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IGFL2 expression and surgical volume: Independent predictors of survival in gastric cancer

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Abstract

This study aimed to assess the impact of surgeons' annual volume and insulin-like growth factor-like family member 2 (IGFL2) expression on gastric cancer prognosis. Clinicopathological data from 475 patients who underwent D2 lymph node dissection were analyzed. IGFL2 expression was evaluated using immunohistochemistry. Patients were divided into training (70%) and validation (30%) groups. Univariate and multivariate Cox regression identified risk factors for overall survival (OS) and disease-free survival (DFS), leading to a clinical prediction model. Model performance was evaluated using C-index. High IGFL2 expression and low surgical volume independently predicted poorer OS and DFS (hazard ratio = 2.13, 2.17, all $P < .01$). Surgeons performing >26 cases annually had higher OS and DFS (hazard ratio = 1.65, 1.58, all $P < .01$). Nomograms integrating surgical volume, IGFL2 expression, grade, TNM staging, and carcinoembryonic antigen showed superior predictive accuracy for OS and DFS compared to TNM alone, with robust C-indices and area under the curve values. Surgeons' annual volume and IGFL2 expression independently predict gastric cancer prognosis, emphasizing the need for specialized training and further research on IGFL2's molecular mechanisms to enhance patient outcomes.

Abbreviations: AUC = area under the curve, CEA = carcinoembryonic antigen, DCA = decision curve analysis, DFS = disease-free survival, FFPE = formalin-fixed paraffin-embedded, GC = gastric cancer, HR = hazard ratio, IGFL2 = insulin-like growth factor-like family member 2, IHC = immunohistochemistry, KM = Kaplan–Meier, OS = overall survival, STAD = stomach adenocarcinomas, TCGA = The Cancer Genome Atlas.

Keywords: clinical prediction model, gastric cancer, IGFL2, surgeons' annual volume

1. Introduction

Gastric cancer, a severe malignancy with a high mortality rate, affects over 1 million individuals worldwide annually, leading to approximately 783,000 fatalities.[1] The incidence rates are significantly higher in Eastern Asia and Eastern Europe than in North America, Northern Europe, and Africa. Recent studies have reported an increasing prevalence of gastric cancer among younger adults in certain regions. The multifaceted etiology of the disease encompasses elements such as helicobacter pylori infection, dietary factors, genetic predispositions, and environmental influences, underscoring the need for comprehensive research and effective preventive strategies.

Surgical treatment is pivotal for managing gastric cancer, primarily targeting complete tumor removal to enhance survival rates.[2] However, this approach faces challenges such as the intricate nature of the surgeries, the risk of postoperative complications, and the necessity for highly skilled surgical teams. Quality control in gastric cancer surgery is critical because it directly influences patient outcomes and prognoses. High-quality surgical interventions characterized by meticulous techniques and thorough management of potential complications can markedly improve the survival rate and quality of life of patients with gastric cancer.[3]

The annual surgical volume of a surgeon or hospital is a crucial factor in the quality control of gastric cancer treatment, with studies yielding varied outcomes. Although higher volumes are often correlated with an improved patient prognosis, this correlation is not consistently evident across all studies. Comprehensive research suggests that higher surgical

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volumes are generally associated with favorable patient outcomes such as enhanced survival rates, more effective lymph node dissections, decreased mortality rates, and shortened hospital stays.[4–6] However, some studies have proposed that the sheer number of surgeries may not be the sole determinant of surgical success, highlighting that the surgeon's expertise and overall surgical care quality may play a more critical role in determining the long-term survival of patients with gastric cancer.[7–9]

Recent advancements in the treatment of gastric cancer have centered on molecular and targeted therapies, including trastuzumab for HER2-positive tumors and immunotherapies aimed at the PD-1/PD-L1 pathways.[10,11] However, obstacles such as tumor heterogeneity, drug resistance, and the challenge of identifying effective biomarkers have impeded this progress. These challenges highlight the urgent need to identify new molecular targets to develop tailored and more effective treatment strategies and enhance patient outcomes in gastric cancer care.

IGFL2, a member of the insulin-like growth factor family, is associated with cell growth.[12] Studies using The Cancer Genome Atlas (TCGA) database have shown that *IGFL2* is overexpressed in various tumor tissues, often correlating with poor prognosis. Its relationship with immune cells, immune-related genes, and low methylation levels indicate its role in oncogenesis.[13] Additionally, mutations in *IGFL2* are linked to adverse outcomes, underscoring its potential as a biomarker for tumor immunotherapy and emphasizing the importance of further investigations in gastric cancer research. Previous studies in our center have found that IGFL2 is an important oncogene in gastric cancer (unpublished data).

In this study, we aimed to assess the impact of the annual volume of gastric cancer surgeries performed by surgeons, the novel molecular marker *IGFL2*, and various clinicopathological factors on overall survival (OS) and disease-free survival (DFS), particularly during the initial phase of laparoscopic surgery at our center. The era prior to 2010, marked by the advent of laparoscopic techniques, featured a predominance of open

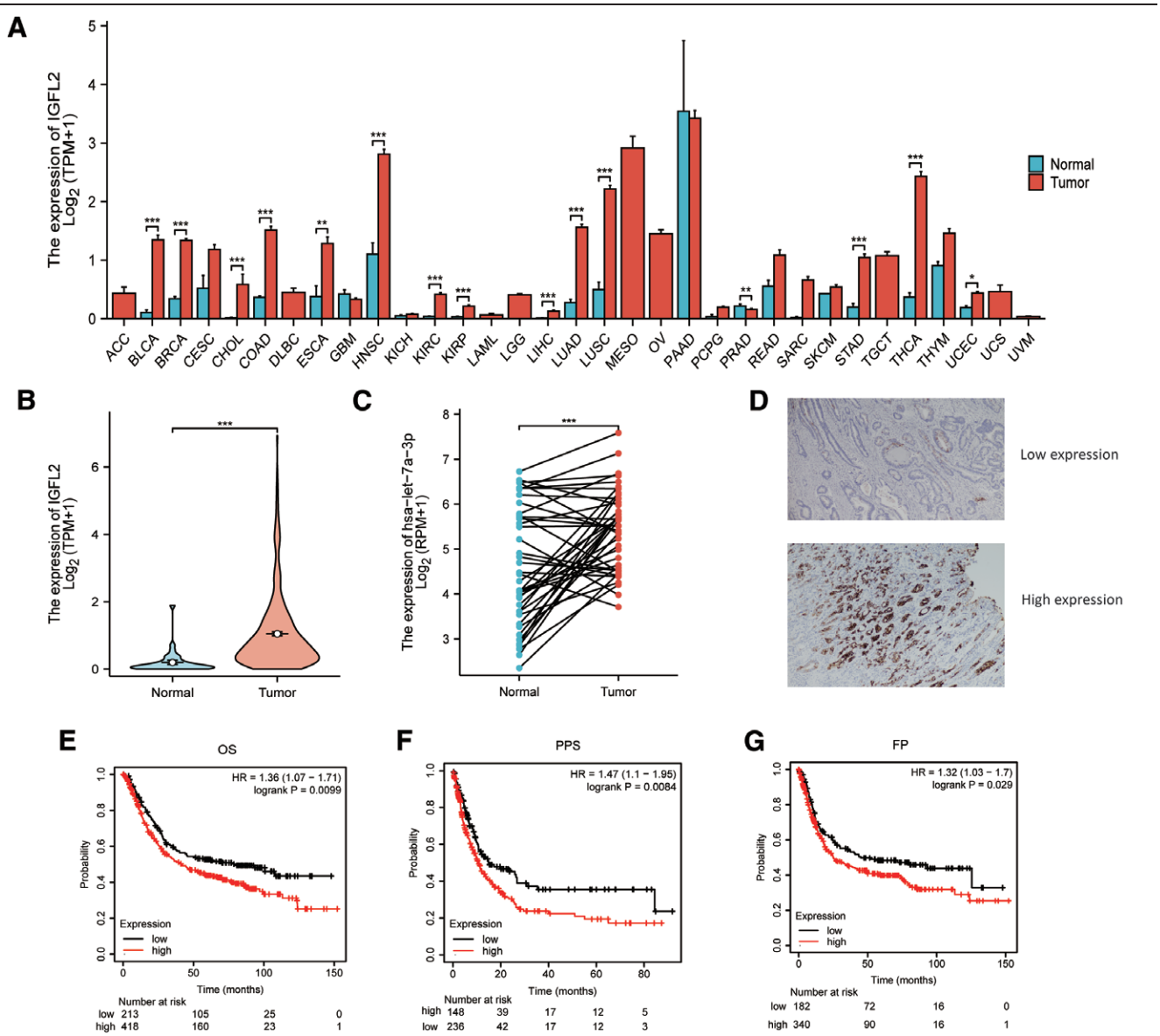

Figure 1. IGFL2 expression and prognosis (A) IGFL2 expression across 33 cancer types, sourced from the TCGA database. (B) Specific IGFL2 expression in stomach adenocarcinoma (STAD) and normal tissues from TCGA. (C) Comparison of IGFL2 expression in 27 paired tumor and normal tissues from TCGA. (D) Representative images of high and low IGFL2 expression in tumor tissues, analyzed via immunohistochemistry (IHC) at Yantai Yuhuangding Hospital. (E–G) Correlation of IGFL2 with overall survival (OS), disease progression (FP), and post-progression survival (PPS), represented in Kaplan–Meier plots.

surgeries with relatively low volumes. Consequently, we focused our analysis on patient data from gastric cancer surgeries performed between 2008 and 2010. This study aimed to determine the effects of high annual surgical volumes and the presence of *IGFL2* on patient prognosis with the goal of enhancing the assessment of surgical quality and identifying potential new drug targets to improve outcomes in gastric cancer treatment.

Table 1

Clinicopathological characteristics of gastric cancer patients in the training and validation cohorts.

Variable names	Train number (%)	Validation number (%)	*t* or χ^2	*P*-value
Number	332	143		
Age	65.151 ± 10.32	64.31 ± 10.62	0.81	.4186
Gender			0.06	.81
Female	120 (36.14)	50 (34.97)		
Male	212 (63.86)	93 (65.03)		
Location			1.58	.66
Lower	123 (37.05)	57 (39.86)		
Middle	119 (35.84)	43 (30.07)		
Others	13 (3.92)	7 (4.90)		
Upper	77 (23.19)	36 (25.17)		
Histological type			0.55	.97
Diffuse type	69 (20.78)	29 (20.28)		
Intestinal type	154 (46.39)	68 (47.55)		
Mixed type	109 (32.83)	46 (32.17)		
Grade			0.03	.98
G1	106 (31.93)	45 (31.47)		
G2	132 (39.76)	58 (40.56)		
G3	94 (28.31)	40 (27.97)		
T			3.18	.36
T1	20 (6.02)	12 (8.39)		
T2	66 (19.88)	23 (16.08)		
T3	154 (46.39)	75 (52.45)		
T4	92 (27.71)	33 (23.08)		
N			0.54	.91
N0	101 (30.42)	41 (28.67)		
N1	91 (27.41)	37 (25.87)		
N2	70 (21.08)	34 (23.78)		
N3	70 (21.08)	31 (21.68)		
M			0.02	.88
M0	310 (93.37)	133 (93.01)		
M1	22 (6.63)	10 (6.99)		
Stage			0.88	.83
I	45 (13.55)	21 (14.68)		
II	109 (32.83)	42 (29.37)		
III	144 (43.37)	67 (46.85)		
IV	34 (10.24)	13 (9.09)		
Event			0.2	.65
Alive	200 (60.24)	83 (58.04)		
Dead	132 (39.76)	60 (41.96)		
IGFL2			0.2	.65
High	163 (49.10)	67 (46.85)		
Low	169 (50.90)	76 (53.15)		
Annual surgical volume			0.14	.71
High	210 (63.25)	93 (65.03)		
Low	122 (36.75)	50 (34.97)		
Tumor size			0.01	.94
<4 cm	145 (43.67)	63 (44.06)		
≥4 cm	187 (56.33)	80 (55.94)		
CEA			1.09	.3
Normal	211 (63.55)	98 (68.53)		
High	121 (36.45)	45 (31.47)		
CA199			0.01	.92
Normal	219 (65.96)	95 (66.43)		
High	113 (34.04)	48 (33.57)		
Surgical approach			0.1	.76
Open surgery	218 (65.66)	96 (67.13)		
Laparoscopy-assisted surgery	114 (34.34)	47 (32.87)		

2. Materials and methods

2.1. Case selection

In this study, we used formalin-fixed paraffin-embedded (FFPE) samples from 475 patients with newly diagnosed and biopsy-confirmed gastric cancer (GC). Patients who underwent D2 lymphadenectomy between June 2008 and April 2010 were recruited from the Yantai Yuhuangding Hospital in Shandong, China. The patients were randomly distributed into the training and validation cohorts in a 7:3 ratio using the random-number method. The inclusion criteria were as follows: hematoxylin and eosin-stained slides displaying invasive tumor sections, comprehensive follow-up and clinicopathological data, no prior cancer treatments, at least 15 examined lymph nodes, and informed consent. Exclusion criteria included the absence of an initial FFPE tumor and normal samples or previous anticancer therapy. All samples were reevaluated by 2 independent pathologists, and TNM staging was updated according to the 8th edition of the American Joint Committee on Cancer staging manual. This study was approved by the review board of Yantai Yuhuangding Hospital (2018207).

2.2. Determination of optimal cutoff value for annual surgical volume

In this study, we used the X-tile software (https://medicine.yale.edu/lab/rimm/research/software/) to determine the optimal cutoff for a surgeon's annual surgical volume. X-tile is an online tool widely used in biomedical research that scans all possible cutoff points, combining them with patient survival data to select the point that produces the most statistically significant difference (based on the log-rank test), thereby maximizing the difference in outcomes between different groups.

2.3. IGFL2 expression in stomach adenocarcinomas (STAD)

We primarily used the Xiantao Academic Online Tool for the following analyses. RNA sequencing data were obtained from TCGA platform. The data were aligned and mapped using the (STAR) algorithm, followed by normalization using transcripts per million and a subsequent log2 transformation. The data were integrated with the corresponding clinical information. We analyzed *IGFL2* expression in various cancer types, focusing on gastric cancer, to determine its correlation with specific clinical pathologies of this disease.

2.4. Kaplan–Meier (KM) plotter database

The KM plotter database (https://kmplot.com/analysis/) was used to assess the prognostic value of *IGFL2* expression in STAD. Patients were categorized into groups based on high or low *IGFL2* expression levels to investigate outcomes such as survival (post-progression survival), first progression (FP), and OS.

2.5. Immunohistochemistry

FFPE specimens were processed for immunohistochemistry (IHC) as previously described. Sections (4 μm thick) were dewaxed in xylene and rehydrated using a graded ethanol series. Endogenous peroxidase activity was quenched with a 1% hydrogen peroxide/methanol solution for 10 minutes, followed by antigen retrieval in a citrate buffer (10 mM, pH 6.0) using microwave treatment for 30 minutes. Blocking was performed using 10% normal rabbit serum for 30 minutes.

The sections were then incubated overnight at 4 °C with the anti-*IGFL2* antibody (1:200 dilution, NBP3-09570, Novus, USA), followed by a 30-minute incubation with a horseradish peroxidase-labeled polymer system (EnVision™, DakoCytomation, Denmark). Color development was facilitated by 0.05% DAB, and the sections were counterstained with modified Harris hematoxylin.

2.6. Evaluation of IHC staining

Two expert pathologists who were blinded to the patients' clinical details and outcomes independently evaluated the IHC-stained sections. They examined 10 high-magnification fields in the tumor area and achieved concordance in approximately 90% of the cases. Discrepancies were resolved by consulting a

Table 2

Univariate analysis of variance on the expression level of IGFL2.

	Number	IGFL2 expression			
Clinical pathological data	**n = 332**	**High (%)**	**Low (%)**	**χ^2**	***P*-value**
Gender					
Female	120 (36.14)	62 (38.04)	58 (34.32)	0.5	.48
Male	212 (63.86)	101 (61.96)	111 (65.68)		
Age					
>60 years	112 (33.73)	53 (15.96)	59 (17.77)	0.87	.35
≤60 years	220 (62.27)	116 (34.94)	104 (31.33)		
Tumor location				1.95	.584
Upper	77 (23.19)	41 (25.15)	36 (21.30)		
Middle	119 (35.84)	61 (37.42)	58 (34.32)		
Lower	123 (37.05)	56 (34.36)	67 (39.64)		
Others	13 (3.92)	5 (3.07)	8 (4.73)		
Tumor size				3.40	.065
<4 cm	211 (63.55)	99 (60.74)	112 (66.27)		
≥4 cm	121 (36.45)	64 (39.26)	57 (33.73)		
Grade				14.27	<.01
G1	106 (31.93)	49 (30.06)	57 (33.73)		
G2 + G3	226 (68.07)	99 (29.82)	127 (38.25)		
T				57.36	<.01
T1 + T2	86 (25.90)	74 (22.23)	12 (3.61)		
T3 + T4	246 (74.10)	95 (28.61)	151 (45.48)		
N				29.05	<.01
N0	101 (30.42)	74 (22.23)	27 (8.13)		
N+	231 (69.57)	95 (28.61)	136 (40.96)		
M				13.93	.0002
0	298 (89.76)	162 (48.80)	136 (40.96)		
1	34 (10.24)	7 (2.11)	27 (8.13)		
CA199				1.64	.20
Normal	219 (65.96)	102 (62.58)	117 (69.23)		
High	113 (34.04)	61 (37.42)	52 (30.77)		
CEA					
High	187 (56.33)	96 (58.90)	91 (53.85)	0.86	.35
Normal	145 (43.67)	67 (41.10)	78 (46.15)		
TNM stage				83.9	<.01
I + II	154 (46.39)	120 (36.14)	34 (10.24)		
III + IV	178 (53.61)	49 (14.76)	129 (38.86)		
Histological type				4.66	.098
Intestinal type	154 (46.39)	78 (47.85)	76 (44.97)		
Diffuse type	69 (20.78)	28 (17.18)	41 (24.26)		
Mixed type	109 (32.83)	57 (34.97)	52 (30.77)		

Table 3

Binary logistic regression analysis of IGFL2 expression.

Clinical pathological data	**N = 332**	**IGFL2 expression**		**OR**	**95% CI**	***P*-value**
Grade				1.97	1.14–3.43	.016
G1	106 (31.93)	49 (30.06)	57 (33.73)			
G2 + G3	226 (68.07)	99 (29.82)	127 (38.25)			
T stage				8.32	4.20–16.46	<.01
T1 + T2	86 (25.90)	74 (22.23)	12 (3.61)			
T3 + T4	246 (74.10)	95 (28.61)	151 (45.48)			
N stage				2.65	1.50–4.71	.001
N0	101 (30.42)	74 (22.23)	27 (8.13)			
N+	231 (69.57)	95 (28.61)	136 (40.96)			
M stage				1.94	0.78–4.84	.157
0	298 (89.76)	162 (48.80)	136 (40.96)			
1	34 (10.24)	7 (2.11)	27 (8.13)			

third expert whose agreement with one of the initial reviewers determined the prevailing assessment. In cases of disagreement, all 3 pathologists collaborated to reach a consensus. *IGFL2* expression was quantified using a semi-quantitative H-score derived from a four-level intensity scale (0 = no staining, 0.5 = weak, 1 = moderate, 1.5 = strong) and the percentage of stained cells (0–100%). Based on the median H-score, patients were categorized into high or low *IGFL2* expression groups.

2.7. Nomogram development

Nomograms were created based on the training cohort data. Survival rates for different factors were determined using KM estimates and evaluated using the log-rank test. Factors with *P*-values below .05 underwent time-dependent multivariable Cox regression to identify significant prognostic indicators using SPSS 22.0. The final nomograms were constructed in R 4.3.2, using the "survival" and' rms' packages, with backward step-wise selection influenced by the likelihood ratio test and Akaike information criterion for optimizing the model.

2.8. Nomogram validation and calibration

To assess the accuracy of the nomograms in predicting survival, the concordance index (C-index) was calculated within

Table 4

Univariate analysis for overall survival (OS) in the training cohort.

Characteristics	Number (%)	Hazard ratio (HR)	95% CI	*P*-value
Age	65.15 ± 10.32	1.008	0.99–1.03	.352
Annual surgical volume				
High	210 (63.25)			
Low	122 (36.75)	1.65	1.16–2.35	.005
CA199				
0	219 (65.96)			
1	113 (34.04)	0.99	0.70–1.42	.97
CEA				
High	187 (56.32)			
Normal	145 (43.68)	0.67	0.44–0.89	.01
Grade				
G1	106 (31.93)			
G2	132 (39.76)	2.01	1.34–3.00	.001
G3	94 (28.31)	3.30	2.05–5.32	0
Histological type				
Diffuse type	69 (20.78)			
Intestinal type	154 (46.39)	0.94	0.59–1.48	.78
Mixed type	109 (32.83)	1.39	0.86–2.24	.18
IGFL2				
High	163 (49.10)			
Low	169 (50.90)	0.47	0.33–0.66	0
Location				
Lower	123 (37.05)			
Middle	119 (35.84)	1.11	0.74–1.68	.61
Others	13 (3.92)	0.92	0.391–2.18	.86
Upper	77 (23.19)	1.11	0.70–1.77	.66
M				
M0	298 (89.76)			
M1	34 (10.24)	17.72	8.34–37.63	0
N				
N0	101 (30.42)			
N1	91 (27.41)	1.43	0.91–2.27	.12
N2	70 (21.08)	2.06	1.28–3.33	.003
N3	70 (21.08)	2.36	1.42–3.93	.001
Sex				
Female	120 (36.14)			
Male	212 (63.86)	0.95	0.67–1.36	.78
Stage				
I	45 (13.55)			
II	109 (32.83)	1.33	0.74–2.37	.34
III	144 (43.37)	2.33	1.33–4.09	.003
IV	34 (10.24)	30.64	12.53–74.96	0
Surgical approach				
0	218 (65.66)			
1	114 (34.34)	0.78	0.54–1.12	.178
T				
T1	20 (6.02)			
T2	66 (19.88)	1.39	0.60–3.25	.446
T3	154 (46.39)	1.71	0.78–3.76	.18
T4	92 (27.71)	2.38	1.06–5.33	.035
Tumor size				
0	211 (63.55)			
1	121 (36.45)	1.29	0.91–1.82	.15

the validation cohort, with values ranging from 0.5 (no prediction capability) to 1.0 (perfect prediction). Calibration for the 1-year, 3-year, and 5-year OS and DFS involved aligning the predicted outcomes with the actual occurrences to adjust for discrepancies.

2.9. Clinical application

The practical utility of the nomograms was evaluated through a decision curve analysis (DCA), which determined their net benefit at various probability thresholds to gauge their effectiveness in informing clinical decisions.

2.10. Statistical analysis

For comparative analyses between 2 groups, continuous variables were assessed using the *t* test, while categorical variables were analyzed with the χ^2 test. OS and DFS were determined from the date of surgery to the event of regional recurrence or distant metastasis (for DFS), or to death or the last clinical follow-up (for OS). The KM method, in conjunction with the log-rank test, was used to calculate DFS and OS rates. Variables identified as significant in univariate analyses were further evaluated using a <multivariate Cox proportional hazards regression analysis. Statistical analyses were performed using R (version 4.3.2) and SPSS software (version 22.0). All tests were bidirectional, and a *P*-value < .05 was deemed statistically significant.

Table 5

Multifactorial Cox regression analysis for overall survival (OS) in the training cohort.

Characteristics	Number (%)	Hazard ratio (HR)	95% CI	*P*-value
Annual surgical volume				
High	210 (63.25)			
Low	122 (36.75)	1.66	1.15–2.40	.007
CEA				
High	187 (56.32)			
Normal	145 (43.68)	0.70	0.49–1.01	.06
Grade				
G1	106 (31.93)			
G2	132 (39.76)	1.96	1.29–2.99	.002
G3	94 (28.31)	2.22	1.28–3.82	.004
IGFL2				
High	163 (49.10)			
Low	169 (50.90)	0.48	0.34–0.69	0
Stage				
I	45 (13.55)			
II	109 (32.83)	1.56	0.86–2.82	.14
III	144 (43.37)	2.22	1.23–4.01	.008
IV	34 (10.24)	25.19	9.89–64.14	0

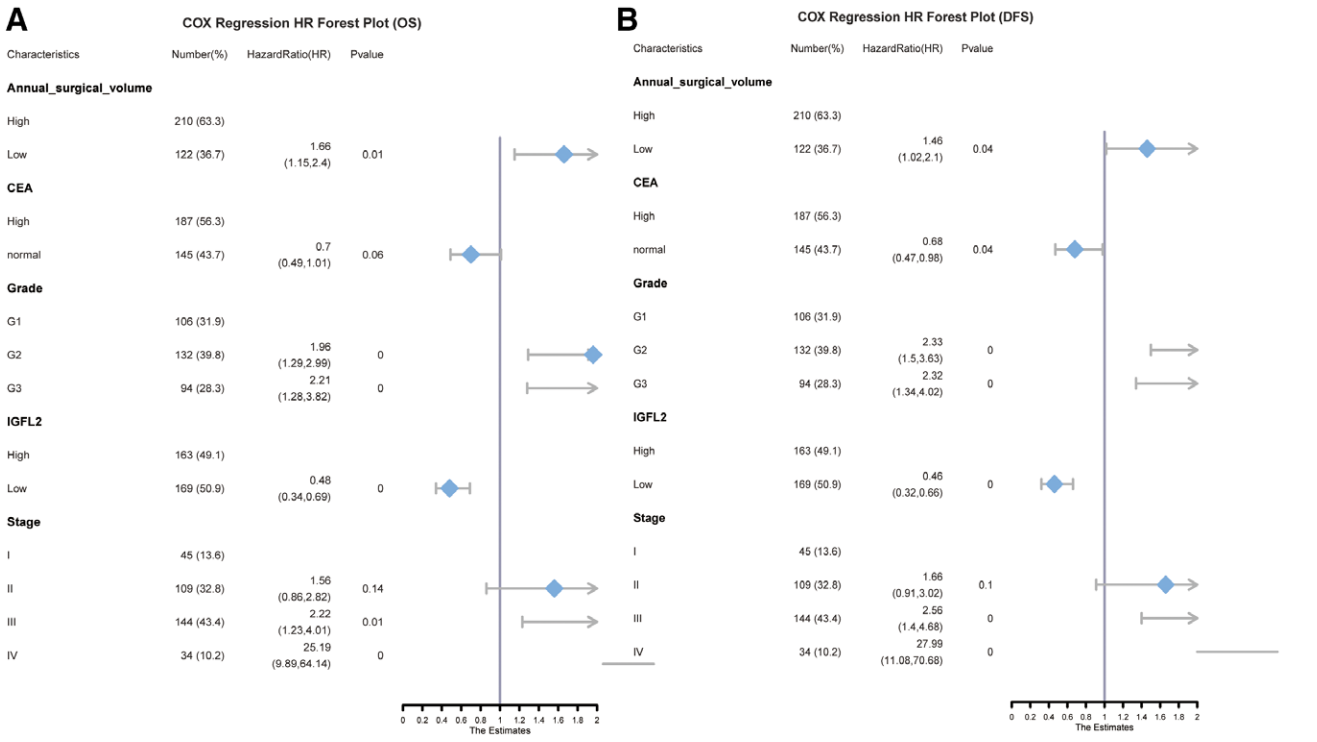

Figure 2. COX regression HR forest plot for OS (A) and PFS (B).

3. Results

3.1. The overexpression of IGFL2 in human gastric cancer

A pan-cancer analysis of 33 cancer types from the TCGA database indicated that *IGFL2* mRNA levels were significantly higher in gastric cancer tissues than in normal tissues ($P < .001$; Fig. 1A). IGFL2 expression was elevated in 375 gastric cancer tissues compared to 32 normal tissues ($P < .01$, Fig. 1B), with a similarly significant increase observed in tumor samples from 27 paired tumor-normal tissues ($P < .01$, Fig. 1C). Immunohistochemical analysis conducted at the Yantai Yuhuangding Hospital revealed that *IGFL2* expression was decreased in well-differentiated specimens and elevated in poorly differentiated specimens (Fig. 1D). Additionally, the analysis of KM plotter database showed that high *IGFL2* expression in STAD was associated with adverse outcomes in first progression (FP), OS, and post-progression survival (Fig. 1E–G).

Based on the X-tile results, the optimal cutoff for a surgeon's annual surgical volume was 26. Comparison of the clinicopathological profiles of the training and validation cohorts revealed no significant differences in key clinicopathological parameters between the 2 sets (Table 1). The association between *IGFL2* expression and primary clinicopathological variables was examined using one-way ANOVA and multivariate logistic regression analyses. One-way ANOVA indicated that grade classifications T stage, N stage, M stage, and overall

Table 6

Univariate analysis for disease-free survival (DFS) in the training cohort.

Characteristics	Number (%)	Hazard ratio (HR)	95% CI	*P*-value
Age	65.15 ± 10.32	1.01	0.99–1.02	.41
Annual surgical volume				
High	210 (63.25)			
Low	122 (36.75)	1.58	1.11–2.25	.01
CA199				
0	219 (65.96)			
1	113 (34.04)	0.97	0.68–1.39	.88
CEA				
High	187 (56.32)			
Normal	145 (43.68)	0.61	0.43–0.87	.01
Grade				
G1	106 (31.93)			
G2	132 (39.76)	2.13	1.42–3.20	.00
G3	94 (28.31)	3.32	2.06–5.35	.00
Histological type				
Diffuse type	69 (20.78)			
Intestinal type	154 (46.39)	0.94	0.59–1.48	.78
Mixed type	109 (32.83)	1.36	0.84–2.19	.21
IGFL2				
High	163 (49.10)			
Low	169 (50.90)	0.47	0.33–0.66	.00
Location				
Lower	123 (37.05)			
Middle	119 (35.84)	1.16	0.77–1.75	.47
Others	13 (3.92)	0.85	0.36–2.02	.71
Upper	77 (23.19)	1.21	0.76–1.92	.42
M				
M0	298 (89.76)			
M1	34 (10.24)	18.51	8.75–39.15	.00
N				
N0	101 (30.42)			
N1	91 (27.41)	1.37	0.86–2.16	.19
N2	70 (21.08)	2.17	1.34–3.51	.00
N3	70 (21.08)	2.42	1.45–4.03	.00
Sex				
Female	120 (36.14)			
Male	212 (63.86)	0.95	0.67–1.36	.78
Stage				
I	45 (13.55)			
II	109 (32.83)	1.30	0.73–2.31	.37
III	144 (43.37)	2.44	1.39–4.28	.00
IV	34 (10.24)	32.76	13.45–79.82	.00
Surgical approach				
0	218 (65.66)			
1	114 (34.34)	0.79	0.55–1.14	.20
T				
T1	20 (6.02)			
T2	66 (19.88)	1.33	0.57–3.09	.51
T3	154 (46.39)	1.93	0.88–4.24	.10
T4	92 (27.71)	2.32	1.03–5.19	.04
Tumor size				
0	211 (63.55)			
1	121 (36.45)	1.32	0.94–1.86	.12

stage were associated with *IGFL2* expression (Table 2). A multivariate logistic regression analysis revealed that Grade classifications, T stage, and N stage were significantly associated with *IGFL2* expression (Table 3).

3.2. Prognostic factors in patients with gastric cancer

We assessed prognostic factors for OS and progression-free survival (PFS) independently. A univariate analysis identified grade, carcinoembryonic antigen (CEA), T stage, N stage, M

Table 7

Multifactorial Cox regression analysis for disease-free survival (DFS) in the training cohort.

Characteristics	Number (%)	Hazard ratio (HR)	95% CI	*P*-value
Annual surgical volume				
High	210 (63.25)			
Low	122 (36.75)	1.463	1.02–2.10	.039
CEA				
High	187 (56.32)			
Normal	145 (43.68)	0.681	0.47–0.98	.037
Grade				
G1	106 (31.93)			
G2	132 (39.76)	2.332	1.50–3.63	0
G3	94 (28.31)	2.324	1.35–4.02	.003
IGFL2				
High	163 (49.10)			
Low	169 (50.90)	0.459	0.32–0.66	0
Stage				
I	45 (13.55)			
II	109 (32.83)	1.661	0.91–3.02	.096
III	144 (43.37)	2.555	1.40–4.68	.002
IV	34 (10.24)	27.987	11.08–70.68	0

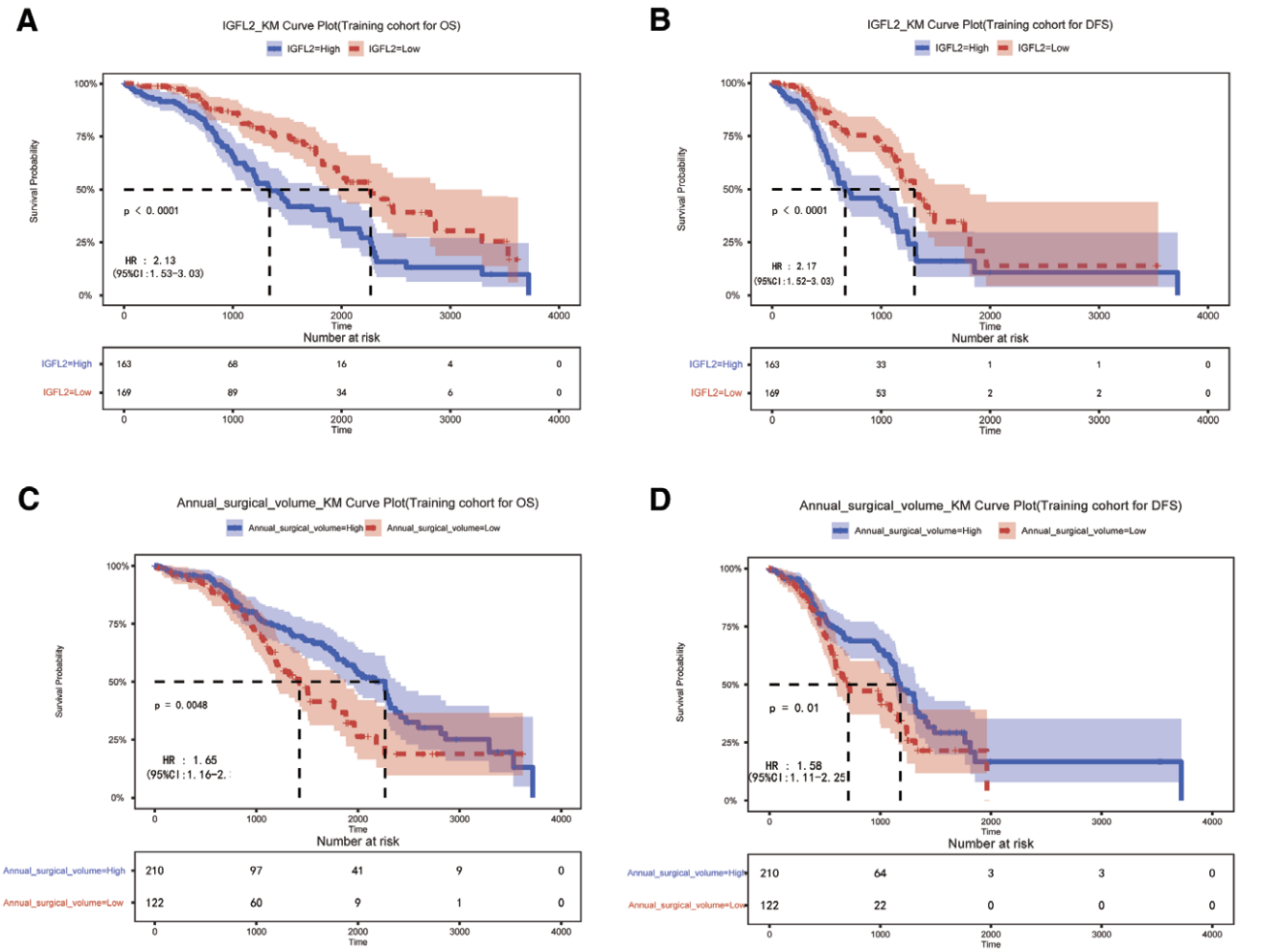

Figure 3. Association of IGFL2 expression (A and B) and annual surgical volume (C and D) with overall survival (OS) and disease-free survival (DFS).

stage, tumor size, *IGFL2*, TNM stage, and annual surgical volume as potential prognostic indicators for OS. Factors with a *P*-value <.05 were subsequently included in a multivariable Cox regression analysis (Table 4, Figure S1A, Supplemental Digital Content, http://links.lww.com/MD/N666). This analysis revealed that TNM stage, tumor grade, *IGFL2* expression, and annual surgical volume were independent prognostic factors (Table 5, Fig. 2A). For DFS, the findings were analogous; a univariate analysis identified similar prognostic factors (Table 6, Figure S1B, Supplemental Digital Content, http://links.lww.com/MD/N666). A multivariate Cox regression analysis determined that TNM stage, CEA levels, grade, *IGFL2* expression, and annual surgical volume were independent prognostic factors (Table 7, Fig. 2B).

Given that grade classification, CEA, and stage are well-established prognostic factors, our analysis focused on the prognostic influence of *IGFL2* expression and annual surgical volume.

3.2. High expression of IGFL2 is associated with poor clinical outcomes

To assess the prognostic significance of *IGFL2* expression in patients with GC, a KM survival analysis was conducted. This

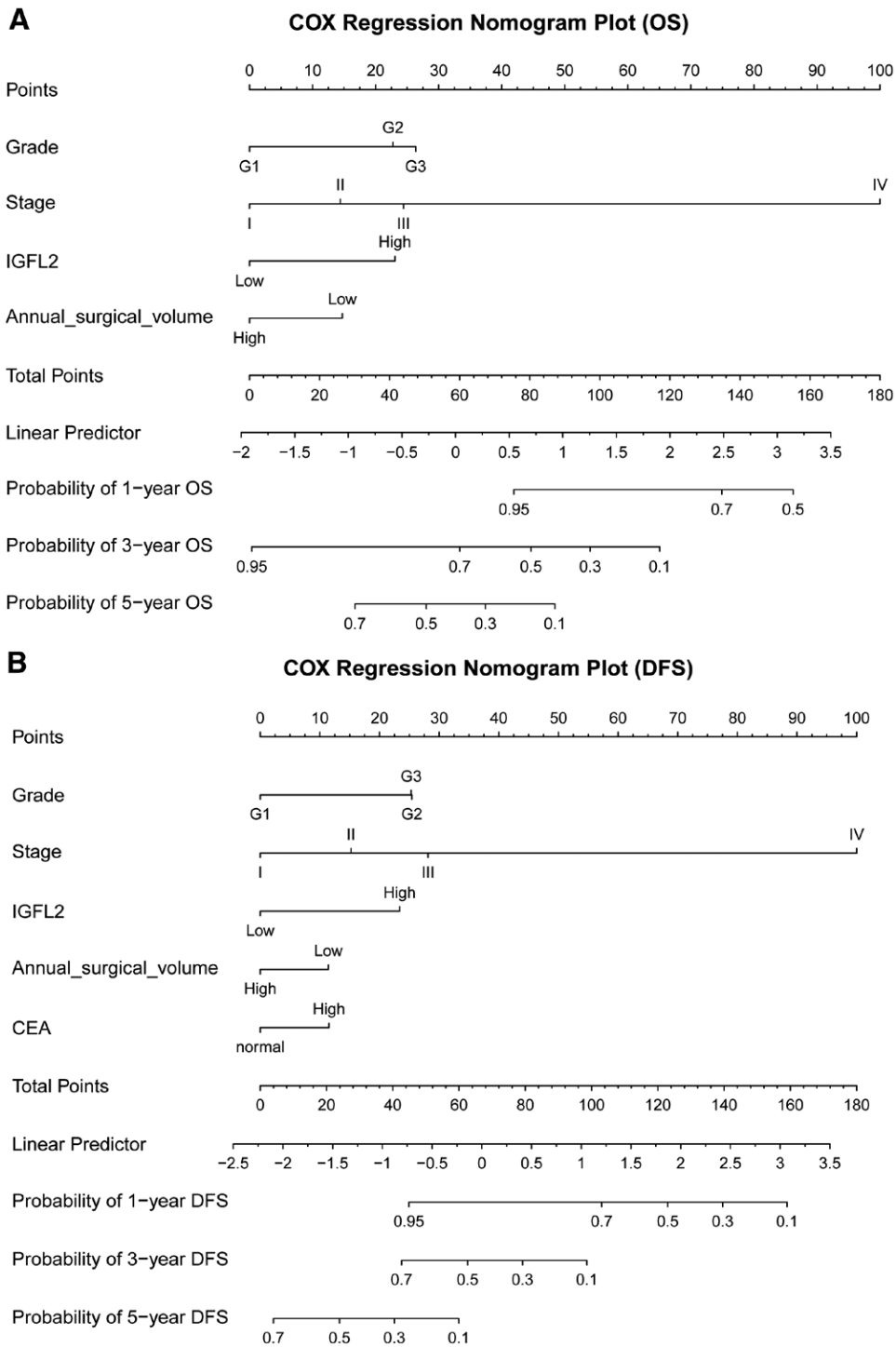

Figure 4. Multivariable Cox regression nomogram for predicting 1-year, 3-year, and 5-year OS (A) and PFS (B) based on independent variables.

analysis revealed that patients with high *IGFL2* expression exhibited lower 3-year OS and DFS compared to those with low *IGFL2* expression (3-year OS: 38.04% vs 51.53%; hazard ratio (HR) = 2.13 [1.53–3.03]; 3-year DFS: 17.79% vs 25.44%; HR = 2.17 [1.52–3.03]; all $P < .01$; Fig. 3A and B).

3.3. Low annual surgical volume is associated with poor clinical outcomes

To evaluate the prognostic impact of the annual surgical volume in patients with GC, a KM survival analysis was performed. The test revealed that surgeons with an annual surgical volume >26 cases had patients with higher 3-year OS and DFS compared to surgeons with a volume <26 cases (3-year OS: 45.08% vs 43.33%; HR = 1.65 [1.16–1.35]; 3-year DFS: 25.23% vs 15.57%; HR = 1.58 [1.11–2.25]; all $P < .01$; Fig. 3C and D).

Nomograms were designed and validated to predict outcomes in patients with GC using key independent survival predictors. Using multivariate Cox regression, we created nomograms for calculating 1-year, 3-year, and 5-year OS and DFS, as illustrated in Fig. 4A and B. These nomograms scored each significant factor, summing them to project the OS and DFS at specified intervals. The training cohort exhibited concordance indices (C-indexes) of 0.732 (95% CI: 0.705–0.759) for OS and 0.742 (95% CI: 0.717–0.767) for DFS, with calibration plots closely aligned with the reference, suggesting model accuracy without the need for recalibration (Fig. 6). The validation cohort C-indexes were 0.749 (95% CI: 0.718–0.780) for OS and 0.753 (95% CI: 0.724–0.783) for DFS.

Receiver operating characteristic analysis confirmed the model's robust with ness, area under the curve (AUC) values surpassing 0.7 in both groups, underscoring clinical applicability. Specifically, the AUCs for the 1-year, 3-year, and 5-year OS in the training cohort were 0.924, 0.773, and 0.796, respectively, and those in the validation cohort were 0.872, 0.742, and 0.941, respectively. For DFS, the training cohort AUCs were 0.746, 0.819, and 0.764, respectively, and for the validation cohort, they were 0.802, 0.809, and

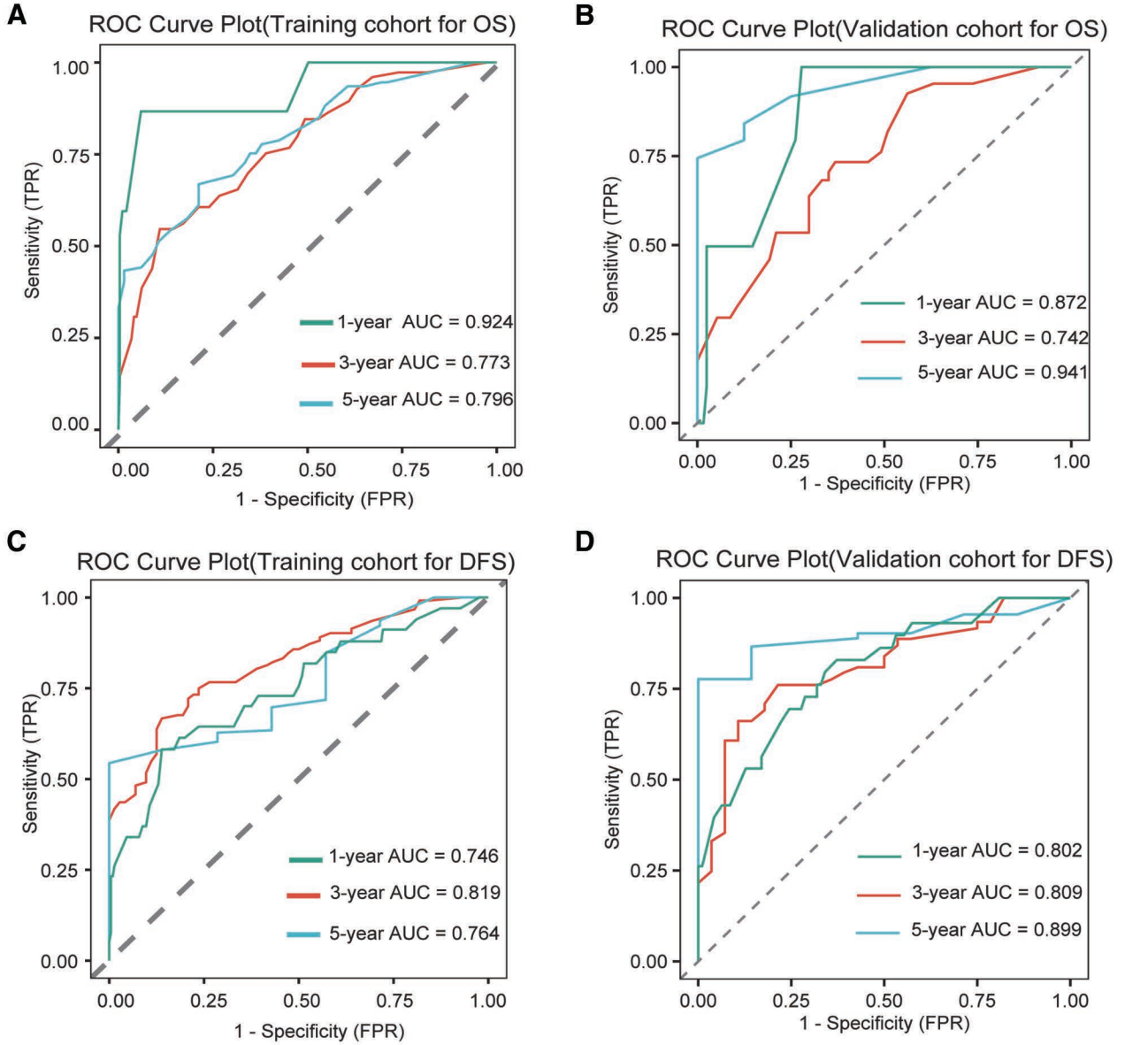

Figure 5. Receiver operating characteristic (ROC) curves for 1-year, 3-year, and 5-year OS and PFS from multivariable Cox regression, evaluating training cohorts (A and B) versus validation cohorts (C and D).

0.899, respectively, indicating strong predictive performance (Fig. 5A–D). Calibration curves showed a good agreement between the predicted and observed survival rates for DFS and OS (Fig. 6). DCA across the 1-year, 3-year, and 5-year OS and PFS intervals demonstrated net benefits, affirming the model's predictive accuracy (Fig. 7). KM plots from the risk model coefficients of the validation cohort showed that higher risk scores were correlated with poorer OS and DFS outcomes (all $P < .01$) (Fig. 8).

Moreover, the predictive performance of the nomograms for both OS and DFS was better than that of the traditional TNM staging system in both the training and validation cohorts (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/N667). The C-indices for TNM staging in predicting OS and DFS were 0.656 (95% CI: 0.628–0.683) and 0.662 (95% CI: 0.634–0.691) in the training cohort, respectively, and 0.700 (95% CI: 0.662–0.738) and 0.687 (95% CI: 0.651–0.723) in the validation cohort, respectively. These values were significantly lower than those obtained from our novel model, highlighting its enhanced predictive capability compared with the conventional TNM staging system.

4. Discussion

Stomach cancer is a significant health concern, particularly in East Asia. Early detection through screening is critical for its management.[14] For patients with advanced gastric cancer, surgery, particularly standard D2 lymph node dissection, is considered the most effective curative approach, and is believed to greatly improve survival rates.[15] Furthermore, the integration of surgery with chemotherapy,[16] targeted therapy,[10] or immunotherapy[11] has markedly improved the survival outcomes of advanced-stage cancer patients, demonstrating a substantial benefit over surgery alone. Therefore, enhancing surgical quality and discovering new therapeutic targets are vital for improving the long-term survival rates of patients with gastric cancer.

Japan's surgical training system plays a crucial role in advancing surgical skills, leading to better patient outcomes in gastric

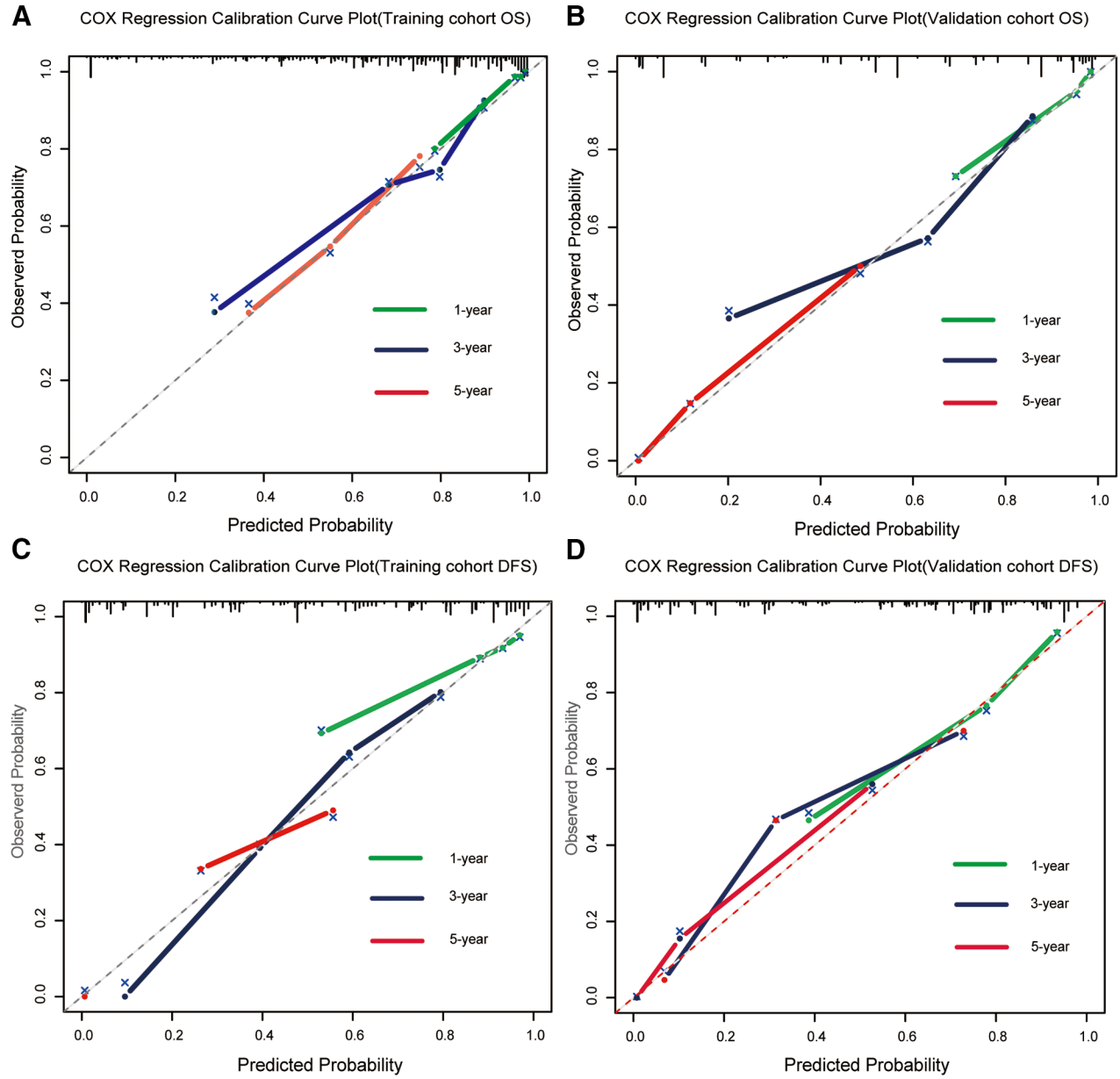

Figure 6. Calibration plots for 1-year, 3-year, and 5-year OS and DFS using multivariable Cox regression in training (A and B) and validation groups (C and D).

cancer treatment.[17–19] Studies comparing the perioperative and long-term survival outcomes between Western patients undergoing gastrectomy before and after training in Japan have shown that post-training participants had higher rates of lymph node dissection, fewer complications, shorter hospital stays, and improved median survival.[20] These findings underscore the importance of comprehensive D2 lymph node dissection training for enhancing surgical proficiency, reducing postoperative complications, and increasing survival rates among patients with gastric cancer.

The relationship between hospital capacity and cancer survival rates has been rigorously examined in Japan. Research has found that the adjusted risk ratios for prevalent cancers, such as gastric and colon cancers, are significantly influenced by hospital capacity, with ratios being 0.76 for stomach cancer and 0.85 for colon cancer.[21] These data underscore the strong association between hospital capacity and the survival rates of patients with cancer. Additional studies have demonstrated that the mortality risks for stomach cancer at low-capacity facilities are 1.36 to 1.82 times greater than those at high-capacity hospitals,[22] suggesting that centralizing patients in specialized hospitals might improve survival outcomes.

In Western regions, such as Europe and the United States, the benchmark for high or low surgical volume is typically approximately 20 cases,[4] indicative of the rarer occurrence of the disease, whereas, in East Asia, it ranges from 20 to 50 cases.[5] In our study, we set the threshold to 26 cases, which aligned with the figures cited in previous studies. Despite the scarcity of data on the effect of individual surgeon volumes on patient survival, our research concentrated on how varying surgical volumes among surgeons affect survival in the Chinese context. The results indicated that both OS and DFS were considerably higher in patients managed by surgeons with higher case volumes, highlighting the importance of surgical expertise in enhancing patient outcomes.

The five-year survival rate in our cohort was notably lower than that reported in Japan, with several contributing factors identified: initially, the incidence of early gastric cancer in our study was approximately 10%, whereas advanced stages accounted for 70% to 80%, in contrast to Japanese statistics.[23] Moreover, unlike Japan's stringent surgical accreditation system,[24,25] which standardizes surgical practices, China has lacked such standardization, with training often being mentor-based and variable in quality. However, recent advancements, such as live-streamed surgeries, have allowed Chinese surgeons to gain insights from global experts and improve their proficiency in advanced surgical techniques. Economic factors also played a role. A decade and a half ago, China's lower development level meant that numerous patients were unable to afford the necessary follow-up treatments, adversely affecting survival rates.

In this study, *IGFL2* expression was a prominent finding. Previous research on *IGFL2* in pancreatic cancer, utilizing the TCGA database, linked high expression to a negative prognosis.[13] Unlike the previous studies, our investigation using clinical samples showed that high *IGFL2* expression was correlated with TNM stage and grade classification. *IGFL2* was also

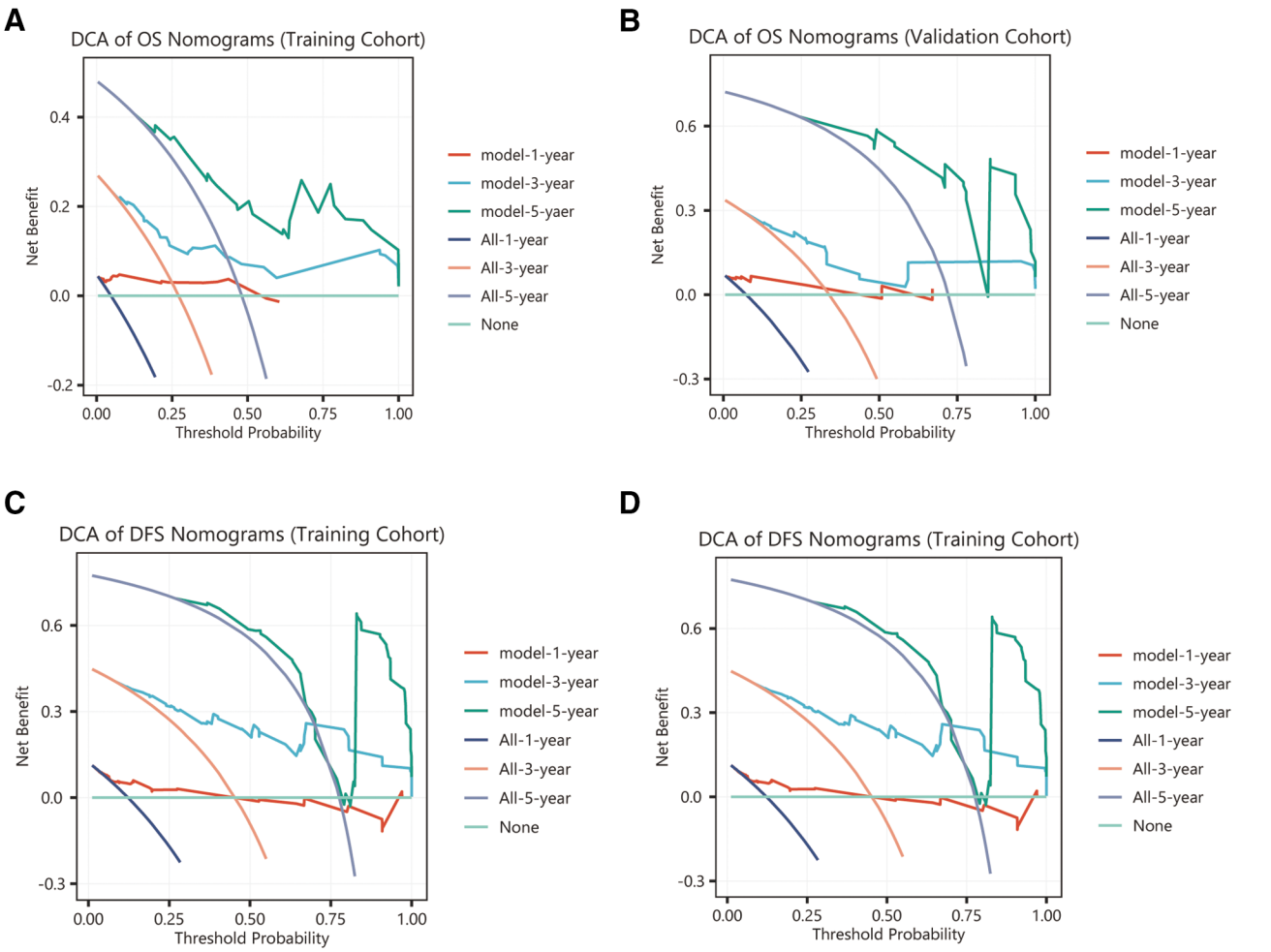

Figure 7. Decision curve analysis (DCA) for 1-year, 3-year, and 5-year OS and DFS from multivariable Cox regression across training cohorts (A and B) and validation cohorts (C and D).

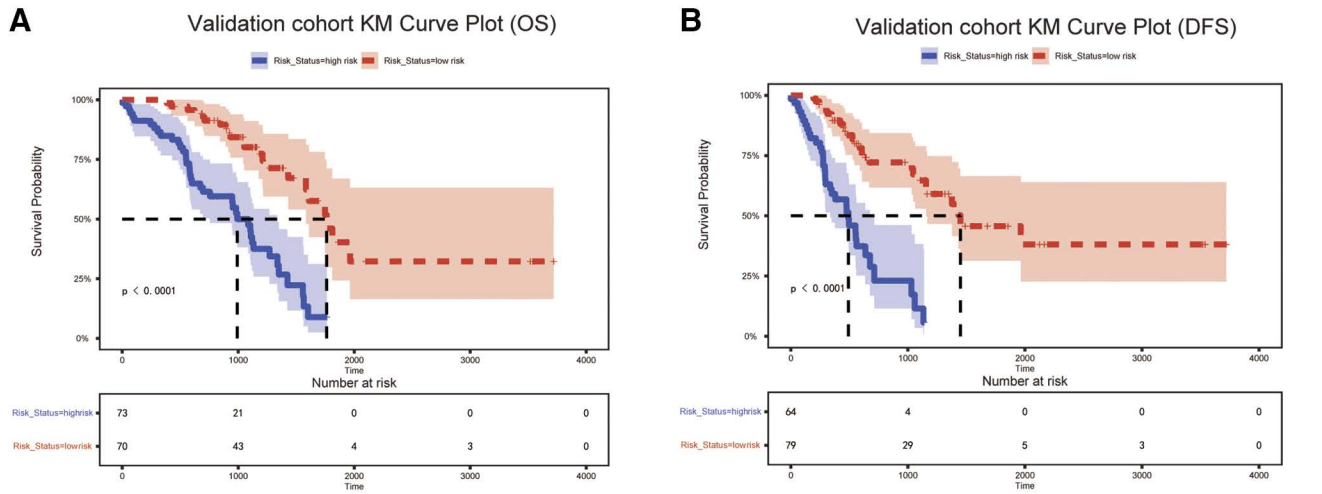

Figure 8. Kaplan–Meier survival plot for high and low-risk groups in the validation cohort about OS (A) and DFS (B).

determined to be an independent risk factor for OS and DFS in our multifactorial Cox regression analysis, suggesting its potential as a novel marker for gastric cancer. Future studies using cellular and animal models are required to explore *IGFL2*'s specific role in gastric cancer development.

Our model, incorporating *IGFL2*, the surgeon's annual surgical volume, TNM staging, CEA levels, and grade, among other factors, was stringently validated within the validation cohort, achieving receiver operating characteristic values >0.7. It outperformed the traditional TNM staging model across various metrics, including the C-index, calibration, and DCA curves. KM curves for the high-risk and low-risk groups, defined by risk coefficients, showed marked differences in survival within the validation cohort, highlighting the model's robustness and predictive precision.

This study has some limitations, notably the time frame from 2008 to 2010, which aligns with the initial phase of laparoscopic surgery at our institution. In this early stage, the survival rates between laparoscopic and open surgeries showed no significant variance, possibly due to nascent adoption and fewer surgeries being performed. Furthermore, the scope of the study was constrained by its small sample size and single-center nature. To corroborate the observed differences in *IGFL2* expression and its prognostic significance, it is imperative to broaden the research to include more centers and a larger sample size to enhance the robustness of the results.

In summary, our findings suggest that the annual surgical volume of gastric cancer surgeons and the expression levels of *IGFL2* are closely associated with patient outcomes. To improve surgical outcomes and patient survival rates, it is crucial to develop a thorough surgical training and accreditation system for gastric cancer surgeons in China. Therefore, *IGFL2* has emerged as a potential therapeutic target. Future efforts should focus on broadening the research base by including more sample centers and increasing the sample size to further investigate the differences in *IGFL2* expression and delve into the underlying mechanisms and immune responses.

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