

# World Journal of *Gastrointestinal Surgery*

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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

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## Retrospective Study

# Nomogram model including *LATS2* expression was constructed to predict the prognosis of advanced gastric cancer after surgery

Nan Sun, Bi-Bo Tan, Yong Li

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## Abstract

### BACKGROUND

Gastric cancer is a leading cause of cancer-related deaths worldwide. Prognostic assessments are typically based on the tumor-node-metastasis (TNM) staging system, which does not account for the molecular heterogeneity of this disease. *LATS2*, a tumor suppressor gene involved in the Hippo signaling pathway, has been identified as a potential prognostic biomarker in gastric cancer.

### AIM

To construct and validate a nomogram model that includes *LATS2* expression to predict the survival prognosis of advanced gastric cancer patients following radical surgery, and compare its predictive performance with traditional TNM staging.

### METHODS

A retrospective analysis of 245 advanced gastric cancer patients from the Fourth Hospital of Hebei Medical University was conducted. The patients were divided into a training group (171 patients) and a validation group (74 patients) to develop and test our prognostic model. The performance of the model was determined using C-indices, receiver operating characteristic curves, calibration plots, and decision curves.

### RESULTS

The model demonstrated a high predictive accuracy with C-indices of 0.829 in the training set and 0.862 in the validation set. Area under the curve values for three-year and five-year survival prediction were significantly robust, suggesting an excellent discrimination ability. Calibration plots confirmed the high concordance between the predictions and actual survival outcomes.

## CONCLUSION

We developed a nomogram model incorporating LATS2 expression, which significantly outperformed conventional TNM staging in predicting the prognosis of advanced gastric cancer patients postsurgery. This model may serve as a valuable tool for individualized patient management, allowing for more accurate stratification and improved clinical outcomes. Further validation in larger patient cohorts will be necessary to establish its generalizability and clinical utility.

**Key Words:** Gastric cancer; *LATS2*; Column line graph; Prognosis; Advanced gastric cancer survival; Molecular biomarkers; Predictive analytics in oncology; Survival analysis

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**Core Tip:** This study focuses on developing a prognostic model for patients with advanced gastric cancer postsurgery by integrating *LATS2* expression and clinicopathological features into a nomogram. It highlights the significance of the *LATS2* gene in improving prognostic predictions beyond traditional tumor-node-metastasis staging. Our model demonstrates excellent predictive accuracy and clinical utility, which indicates its potential for enhancing individualized patient care through better risk stratification. Future studies should focus on external validation to confirm the model's applicability across diverse patient populations.

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## INTRODUCTION

Gastric cancer ranks fifth and fourth among all malignant tumors globally in terms of incidence and mortality, respectively[1], and poses a serious threat to human health. The prognosis of gastric cancer remains unsatisfactory because there are no specific and obvious symptoms during the early stages, thus most patients are at an advanced stage at the time of presentation[2]. The poor prognosis of advanced gastric cancer may be related, in part, to the heterogeneous nature of gastric cancer, which involves various gene mutations and molecular signaling pathways, some of which may be exploited for prognosis and targeted drug therapy[3-6].

Nomograms have been used to predict the survival prognosis of cancer patients through the construction of multifactorial regression models. These models integrate multiple clinical factors based on the relative degree of contribution of each to the outcome variables, followed by visualization of the data[7]. Nomograms have been used for colorectal cancer[8], lung adenocarcinoma[9], breast cancer[10], endometrial stromal sarcoma[11], and other tumors to accurately predict patient prognosis.

Large tumor suppressor kinase (LATS) was first discovered in *Drosophila melanogaster* in 1995. An ortholog was found to exist in humans in subsequent studies, which included LATS1 and LATS2[12]. LATS is a core member of the Hippo signaling pathway and plays an important role in maintaining cellular homeostasis[13,14]. LATS also has a role in the development of gastric cancer by inhibiting tumor cell proliferation and promoting apoptosis[15,16].

In this study, 245 gastric cancer patients were retrospectively analyzed to determine the clinical value of *LATS2* expression on the survival prognosis of patients with advanced gastric cancer. *LATS2* was incorporated into a prognostic prediction model of postoperative gastric cancer patients to generate a model that enables the prognostic assessment of patients with advanced gastric cancer. The results were visualized in the form of a nomogram and the predictive efficacy of the model was evaluated.

## MATERIALS AND METHODS

### Research subjects

A total of 245 patients with advanced gastric cancer who underwent surgery in the Department of Surgery at the Fourth Affiliated Hospital of Hebei Medical University from March 2015 to March 2017 were retrospectively selected. The patients were randomly divided into a training group and a validation group at a 7:3 ratio. The training group was used to screen variables and construct models, whereas the validation group was used to validate the models obtained from the training group. The tumor were surgically resected and analyzed for pathology and by immunohistochemical staining. The tumor-node-metastasis (TNM) stage was determined according to the AJCC 8<sup>th</sup> edition standard TNM staging system. The data in were obtained from the postoperative pathology reports and the patient clinical information was collected through the hospital's independent information system. For immunohistochemistry, the intensity and



extent of staining were assessed semi-quantitatively, with scores of 0-3 defined as low expression and scores of 4-9 defined as high expression. This was a retrospective study approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval No. 2019ME0039).

**Inclusion criteria:** (1) Confirmed diagnosis of advanced gastric cancer along with radical gastrectomy (D2 lymph node dissection, R0 resection); (2) M0 patients without distant metastasis; (3) Diagnosis of primary gastric adenocarcinoma, which was clearly defined by postoperative pathology and immunohistochemical staining; (4) Complete medical records and immunohistochemistry analysis data; (5) No chemotherapy, radiotherapy, immunotherapy, or other tumor present; and (6) The depth of cancer cell invasion reached the muscle layer, serous layer, or extraserous layer (T stage  $\geq$  T2).

**Exclusion criteria:** (1) Patients aged  $< 18$  years old and survival time  $< 1$  month; (2) Combination of severe anemia, infection, autoimmune disease, hematologic disease, or inflammation in the last month; (3) Combination of severe brain, heart, liver, kidney, or other vital organ disease; (4) Recurrence, combination of distant metastasis, or history of other malignant neoplasms; (5) Recent use of antibiotics, anti-inflammatory drugs; and (6) Incomplete pathological data or postoperative loss of patient contact.

### Observation indicators

The collected clinical data included: gender, age, comorbidities (hypertension, diabetes mellitus, chronic lung disease), history of smoking, LATS2, history of alcohol consumption, tumor size, lymphatic invasion, T-stage, and N stage.

### Survival follow-up

Follow-up data were obtained from inpatient medical records, outpatient medical records, and telephone consultations. Patients were monitored every three months during the first two years following surgery and every six months after two years. Overall survival (OS) was defined as the time from the start of treatment to death from any cause. For patients lacking study endpoints, we recorded the latest follow-up date, which was January 31, 2022, for the included patients. Local recurrence or distant metastasis was determined based on a computed tomography (CT)-enhanced scan, fiberoptic gastroscopy biopsy, bone scan, magnetic resonance imaging, or positron emission tomography/CT.

### Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as the median and interquartile range. Differences in the distribution of categorical variables between the training and validation groups were tested using a chi-square test or Fisher's exact test. Differences in the distribution of continuous variables between the two groups were tested using a *t*-test. Hazard ratios and 95%CI for each risk factor were calculated using a one-way Cox regression. Significant effects from the unifactorial analysis were included in the multifactorial Cox regression based on Akaike information criteria. Significant clinical variables in the multifactorial analysis were independent predictors of overall survival and were used to construct nomogram plots to estimate three-year and five-year overall and progression-free survival rates as well as to generate Kaplan-Meier survival curves. The C-index and receiver operating characteristic (ROC) curves were plotted, which were used to assess the discriminatory ability of the nomogram charts. C-index and an area under curve (AUC)  $\geq 0.7$  indicated that the nomogram charts had good predictive discriminatory ability. Calibration plots were used to assess the gap between the predicted and actual results of the nomogram graphs. A decision curve analysis was used to assess the clinical benefit of the nomogram charts. *P*-values were used for all statistical analyses and *P*  $< 0.05$  was considered statistically significant. Statistical analysis and plotting of the data were done using R 4.2.1 (<http://www.R-project.org/>) software and the RStudio environment.

## RESULTS

### Analysis of general clinical data

A total of 245 patients were randomly divided into a training group (171) and a validation group (74) in a 7:3 ratio. Among all patients, the majority were male (80.41%) and most of them were older than 65 years (60.00%) (Table 1). More than half of the patients did not have hypertension (64.90%), diabetes mellitus (90.61%), or chronic lung disease (96.33%), whereas a minority had no history of smoking (8.98%). Most of the patients exhibited lymphatic invasion (81.63%) and high LATS2 expression (66.90%). Approximately half of the patients had a history of alcohol consumption. Most patients had a tumor diameter greater than 5 cm (83.67%) and staged as T4 (72.24%) and N3 (30.61%).

### Unifactorial and multifactorial Cox analysis

Based on a unifactorial Cox analysis, age, lymphatic invasion, LATS2 expression, tumor size, T stage, and N stage had predictive value (Table 2). In a multifactorial Cox analysis, all of the above factors had independent predictive value, except for age, which was included in the nomogram model. As shown in Figure 1, the survival rate of patients with high LATS2 expression was higher compared with that of low-expressing patients.

### Establishment and validation of a nomogram

Based on the results of a multifactorial Cox analysis, lymphatic invasion, LATS2, tumor size, T, and N were included in the nomogram (Figure 2), and the consistency indices (C-index) of the three clinical prediction models, namely TN staging, TN staging combined with LATS2, and the nomogram model, were calculated, respectively, according to the

Table 1 Clinical information, *n* (%)

Characteristics	All patients cases (%) / median (IQR)	Training group cases (%) / median (IQR)	Validation group cases (%) / median (IQR)	<i>P</i> value
Sex				
Male	197 (80.41)	142 (83.04)	55 (74.32)	0.16
Female	48 (19.59)	29 (16.96)	19 (25.68)	
Age				
< 65	98 (40.00)	64 (37.43)	34 (45.95)	0.27
≥ 65	147 (60.00)	107 (62.57)	40 (54.05)	
Hypertension				
No	159 (64.90)	115 (67.25)	44 (59.46)	0.30
Yes	86 (35.10)	56 (32.75)	30 (40.54)	
Diabetes				
Yes	23 (9.39)	13 (7.60)	10 (13.51)	0.22
No	222 (90.61)	158 (92.40)	64 (86.49)	
Chronic lung disease				
Yes	9 (3.67)	6 (3.51)	3 (4.05)	1
No	236 (96.33)	165 (96.49)	71 (95.95)	
Smoking				
Yes	223 (91.02)	154 (90.06)	69 (93.24)	0.58
No	22 (8.98)	17 (9.94)	5 (6.76)	
Lymphatic invasion				
Yes	200 (81.63)	140 (81.87)	60 (81.08)	1
No	45 (18.37)	31 (18.13)	14 (18.92)	
LATS2				
High	164 (66.90)	121 (70.70)	43 (58.10)	0.60
Low	81 (33.10)	50 (29.30)	31 (41.80)	
Alcohol consumption				
Yes	135 (55.10)	93 (54.39)	42 (56.76)	0.84
No	110 (44.90)	78 (45.61)	32 (43.24)	
Tumor size				
> 5 cm	205 (83.67)	145 (84.80)	60 (81.08)	0.59
≤ 5 cm	40 (16.33)	26 (15.20)	14 (18.92)	
T stage				
2	45 (18.37)	26 (15.20)	19 (25.68)	0.11
3	23 (9.39)	15 (8.77)	8 (10.81)	
4	177 (72.24)	130 (76.03)	47 (63.51)	
N stage				
0	74 (30.20)	54 (31.58)	20 (27.03)	0.62
1	45 (18.37)	28 (16.37)	17 (22.97)	
2	51 (20.82)	35 (20.47)	16 (21.62)	
3	75 (30.61)	54 (31.58)	21 (28.38)	

IQR: Interquartile range.

**Table 2 Unifactorial and multifactorial cox analysis**

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Sex						
Male	Reference					
Female	0.700	0.397-1.233	0.217			
Age						
< 65	Reference			Reference		0.199
≥ 65	6.632	4.026-10.926	< 0.001	1.780	0.739-4.286	
Hypertension						
No	1.202	0.800-1.812	0.378			
Yes	Reference					
Diabetes						
Yes	1.256	0.608-2.594	0.537			
No	Reference					
Chronic lung disease						
Yes	0.807	0.255-2.552	0.716			
No	Reference					
Smoking						
Yes	0.900	0.604-1.312	0.605			
No	Reference					
Lymphatic invasion						
Yes	13.121	7.840-21.959	< 0.001	3.251	1.519-6.960	0.002
No	Reference			Reference		
LATS2						
High	0.327	0.217-0.495	< 0.001	0.522	0.307-0.887	0.016
Low	Reference			Reference		
Alcohol consumption						
Yes	1.186	0.796-1.767	0.402			
No	Reference					
Tumor size						
> 5 cm	Reference			Reference		
≤ 5 cm	319.955	42.319-2419.010	< 0.001	79.564	8.657-731.251	< 0.001
T stage						
2	Reference					
3	6.691	2.407-18.598	< 0.001	9.620	3.390-27.300	< 0.001
4	5.452	2.372-12.536	< 0.001	4.156	1.753-9.850	< 0.001
N stage						
0	Reference					
1	1.650	0.824-3.304	0.158	1.762	0.872-3.563	0.115

2	2.237	1.186-4.220	0.013	2.248	1.155-4.376	0.017
3	4.332	2.452-7.653	< 0.001	3.874	2.127-7.056	< 0.001

HR: Hazard ratio.

**Table 3 Model consistency index (c-index)**

Variables		Training group		Validation group	
		C-index	95%CI	C-index	95%CI
Overall survival	TN stage	0.702	0.653-0.751	0.756	0.682-0.830
	TN stage + LATS2	0.785	0.742-0.828	0.830	0.761-0.899
	Nomogram	0.829	0.788-0.870	0.862	0.805-0.919

results of the clinical data. After comparing the three clinical prediction models, we concluded that the nomogram model had accurate clinical prognostic prediction (Table 3). The C-indexes of the training and validation sets were 0.829 and 0.862, respectively, which were higher compared with those of the two models, TN staging, and TN staging combined with LATS2. The three-year and five-year AUC of TN staging combined with LATS2 in the training set were higher compared with those of the TN staging model, indicating that LATS2 has a positive significance for the prognosis of progressive gastric cancer. The three-year and five-year AUC of the training set of the nomogram graph model were 0.8723 and 0.8525, respectively, which were higher compared with those of the two models of TN staging and TN staging combined with LATS2, which suggests that our model has a good predictive performance (Figure 3). Similarly, the three-year and five-year AUC of the validation set nomogram model were 0.9129 and 0.8763, respectively (Figure 4), indicating that it had a good discriminatory ability. As shown in Figures 5 and 6, the prognosis predicted by the nomogram model was in high agreement with the actual real-world situation.

## DISCUSSION

Accurate prediction of postoperative prognosis is important for optimizing treatment strategies and improving outcomes in patients with advanced gastric cancer. In this study, we developed and validated a prognostic model incorporating LATS2 expression and clinicopathological characteristics to predict overall survival at three and five years following radical surgery for advanced gastric cancer.

Several findings indicate that our nomogram model has significant clinical value for postoperative prognosis prediction. First, the model showed good discrimination, with C-indices of 0.829 and 0.862 in the training and validation sets, respectively. The AUCs at three and five years were also high, ranging from 0.8525 to 0.9129, further demonstrating the strong predictive accuracy. Calibration plots revealed a high level of agreement between the predicted and actual survival. In addition, a decision curve analysis showed that the predictions using our model resulted in a superior net benefit compared with predictions based on TNM staging alone or TNM combined with LATS2 across a wide range of threshold probabilities. Taken together, the results provide solid evidence that the model can accurately stratify patients by prognostic risk.

Of note, the incorporation of LATS2 expression data improved model performance over TNM staging alone. High LATS2 expression was associated with a significantly better prognosis, which is consistent with its known tumor suppressive function. As an important component of the Hippo signaling pathway, which regulates cell proliferation and apoptosis, dysregulation of LATS2 affects key oncogenic mechanisms in gastric cancer. Our findings indicate that LATS2 merits inclusion as a prognostic biomarker, lending additional risk stratification information beyond standard clinicopathological factors.

In clinical practice, TNM staging is primarily used to roughly predict prognosis; however, it lacks individualization and accuracy in predicting postoperative treatment and prognosis[17]. The construction of effective prognostic tools is of great significance for the individualized treatment of patients, for whom the nomogram has attracted much attention in recent years because of its convenient and intuitive clinical application[18]. Some models for predicting patient prognosis in gastric cancer have been reported, such as a gastric cancer prognosis model based on oxidative stress genes[19], and a model related to scorched death[20]; however, there are many candidate genes involved and research is immature, so the clinical feasibility is not high. For example, age, race, marital status, TNM stage, surgery, chemotherapy, grade, and the number of positive regional nodes can be used to predict the survival of gastric cancer patients[21]; however, the C-index and area under the ROC curve are low, thus the accuracy of prognosis for gastric cancer is not high. To more accurately predict the prognosis of patients with gastric cancer following surgery and for clinical application, it is significant to combine biomarkers that have an important role in gastric cancer with clinicopathological features.

The user-friendly visual format of the nomogram facilitates its application to clinical practice. By mapping the profiles of individual patients onto the diagram, physicians can readily estimate three- and five-year survival probabilities. This

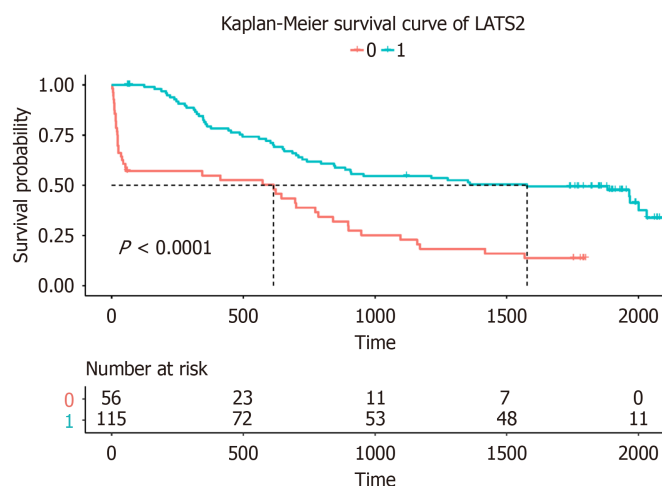


Figure 1 Kaplan-Meier survival curve for LATS2 expression.

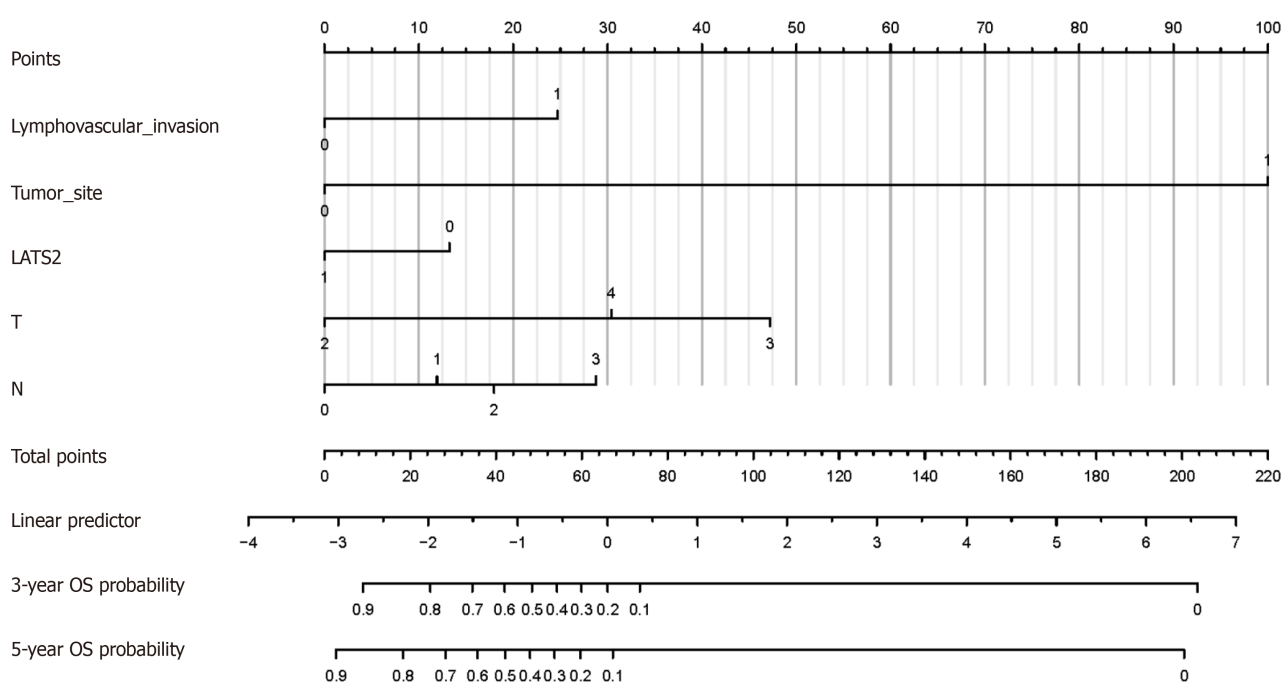


Figure 2 Nomogram consisting of lymphatic invasion, LATS2, tumor size, and T and N stages.

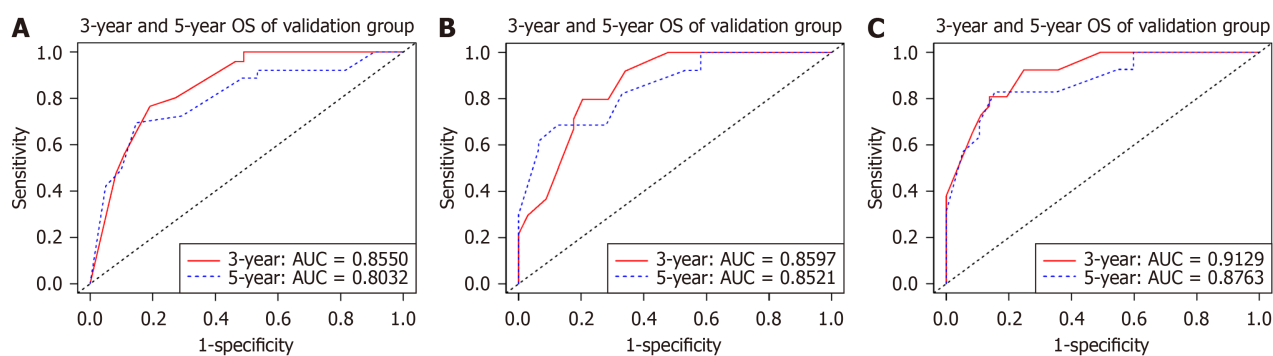
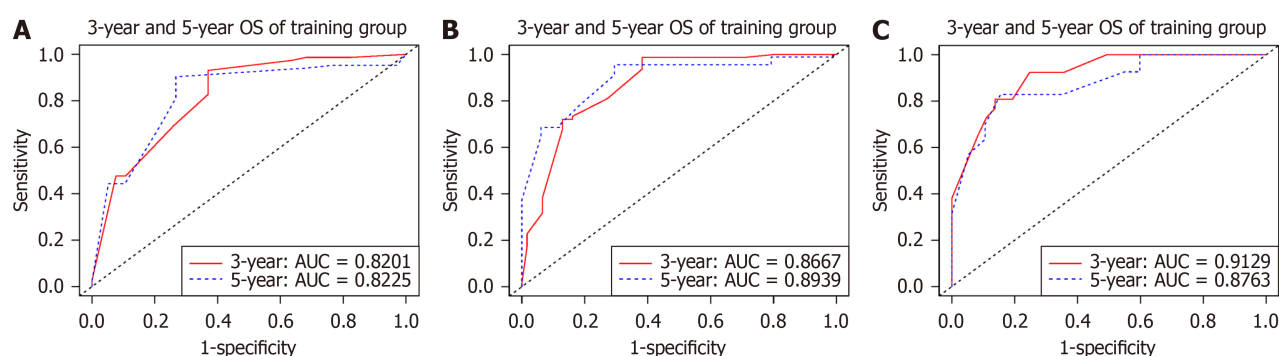
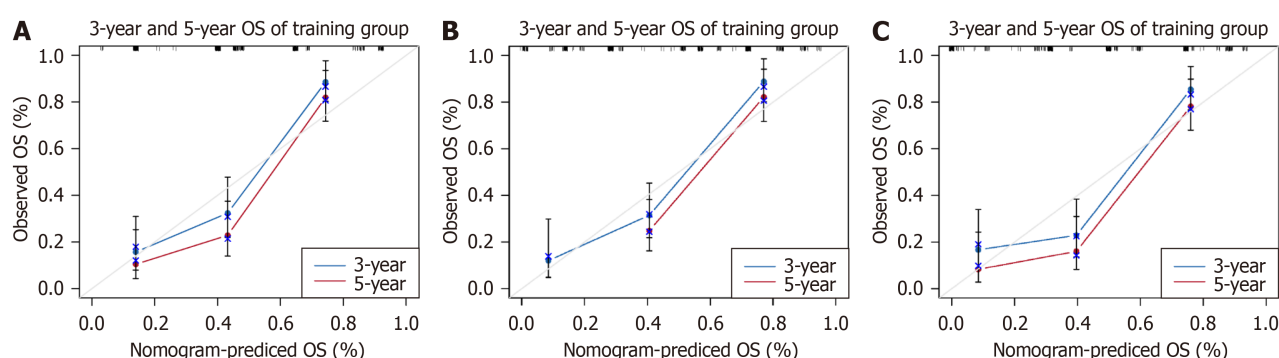


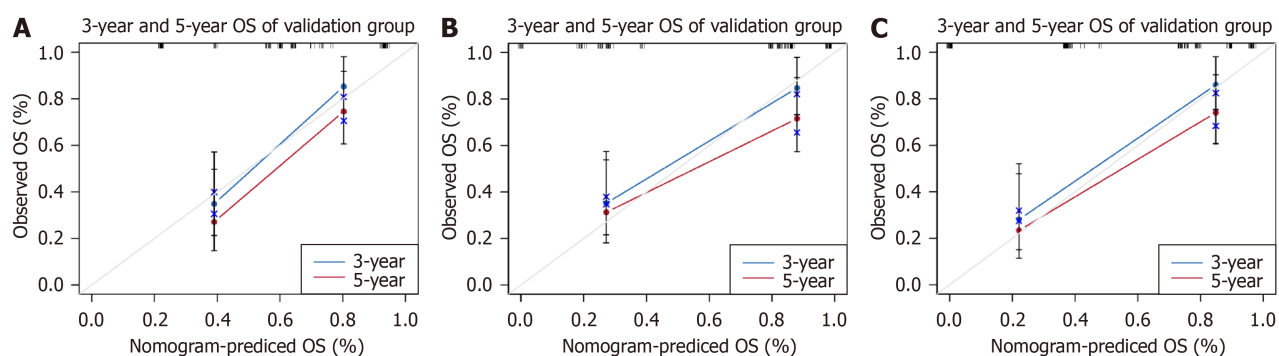
Figure 3 Receiver operating characteristic curve of training set. A: Receiver operating characteristic (ROC) curve of TN stage; B: ROC curve of TN stage + LATS2; C: ROC curve of the target model.



**Figure 4 Receiver operating characteristic curve of validation set.** A: Receiver operating characteristic (ROC) curve of TN stage; B: ROC curve of TN stage + LATS2; C: ROC curve of the target model.



**Figure 5 Calibration diagram of training set.** A: Calibration diagram of TN stage; B: Calibration diagram of TN stage + LATS2; C: Calibration plot of the target model.



**Figure 6 Calibration diagram of validation set.** A: Calibration diagram of TN stage; B: Calibration diagram of TN stage + LATS2; C: Calibration plot of the target model.

may facilitate important management decisions, such as selecting high-risk patients likely to benefit from adjuvant chemotherapy or more intensive follow-up. Dynamic risk assessment at successive time points may also help to determine if and when to modify treatment regimens.

By enabling more accurate risk stratification and prognosis prediction, this model has the potential to significantly improve clinical decision-making and outcomes for patients undergoing radical surgery for advanced gastric cancer. The next step will be an external validation of the model using patient cohorts from other centers. Broader validation will provide further support for its generalizability and clinical utility. The *LATS* gene family is a core component of the Hippo pathway and an important regulator of homeostasis *in vivo*, of which *LATS2* expression is low in gastric cancer tissues[16]. Previous studies have confirmed that in gastric cancer, *LATS2* is involved in tumor cell growth, invasion, migration[22–24], and mesenchymal transformation[25]. Previous studies have confirmed that *LATS2* expression in gastric cancer is closely associated with clinicopathological factors[26] and the survival rate of gastric cancer patients[27].

Some limitations should be acknowledged when interpreting our results. First, the sample size, though adequately powered for model development and internal validation, was relatively small and derived from a single center. Thus, large prospective studies are warranted to validate these findings. Second, data on certain potential prognostic variables,



such as the Lauren classification and Borrmann classification, were not available for inclusion. Future models incorporating a more comprehensive set of clinical and molecular data may improve the prognostic accuracy. Finally, the current study lacked an external validation set. Validating the model using an independent patient population will also be essential to confirm its wider applicability.

## CONCLUSION

In conclusion, we developed an internally validated, robust prognostic model for advanced gastric cancer after radical surgery, incorporating both tumor biomarkers and clinicopathological data. The results indicate that the model enables superior discrimination of low- *vs* high-risk patients compared with standard prognostic approaches. Following additional external validation, translation of this prognostic tool into clinical practice may significantly assist therapeutic decision-making and ultimately improve patient outcomes. The next steps will be to expand validation of the model across multiple centers as well as investigator-initiated trials to evaluate its impact on clinical management and survival.

## ARTICLE HIGHLIGHTS

### Research background

Gastric cancer is a significant global health concern, ranking fifth in incidence and fourth in mortality among all cancers. The prognosis is often poor due to late-stage diagnosis. Molecular signaling pathways and gene mutations, like those involving the *LATS* gene, play a crucial role in the pathogenesis of gastric cancer, affecting prognosis and treatment options.

### Research motivation

There is a need for more accurate prognostic models for advanced gastric cancer that can incorporate molecular biomarkers like LATS2 expression. This would improve individual prognosis assessments and aid in personalizing treatment strategies.

### Research objectives

The objective of this research is to construct a nomogram model based on LATS2 expression and evaluate its predictive accuracy for the survival prognosis of patients with advanced gastric cancer post-surgery.

### Research methods

The study retrospectively analyzed clinical data of 245 advanced gastric cancer patients, dividing them into a training group and a validation group. Univariate and multivariate Cox regression analyses were used to assess the prognostic value of LATS2 expression. The model's performance was analyzed through various statistical methods including C-index, receiver operating characteristic curves, calibration curves, and decision curves.

### Research results

The nomogram model demonstrated high C-indexes and area under curve values, indicating strong predictive accuracy. Calibration plots showed high agreement between predicted and actual survival, and decision curves indicated the model's superior net benefit over tumor-node-metastasis (TNM) staging alone.

### Research conclusions

The nomogram model incorporating LATS2 expression provided significant clinical value in predicting the postoperative prognosis of advanced gastric cancer patients. It showed superior discrimination and net clinical benefit compared to TNM staging alone.

### Research perspectives

The study suggests that the developed model can assist in clinical decision-making, but acknowledges limitations such as the small, single-center sample size. Future research should aim at external validation and include more comprehensive clinical and molecular data to optimize prognostic accuracy.

## FOOTNOTES

**Author contributions:** Sun N designed the research study; Sun N, Tan BB and Li Y performed the research; Sun N and Tan BB contributed analytic tools; Sun N and Li Y analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

**Institutional review board statement:** This was a retrospective study approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval No. 2019ME0039).

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** All authors claim no conflicts of interest.

**Data sharing statement:** Raw data, statistical codes and datasets are available from the corresponding author.

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