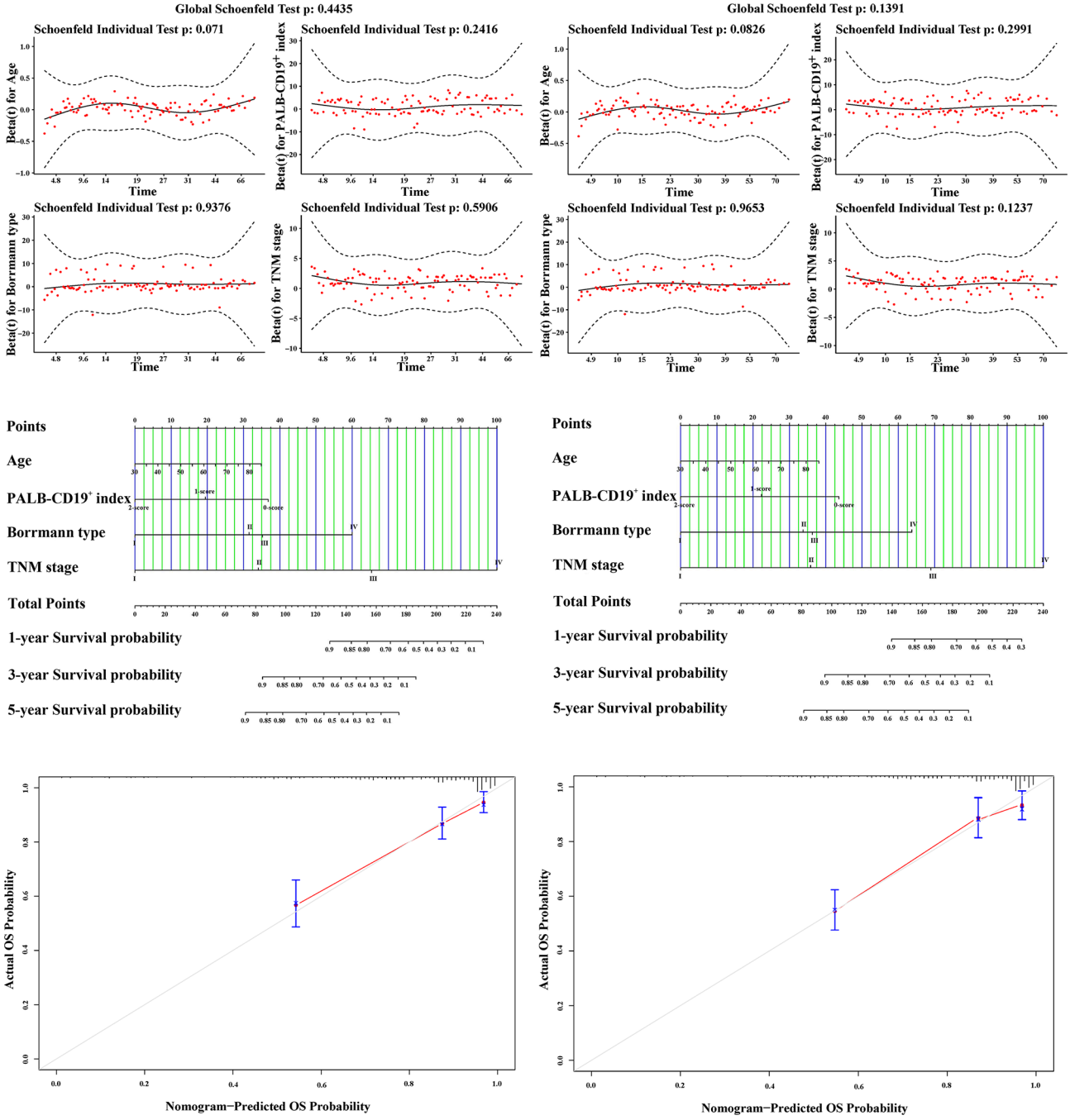

Fig. 8 Nomograms of PFS and OS. (**A**) Global Schoenfeld curve of PFS; (**B**) global Schoenfeld curve of OS; (**C**) nomogram of PFS; (**D**) nomogram of OS; (**E**) calibration curve of PFS in the validation set; (**F**) calibration curve of OS in the validation set

Additionally, integrating this index into multicentre studies with larger, diverse populations would validate its generalizability and increase its clinical utility. With the increasing accessibility of high-throughput omics technologies, combining the PALB-CD19$^+$ index with other promising biomarkers, such as ctDNA, tumour-infiltrating immune cells, or advanced imaging metrics, may provide a more comprehensive assessment of patient prognosis. Furthermore, exploring the role of this index in the context of emerging therapeutic approaches, such as immunotherapy and targeted therapies, could deepen our understanding of its clinical value and offer novel insights into the management of GC. These advancements not only refine prognostic tools but also contribute to precision oncology, ultimately improving outcomes for patients with GC.

This study has several limitations. First, as a single-centre study, it may be subject to selection bias. Future

research should validate these findings in larger, multicentre patient populations to increase the generalizability and reliability of the results. Such research would better encompass patients from different regions, ethnicities, and treatment strategies. Second, although this study includes both training and validation cohorts, the overall sample size remains relatively limited, and external validation is lacking. This may lead to insufficient statistical power, particularly in subgroup analyses, such as those based on TNM staging or molecular subtypes. Expanding the sample size and incorporating external validation could further enhance the stability and reliability of the conclusions. Additionally, due to the limitations of the study design, certain variables that might influence the results were not included in the analysis. For example, blood parameters such as C-reactive protein (CRP), coagulation markers, and circulating tumour DNA (ctDNA) may play critical roles in patient prognosis. Future studies should broaden the scope to include these potential key factors and refine the predictive model. Finally, this study relied solely on static data collected at the time of diagnosis and did not explore the dynamic changes in the PALB-CD19$^+$ index during the treatment process or its predictive value over time. Longitudinal follow-up studies are needed to assess the role of this index in monitoring treatment response and predicting disease progression. To address these limitations, future studies should incorporate larger, multicentre cohorts, include a broader range of clinical and molecular variables, and integrate dynamic, longitudinal data to comprehensively evaluate the predictive value of the PALB-CD19$^+$ index.

Conclusion

The PALB-CD19$^+$ index exhibits potential prognostic value in predicting surgical outcomes in GC patients. Its ability to integrate nutritional and immune parameters may provide clinicians with a novel and comprehensive tool for identifying high-risk patients and guiding personalized treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13715-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
Writing-original draft and Writing-review & editing: Hongming Pan and Hao Sun; Data curation and Investigation: Yanjiao Zuo; Methodology and Supervision: Ruihu Zhao; Resources, Funding acquisition, and Project administration: Yingwei Xue and Hongjiang Song.

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Data availability
The authors promise to provide the original data supporting this study without reservation.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Harbin Medical University Cancer Hospital. Due to the retrospective nature of this investigation, the Ethics Committee of Harbin Medical University Cancer Hospital decided to waive informed consent.

Patient consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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