Optimizing Clinical Outcomes: A Nomogram for Predicting Gastric Cancer Survival in Elderly Patients Following Gastrectomy

Jun Li[1], Jiang Zhu[2,3], Xu Song[1], Yuhang Zhou[1], Jin Zhang[1]
[1]Department of General Surgery, Affiliated Hospital of Jiangsu University, Jiangsu, China
[2]Department of Hepatobiliary Surgery, Danyang City People's Hospital, Jiangsu 212300, China
[3]Department of Hepatobiliary Surgery, Danyang Hospital Affiliated to Nantong University, Jiangsu 212300, China

Corresponding author: Jin Zhang (e-mail: Zhangjinjsdx@163.com).

ABSTRACT **Background:** Owing to the aging global population, the prevalence of gastric cancer (GC) in the elderly is on the increase. The study aimed to investigate risk variables correlated with cancer-specific survival (CSS) and to construct and validate a nomogram to calculate the probability of CSS after gastrectomy in elderly patients with non-metastatic GC.

Methods: Overall, 5462 postgastrectomy patients with geriatric non-metastatic GC who were diagnosed between 2006 and 2015, and 1078 patients diagnosed between 2004 and 2005 from the Surveillance, Epidemiology, and End Results (SEER) database were incorporated in this study. We randomly selected 3846 patients from the 5462 patients to constitute the training cohort to construct the nomogram, and the other 1616 patients were used for internal validation. Additionally, the other 1078 patients were used for external validation. CSS predictors were screened using univariate Cox proportional hazards regression analysis, Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis, Random Survival Forest (RSF), and multivariate Cox proportional hazards regression analysis. A model for predicting CSS was developed using Cox proportional hazards regression analysis, and both static and dynamic web-based nomograms were provided.

Results: A total of 10 variables, including gender, age, race, tumor size, primary site, grade, positive lymph nodes (PLNs), examined lymph nodes (ELNs), T stage, and months from diagnosis to treatment (MFDTT), were incorporated in the development of the nomogram. The areas under the curve (AUCs) for the training cohort at 3, 5, and 10 years were 0.780 (95% CI, 0.765–0.795), 0.792 (95% CI, 0.778–0.807), and 0.803 (95% CI, 0.781–0.826). Following internal validation, these values were 0.809 (95% CI, 0.789–0.830), 0.822 (95% CI, 0.801–0.843), and 0.824 (95% CI, 0.793–0.854). The model-predicted CSS converges with the actual CSS according to the calibration curves. The nomogram showed higher clinical benefit than the TNM staging system, according to the decision curve analysis (DCA) for all three cohorts. The nomogram score was utilized as a basis for grouping high- and low-risk patients, and significant statistical differences ($p<0.0001$) were demonstrated between the two groups in the Kaplan–Meier (K-M) curves.

Conclusions: Our novel nomogram can conveniently and accurately predict CSS in elderly patients with non-metastatic GC after gastrectomy, which can assist clinicians in adopting individualized treatment strategies to improve the prognosis of elderly patients with GC.

INDEX TERMS nomogram, gastric cancer, prognosis, risk factors, SEER database.

I. INTRODUCTION

GGastric cancer (GC) poses a significant global health threat, ranking fifth in terms of cancer-specific morbidity and third in terms of cancer-specific mortality(1). Over 1 million new cases of GC are diagnosed annually, and most cases occur in elderly patients (≥65 years)(2). With ongoing global aging and the prevalence of cancer-causing factors, GC has become a major burden on the health of elderly patients.

In the treatment of non-metastatic GC, gastroplasty with standardized lymphadenectomy D2 remains the mainstay(3). Although diagnostic technology and therapeutic strategies have improved considerably, the survival time of elderly patients with GC remains worrisome and may be due to frailty,

poor nutrition, and an inflammatory background caused by the decline of physiologic systems in elderly patients(4,5). Furthermore, elderly patients frequently exhibit insidious onset of disease and develop complications in multiple organ systems, both of which contribute to short survival time(6,7). In current clinical practice, the 8th AJCC TNM staging system is used as a guideline for assessing prognosis and adjuvant therapy intensively. However, the TNM staging also has limitations in prognostic assessment(8,9). Differences in tumor biology and molecular genetic characteristics often lead to a heterogeneous prognosis of GC with the same stage(10). The prognostic factors of elderly patients with GC after gastrectomy are more complex and diverse; moreover, studies on the prognosis of this particular group have been deficient. Therefore, it is essential to design an individually tailored model for evaluating the prognosis of elderly patients with GC after gastrectomy to optimize treatment strategies.

This study aimed to investigate risk variables correlated with cancer-specific survival (CSS) and to construct and validate a nomogram to calculate the probability of CSS after gastrectomy in elderly patients with non-metastatic GC. Data from the Surveillance, Epidemiology, and End Results (SEER) database served as the basis for the construction and validation of the nomogram, which can accurately predict the long-term CSS after gastrectomy in elderly patients with non-metastatic GC and contribute to enhanced clinical benefits.

II. MATERIALS AND METHODS

A. DATA EXTRACTION

Based on data from the SEER database, 5462 elderly postgastrectomy patients with GC who were diagnosed between 2006 and 2015 were included in this retrospective cohort study. A 7:3 ratio was used to divide the patients into a training cohort (n=3846) and an internal validation cohort (n=1616). Additionally, we enrolled 1078 patients who were diagnosed between 2004 and 2005 as the external verification cohort. Informed consent and approval from the institutional ethics review board were not necessary since the SEER database is open to the public. All personal privacy data had been deleted before the SEER database was made available.

This study's inclusion criteria were as follows:
1) Age of diagnosis ≥65 years;
2) Diagnosed between 2006 and 2015;
3) Pathological diagnosis of gastric cancer; and
4) Patients with GC as the first and only primary malignancy.

The following were the exclusion criteria:
1) Death due to other causes or cases where the cause of death was unknown;
2) Cases with unknown survival status or racial information;
3) Patients who did not undergo gastrectomy or those with missing surgical information; and
4) Cases with an unknown stage or AJCC IV stage.

The procedures for inclusion and exclusion are described in Figure 1. From the SEER database, baseline information was extracted, including gender, age, race, marital status, primary tumor site, histologic type, grade, primary site surgery, radiation therapy, chemotherapy, tumor size, tumor extension, ELNs, PLNs, AJCC stage, MFDTT, survival time, cause of death, and vital status. The risk of non-cancer deaths is significantly increased in elderly patients, as they frequently have comorbidities(11). Given the impact of comorbidities on overall survival, we identified CSS as a key outcome. CSS is defined as the period from the cancer diagnosis to either cancer-specific death or the designated follow-up deadline.

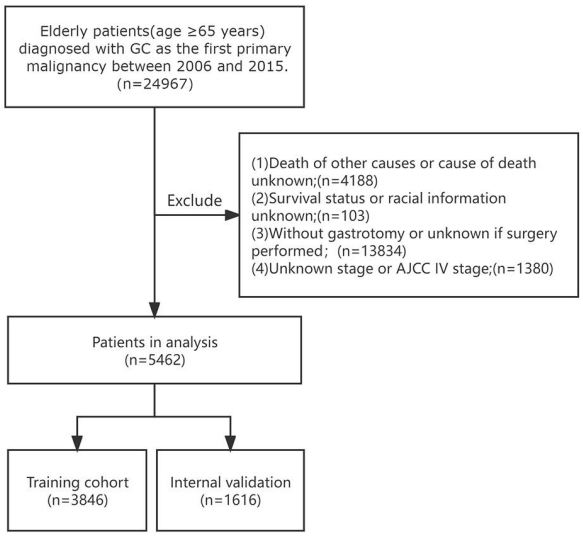


FIGURE 1. Flowchart showing the selection procedure of elderly patients with stage I–III gastric cancer from the surveillance, epidemiology, and end results (SEER) database.

B. RECLASSIFICATION OF VARIABLES

The 8th edition of the AJCC guidelines was used to reclassify the T stage, N stage, and TNM stages of all patients. Tumor size was stratified into three groups: <2 cm, 2–3 cm, and >3 cm, as well as the ELN, specifically 1–15 and ≥16(12–14). The primary site of the tumor was reclassified as cardia/fundus, body/antrum/pylorus, lesser curvature/greater curvature, and overlapping/stomach NOS according to the anatomical structure of the stomach. Since grade IV tumors are less common, a single category was created encompassing grade III and IV cases. Therefore, a total of three groups were developed based on the tumor grade: grade I/II, grade III/IV, and unknown.

C. SELECTION OF PREDICTORS

To identify possible risk factors for CSS, all variables in the training cohort were analyzed using univariate Cox regression analysis. Afterwards, the Spearman correlation analysis and multiple covariance analysis, including the significant covariates ($p < 0.05$) were performed to prevent

multicollinearity between variables from reducing the stability and accuracy of the model. We employed LASSO regression analysis and RSF to conduct a thorough screening of significant factors. Subsequently, we identified independent predictors for CSS through multivariate Cox regression analysis. Therefore, surgery, histologic type, and marital status were excluded. Ten variables, including age, gender, race, primary site, grade, tumor size, ELNs, T stage, PLNs, and MFDTT were used to construct the nomogram.

D. STATISTICAL ANALYSIS

R software version 4.2.3 was used for the statistical analyses. Differences in the distribution of data between the groups were examined using t test, x2 test, and the Mann–Whitney U test. Using univariate analysis and LASSO regression analysis, we selected 13 variables as the potential predictors for CSS. RSF was used to justify the importance of these factors. Multivariate Cox proportional hazards regression was used as the final method to identify independent risk factors for CSS and to construct the predictive model. Calibration curves were effectively used to evaluate the difference between predicted outcomes and actual values. Time-dependent receiver operating characteristic (ROC) curves and DCA were plotted to assess the nomogram and to compare it with the AJCC TNM staging system. Using risk scoring, the model could be used to accurately recognize high-risk and low-risk patients. The difference in survival between high-risk and low-risk patients was clearly illustrated using the Kaplan–Meier (K-M) curve. P values were bilateral, and $p < 0.05$ was defined as statistical significance.

III. RESULTS

A. PATIENTS' BASELINE CHARACTERISTICS

The clinical information of 5426 elderly patients with nonmetastatic GC were extracted from the SEER database. All the included patients had undergone gastrectomy and lymphadenectomy. To construct the nomogram, 3846 participants were used as the training cohort, while the other 1616 participants were used for internal validation. The demographic characteristics and clinicopathological features of all patients are summarized in Table 1. In parallel, Supplementary Table 1 summarizes the baseline characteristics of patients diagnosed in 2004 and 2005 who were included in the external validation cohort (n = 1078).

B. PREDICTOR SELECTION

To explore potential predictors for CSS, univariate analysis was first performed on the training cohort using Cox proportional risk regression. Our results suggested that chemotherapy and radiotherapy were not potential risk factors for CSS (Figure 2). The Spearman correlation analysis was conducted to avoid the effects of multicollinearity on the models. Significant correlations between TNM stage and several variables were demonstrated, and the same results existed for N stage and PLNs (Supplementary Figure 1). Multiple analyses of covariance of 13 variables with TNM stage and N stage removed showed that the variance inflation factors (VIFs) for all variables were less than 2 (Supplementary Table 2). In the LASSO regression analysis, 13 variables including gender, age, race, marital status, primary site, histologic type, grade, surgery, tumor size, T stage, ELNs, PLNs, and MFDTT were considered. The two Cox proportional hazards models (model 1 (13 variables) and model 2 (8 variables)) were constructed and compared using C-index and AUCs at 3, 5, and 10 years when $\log\lambda$ took the values of -5.625787 and -3.113876 (Figure 3). The results indicated that the C-index and AUCs of model 1 were higher than those of model 2 (Supplementary Table 3), and 13 variables were retained for further analyses.

To further validate the importance of these variables, a nonparametric method was developed to calculate the importance scores for each predictor using RSF. PLNs were revealed to be the most influential factor for CSS, followed by T stage, age, and ELNs, while the importance scores for surgery and histologic type were negative (Figure 4). Based on the multivariate COX regression analysis, marital status was not independently associated with CSS ($P>0.05$) (Figure 5). Ultimately, ten variables, including age, gender, race, primary site, tumor size, grade, PLNs, ELNs, T stage, and MFDTT, were confirmed to construct the predictive model.

C. CONSTRUCTION AND VALIDATION OF THE NOMOGRAM

According to the multivariate Cox regression analysis in the training cohort, ten significant risk factors were integrated into a nomogram that can predict the 3-, 5-, and 10-year CSS probabilities (Figure 6). Excellent calibration capability of the nomogram can be observed in the calibration curves for the three cohorts shown in Figure 7 A-C. Furthermore, the time-dependent ROC curves were implemented to evaluate the accurate predictability for 3-, 5-, 10-year CSS. The AUC values in the training cohort were 0.780 (95% CI, 0.765–0.795), 0.792 (95% CI, 0.778–0.807), and 0.803 (95% CI, 0.781–0.826) for 3-, 5-, 10-year CSS, respectively. In comparison, the AUC values for the AJCC TNM staging system in predicting 3-, 5-, 10-year CSS were 0.749 (95% CI, 0.735–0.764), 0.765 (95% CI, 0.750–0.780), and 0.761 (95% CI, 0.737–0.785), respectively (Figure 8 A). Similar results were obtained when the nomogram was checked using the internal and external validation cohorts (Figure 8 B,C).

TABLE 1. Patients' demographics and baseline characteristics

Characteristic	Total (n = 5462)	Training cohort(n = 3846)	Validation cohort (n = 1616)	p-value
Sex				0.088
Male	3271 (59.89%)	2275 (59.15%)	996 (61.63%)	
Female	2191 (40.11%)	1571 (40.85%)	620 (38.37%)	
Age (Mean ± SD)	74 ± 7	74 ± 7	74 ± 7	0.444
Race				0.878
White	3593 (65.78%)	2538 (65.99%)	1055 (65.28%)	
Black	566 (10.36%)	402 (10.45%)	164 (10.15%)	
Asian or Pacific Islander	1261 (23.09%)	877 (22.80%)	384 (23.76%)	
American Indian/Alaska Native	42 (0.77%)	29 (0.75%)	13 (0.80%)	
Marital Status				0.060
Married	3334 (61.04%)	2350 (61.10%)	984 (60.89%)	
Unmarried	1940 (35.52%)	1378 (35.83%)	562 (34.78%)	
Unknown	188 (3.44%)	118 (3.07%)	70 (4.33%)	
Primary Site				0.658
Cardia/Fundus	1484 (27.17%)	1047 (27.22%)	437 (27.04%)	
Body/antrum/Pylorus	2254 (41.27%)	1568 (40.77%)	686 (42.45%)	
Lesser/Greater curvature	890 (16.29%)	636 (16.54%)	254 (15.72%)	
Overlapping/Stomach, NOS	834 (15.27%)	595 (15.47%)	239 (14.79%)	
Histologic Type				0.980
Adenocarcinoma	3986 (72.98%)	2806 (72.96%)	1180 (73.02%)	
Signet ring cell carcinoma	869 (15.91%)	614 (15.96%)	255 (15.78%)	
Others/Unknown	607 (11.11%)	426 (11.08%)	181 (11.20%)	
Grade				0.259
I/II	1742 (31.89%)	1246 (32.40%)	496 (30.69%)	
III/IV	3455 (63.26%)	2407 (62.58%)	1048 (64.85%)	
Unknown	265 (4.85%)	193 (5.02%)	72 (4.46%)	
Surgery				0.094
Near total or total gastrectomy	4330 (79.27%)	3026 (78.68%)	1304 (80.69%)	
Others	1132 (20.73%)	820 (21.32%)	312 (19.31%)	
Tumor Size				0.658
< 2 cm	701 (12.83%)	494 (12.84%)	207 (12.81%)	
2–3 cm	971 (17.78%)	673 (17.50%)	298 (18.44%)	
> 3 cm	3355 (61.42%)	2363 (61.44%)	992 (61.39%)	
Unknown	435 (7.96%)	316 (8.22%)	119 (7.36%)	
T Stage				0.826
T1	1206 (22.08%)	860 (22.36%)	346 (21.41%)	
T2	665 (12.18%)	469 (12.19%)	196 (12.13%)	
T3	2115 (38.72%)	1470 (38.22%)	645 (39.91%)	
T4a	1125 (20.60%)	798 (20.75%)	327 (20.24%)	
T4b	351 (6.43%)	249 (6.47%)	102 (6.31%)	
N Stage				0.487
N0	2327 (42.60%)	1660 (43.16%)	667 (41.27%)	
N1	1021 (18.69%)	713 (18.54%)	308 (19.06%)	
N2	924 (16.92%)	630 (16.38%)	294 (18.19%)	
N3a	822 (15.05%)	583 (15.16%)	239 (14.79%)	
N3b	368 (6.74%)	260 (6.76%)	108 (6.68%)	
TNM Stage				0.429
I	1488 (27.24%)	1048 (27.25%)	440 (27.23%)	
II	1671 (30.59%)	1195 (31.07%)	476 (29.46%)	
III	2303 (42.16%)	1603 (41.68%)	700 (43.32%)	
ELNs				0.968
Nodes < 16	2820 (51.63%)	1985 (51.61%)	835 (51.67%)	
Nodes ≥ 16	2642 (48.37%)	1861 (48.39%)	781 (48.33%)	
PLNs, Median (IQR)	1.0 (0.0, 5.8)	1.0 (0.0, 5.0)	1.0 (0.0, 6.0)	0.292
Radiation				0.482
Yes	1539 (28.18%)	1073 (27.90%)	466 (28.84%)	
No/Unknown	3923 (71.82%)	2773 (72.10%)	1150 (71.16%)	
Chemotherapy				0.992
Yes	2424 (44.38%)	1707 (44.38%)	717 (44.37%)	
No/Unknown	3038 (55.62%)	2139 (55.62%)	899 (55.63%)	
MFDTT (Months), Median (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.924
Time (Months), (Mean ± SD)	50 ± 48	49 ± 47	51 ± 49	0.120
Status				0.241
Dead	3582 (65.58%)	2541 (66.07%)	1041 (64.42%)	
Alive/Off	1880 (34.42%)	1305 (33.93%)	575 (35.58%)	

Abbreviations: SD, standard deviation; IQR, interquartile range; MFDTT, Months from diagnosis to treatment; ELNs, Examined lymph nodes; PLNs, Positive lymph nodes

SUPPLEMENTARY TABLE 1. Patient demographics and baseline characteristics in external validation cohort

Characteristic	External validation cohortn = 1078
Gender	
Male	633 (58.72%)
Female	445 (41.28%)
Age	
Mean ± SD	75 ± 7
Race	
White	727 (67.44%)
Black	116 (10.76%)
Asian or Pacific Islander	226 (20.96%)
American Indian/Alaska Native	9 (0.83%)
Marital Status	
Married	639 (59.28%)
Unmarried	421 (39.05%)
Unknown	18 (1.67%)
Primary Site	
Cardia/Fundus	288 (26.72%)
Body/antrum/Pylorus	449 (41.65%)
Lesser/Greater curvature	165 (15.31%)
Overlapping/Stomach,NOS	176 (16.33%)
Histologic Type	
Adenocarcinoma	824 (76.44%)
Signet ring cell carcinoma	179 (16.60%)
Others/Unknown	75 (6.96%)
Grade	
I/II	326 (30.24%)
III/IV	713 (66.14%)
Unknown	39 (3.62%)
Surgery	
Near total or total gastrectomy	857 (79.50%)
Others	221 (20.50%)
Tumor Size	
< 2cm	94 (8.72%)
2-3cm	171 (15.86%)
> 3cm	726 (67.35%)
Unknown	87 (8.07%)
T Stage	
T1	184 (17.07%)
T2	112 (10.39%)
T3	397 (36.83%)
T4a	282 (26.16%)
T4b	103 (9.55%)
N Stage	
N0	357 (33.12%)
N1	215 (19.94%)
N2	212 (19.67%)
N3a	204 (18.92%)
N3b	90 (8.35%)
TNM Stage	
I	231 (21.43%)
II	278 (25.79%)
III	569 (52.78%)
ELNs	
Nodes<16	688 (63.82%)
Nodes>=16	390 (36.18%)
PLNs	
Median (IQR)	2.0 (0.0, 7.0)
Radiation	
Yes	295 (27.37%)
No/Unknown	783 (72.63%)
Chemotherapy	
Yes	368 (34.14%)
No/Unknown	710 (65.86%)
MFDTT(Months)	
Median (IQR)	1.00 (0.00, 1.00)
Status	
Dead	898 (83.30%)
Alive/Off	180 (16.70%)
Time(Months)	
Mean ± SD	48 ± 65

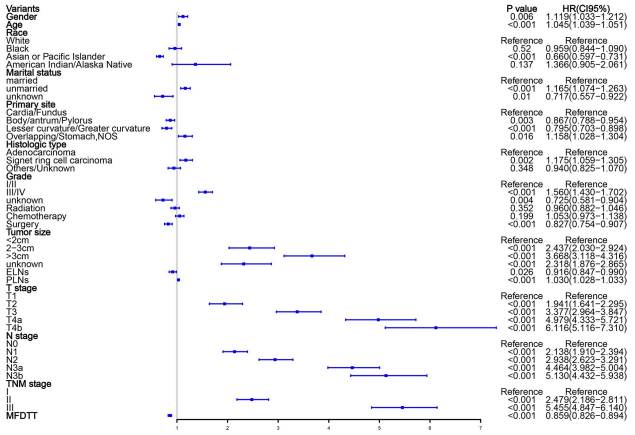
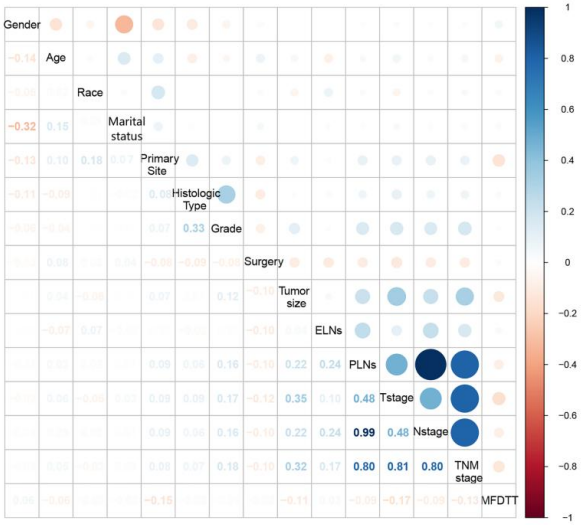


FIGURE 2. Univariate Cox regression analyses of factors associated with CSS in patients with gastric cancer in the training cohort. CSS, cancer-specific survival.



Supplementary figure 1. Correlation Heatmap for variables selected by univariate Cox regression analyse .

SUPPLEMENTARY TABLE 2. The result of VIF test.

Variables	VIF
Gender	1.180098
Age	1.095232
Race	1.03037
Marital Status	1.155658
Primary Site	1.098295
Histologic Type	1.133517
Grade	1.11933
Surgery	1.061358
Tumor Size	1.121582
ELNs	1.076058
PLNs	1.080221
T Stage	1.174414
MFDTT	1.040242

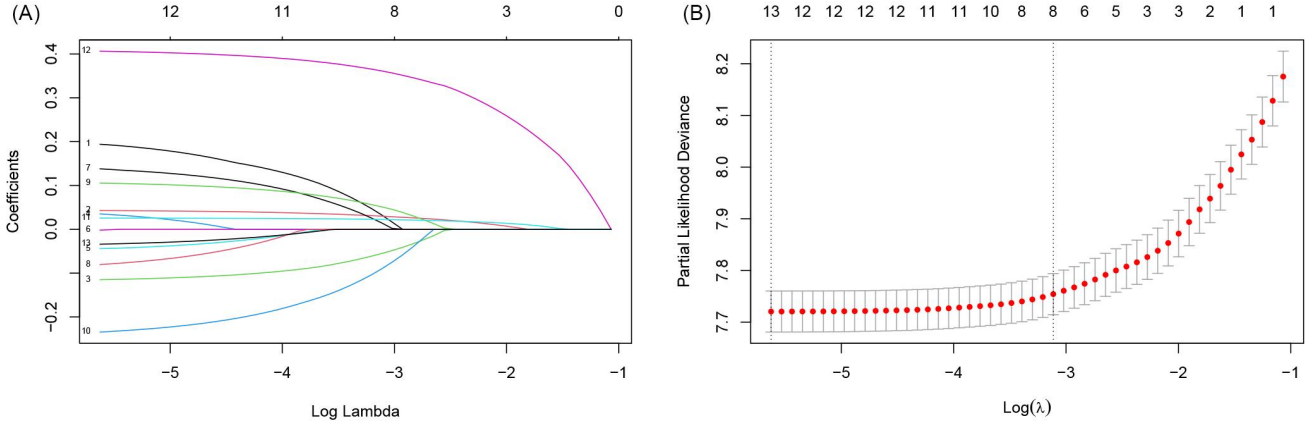


FIGURE 3. Predictor selection for LASSO regression analysis. (A) LASSO coefficient profiles of the 13 variables; (B) the selection process of the optimum value of the parameter l in the Lasso regression model using the cross-validation method. LASSO, least absolute shrinkage and selection operator.

SUPPLEMENTARY TABLE 3. Discriminatory ability of model 1 and model 2 to predict CSS in training cohort.

	Model1	Model2
C-index	0.717	0.701
3-years AUC	0.777	0.775
5-years AUC	0.790	0.788
10-years AUC	0.802	0.801

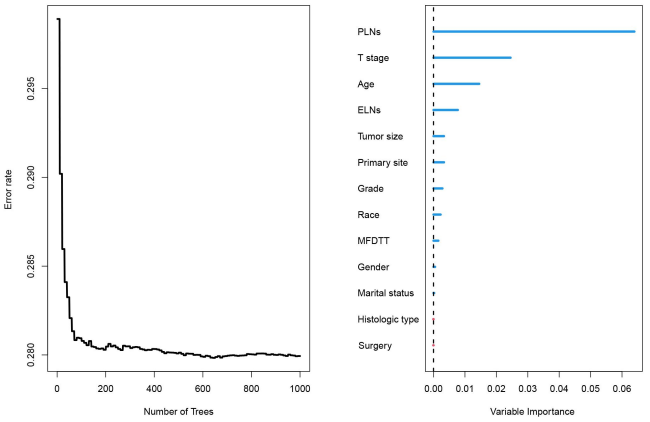


FIGURE 4. Analysis of postoperative CSS in elderly GC patients based on random survival forests. (A) Error rate of random survival forest; (B) Out-of-bag variable importance ranking. CSS, cancer-specific survival.

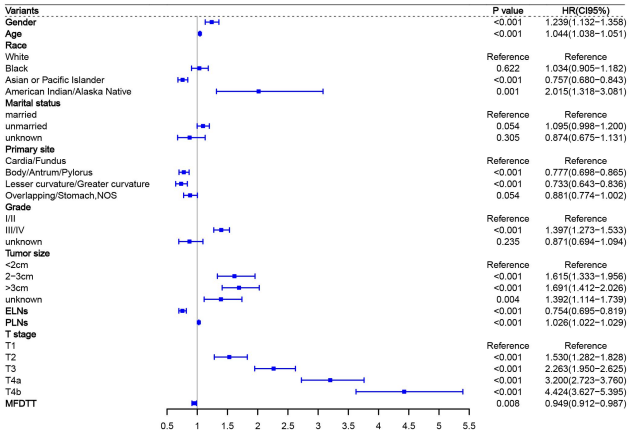


FIGURE 5. Multivariate Cox regression analyses of factors associated with CSS in elderly patients with GC in the training cohort. CSS, cancer-specific survival.

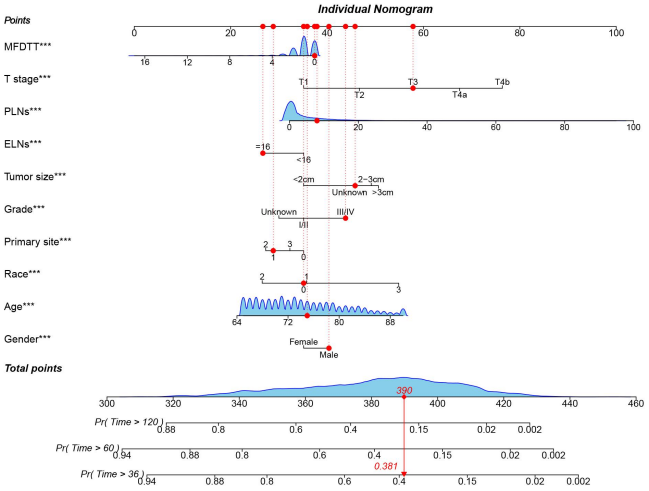


FIGURE 6. Nomogram used to predict 3-, 5-, 10-year CSS in elderly patients with GC who underwent gastrectomy. CSS, cancer-specific survival.

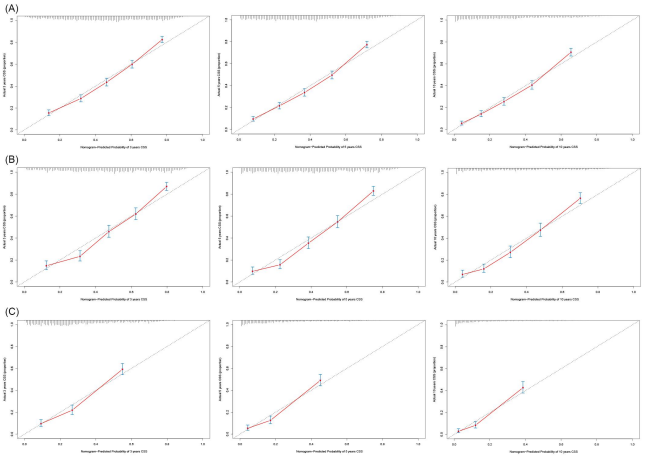


FIGURE 7. Calibration plots of the nomogram and TNM staging system for predicting CSS at 3, 5, and 10 years in the training cohort (A), the validation cohort (B), and the external validation cohort (C). CSS, cancer-specific survival.

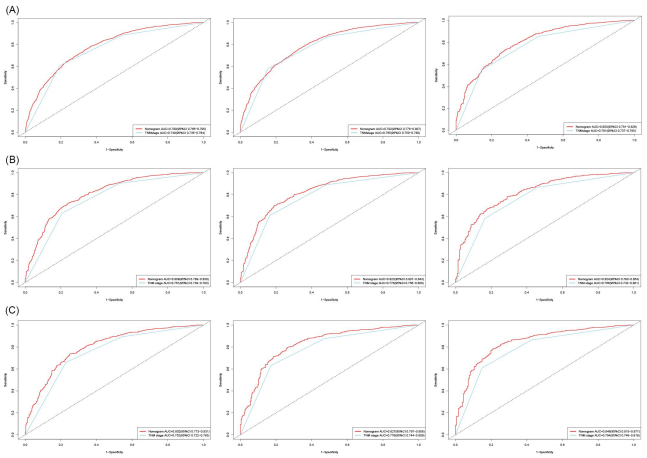


FIGURE 8. Time-dependent ROC curves of the nomogram and TNM staging system for predicting CSS at 3, 5, and 10 years in the training cohort (A), the validation cohort (B), and the external validation cohort (C). DCA, decision curve analysis; CSS, cancer-specific survival.

D. CLINICAL APPLICATION OF THE NOMOGRAM

Clinical effectiveness of the nomogram was estimated using DCA. Owing to its superior net benefit in predicting 3-, 5-, and 10-year CSS at most risk thresholds, the nomogram showed excellent clinical applicability compared to the TNM staging system (Figure 9 A–C). Moreover, patients were categorized into high-risk and low-risk groups according to the risk scores achieved from the nomogram. In three cohorts, K-M curves showed reduced CSS for patients in the high-risk group compared with those in the low-risk group ($P<0.0001$), signifying that the nomogram was effective in identifying patients with poorer prognoses (Figure 10A–C). A web-based dynamic nomogram (https://nomo888.shinyapps.io/dynnomapp/) that can predict CSS at different time points based on individual data was generated to facilitate the clinical application of the nomogram. The interface of the dynamic nomogram is shown in Figure 11.

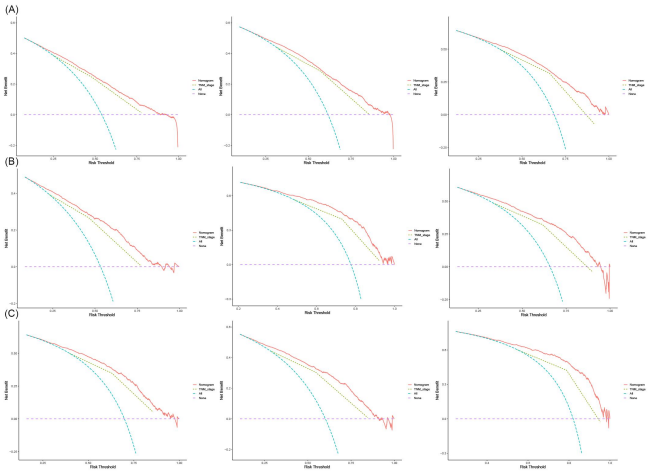


FIGURE 9. DCA of the nomogram and TNM staging system for predicting CSS at 3, 5, and 10 years in the training cohort (A), the validation cohort (B), and the external validation cohort (C). CSS, cancer-specific survival; DCA, decision curve analysis.

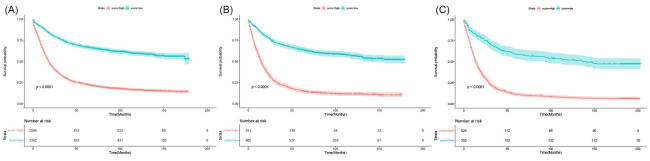


FIGURE 10. K-M curves for CSS in the training cohort (A), the validation cohort (B), and the external validation cohort (C). CSS, cancer-specific survival.

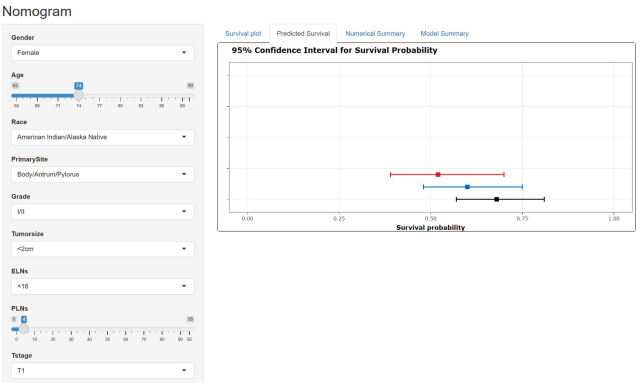


FIGURE 11. Working interface for the online nomogram.

IV. DISCUSSION

Owing to the longer life expectancy and universal application of gastroscopy in recent years, the number of elderly patients with GC is expected to further increase(15).The predominant treatment for elderly patients with grade I-III GC remains radical gastrectomy. Compared to younger patients, elderly patients usually have a longer recovery time and poorer survival after surgery due to the deterioration of physiological systems and functions of various organs(5,16). In most cases, postoperative adjunctive therapeutic measures and strategies for follow-up are generally guided by the TNM stage(12). However, many proven risk factors for prognosis, such as age, tumor size, and operation modality, are omitted in the TNM staging system. Therefore, the TNM staging system has significant limitations in providing a comprehensive assessment prognosis in individual patients(17–19). With a nomogram, clinicopathological and demographic characteristics can be incorporated into a comprehensive model to predict individual CSS. Compared with the TNM staging system, our nomogram was more outstanding in predictive sensitivity, accuracy, and specificity(18). In the past few years, the prognosis of elderly patients with non-metastatic GC has been studied in a few studies; however, most of these studies had small sample sizes(20,21). On the basis of the SEER database, we identified 10 independent prognostic factors for elderly patients undergoing gastrectomy. The nomogram constructed with these variables was able to accurately and conveniently predict CSS after gastrectomy in elderly patients with non-metastatic GC, and the accuracy of the nomogram was evaluated in internal and external validation cohorts.

Lymph node metastasis plays a vital role in survival time and clinical treatment decisions for patients with GC(22). Numerous surveys have demonstrated that the removal of a sufficient number of lymph nodes is significantly associated with long-term survival. A greater number of ELNs, which means fewer lymph node omissions, was directly correlated with enhanced survival(19,23–25). This is also consistent with our findings that PLNs have the most significant influences on the prognosis of elderly patients with GC; furthermore, ELNs were included in the nomogram as an independent predictor for CSS. Petrelli et al. found that cancers located in the upper third of the stomach significantly increase the risk of mortality across all causes(26). Similar results were observed in our study: patients in whom the primary tumor site was the cardia/fundus received higher risk scores, which also predicted lower CSS. The high aggressiveness and metastatic tendency exhibited by both poorly differentiated and undifferentiated carcinomas frequently lead to poorer prognoses(27,28). Patients with a better degree of differentiation experience slower cancer advancement and usually have more opportunities to choose better therapeutic measures to maximize the survival rate. Radiotherapy and chemotherapy have also been shown in several studies to significantly improve the prognosis of patients with gastric cancer(29–32). However, in our study, radiotherapy and chemotherapy were not incorporated into the predicted model as independent predictors for CSS, owing to incomplete patient information from the SEER database, including the regimens and cycles of adjuvant chemotherapy and radiotherapy. In addition, the frailty and comorbidities prevalent in elderly patients can lead to a weaker role for radiotherapy and chemotherapy in prolonging the CSS. Nerve invasion and vascular invasion have been recognized to be significantly correlated with prognosis and recurrence in GC patients in many studies(33–35). Furthermore, tumor markers, such as carcinoembryonic antigen (CEA), CA-199 and CA-125, and immune system signaling molecules, such as Lymphocyte-to-C-reactive protein ratio (LCR), neutrophil-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), have also been declared to significantly influence the prognosis of GC patients(36–38). These indicators could not be validated in our research due to the paucity of patient information from the SEER database. Furthermore, the tumor immune microenvironment and the concept of immunoscore have provided novel insight into the assessment of tumors(39–41).

Through our comprehensive analysis, we identified 10 factors that were then used to develop a convenient and accurate nomogram for predicting the CSS after gastrectomy in elderly patients with non-metastatic GC. The comparison of the model to the TNM staging system demonstrated that it offers a more accurate and comprehensive estimation of prognosis. The factors included in the nomogram were conveniently obtained in clinical work without additional testing, indicating that the nomogram has a high potential application value.

This study has some limitations. First, selection bias may have occurred owing to the model's retrospective nature. Second, the limited information available in the SEER database restricted our ability to explore more multivariate factors associated with the prognosis of patient with GC. Third, multicenter prospective studies with larger populations are necessary to confirm the present results before clinical application.

V. CONCLUSION

We constructed a new nomogram based on data from the SEER database to predict long-term CSS after gastrectomy in elderly patients with non-metastatic GC. The online nomogram makes it more convenient to accurately distinguish high-risk patients from other patients and provides a reference to individualized clinical treatment strategies.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

JL and JZ conceived and designed the study. XS, JZ, and YHZ performed a literature search. JL wrote the manuscript. JZ critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors are grateful to all the patients, researchers, and institutions that participated in the SEER database.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: https://seer.cancer.gov/.

REFERENCES

[1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," CA Cancer J Clin, vol. 68, no. 6, pp. 394-424, 2018, doi:10.3322/caac.21492.

[2] J. Machlowska, J. Baj, M. Sitarz, R. Maciejewski, and R. Sitarz, "Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies," Int J Mol Sci, vol. 21, no. 11, p. 4012, 2020, doi:10.3390/ijms21114012.

[3] C. Allemani, H. K. Weir, H. Carreira, et al., "Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2)," Lancet, vol. 385, no. 9972, pp. 977-1010, 2015, doi:10.1016/S0140-6736(14)62038-9.

[4] "Frailty in Older People," Lancet, vol. 381, no. 9868, pp. 752-762, 2013, doi:10.1016/S0140-6736(12)62167-9.

[5] T. Matsunaga, R. Ishiguro, W. Miyauchi, et al., "Appraisal of long-time outcomes after curative surgery in elderly patients with gastric cancer: a propensity score matching analysis," BMC Surg, vol. 21, p. 33, 2021, doi:10.1186/s12893-021-01046-0.

[6] H. Yazici, A. C. Esmer, A. Eren Kayaci, and S. C. Yegen, "Gastrıc cancer surgery in elderly patients: promising results from a mid-western population," BMC Geriatr, vol. 23, no. 1, p. 529, 2023, doi:10.1186/s12877-023-04206-4.

[7] Y. Choi, N. Kim, K. W. Kim, et al., "Gastric cancer in older patients: a retrospective study and literature review," Ann Geriatr Med Res, vol. 26, no. 1, pp. 33-41, 2022, doi:10.4235/agmr.21.0144.
[8] J. A. Ajani, T. A. D'Amico, D. J. Bentrem, et al., "Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology," J Natl Compr Canc Netw, vol. 20, no. 2, pp. 167-192, 2022, doi:10.6004/jnccn.2022.0008.
[9] J. Lu, Z. F. Zheng, J. W. Xie, et al., "Is the 8th Edition of the AJCC TNM Staging System Sufficiently Reasonable for All Patients with Noncardia Gastric Cancer? A 12,549-Patient International Database Study," Ann Surg Oncol, vol. 25, no. 7, pp. 2002-2011, 2018, doi:10.1245/s10434-018-6447-0.
[10] X. Y. Zhang and P. Y. Zhang, "Gastric cancer: somatic genetics as a guide to therapy," J Med Genet., vol. 54, no. 5, pp. 305-312, 2017, doi:10.1136/jmedgenet-2016-104171.
[11] I. Akushevich, J. Kravchenko, A. P. Yashkin, et al., "Time trends in the prevalence of cancer and non-cancer diseases among older U.S. adults: Medicare-based analysis," Exp Gerontol., vol. 110, pp. 267-276, 2018, doi:10.1016/j.exger.2018.06.017.
[12] J. A. Ajani, T. A. D'Amico, D. J. Bentrem, et al., "Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology," J Natl Compr Canc Netw, vol. 20, no. 2, pp. 167-192, 2022, doi:10.6004/jnccn.2022.0008.
[13] Z. Wang, J. Liu, Y. Luo, et al., "Establishment and verification of a nomogram for predicting the risk of lymph node metastasis in early gastric cancer," Rev Esp Enferm Dig, vol. 113, no. 6, pp. 411-417, 2021, doi:10.17235/reed.2020.7102/2020.
[14] G. Nie, H. Zhang, J. Yan, D. Xie, H. Zhang, and X. Li, "Construction and validation of a novel nomogram to predict cancer-specific survival in patients with gastric adenocarcinoma," Front Oncol, vol. 13, p. 1114847, 2023, doi:10.3389/fonc.2023.1114847.
[15] J. Schendel, E. Jost, M. Mah, et al., "Gastric cancer management in elderly patients: a population-based study of treatment patterns and outcomes in gastric cancer patients $\geq$75 years from Alberta, Canada," Am J Surg, vol. 221, no. 4, pp. 839-843, 2021, doi:10.1016/j.amjsurg.2020.03.006.
[16] S. D. Nelen, R. H. A. Verhoeven, V. E. P. P. Lemmens, J. H. W. de Wilt, and K. Bosscha, "Increasing survival gap between young and elderly gastric cancer patients," Gastric Cancer, vol. 20, no. 6, pp. 919-928, 2017, doi:10.1007/s10120-017-0708-7.
[17] Y. Chen, Y. Jia, Z. Peng, and G. Wang, "The prognostic role of tumor size in stage T1 gastric cancer," World J Surg Oncol, vol. 20, no. 1, p. 135, 2022, doi:10.1186/s12957-022-02596-0.
[18] G. M. Mranda, Y. Xue, X. G. Zhou, et al., "Revisiting the 8th AJCC system for gastric cancer: A review on validations, nomograms, lymph nodes impact, and proposed modifications," Ann Med Surg, vol. 75, 2022, doi:10.1016/j.amsu.2022.103411.
[19] M. Sierzega, L. Bobrzynski, P. Kolodziejczyk, et al., "Nomogram-Based Prognostic Evaluation of Gastric Cancer Patients with Low Counts of Examined Lymph Nodes Outperforms the Predictive Ability of the 7th and 8th Editions of the American Joint Committee on Cancer Staging System," J Gastrointest Surg, vol. 27, no. 1, pp. 7-16, 2023, doi:10.1007/s11605-022-05334-9.
[20] T. Tatara, S. Suzuki, S. Kanaji, et al., "Lymphopenia predicts poor prognosis in older gastric cancer patients after curative gastrectomy," Geriatr Gerontol Int, vol. 19, no. 12, pp. 1215-1219, 2019, doi:10.1111/ggi.13794.
[21] M. Roberto, A. Botticelli, L. Strigari, et al., "Prognosis of elderly gastric cancer patients after surgery: a nomogram to predict survival," Med Oncol, vol. 35, no. 7, p. 111, 2018, doi:10.1007/s12032-018-1166-8.
[22] C. Díaz Del Arco, L. Ortega Medina, L. Estrada Muñoz, S. García Gómez de Las Heras, and M. J. Fernández Aceñero, "Pathologic lymph node staging of gastric cancer," Am J Clin Pathol, vol. 156, no. 5, pp. 749-765, 2021, doi:10.1093/ajcp/aqab031.
[23] H. Li, D. Lin, Z. Yu, et al., "A nomogram model based on the number of examined lymph nodes-related signature to predict prognosis and guide clinical therapy in gastric cancer," Front Immunol, vol. 13, p. 947802, 2022, doi:10.3389/fimmu.2022.947802.
[24] L. Zhao, W. Han, X. Yang, et al., "Exceeding 30 ELNs is strongly recommended for pT3-4N0 patients with gastric cancer: A multicenter study of survival, recurrence, and prediction model," Cancer Sci, vol. 112, no. 8, pp. 3266-3277, 2021, doi:10.1111/cas.15003.
[25] J. Back, V. Sallinen, A. Kokkola, and P. Puolakkainen, "Surgical and oncological outcomes of D1 versus D2 gastrectomy among elderly patients treated for gastric cancer," Scand J Surg, vol. 111, no. 2, p. 14574969221096193, 2022, doi:10.1177/14574969221096193.
[26] F. Petrelli, M. Ghidini, S. Barni, et al., "Prognostic role of primary tumor location in non-metastatic gastric cancer: a systematic review and meta-analysis of 50 studies," Ann Surg Oncol, vol. 24, no. 9, pp. 2655-2668, 2017, doi:10.1245/s10434-017-5832-4.
[27] S. Zhang, L. Zheng, Y. Zhang, et al., "A web-based prediction model for long-term cancer-specific survival of middle-aged patients with early-stage gastric cancer: a multi-institutional retrospective study," J Cancer Res Clin Oncol., published online September 15, 2023, doi:10.1007/s00432-023-05405-7.
[28] H. Lu, Y. Sun, Z. Zhu, H. Xu, R. Huang, and B. Huang, "Differentiated/undifferentiated mixed type is a prognostic factor for T2/T3 gastric cancer patients," Expert Rev Gastroenterol Hepatol, vol. 15, no. 11, pp. 1329-1336, 2021, doi:10.1080/17474124.2021.1973430.
[29] S. H. Park, D. H. Lim, T. S. Sohn, et al., "A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial☆," Ann Oncol, vol. 32, no. 3, pp. 368-374, 2021, doi:10.1016/j.annonc.2020.11.017.
[30] N. Zhang, Q. Fei, J. Gu, L. Yin, and X. He, "Progress of preoperative and postoperative radiotherapy in gastric cancer," World J Surg Oncol, vol. 16, no. 1, p. 187, 2018, doi:10.1186/s12957-018-1490-7.
[31] Y. W. Zhang, Y. L. Zhang, H. Pan, et al., "Chemotherapy for patients with gastric cancer after complete resection: a network meta-analysis," World J Gastroenterol, vol. 20, no. 2, pp. 584-592, 2014, doi:10.3748/wjg.v20.i2.584.
[32] D. H. Ilson, "Advances in the treatment of gastric cancer," Curr Opin Gastroenterol, vol. 36, no. 6, pp. 525-529, 2020, doi:10.1097/MOG.0000000000000679.
[33] W. You, Z. Cai, N. Sheng, et al., "Construction and validation of convenient clinicopathologic signatures for predicting the prognosis of stage I-III gastric cancer," Front Oncol, vol. 12, p. 848783, 2022, doi:10.3389/fonc.2022.848783.
[34] C. Li, M. Wang, X. Cheng, Y. Jiang, and H. Xiao, "Nerve invasion as an independent predictor of poor prognosis in gastric cancer after curative resection," Med (Baltim), vol. 101, no. 33, p. e30084, 2022, doi:10.1097/MD.0000000000030084.
[35] K. Chang, B. Song, I. G. Do, et al., "Venous invasion and perineural invasion as upstaging and poor prognostic factors in N0 gastric cancers," Anticancer Res, vol. 41, no. 11, pp. 5803-5810, 2021, doi:10.21873/anticanres.15397.
[36] "Association of clinical parameters and prognosis with the pretreatment systemic immune-inflammation index (SII) in patients with gastric cancer," J Coll Physicians Surg Pak., published online January 1, 2021, pp. 83-88, doi:10.29271/jcpsp.2021.01.83.
[37] M. Yildirim and B. Koca, "Lymphocyte C-reactive protein ratio: A new biomarker to predict early complications after gastrointestinal oncologic surgery," CBM, vol. 31, no. 4, pp. 409-417, 2021, doi:10.3233/CBM-210251.
[38] X. Wang, M. Mao, S. Zhu, et al., "A novel nomogram integrated with inflammation-based factors to predict the prognosis of gastric cancer patients," Adv Ther, vol. 37, no. 6, pp. 2902-2915, 2020, doi:10.1007/s12325-020-01356-4.
[39] A. Rojas, P. Araya, I. Gonzalez, and E. Morales, "Gastric tumor microenvironment," Adv Exp Med Biol, vol. 1226, pp. 23-35, 2020, doi:10.1007/978-3-030-36214-0_2.
[40] D. Zeng, M. Li, R. Zhou, et al., "Tumor microenvironment characterization in gastric cancer identifies prognostic and immunotherapeutically relevant gene signatures," Cancer Immunol Res, vol. 7, no. 5, pp. 737-750, 2019, doi:10.1158/2326-6066.CIR-18-0436.
[41] F. Marliot, F. Pagès, and J. Galon, "Usefulness and robustness of Immunoscore for personalized management of cancer patients," Oncoimmunology, vol. 9, no. 1, p. 1832324, 2020, doi:10.1080/2162402X.2020.1832324.