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ORIGINAL RESEARCH

Prognostic Value of Inflammatory Indices in Papillary Gastric Carcinoma with Different Proportions of Papillary Components

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Purpose: To evaluate the prognostic significance of peripheral inflammatory indices in patients with advantage papillary gastric carcinoma (APGC) and non-advantage papillary gastric carcinoma (NAPGC).

Methods: The study retrospectively analyzed 270 patients who underwent radical surgery. Patients were stratified into APGC (n=133) and NAPGC (n=137) cohorts based on papillary component proportion (≥50% papillary histology for APGC, <50% for NAPGC). Receiver operating characteristic curve analysis was performed to assess the sensitivity of inflammatory indices for prognostic prediction. Overall survival was analyzed using Kaplan–Meier survival and Log rank tests. The relationship between inflammatory indicators and clinicopathological characteristics was examined. Independent prognostic risk factors were identified using the Cox regression model and integrated into a nomogram, with calibration plots and decision curves used to evaluate predictive performance.

Results: Compared to NAPGC patients, APGC patients demonstrated higher pT stage and carcinoembryonic antigen (CEA) levels, with poorer survival outcomes. Stage III APGC patients showed higher peripheral blood neutrophil ratios than NAPGC patients. For APGC, neutrophil-to-lymphocyte ratio (NLR) and CEA were identified as independent prognostic factors, while for NAPGC, systemic immune-inflammatory index (SII), age, and pN stage were determined to be independent prognostic factors.

Conclusion: Significant differences exist in clinicopathological characteristics, peripheral blood inflammatory indices, and prognosis between APGC and NAPGC patients. The nomogram incorporating inflammatory indices NLR and SII effectively predicts prognosis in both APGC and NAPGC patients.

Keywords: gastric cancer, papillary carcinoma, inflammatory index, prognosis, nomogram

Introduction

Gastric cancer (GC) represents a significant global health burden, ranking as the sixth most common malignancy worldwide with an annual mortality of approximately 768,793 cases.[1] The significant heterogeneity of GC contributes to poor outcomes in certain patients, particularly as reflected in the diverse spectrum of histological patterns.[2,3] According to the World Health Organization classification,[4] GCs are categorized into four primary histological patterns: tubular, papillary, mucinous, and poorly cohesive carcinomas. Within this histological spectrum, papillary gastric carcinoma (PGC) represents a unique and well-defined subtype, constituting 5%-10% of all GC cases.[4] Accurate diagnosis of PGC necessitates thorough pathological examination of biopsy specimens. Morphologically, PGC is distinguished by its well-differentiated architecture featuring mildly atypical cells characterized by eosinophilic cytoplasm and polarized nuclei. The hallmark of this carcinoma lies in its distinctive elongated, finger-like projections, which are lined by cylindrical or cuboidal cells and supported by a fibrovascular connective tissue core.[4–6]

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The clinical diagnosis of PGC rests on the predominance of papillary adenocarcinoma within the tumor mass. The disease manifests with distinctive clinical features, including predominant occurrence in elderly populations, preferential localization to the upper third of the stomach, high differentiation status, frequent microsatellite instability (MSI), and marked tendency toward early lymphatic and hepatic metastasis. These aggressive characteristics collectively contribute to diminished survival time.[7–9] Furthermore, when considering endoscopic submucosal dissection for early GC diagnosed as PGC, careful evaluation is essential due to the risk of lymph node metastasis and potential need for subsequent surgical intervention.[10] Despite its relatively low prevalence among histological subtypes, accurate identification of high-risk papillary carcinoma is essential for determining prognosis and optimizing treatment strategies, given its potential for aggressive behavior.

The proportion of papillary components within tumor tissue significantly influences patient outcomes. Wang et al[7] classified PGC into advantage papillary gastric carcinoma (APGC) and non-advantage papillary gastric carcinoma (NAPGC) based on the percentage of characteristic papillary structures within tumor tissue. Their research demonstrated marked differences in biological behavior and clinical outcomes between these two subtypes. While APGC typically shows better differentiation, it paradoxically exhibits shorter median survival compared to NAPGC. Therefore, there is a pressing need to identify reliable clinical biomarkers for both APGC and NAPGC patients at high risk, enabling more accurate prognostic stratification.

Immunotherapy has revolutionized the treatment paradigm for various advanced malignancies in recent years. PD-L1, as a core target of immune checkpoints, has seen its inhibitors become a standard treatment option for advanced GC—particularly in PD-L1-positive patients—by reversing the immunosuppressive state of the tumor microenvironment, significantly improving survival outcomes.[11] However, a significant proportion of patients fail to respond to immune checkpoint therapy due to individual variations in host factors and the tumor microenvironment.[12] The peripheral immune system, as a crucial component of tumor immunity, has shown promising potential in predicting immunotherapy response[13] and significantly influences tumor progression. Studies have demonstrated that inflammatory indices derived from peripheral blood, including the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-inflammation Index (SII), serve as effective predictors of immunotherapy response, distant metastasis, and clinical outcomes in GC.[14–17] While research examining the prognostic value of peripheral blood inflammatory indices in papillary carcinoma has largely concentrated on thyroid cancer,[18] the relationship between PGC and peripheral immune inflammatory responses remains unexplored. Therefore, investigation is warranted to determine whether peripheral blood inflammatory markers can effectively distinguish immune profiles and predict prognosis between APGC and NAPGC patients.

Methods

Patients

This retrospective study analyzed patients with pathologically confirmed PGC who underwent radical surgery at the Department of Gastrointestinal Surgery, Harbin Medical University Cancer Hospital between March 2011 and December 2016. Among 4,611 patients receiving radical surgery during this period, 270 were diagnosed with PGC, accounting for 5.9% of the cohort. GC diagnosis was established through pathological examination of postoperative tissue specimens. Preoperative evaluations included magnetic resonance imaging/gastric computed tomography (CT), abdominal ultrasonography, chest radiography, electrocardiography, comprehensive hematological tests, and tumor marker assessments. When clinically indicated, selected patients underwent positron emission tomography (PET)/CT. Follow-up continued until death or for a maximum duration of 5 years.

The study excluded patients with: (1) prior chemotherapy, (2) severe cardiac conditions, (3) hematologic malignancies, (4) active severe infections, (5) autoimmune disorders, and (6) platelet transfusion therapy within 3 months before surgery.

Adjuvant chemotherapy was administered according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[19] For patients with stage II or IIIGC, the primary treatment protocols consisted of either oxaliplatin plus capecitabine (XELOX) or oxaliplatin plus S-1 (SOX).

Clinicopathological Data

Patient clinicopathological data were maintained in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No.2013SR087424, http://www.sgihmu.com). This database encompasses comprehensive patient information including sex, age, tumor characteristics (size and location), histological type, pTNM stage (according to the eighth edition of the American Joint Commission on Cancer), postoperative chemotherapy regimens, and laboratory findings. Postoperative surveillance consisted of tumor marker assessments and radiological evaluations (ultrasound, CT, and gastroscopy) at 3–6 month intervals.

Diagnosis of Papillary Carcinoma

Pathological diagnosis was established through independent evaluation by two institutional pathologists using hematoxylin and eosin-stained paraffin sections. Tumors were classified as APGC when papillary components constituted the major architectural pattern of the tumor, accounting for 50% or more of the tumor component proportions. In contrast, tumors with a lower proportion of papillary features, comprising less than 50% of the tumor component proportions, were designated as NAPGC[7] (Figure 1).

Blood Sample

Fasting blood samples were collected from the cubital vein on the day following admission. Two milliliters of venous blood were obtained and processed in the hematology laboratory for serum separation and measurement of preoperative biomarkers including CEA and CA19-9, followed by inflammatory index calculations. The inflammatory indices were calculated using the following formulas: NLR = N/L, PLR = P/L, and SII = N×P/L, where N represents neutrophil count, L represents lymphocyte count, and P represents platelet count.

Statistical Analysis

Overall survival (OS) was defined as the interval from surgery to either death or last documented survival status, including patients who remained alive at final follow-up. The prognostic discriminatory power of inflammatory indices for APGC and NAPGC was evaluated using receiver operating characteristic (ROC) curves. Optimal cutoff values were determined using the Youden index, calculated as sensitivity - (1-specificity), with the maximum value selected as the optimal threshold. Time-dependent ROC (T-ROC) analysis was employed to assess and compare the prognostic accuracy of different inflammatory indices through area under the curve (AUC) values.

Associations between inflammatory indices and clinicopathological parameters were assessed using the chi-square test. Survival curves were generated using the Kaplan-Meier method and compared using the Log rank test. Independent prognostic factors were identified through univariate and multivariate Cox regression analyses for each group. These factors were subsequently incorporated into prognostic nomograms using R software with the "SvyNom" and "rms" packages. The nomograms' predictive accuracy was evaluated using calibration plots and decision curve analysis, implemented through the "survival" and "rms" packages and "stdca.R" files.

Statistical analyses were performed using GraphPad Prism 8, SPSS version 25.0 (SPSS Inc., Chicago, IL, USA), and R software version 4.1.2. Statistical significance was defined as $P < 0.05$.

Results

Clinical Characteristics

The study included a total of 270 cases of papillary carcinoma, consisting of 133 cases of APGC and 137 cases of NAPGC. The APGC group comprised 110 male and 23 female patients with an average age of 60.8 years. The distribution of pTNM stages in the APGC group was as follows: 24 patients had stage I, 42 had stage II, and 67 had stage III. The NAPGC group consisted of 108 male and 29 female patients with an average age of 60.3 years. The distribution of pTNM stages in the NAPGC group was similar, with 28 patients had stage I, 47 had stage II, and 62 had stage III.

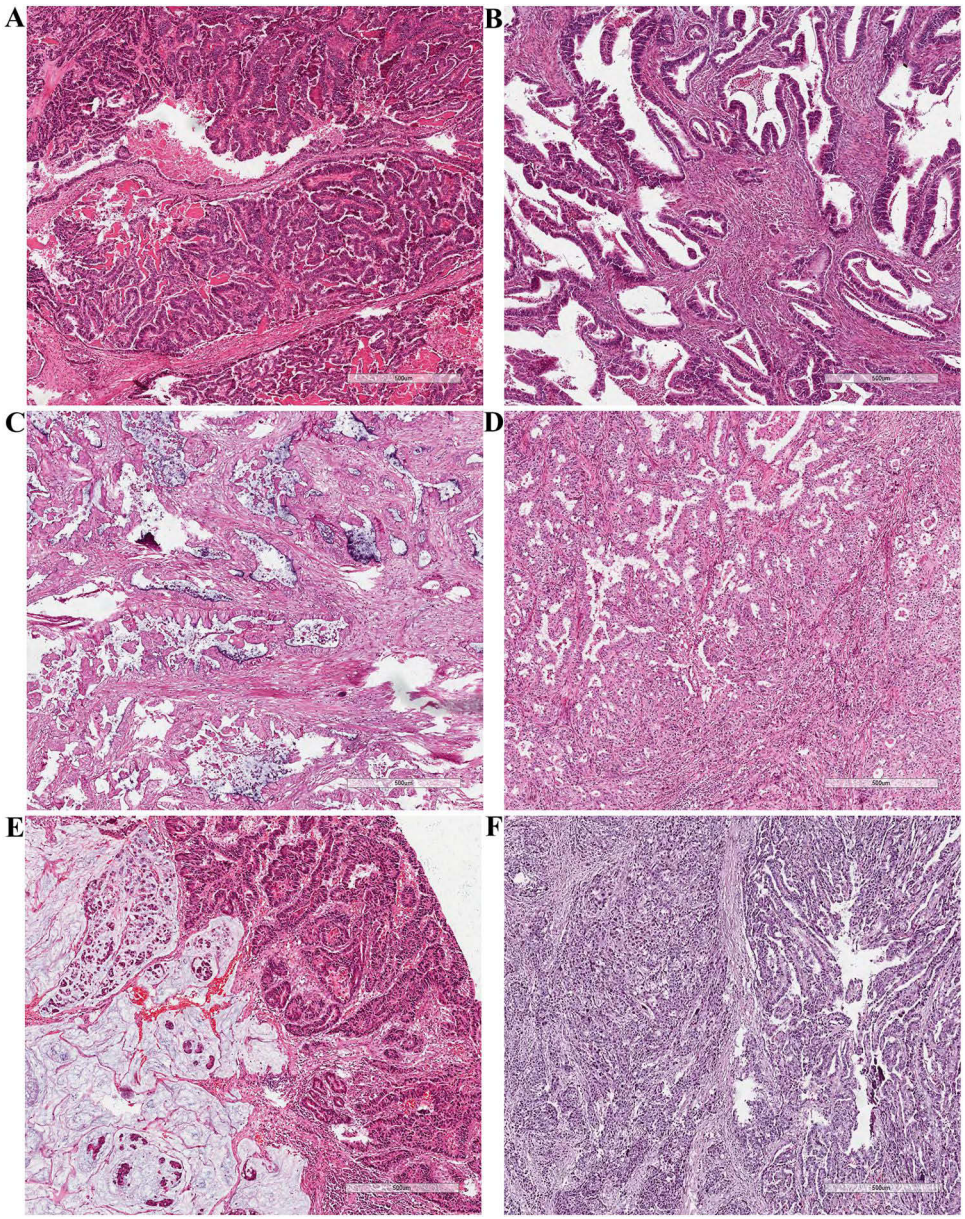

Figure 1 Resentative microscopic images of hematoxylin and eosin staining in pathological samples. (**A**) APGC. (**B–F**) NAPGC: (**B**) Well-differentiated tubular adenocarcinoma as the predominant component; (**C**) Moderately differentiated tubular adenocarcinoma as the predominant component; (**D**) Poorly differentiated tubular adenocarcinoma as the predominant component; (**E**) Mucinous adenocarcinoma as the predominant component; (**F**) Poorly cohesive carcinoma as the predominant component.

Abbreviations: APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma.

Notably, APGC exhibited significantly higher proportions of pT4 stage tumors and elevated carcinoembryonic antigen (CEA) levels (>5ng/mL) compared to NAPGC. In the APGC group, 41.4% of patients had pT4 stage tumors, and 37.5% had elevated CEA levels. In contrast, only 20.4% of patients in the NAPGC group had pT4 stage tumors, and 23.1% had elevated CEA levels (Table 1). These findings suggest that APGC may be associated with more advanced tumor stages and higher tumor marker levels compared to NAPGC.

Survival Differences Between APGC and NAPGC

Survival curve analysis revealed notable differences in the 5-year survival rates between patients with APGC and those with NAPGC. The 5-year survival rate for patients with APGC was 58.5%, while patients with NAPGC had

Table 1 Basic Characteristics of Patients

Characteristics	APGC (n=133)	NAPGC (n=137)	P value
Sex, n (%)			0.420
Male	110 (82.7%)	108 (78.8%)	
Female	23 (17.3%)	29 (21.2%)	
Age, mean ± sd	60.774 ± 8.2624	60.307 ± 8.625	0.650
Local, n (%)			0.096
Upper third	20 (15%)	30 (21.9%)	
Middle third	23 (17.3%)	19 (13.9%)	
Lower third	86 (64.7%)	88 (64.2%)	
Total stomach	4 (3%)	0 (0%)	
Tumor size, median (IQR)	50 (40, 70)	50 (40, 70)	0.375
pT stage, n (%)			**< 0.001**
pT1	12 (9%)	17 (12.4%)	
pT2	32 (24.1%)	22 (16.1%)	
pT3	34 (25.6%)	70 (51.1%)	
pT4	55 (41.4%)	28 (20.4%)	
pN stage, n (%)			0.363
pN0	45 (33.8%)	46 (33.6%)	
pN1	20 (15%)	30 (21.9%)	
pN2	29 (21.8%)	31 (22.6%)	
pN3	39 (29.3%)	30 (21.9%)	
pTNM, n (%)			0.697
I	24 (18%)	28 (20.4%)	
II	42 (31.6%)	47 (34.3%)	
III	67 (50.4%)	62 (45.3%)	
HER-2, n (%)			0.150
0	42 (31.6%)	41 (31.3%)	
1+	23 (17.3%)	37 (28.2%)	
2+	31 (23.3%)	22 (16.8%)	
3+	37 (27.8%)	31 (23.7%)	
Postoperative chemotherapy, n (%)			0.535
Without	72 (54.1%)	69 (50.4%)	
With	61 (45.9%)	68 (49.6%)	
CEA, n (%)			**0.011**

(*Continued*)

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Table 1 (Continued).

Characteristics	APGC (n=133)	NAPGC (n=137)	P value
≤5ng/mL	80 (62.5%)	103 (76.9%)	
>5ng/mL	48 (37.5%)	31 (23.1%)	
CA19-9, n (%)			0.185
≤6U/mL	41 (31.8%)	33 (24.4%)	
>6U/mL	88 (68.2%)	102 (75.6%)	

Note: Statistical significance ($p<0.05$) is highlighted in bold.
Abbreviations: APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9.

a considerably higher rate of 78.5% (Figure 2A). Further subgroup analysis based on different pTNM stages provided additional insights. For patients with stage I+II disease, the 5-year survival rates were 74.5% and 87.8% for APGC and NAPGC, respectively. In the case of stage III disease, patients with APGC had a 5-year survival rate of 42.9%, whereas those with NAPGC had a rate of 59.8% (Figure 2B and C). Moreover, poorer survival outcomes were observed in specific subgroups of APGC patients. Those with pT3-T4 stage tumors and those with pN0-N1 lymph node involvement experienced significantly lower survival rates compared to their NAPGC counterparts (Figure 2D–G).

Inflammatory Indices in APGC and NAPGC

Analysis of peripheral circulating immune cells, including neutrophil count, lymphocyte count, and platelet count, was performed according to pTNM stage. A higher neutrophil percentage was observed in patients with APGC compared to those with NAPGC, particularly in patients with stage III tumors (Figure 3A). No significant differences were found in lymphocyte percentage or platelet counts between the APGC and NAPGC groups (Figure 3B and C).

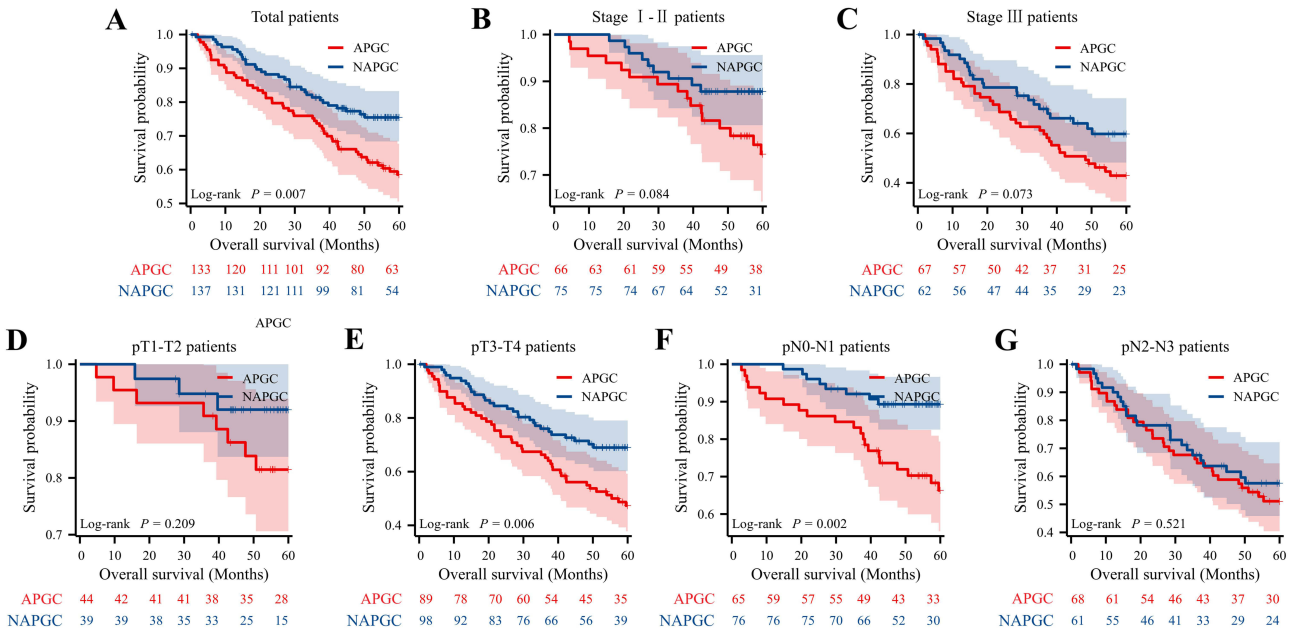

Figure 2 Kaplan-Meier survival curves for patients with APGC and NAPGC. (**A**) All patients. (**B**) Patients with stage I+II tumors. (**C**) Patients with stage III tumors. (**D**) Patients with pT1-T2 tumors. (**E**) Patients with pT3-T4 tumors. (**F**) Patients with pN0-N1 tumors. (**G**) Patients with pN2-N3 tumors.
Abbreviations: APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma.

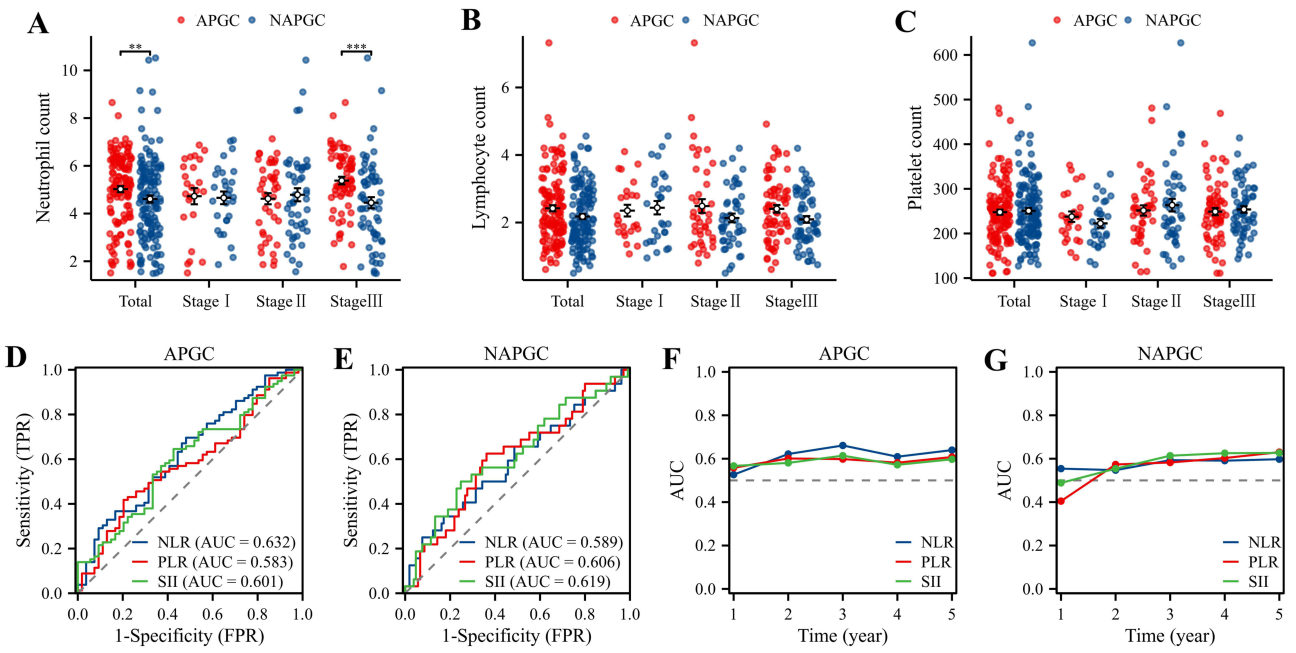

Figure 3 (**A-C**) Difference in neutrophil, lymphocyte, and platelet counts between patients with APGC and NAPGC based on the pTNM stage. (**D** and **E**) ROC curves for NLR, PLR, and SII in patients with APGC and NAPGC. (**F** and **G**) T-ROC curves for NLR, PLR and SII in patients with APGC and NAPGC. ***P*<0.01, ****P*<0.001.
Abbreviations: APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma; ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; T-ROC, time-dependent receiver operating characteristic.

The AUC for the predictive markers in APGC patients was 0.632 (0.536–0.728) for NLR, 0.583 (0.485–0.681) for PLR, and 0.601 (0.504–0.699) for SII (Figure 3D). NLR demonstrated the highest accuracy in predicting prognosis for APGC patients. The Youden index cutoff value for the NLR ROC curve in APGC patients was 2.39. For NAPGC patients, the AUC (95% CI) was 0.589 (0.471–0.707) for NLR, 0.606 (0.492–0.720) for PLR, and 0.619 (0.504–0.734) for SII (Figure 3E). SII exhibited the best accuracy in predicting prognosis for NAPGC patients. The Youden index cutoff value for the SII ROC curve in NAPGC patients was 666.71.

A comparative analysis of the prognostic values of NLR, PLR, and SII in APGC and NAPGC using T-ROC was conducted. In APGC patients, the AUC of NLR was higher than that of PLR and SII. The AUC values of NLR for 1-year, 3-year, and 5-year OS in APGC patients were 0.527, 0.660, and 0.640, respectively (Figure 3F). In NAPGC patients, the AUC of SII was higher than that of NLR and PLR. The AUC values of SII for 1-year, 3-year, and 5-year OS in NAPGC patients were 0.489, 0.614, and 0.627, respectively (Figure 3G).

In conclusion, NLR and SII were identified as the most suitable inflammatory indices for predicting prognosis in APGC and NAPGC patients, respectively.

Relationship Between the Inflammatory Indices and Clinicopathological Characteristics of Patients

The correlations between inflammatory indices and clinicopathological features were investigated. In APGC patients, no significant relationship was found between NLR and tumor size or age (Figure 4A and B). Chi-square analysis also indicated no correlation between NLR and the clinicopathological characteristics of APGC patients (Figure 4C).

In NAPGC patients, SII showed no significant correlation with age but demonstrated a positive correlation trend with tumor size (Figure 4D and E). This finding suggests that larger tumor size may have a significant effect on the surrounding immune microenvironment. However, chi-square analysis revealed no correlation between SII and the clinicopathological characteristics of NAPGC patients (Figure 4F).

Although the results were not statistically significant, higher NLR and SII appeared to be associated with GC progression. Further verification of these findings through an expansion of the sample size is warranted.

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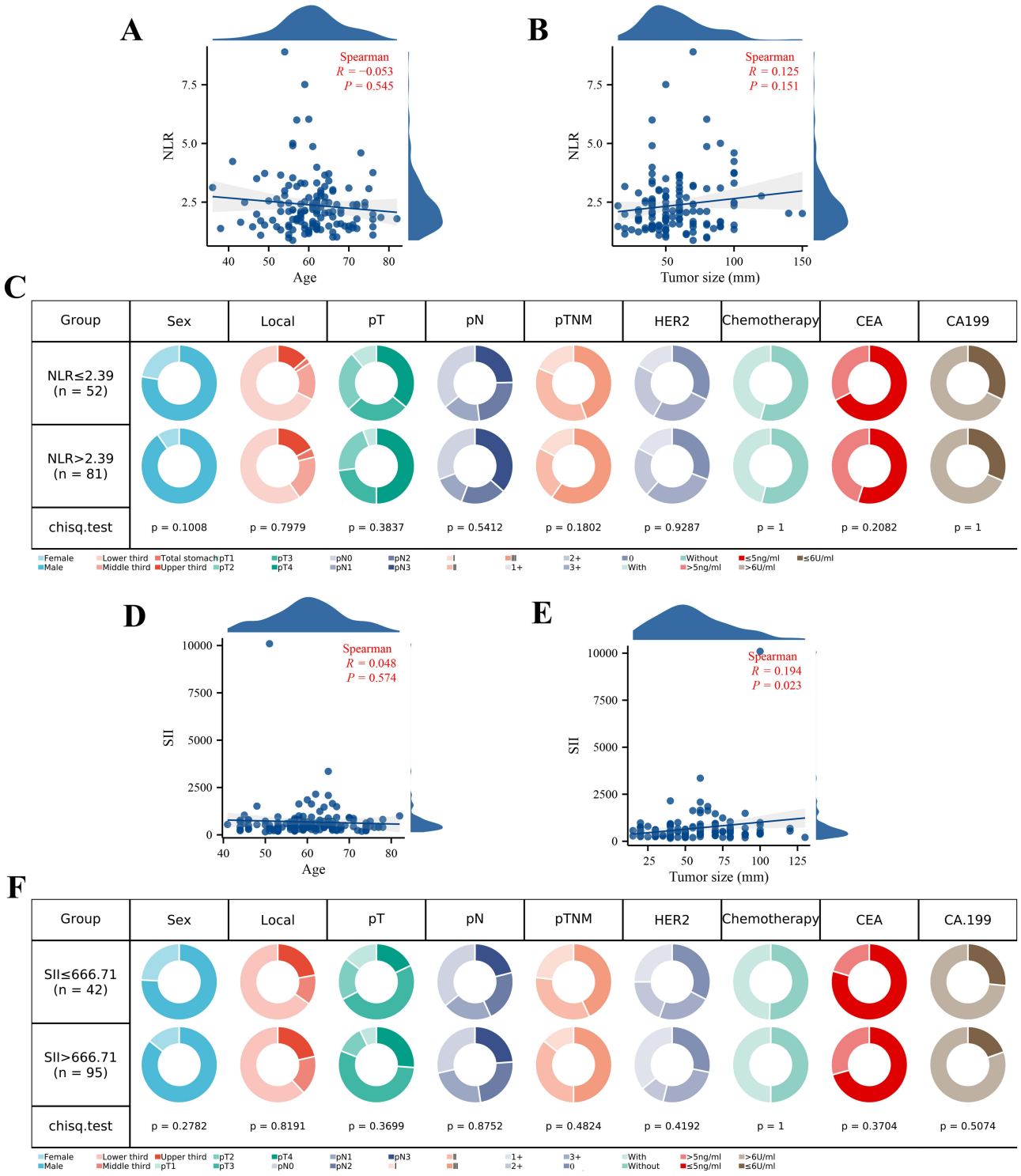

Figure 4 (**A** and **B**) Association of NLR with age and tumor size in patients with APGC. (**C**) Chi-square analysis of the association between NLR and clinicopathological features in APGC patients. (**D** and **E**) Association of SII and age, tumor size in patients with NAPGC. (**F**) Chi-square analysis of the association between SII and clinicopathological features in NAPGC patients.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index. APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma.

Inflammatory Indices and Patient Survival

In patients with APGC, the 5-year survival rates differed based on NLR values. Patients with NLR ≤ 2.39 had a 5-year survival rate of 67.0%, while those with NLR > 2.39 had a lower rate of 45.4% (Figure 5A). When stratified by pTNM stage, the 5-year survival rates for patients with stage I+II tumors were 78.5% for NLR ≤ 2.39 and 66.3% for NLR > 2.39. In patients with stage III tumors, the 5-year survival rates were 52.8% for NLR ≤ 2.39 and 32.3% for NLR > 2.39 (Figure 5B and C).

Similarly, in patients with NAPGC, the 5-year survival rates varied based on SII values. Patients with SII ≤ 666.71 had a higher 5-year survival rate of 82.2%, compared to 61.2% for those with SII > 666.71 (Figure 5D). When analyzed by pTNM stage, the 5-year survival rates for patients with stage I+II tumors were 90.6% for SII ≤ 666.71 and 81.0% for SII > 666.71. In patients with stage III tumors, the 5-year survival rates were 70.6% for SII ≤ 666.71 and 40.7% for SII > 666.71 (Figure 5E and F).

Univariate and Multivariate Analyses in APGC and NAPGC

Cox regression analysis was performed to identify independent prognostic factors for APGC and NAPGC. Multivariate analysis revealed that CEA levels and NLR were independent prognostic variables for patients with APGC (Table 2). In contrast, age, pN stage, and SII were found to be independent predictive variables for patients with NAPGC, as determined by multivariate analysis (Table 3).

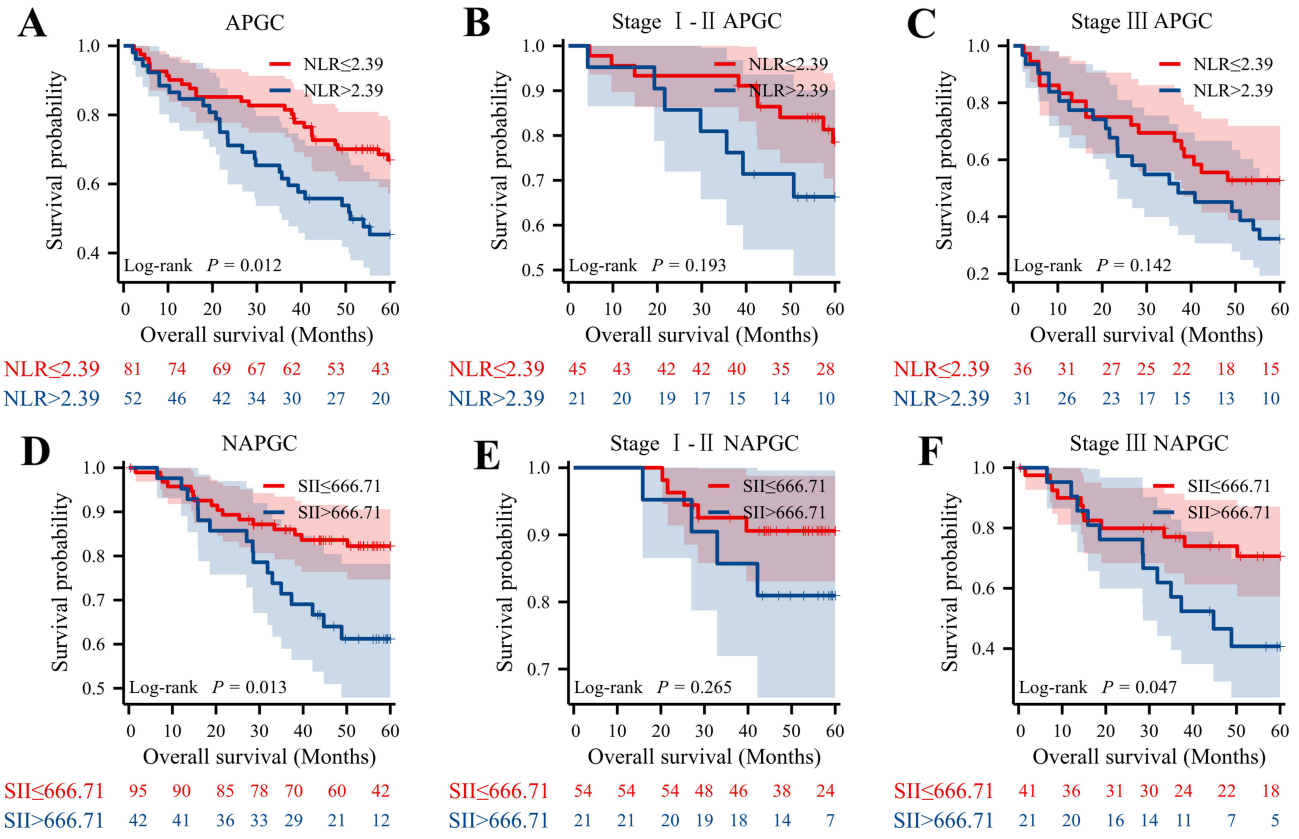

Figure 5 (**A-C**) Kaplan-Meier survival curves for APGC patients based on NLR in all stages, stage I-II, and stage III. (**D-F**) Kaplan-Meier survival curves for NAPGC patients based on SII in all stages, stage I-II, and stage III.

Abbreviations: APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index.

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Table 2 Prognostic Factors of Patients with APGC by Univariate and Multivariate Analyses Based on Cox Regression Analysis

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex		0.695		
Male	1			
Female	0.860 (0.406–1.823)			
Age (years)	1.028 (0.995–1.063)	0.095		
Tumor location		0.216		
Upper third	1			
Middle third	1.420 (0.607–3.324)	0.419		
Lower third	0.717 (0.340–1.512)	0.382		
Total stomach	1.163 (0.251–5.385)	0.847		
Tumor size (mm)	1.017 (0.007–1.027)	**0.001**	1.009 (0.998–1.021)	0.119
pT stage		**0.002**		0.128
pT1	1		1	
pT2	0.628 (0.150–2.630)	0.525	0.551 (0.131–2.320)	0.357
pT3	1.909 (0.548–6.644)	0.310	1.227 (0.340–4.427)	0.619
pT4	3.206 (0.981–10.481)	0.054	1.755 (0.506–6.084)	0.267
pN stage		0.114		
pN0	1			
pN1	2.177 (0.916–5.173)	0.078		
pN2	2.044 (0.932–4.481)	0.074		
pN3	2.330 (1.138–4.771)	0.021		
HER-2		0.547		
0	1			
1+	0.622 (0.245–1.578)	0.318		
2+	1.200 (0.591–2.435)	0.614		
3+	1.168 (0.596–2.289)	0.650		
Postoperative chemotherapy				
Without	1			
With	0.837 (0.488–1.436)	0.518		
CEA				
≤5ng/mL	1			
>5ng/mL	2.264 (1.306–3.928)	**0.004**	1.773 (1.009–3.115)	**0.047**

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
CA-199				
≤6U/mL	1			
>6U/mL	1.113 (0621–1.992)	0.720		
NLR	1.380 (1.157–1.645)	**< 0.001**	1.261 (1.038–1.532)	**0.019**

Note: Statistical significance ($p<0.05$) is highlighted in bold.
Abbreviations: APGC, advantage papillary gastric carcinoma; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; NLR, neutrophil-to-lymphocyte ratio.

Table 3 Prognostic Factors of Patients with NAPGC by Univariate and Multivariate Analyses Based on Cox Regression Analysis

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex		0.911		
Male	1			
Female	1.049 (0.454–2.426)			
Age(years)	1.048 (1.007–1.092)	**0.022**	1.053 (1.009–1.100)	**0.019**
Tumor location		0.547		
Upper third	1			
Middle third	0.523 (0.142–1.933)	0.331		
Lower third	0.705 (0.321–1.550)	0.385		
Tumor size (mm)	1.020 (1.008–1.033)	0.001	1.005 (0.989–1.021)	0.529
pT stage		0.057		
pT1	1			
pT2	1.559 (0.141–17.198)	0.717		
pT3	4.985 (0.665–37.351)	0.118		
pT4	7.878 (1.017–61.032)	0.048		
pN stage		**0.002**		**0.006**
pN0	1		1	
pN1	4.916 (0.992–24.358)	0.051	3.667 (0.707–19.028)	0.122
pN2	10.257 (2.272–46.313)	0.002	10.045 (2.150–46.929)	0.003
pN3	13.828 (3.117–61.340)	0.001	11.394 (2.425–53.525)	0.002
HER-2		0.617		
0	1			
1+	1.622 (0.668–4.134)	0.275		

(*Continued*)

Table 3 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
2+	1.186 (0.388–3.624)	0.765		
3+	0.935 (0.324–2.694)	0.900		
Postoperative chemotherapy				
Without	1			
With	0.777 (0.387–1.563)	0.480		
CEA				
≤5ng/mL	1			
>5ng/mL	1.928 (0.923–4.024)	0.081		
CA-199				
≤6U/mL	1			
>6U/mL	1.052 (0.455–2.432)	0.906		
SII	1.000 (1.000–1.000)	**0.035**	1.000 (1.000–1.001)	**0.021**

Note: Statistical significance ($p<0.05$) is highlighted in bold.
Abbreviations: NAPGC, non-advantage papillary gastric carcinoma; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; SII, systemic immune-inflammatory index.

Nomogram for Predicting APGC and NAPGC

We found that CEA levels and NLR were independent prognostic factors for patients with APGC, while age, pN stage, and SII were independent predictive variables for patients with NAPGC. These factors were integrated to construct nomograms for each subtype (Figure 6A and B).

For patients with APGC, the AUC values for predicting 3-year and 5-year OS were 0.716 and 0.723, respectively. The sensitivity values were 65.6% for 3-year OS and 75.8% for 5-year OS, while the specificity values were 69.8% for 3-year OS and 63.4% for 5-year OS (Figure 6C).

In patients with NAPGC, the AUC values for predicting 3-year and 5-year OS were 0.796 and 0.784, respectively. The sensitivity values were 72.1% for 3-year OS and 65.5% for 5-year OS, while the specificity values were 85.7% for 3-year OS and 86.4% for 5-year OS (Figure 6D).

To validate the predictive capabilities of the nomograms, decision curve analysis and calibration plots were generated. The prognostic calibration curve plots indicated that the nomograms for APGC and NAPGC effectively predicted 1-year, 3-year, and 5-year OS (Figure 6E and F). Furthermore, the decision curve analysis demonstrated that the nomograms could provide more prediction benefits compared to the pTNM stage alone (Figure 6G–J).

Discussion

PGC, a rare form of GC, is associated with a poor prognosis and exhibits distinct disparities compared to other pathological types in terms of age at disease onset, tumor location, and tumor invasiveness. Patients over 65 years of age are more prone to develop PGC, which predominantly affects the upper portion of the stomach and is frequently linked to a high risk of lymph node and liver metastases.[7,8,10] Due to differences in the proportion and growth pattern of papillary components, some patients with PGC have a potentially high risk of poor outcomes.

Micropapillary carcinoma is a distinct GC subtype characterized by clusters of tumor cells surrounded by clear spaces, lacking fibrovascular cores.[4] Roh et al analyzed 11 cases of micropapillary carcinoma and found that this growth pattern did not significantly affect patient prognosis.[20] In contrast, Zhang et al analyzed 32 cases of micropapillary

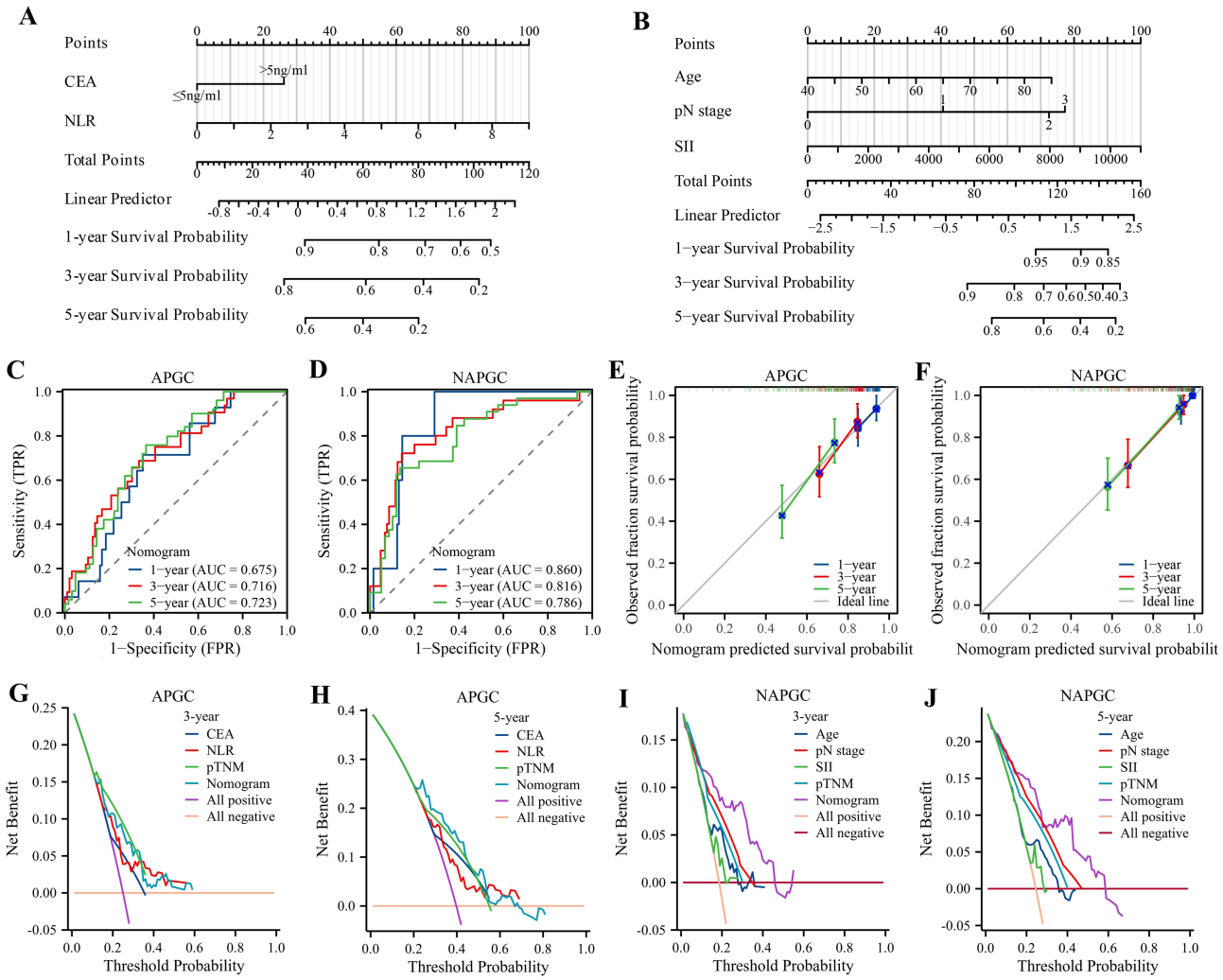

Figure 6 (**A** and **B**) Nomogram model predicting the 1-, 3- and 5-year survival rates of patients with APGC and NAPGC. (**C** and **D**) ROC curves of the nomogram predicting the 1-, 3-year and 5-year survival rates in patients with APGC and NAPGC. (**E** and **F**)The prognostic calibration curve plots in patients with APGC and NAPGC based on nomogram. (**G-J**) The decision curve analysis of 3- and 5-year survival in patients with APGC and NAPGC.
Abbreviations: ROC, receiver operating characteristic; APGC, advantage papillary gastric carcinoma; NAPGC, non-advantage papillary gastric carcinoma.

carcinoma and reported a significantly lower OS rate in patients with papillary components located in cystic spaces compared to those with papillary components infiltrating fibrous septa.[21]

In our study, patients were stratified into APGC and NAPGC groups based on the proportion of papillary adenocarcinoma in the pathological types. After expanding the sample size, we found that the 5-year survival rate of APGC was significantly lower than that of NAPGC (58.5% vs 78.5%). This finding confirms that the proportion of papillary adenocarcinoma significantly influences the prognosis of GC. Furthermore, chi-square analysis revealed that APGC exhibited a more aggressive phenotype compared to NAPGC, as evidenced by higher proportions of pT4 stage tumors and elevated CEA levels (>5 ng/mL). The deeper invasion of APGC might be attributed to its exophytic growth pattern, characterized by slow proliferation and abundant stromal components within the tumor. Despite this, the cancer cells possess the ability to infiltrate deeper layers by migrating along ducts, blood vessels, and other pathways. According to a study by Lee et al,[10] early PGC exhibits a higher rate of lymph node metastasis, which is closely associated with the presence of submucosal invasion. These findings are consistent with the results of our research, highlighting the increased invasive potential associated with APGC. Moreover, APGC is associated with higher levels of CEA, which might be related to its more advanced T stage. Numerous studies have demonstrated that CEA levels increase with the progression of the T stage in GC.[22,23] This suggests that the elevated CEA levels observed in APGC could be

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a consequence of its propensity for deeper invasion and higher T stage classification compared to NAPGC. Based on these findings, we propose that differentiating APGC from NAPGC by assessing the proportion of papillary structures in clinical practice holds crucial implications for predicting the prognosis of GC patients. Incorporating this histological distinction into pathological diagnostic protocols may provide valuable insights into disease outcomes and guide personalized treatment strategies. Further research is warranted to validate these results and establish standardized criteria for the clinical application of this prognostic indicator.

Peripheral blood inflammatory markers are crucial indicators reflecting the body's inflammatory status and hold significant value in the diagnosis, differential diagnosis, and prognostic evaluation of various diseases, including infectious diseases, autoimmune disorders, and malignant tumors.[24,25] Elevated levels of these markers can be used to assess disease severity, treatment efficacy, and predict prognosis. As readily available systemic inflammatory markers, peripheral blood indicators (including NLR, PLR, and SII) demonstrate significant prognostic value in GC, with elevated NLR suggesting poor prognosis, particularly pronounced in advanced GC patients.[26,27] However, these indicators show relatively weaker prognostic value in other solid tumors such as colorectal cancer and lung cancer, possibly due to differences in inflammatory microenvironment and immune response characteristics among different tumors.[28] The prognostic threshold values of NLR vary across different cancer types, with GC commonly reported at 2.5–3, while other cancers show greater variation.[28] Given the significant prognostic differences between APGC and NAPGC, we evaluated the clinical diagnostic value of peripheral blood inflammatory markers separately in these two patient groups. In this investigation, differences existed in peripheral immune cell counts between APGC and NAPGC. The ROC analysis highlighted that NLR exhibited the largest AUC in APGC, while SII showed the highest AUC in patients with NAPGC. Both factors were independent risk indicators associated with patient prognosis. These findings also indicate neutrophils, lymphocytes, and platelets may play different functions in APGC and NAPGC. In NAPGC, SII displayed a negative correlation with age. Elderly patients with malignant tumors often exhibit weakened immune response to diseases,[29] which is usually attributed to systemic immune aging, such as reduced T-cell receptor diversity and a decline in cytotoxic cell capacity, possibly leading to the poor immunity of elderly patients.[30,31] However, this correlation was not evident in APGC, suggesting the unique effect of age on peripheral immunity in NAPGC. These immune differences further support our previous hypothesis that APGC and NAPGC may belong to two different subtypes.

A more precise and personalized assessment of a patient's prognosis can be achieved by integrating peripheral blood inflammatory indices with clinicopathological features such as peripheral blood prognostic markers and age.[32,33] This integrated staging approach significantly enhances the postoperative prognostic judgment of patients with GC.[34] We have found that there are not only differences in biological behavior between APGC and NAPGC, but also differences in peripheral blood immunity. These differences led to the development of a nomogram tailored to evaluate patient prognosis based on these distinct pathological subtypes. The results revealed pT stage and NLR as independent risk factors linked to APGC prognosis, while age, pN stage, and SII emerged as independent risk factors associated with NAPGC prognosis. By combining these variables, a nomogram could be created, and ROC analysis showed that the AUC values for APGC patients' 3-year and 5-year OS were 0.716 and 0.723, while those for NAPGC patients were 0.796 and 0.784. Both calibration plots and decision curves analysis confirmed the nomogram's robust predictive performance. The C-index was 0.682(0.647–0.717) in PGC and 0.772(0.733–0.811) in NAPGC. The nomogram riskscore is more beneficial than pTNM stage and deserves further promotion in clinical practice.

Although established biomarkers such as MSI statusand PD-L1 expressionare widely adopted in GC immunotherapy, their detection requires specialized molecular profiling (eg, high-throughput sequencing or immunohistochemistry), which remains inaccessible in most healthcare settings globally—particularly for rare subtypes like PGC due to limited tissue availability. In resource-constrained PGC management, NLR and SII serve as real-time, non-invasive, and cost-effective proxies for systemic inflammation.[35] The dynamic changes of these indicators during immunotherapy, which cannot be achieved through static tissue biomarkers such as MSI/PD-L1, can achieve real-time treatment enhancement and early recurrence prediction.[36–38] Furthermore, threshold-based stratification using inflammatory indices may optimize patient selection for immunotherapy and refine therapeutic strategies.[16] In conclusion, inflammatory indices like

NLR and SII warrant further investigation in GC immunotherapy, especially for rare subtypes such as PGC, given their potential to bridge biomarker accessibility gaps and enhance dynamic risk assessment.

Limitations

Although this study presents unique findings, it has some limitations. This study had a retrospective study design and involved only a single center. In the future, multicenter studies will be necessary to further validate our research findings. Second, the long study duration and the absence of certain pathological characteristics such as nerve infiltration and venous invasion are factors possibly affecting the prognosis of APGC and NAPGC; therefore, it may not be possible to determine whether these pathological characteristics can be integrated with the inflammatory indices to construct the nomogram. Finally, incomplete MSI and PD-L1 data limit our ability to associate them with PGC. Prospective studies of standardized biomarker testing are needed in the future to validate the relationships between these emerging therapeutic targets and PGC biology.

Conclusion

In conclusion, this study reveals significant differences in clinicopathological characteristics, peripheral blood inflammatory indices, and prognosis between patients with APGC and NAPGC. The developed nomograms, which incorporate the inflammatory indices NLR for APGC and SII for NAPGC, along with other independent prognostic factors, effectively predict the prognosis of patients in both subgroups, providing a valuable tool for personalized risk assessment and guiding clinical decision-making.

Data Sharing Statement

All relevant patient data were stored in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright no. 2013SR087424).

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical standards of the Institutional Review Board of Harbin Medical University Cancer Hospital (Approval No. 2019-22-IIT), the Ethical Review Measures for Biomedical Research Involving Human Subjects of China, and the principles of the Declaration of Helsinki (1964) and its later amendments. Written informed consent was obtained from all participants or their legal guardians prior to enrollment. For patients with advanced cancer who exhibited compromised decision-making capacity or significant emotional vulnerability, informed consent was obtained from legally authorized representatives in accordance with Paragraph 28 of the Declaration of Helsinki and relevant Chinese regulations, as full disclosure was deemed potentially harmful to these participants. The study protocol, including the consent procedures, was reviewed and approved by the Ethics Committee of Harbin Medical University Cancer Hospital. All methods were performed in compliance with institutional and national ethical guidelines for biomedical research involving human subjects.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: classification, histology and application of molecular pathology. *J Gastrointest Oncol*. 2012;3(3):251–261. doi:10.3978/j.issn.2078-6891.2012.021
3. Kuwata T. Molecular classification and intratumoral heterogeneity of gastric adenocarcinoma. *Pathol Int*. 2024;74(6):301–316. doi:10.1111/pin.13427
4. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182–188. doi:10.1111/his.13975
5. Uesugi N, Sugai T, Sugimoto R, et al. Clinicopathological and molecular stability and methylation analyses of gastric papillary adenocarcinoma. *Pathology*. 2017;49(6):596–603. doi:10.1016/j.pathol.2017.07.004
6. Uefuji K, Ichikura T, Tamakuma S. Clinical and prognostic characteristics of papillary clear carcinoma of stomach. *Surg Today*. 1996;26(3):158–163. doi:10.1007/BF00311499
7. Wang X, Deng J, Liang H. Well differentiated carcinoma with a poor prognosis: a retrospective analysis of papillary gastric adenocarcinoma. *Surg Today*. 2021;51(8):1387–1396. doi:10.1007/s00595-021-02289-3
8. Yasuda K, Adachi Y, Shiraishi N, Maeo S, Kitano S. Papillary adenocarcinoma of the stomach. *Gastric Cancer*. 2000;3(1):33–38. doi:10.1007/PL00011687
9. Arai T, Komatsu A, Kanazawa N, Nonaka K, Ishiwata T. Clinicopathological and molecular characteristics of gastric papillary adenocarcinoma. *Pathol Int*. 2023;73(8):358–366. doi:10.1111/pin.13345
10. Lee HJ, Kim GH, Park DY, et al. Is endoscopic submucosal dissection safe for papillary adenocarcinoma of the stomach. *World J Gastroenterol*. 2015;21(13):3944–3952. doi:10.3748/wjg.v21.i13.3944
11. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin*. 2021;71(3):264–279. doi:10.3322/caac.21657
12. Kubli SP, Berger T, Araujo DV, Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. *Nat Rev Drug Discov*. 2021;20(12):899–919. doi:10.1038/s41573-021-00155-y
13. Nixon AB, Schalper KA, Jacobs I, Potluri S, Wang IM, Fleener C. Peripheral immune-based biomarkers in cancer immunotherapy: can we realize their predictive potential. *J Immunother Cancer*. 2019;7(1):325. doi:10.1186/s40425-019-0799-2
14. Dong Q, Zhao F, Li Y, et al. The correlation between systemic inflammatory markers and efficiency for advanced gastric cancer patients treated with ICIs combined with chemotherapy. *Immunology*. 2024;172(1):77–90. doi:10.1111/imm.13759
15. Liu J, Sun R, Cai K, Xu Y, Yuan W. A nomogram combining neutrophil to lymphocyte ratio (NLR) and prognostic nutritional index (PNI) to predict distant metastasis in gastric cancer. *Sci Rep*. 2024;14(1):15391. doi:10.1038/s41598-024-65307-7
16. Fu M, Zhang X, Shen F, Ma J, Li Z. Prognostic value of peripheral blood neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, pan-immune-inflammation value and systemic immune-inflammation index for the efficacy of immunotherapy in patients with advanced gastric cancer. *Immunotherapy*. 2024;16:551–563. doi:10.2217/imt-2024-0031
17. Jing Y, Ren M, Li X, et al. The effect of Systemic Immune-Inflammatory Index (SII) and Prognostic Nutritional Index (PNI) in early gastric cancer. *J Inflamm Res*. 2024;17:10273–10287. doi:10.2147/JIR.S499094
18. Cai Y, Zhao L, Zhang Y, Luo D. Association between blood inflammatory indicators and prognosis of papillary thyroid carcinoma: a narrative review. *Gland Surg*. 2024;13(6):1088–1096. doi:10.21037/gs-24-72
19. Ajani JA, Bentrem DJ, Besh S, et al. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw*. 2013;11(5):531–546. doi:10.6004/jnccn.2013.0070
20. Roh JH, Srivastava A, Lauwers GY, et al. Micropapillary carcinoma of stomach: a clinicopathologic and immunohistochemical study of 11 cases. *Am J Surg Pathol*. 2010;34(8):1139–1146. doi:10.1097/PAS.0b013e3181e7043b
21. Zhang Q, Ming J, Zhang S, Li B, Yin L, Qiu X. Micropapillary component in gastric adenocarcinoma: an aggressive variant associated with poor prognosis. *Gastric Cancer*. 2015;18(1):93–99. doi:10.1007/s10120-014-0350-6
22. Gwak HK, Lee JH, Park SG. Preliminary evaluation of clinical utility of CYFRA 21-1, CA 72-4, NSE, CA19-9 and CEA in stomach cancer. *Asian Pac J Cancer Prev*. 2014;15(12):4933–4938. doi:10.7314/APJCP.2014.15.12.4933
23. Cidón EU, Bustamante R. Gastric cancer: tumor markers as predictive factors for preoperative staging. *J Gastrointest Cancer*. 2011;42(3):127–130. doi:10.1007/s12029-010-9161-0
24. Prasetya IB, Jo L, Sungono V, El-Khobar KE, Wijaya RS, Wijaya RS. Prognostic value of inflammatory markers in patients with COVID-19 in Indonesia. *Clin Epidemiol Glob Health*. 2021;11:100803. doi:10.1016/j.cegh.2021.100803
25. Markanday A. Acute phase reactants in infections: evidence-based review and a guide for clinicians. *Open Forum Infect Dis*. 2015;2(3):ofv098. doi:10.1093/ofid/ofv098
26. Han QY, Zhang X, Jg Z, et al. Pre-operative neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with gastric cancer. *Int Immunopharmacol*. 2022;113(Pt A):109371. doi:10.1016/j.intimp.2022.109371
27. Chen J, Hong D, Zhai Y, Shen P. Meta-analysis of associations between neutrophil-to-lymphocyte ratio and prognosis of gastric cancer. *World J Surg Oncol*. 2015;13:122. doi:10.1186/s12957-015-0530-9
28. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106(6):dju124. doi:10.1093/jnci/dju124
29. Blacher E, Tsai C, Litichevskiy L, et al. Aging disrupts circadian gene regulation and function in macrophages. *Nat Immunol*. 2022;23(2):229–236. doi:10.1038/s41590-021-01083-0
30. Britanova OV, Putintseva EV, Shugay M, et al. Age-related decrease in TCR repertoire diversity measured with deep and normalized sequence profiling. *J Immunol*. 2014;192(6):2689–2698. doi:10.4049/jimmunol.1302064

31. Solana R, Mariani E. NK and NK/T cells in human senescence. *Vaccine*. 2000;18(16):1613–1620. doi:10.1016/S0264-410X(99)00495-8
32. Li Z, Li S, Ying X, et al. The clinical value and usage of inflammatory and nutritional markers in survival prediction for gastric cancer patients with neoadjuvant chemotherapy and D2 lymphadenectomy. *Gastric Cancer*. 2020;23(3):540–549. doi:10.1007/s10120-019-01027-6
33. Shi H, Wang H, Pan J, Liu Z, Li Z. Comparing prognostic value of preoperative platelet indexes in patients with resectable gastric cancer. *Sci Rep*. 2022;12(1):6480. doi:10.1038/s41598-022-10511-6
34. Li L, Zeng Q, Xue N, et al. A nomogram based on aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio to predict prognosis after surgery in gastric cancer patients. *Cancer Control*. 2020;27(1):1073274820954458. doi:10.1177/1073274820954458
35. Matsas S, Pn A Jr, Del Giglio A. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as biomarkers to prognosticate survival in advanced gastric cancer patients in the era of immunotherapy: a systematic review and meta-analysis. *J Gastrointest Oncol*. 2024;15(1):33–51. doi:10.21037/jgo-23-808
36. Mireştean CC, Stan MC, Schenker M, et al. Immunotherapy with PD-1 inhibitor nivolumab in recurrent/metastatic platinum refractory head and neck cancers-early experiences from Romania and literature review. *Diagnostics*. 2023;13(16):2620. doi:10.3390/diagnostics13162620
37. Haas M, Lein A, Fuereder T, et al. Early on-treatment C-reactive protein and its kinetics predict survival and response in recurrent and/or metastatic head and neck cancer patients receiving first-line pembrolizumab. *Invest New Drugs*. 2023;41(5):727–736. doi:10.1007/s10637-023-01388-x
38. Hamai Y, Emi M, Ibuki Y, et al. Ability of blood cell parameters to predict clinical outcomes of nivolumab monotherapy in advanced esophageal squamous cell carcinoma. *Onco Targets Ther*. 2023;16:263–273. doi:10.2147/OTT.S404926