ORIGINAL RESEARCH

Characteristics and Predictors of Long-Time Survivors in Non-Metastatic Gastric Signet Ring Cell Carcinoma: A Large Population-Based Study

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Objective: Gastric signet ring cell carcinoma (SRCC) is a distinct entity with a relatively poor prognosis. This study analyzed the clinicopathological characteristics of long-time survivors (LTSs) and identified independent predictors of long-term survival (LTS) in non-metastatic gastric SRCC.

Methods: Data from 3906 patients with non-metastatic gastric SRCC were retrieved from Surveillance, Epidemiology and End Results according to the inclusion and exclusion criteria. Patients were randomly divided into training and validation cohorts. Predictors of LTS in the training cohort were identified by multivariate logistic regression. A nomogram-based predictive model for LTS was constructed in non-metastatic gastric SRCC.

Results: There were 800 patients who survived for >5 years and were defined as TLSs. Young age, other race (not black or white population), female gender, married status, small tumor size, low tumor infiltration, and negative lymph node involvement were independent predictors of LTS in non-metastatic gastric SRCC. These seven variables were incorporated into a nomogram model for predicting LTS. The calibration curve showed good consistency between observed and predicted probability of LTS, and the receiver operating characteristic curve showed acceptable discriminative capacity in the training and validation cohorts.

Conclusion: This study provides an overview of the features of patients with non-metastatic gastric SRCC. Age, race, sex, marital status, tumor size, tumor infiltration, and lymph node involvement were identified as independent predictors of LTS.

Keywords: gastric cancer, signet ring cell carcinoma, long-time survivor, nomogram

Introduction

Gastric cancer is a lethal malignancy that accounts for approximately 8.27% of new cancer cases arising from the digestive system.[1] Histopathologically, most gastric tumors are adenocarcinomas.[2] Signet ring cell carcinoma (SRCC) is a relatively rare histological type with an extremely poor prognosis due to rapid tumor growth and diffuse infiltration into surrounding tissues;[3] it accounts for 16.8% of all gastric cancer cases.[4] SRCC is characterized by predominant intracytoplasmic mucin production in tumor cells (>50% size of cell) with the unique appearance of a signet ring.[5,6] A population-based analysis indicated that patients with gastric SRCC have significantly worse 5-year and 10-year survival rates than those with gastric adenocarcinoma (5-year survival: 19.2% vs 25.8%; 10-year survival: 16.0% vs 22.1%).[4] The baseline demographics and clinical characteristics of gastric SRCC are also distinct from those of common gastric adenocarcinoma, including the mean age of onset, gender ratio, obesity prevalence, tumor grade, and advanced tumor stage.[4,7,8]

Despite the overall dismal prognosis of gastric SRCC, the long-term survival (LTS) of patients with gastric SRCC has improved in recent decades owing to endoscopic treatment, surgery, and adjuvant and neoadjuvant treatments for early-stage

patients, as well as systemic chemotherapy, hyperthermic intraperitoneal chemotherapy, and immunotherapy for metastatic patients.[9] However, there are limited data on the optimal management of non-metastatic gastric SRCC possibly because of the rarity of this specific tumor type. Investigating the specific characteristics of patients with gastric SRCC who survive for a long time is thus critical.

In this study, long-term survivors (LTSs) were defined as patients with a cancer-specific survival (CSS) of >5 years.[10,11] Early death (ED) was defined as cancer-specific death within 5 years from the diagnosis of non-metastatic gastric SRCC. Eligible patients were identified from the Surveillance, Epidemiology and End Results (SEER) database, and the clinicopathological characteristics of non-LTSs and LTSs were compared. Independent predictors of LTS were identified and used to construct and validate a nomogram model to predict LTS in non-metastatic gastric SRCC.

Materials and Methods
Data Source and Patient Selection
Patients with non-metastatic gastric SRCC were collected from the SEER database between 2004 and 2015 using SEER*State (version 8.3.6). The SEER database includes population-based data from 18 registration centers, which covers approximately 30% of the US population.[12] The SEER database includes data on demographics, cancer incidence, tumor-related clinicopathological features, and cancer treatment, thereby providing accessible information for clinical studies of malignant tumors, especially for rare tumor entities.[13] Ethical approval was obtained from the Ethics Committee of the Affiliated Hospital of the Medical School of Ningbo University. Written informed consent was not required in this SEER-based retrospective study.

First, 12,846 patients with gastric SRCC were identified from the SEER database between 2004 and 2015 according to the International Classification of Diseases in Oncology (ICD-O-3) (ICD-O-3: 8490). Patients were included if they met the following criteria: (1) patient age ≥18 years; (2) pathologically confirmed gastric SRCC; (3) single primary tumor; (4) active follow-up data; (5) survival time ≥1 month, which might be, otherwise, caused by perioperative complications; (6) clear cause of death; (7) non-metastatic patients with known TNM stage. As a result, 3906 eligible patients were enrolled in the study (Figure 1). Patients were divided into three groups according to age as follows: ≤50 years, 51–70 years, and >70 years.[14]

LTSs were defined as patients with cancer-specific survival (CSS) >5 years. Patients with CSS <5 years were defined as non-LTSs.

For each patient, demographics, tumor features, treatment regimens, and patient survival data were retrieved from the SEER database.

Establishment and Validation of the Nomogram
Patients were randomly divided into the training group (N = 2759) and validation group (N = 1147) at a ratio of 7:3 by setting seed in R software. Independent predictors of LTS were identified by univariate and multivariate logistic regression analyses. Seven independent risk factors (age, race, sex, marital status, tumor size, T stage, and N stage) were used to construct a nomogram model to predict LTS.

The discrimination of the nomogram-based LTS prediction was assessed using a calibration plot in both cohorts. The C-index was also calculated. The predictive accuracy of the nomogram was evaluated using a receiver operating characteristic (ROC) curve and the area under the curve (AUC).

Statistical Analysis
The significance of differences in clinicopathological characteristics between LTSs and non-LTSs was evaluated using the chi square test. Outcomes of interest included overall survival (OS: the time interval from initial diagnosis to all-cause death) and CSS (the duration from initial diagnosis to death caused by gastric cancer). Survival curves were plotted using the Kaplan-Meier method, and survival differences were evaluated using the Log rank test. Potential predictors of LTS were identified by univariate logistic regression analysis, and variables with a P value <0.1 in the univariate analysis were included in the multivariate analysis. Results are expressed as odds ratio (OR) and 95% confidence interval (CI).
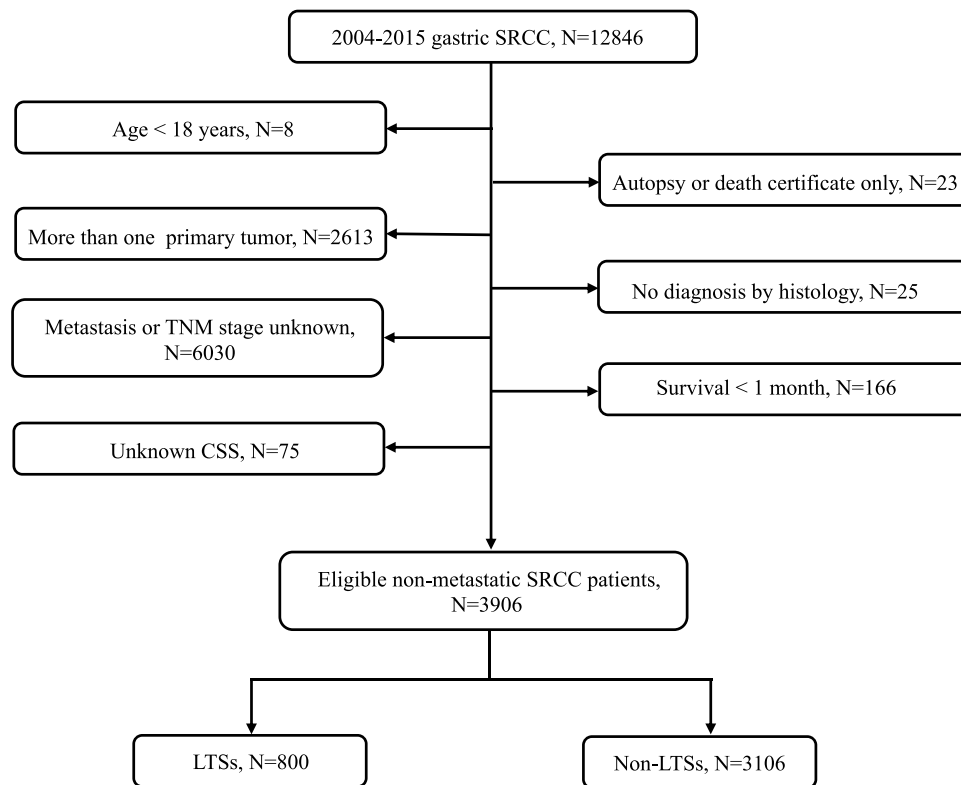
Figure 1 Flow chart of patient selection.
Abbreviations: SRCC, signet ring cell carcinoma; CSS, cancer-specific survival; LTSs, long-time survivors.

SPSS statistics version 26.0 software (SPSS Inc, Chicago, United States) and R version 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. A two-sided P value <0.05 indicated statistical significance.

Results

Baseline Characteristics of Patients

In total, 3906 patients with non-metastatic gastric SRCC were included according to the inclusion and exclusion criteria. The baseline characteristics of the patients are shown in Table 1. Specifically, 21.79% of patients were ≤50 years old (N = 851), 46.16% were 51–70 years old (N = 1803), and 32.05% were >70 years old (N = 1252). Most of the patients were white (N = 2642, 67.64%). There were no significant differences between the number of men (N = 2059, 52.71%) and women (N = 1847, 47.29%). Regarding marital status, 58.50% of the patients were married (N = 2285) and 37.15% were unmarried (N = 1451). Most patients showed poorly differentiated tumors (N = 3204, 82.03%). Patients were divided into different groups according to tumor size (Table 1). Regarding T stage, 30.18% (N = 1179), 42.01% (N = 1641), 23.02% (N = 899), and 4.79% (N = 187) of the patients had T1, T2, T3, and T4 tumors, respectively. Over half of the patients had no lymph node involvement (N = 2013, 51.54%), 32.51% had N1 stage (N = 1270), and 15.95% had N2 stage (N = 623). Most patients underwent surgery (N = 2896, 74.14%), 36.82% received radiation (N = 1438), and 57.76% received chemotherapy (N = 2256).

Differences in Clinicopathological Characteristics Between LTSs and Non-LTSs

The clinicopathological features of LTSs and non-TLSs were compared. Most variables were significantly different between the two groups (Table 2). There was a higher number of young patients (≤50 years) in the LTS group than in the non-LTS group. Regarding race, other race (except black and white) was more common among LTSs. The proportion of women (50.88%) and married patients (66.62%) was higher among LTSs.

Table 1 Clinicopathological Characteristics of Included Patients

Characteristics	Number	Percentage (%)
Total	3906	100
Age		
≤50	851	21.79
51–70	1803	46.16
>70	1252	32.05
Race		
Black	494	12.65
White	2642	67.64
Other	754	19.30
Unknown	16	0.41
Sex		
Male	2059	52.71
Female	1847	47.29
Marital status		
Married	2285	58.50
Unmarried	1451	37.15
Unknown	170	4.35
Tumor grade		
Well/moderately	103	2.64
Poorly	3204	82.03
Undifferentiated	123	3.15
Unknown	476	12.19
Tumor size (cm)		
≤2	678	17.36
2.1–4	853	21.84
4.1–6	561	14.36
>6	778	19.92
Unknown	1036	26.52
T stage		
T1	1179	30.18
T2	1641	42.01
T3	899	23.02
T4	187	4.79
N stage		
N0	2013	51.54
N1	1270	32.51
N2	623	15.95
Surgery		
Yes	2896	74.14
No/unknown	1010	25.86
Radiation		
Yes	1438	36.82
No/unknown	2468	63.18
Chemotherapy		
Yes	2256	57.76
No/unknown	1650	42.24

Predictors of LTS in Non-Metastatic Gastric SRCC

Patients were randomly assigned to training and validation cohorts at a ratio of 7:3. Predictors of LTS were identified using univariate logistic regression analysis. Age, race, sex, marital status, tumor size, T stage, and N stage were associated with LTS (Table 3). These variables were incorporated into the multivariate logistic regression analysis, which

Table 2 Differences of Clinicopathological Characteristics Between Non-LTSs and LTSs in Non-metastatic Gastric SRCC

	Non-LTSs			LTSs	P
	≤2 Years	2–5 Years	Total		
Total	2167	939	3106	800	
Age					<0.001
≤50	380 (17.54)	232 (24.71)	612 (19.7)	239 (29.88)	
51–70	946 (43.65)	460 (48.99)	1406 (45.27)	397 (49.62)	
>70	841 (38.81)	247 (26.3)	1088 (35.03)	164 (20.5)	
Race					<0.001
Black	290 (13.38)	111 (11.82)	401 (12.91)	93 (11.62)	
White	1524 (70.33)	637 (67.84)	2161 (69.58)	481 (60.12)	
Other	347 (16.01)	185 (19.7)	532 (17.13)	222 (27.75)	
Unknown	6 (0.28)	6 (0.64)	12 (0.39)	4 (0.5)	
Sex					0.025
Male	1172 (54.08)	494 (52.61)	1666 (53.64)	393 (49.12)	
Female	995 (45.92)	445 (47.39)	1440 (46.36)	407 (50.88)	
Marital status					<0.001
Married	1175 (54.22)	577 (61.45)	1752 (56.41)	533 (66.62)	
Unmarried	891 (41.12)	321 (34.19)	1212 (39.02)	239 (29.88)	
Unknown	101 (4.66)	41 (4.37)	142 (4.57)	28 (3.5)	
Tumor grade					0.012
Well/moderately	56 (2.58)	31 (3.3)	87 (2.8)	16 (2)	
Poorly	1738 (80.2)	780 (83.07)	2518 (81.07)	686 (85.75)	
Undifferentiated	66 (3.05)	32 (3.41)	98 (3.16)	25 (3.12)	
Unknown	307 (14.17)	96 (10.22)	403 (12.97)	73 (9.12)	
Tumor size (cm)					<0.001
≤2	240 (11.08)	203 (21.62)	443 (14.26)	235 (29.38)	
2.1–4	397 (18.32)	236 (25.13)	633 (20.38)	220 (27.5)	
4.1–6	293 (13.52)	152 (16.19)	445 (14.33)	116 (14.5)	
>6	507 (23.4)	167 (17.78)	674 (21.7)	104 (13)	
Unknown	730 (33.69)	181 (19.28)	911 (29.33)	125 (15.62)	
T stage					<0.001
T1	534 (24.64)	274 (29.18)	808 (26.01)	371 (46.38)	
T2	876 (40.42)	440 (46.86)	1316 (42.37)	325 (40.62)	
T3	598 (27.6)	205 (21.83)	803 (25.85)	96 (12)	
T4	159 (7.34)	20 (2.13)	179 (5.76)	8 (1)	
N stage					<0.001
N0	1053 (48.59)	460 (48.99)	1513 (48.71)	500 (62.5)	
N1	720 (33.23)	326 (34.72)	1046 (33.68)	224 (28)	
N2	394 (18.18)	153 (16.29)	547 (17.61)	76 (9.5)	
Surgery					<0.001
Yes	1290 (59.53)	826 (87.97)	2116 (68.13)	780 (97.5)	
No/unknown	877 (40.47)	113 (12.03)	990 (31.87)	20 (2.5)	
Radiation					0.41
Yes	775 (35.76)	379 (40.36)	1154 (37.15)	284 (35.5)	
No/unknown	1392 (64.24)	560 (59.64)	1952 (62.85)	516 (64.5)	
Chemotherapy					<0.001
Yes	1292 (59.62)	583 (62.09)	1875 (60.37)	381 (47.62)	
No/unknown	875 (40.38)	356 (37.91)	1231 (39.63)	419 (52.38)	

Abbreviations: LTSs, long-time survivors; SRCC, signet ring cell carcinoma.

Table 3 Logistic Regression Analysis to Identify Predictors of Long-Time Survival in Non-Metastatic Gastric SRCC in the Training Cohort

	Unadjusted Logistic Regression		Adjusted Logistic Regression	
	OR (95% CI)	P	OR (95% CI)	P
Age				
>70	Reference		Reference	
51–70	1.87 (1.54–2.29)	<0.001	2.01 (1.63–2.49)	<0.001
≤50	2.59 (2.08–3.24)	<0.001	2.87 (2.27–3.64)	<0.001
Race				
Black	Reference		Reference	
White	0.96 (0.75–1.23)	0.744	0.98 (0.75–1.28)	0.870
Other	1.80 (1.37–2.38)	<0.001	1.57 (1.17–2.13)	0.003
Unknown	1.44 (0.39–4.23)	0.538	1.04 (0.27–3.27)	0.945
Sex				
Male	Reference		Reference	
Female	1.19 (1.03–1.40)	0.023	1.21 (1.02–1.43)	0.028
Marital status				
Unmarried	Reference		Reference	
Married	1.54 (1.30–1.83)	<0.001	1.59 (1.32–1.92)	<0.001
Unknown	1.00 (0.64–1.51)	1	0.98 (0.61–1.52)	0.920
Tumor grade				
Well/moderately	Reference			
Poorly	1.48 (0.89–2.63)	0.154		
Undifferentiated	1.39 (0.70–2.81)	0.353		
Unknown	0.98 (0.56–1.83)	0.960		
Tumor size (cm)				
>6	Reference		Reference	
4.1–6	1.67 (1.26–2.26)	<0.001	1.55 (1.14–2.09)	0.005
2.1–4	2.25 (1.75–2.92)	<0.001	1.60 (1.22–2.10)	<0.001
≤2	3.44 (2.66–4.47)	<0.001	1.53 (1.13–2.07)	0.006
Unknown	0.89 (0.67–1.18)	0.408	0.53 (0.39–0.73)	<0.001
T stage				
T4	Reference		Reference	
T3	2.67 (1.36–6.07)	0.009	2.60 (1.28–6.02)	0.014
T2	5.53 (2.88–12.34)	<0.001	4.88 (2.48–11.09)	<0.001
T1	10.27 (5.34–22.95)	<0.001	9.27 (4.72–21.00)	<0.001
N stage				
N2	Reference		Reference	
N1	1.54 (1.17–2.05)	0.002	1.38 (1.03–1.86)	0.031
N0	2.38 (1.84–3.11)	<0.001	1.96 (1.45–2.66)	<0.001

Abbreviations: SRCC, signet ring cell carcinoma; OR, odds ratio; CI, confidence interval.

showed that younger age, other race (not black or white population), female gender (OR = 1.21, P = 0.028), married status (OR = 1.59, P < 0.001), small tumor size, less advanced T stage, and less advanced N stage were significant independent predictors of LTS (Table 3).

Establishment and Validation of a Nomogram

According to the results of the multivariate logistic regression analysis, age, race, sex, marital status, tumor size, T stage, and N stage were incorporated into a nomogram to predict the probability of LTS in a specific individual. As shown in Figure 2, T stage was the most important predictor of LTS with a maximal score of 100. Other variables had various effects on the probability of LTS.
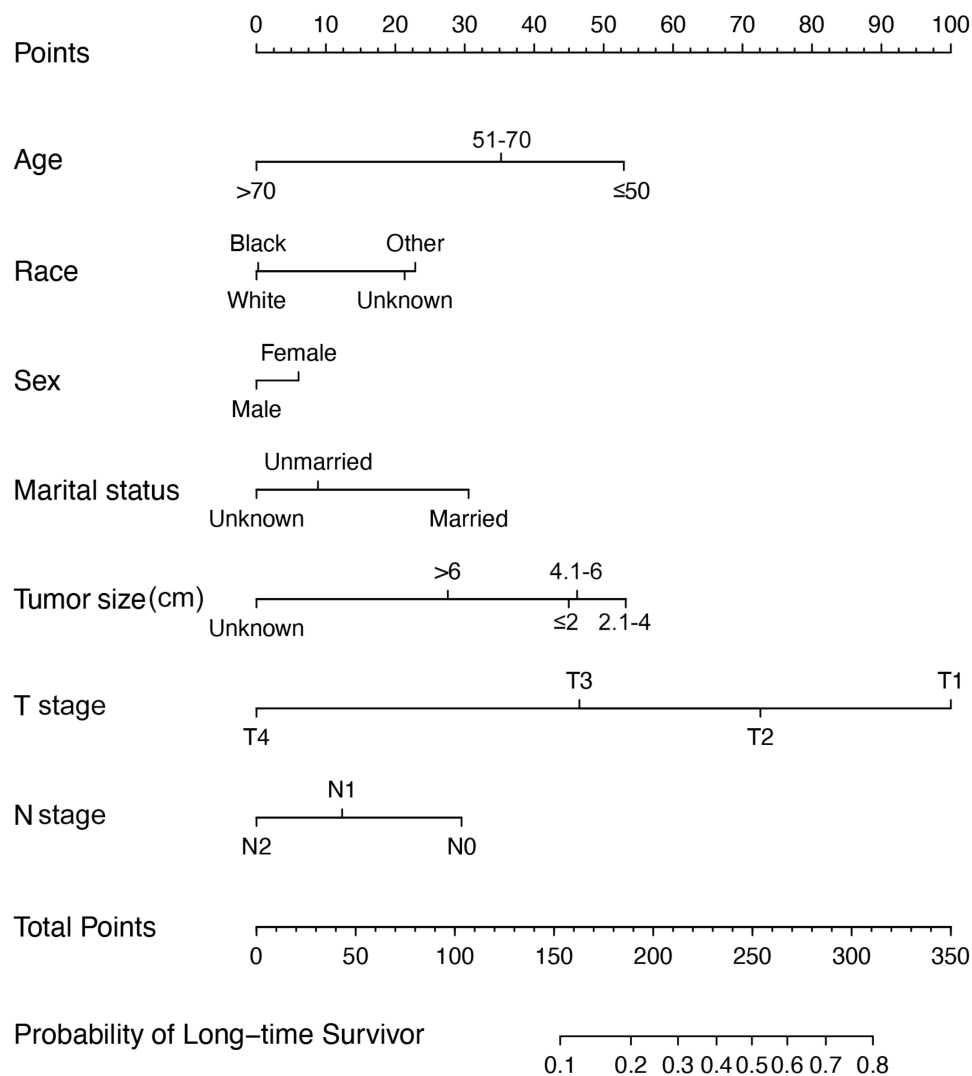
Figure 2 Nomogram to predict the probability of long-time survival. For example, there was a 73-year old (0 point), white (0 point), married (30 points) man (0 point) with gastric SRCC. The tumor was > 6 cm (approximately 30 points), T1 stage (100 points), and negative lymph node involvement (30 points). The total score was 190 points. For this specific patient, the probability of long-time survival was approximately 0.2.

The nomogram showed good accuracy in predicting LTS in the training cohort, with a C-index of 0.745 (Figure 3A). The calibration plot showed good agreement between predicted and observed LTS (Figure 3A). Similarly, the C-index was 0.720 for the nomogram-based LTS prediction in the validation cohort (Figure 3B). The calibration curve showed good consistency between observed and predicted LTS probability. Finally, a ROC curve was generated to evaluate the predictive power of the nomogram-based prediction model for LTS. The AUC values were 0.745 and 0.720 in the training and validation cohorts, respectively (Figure 4).

Age Was an Independent Predictor of LTS in Non-Metastatic Gastric SRCC

Multivariate logistic regression analysis identified age as an independent predictor of LTS. To further examine the association between age and the probability of LTS, we analyzed patient survival stratified by age at diagnosis. As shown in Supplementary Figure 1, patients ≤50 years of age had the best survival, whereas those >70 years had the poorest prognosis.

Discussion

Gastric SRCC is a rare histological type of gastric cancer and is associated with poor survival compared with adenocarcinoma. The incidence of gastric SRCC is increasing, resulting in a considerable health burden to patients.[15]
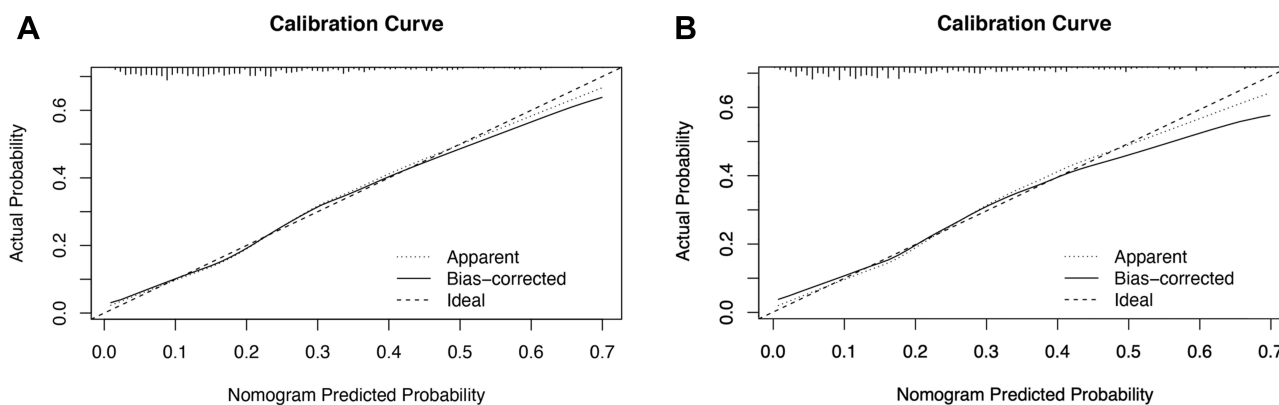
Figure 3 Calibration curve of nomogram-predicted and actual probability of long-time survival in the training cohort (**A**, N = 2759) and the validation cohort (**B**, N = 1147).
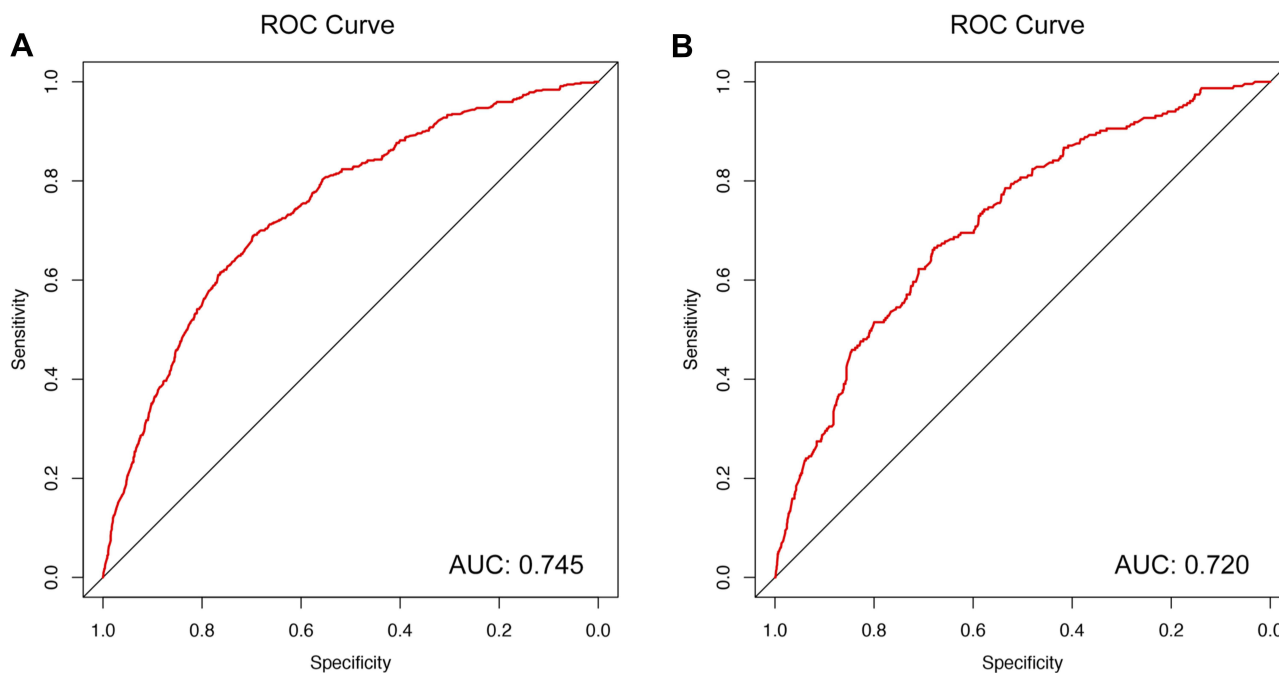

Figure 4 Receiver operating characteristic (ROC) curve and area under the ROC curve (AUCs) in the training cohort (**A**, N = 2759) and the validation cohort (**B**, N = 1147).
Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve.

Therefore, assessing the clinicopathological features of gastric SRCC is important. In addition, investigating the characteristics of LTSs may provide information essential for improving the clinical management of these patients. However, because of the rarity of gastric SRCC and the small sample size, demographic or survival analyses in a single institution are difficult. Here, we used the SEER database to examine the characteristics of LTSs among patients with non-metastatic gastric SRCC and identified predictors of LTS.

To the best of our knowledge, this is the first large population-based study investigating the characteristics of LTSs in non-metastatic gastric SRCC. Consistent with previous studies,[16,17] the incidence of gastric SRCC was higher among women, who accounted for 47.29% of patients in this study. Poorly differentiated or undifferentiated tumors accounted for the majority of tumors (85.18%), which was consistent with previous reports.[18] Comparison of the clinicopathological features of LTSs and non-LTSs showed that LTSs included a higher proportion of young patients (≤50 years, 29.88%), other ethnicity (27.75%), female patients (50.88%), married patients (66.62%), those with a relatively smaller tumor size, and less advanced T and N stages (Table 2).

We further examined the independent predictors of LTS. Multivariate logistic regression analysis revealed that younger age, other race (not black or white population), female gender, married status, small tumor size, and less advanced T and N stages significantly predicted LTS. Age was a strong independent predictor of LTS. As shown in Table 3, patients ≤50 years and patients 51–70 years had a two-fold higher probability of LTS than those >70 years of age. The relatively better LTS in the young population was further confirmed by the survival curve (Supplementary Figure 1). Age at diagnosis is an independent predictor in several malignancies, such as colorectal cancer[19] and hepatocellular carcinoma.[20] Saito et al analyzed 1473 gastric cancer patients who underwent curative gastrectomy and showed that age was an independent prognostic factor, although lymph node dissection was relatively limited and the proportion of patients receiving chemotherapy was lower among elderly patients.[21] Consistently, a Japanese team demonstrated that more extensive lymph node dissection and fewer peri-operative complications might explain the better survival in young patients with gastric cancer.[22] In addition, married patients were more likely to have LTS than unmarried patients. Spousal support is important for the active treatment and surveillance of patients after a cancer diagnosis,[23,24] whereas unmarried patients are more likely to experience undertreatment and lack of social support.[25]

In addition to the demographic and tumor-specific factors analyzed in this study, several studies have demonstrated that molecular biomarkers are associated with patient prognosis in gastric cancer. Chen et al reported that the GALNT14-rs9679162 genotype was an effective predictor of prognosis in gastric SRCC.[26] These authors combined clinicopathological parameters with the GALNT14-rs9679162 genotype to develop a scoring system for stratifying advanced gastric SRCC patients into three distinguishable prognostic subgroups. However, most diagnostic and prognostic biomarkers of gastric SRCC are observed in the laboratory. For instance, hsa-miR-665 and hsa-miR-95 are downregulated in gastric SRCC and may be related to tumor invasion, metastasis, and chemoresistance.[27]

The present study had several limitations. Firstly, selection bias is unavoidable due to the retrospective nature of the study. Although multivariate logistic regression analysis revealed that age was an independent predictor of LTS in non-metastatic gastric SRCC, the relatively poorer survival of elderly patients might also be associated with inadequate lymph node dissection and less intensive treatment. However, these data cannot be retrieved from the SEER database. Secondly, although the performance of the model was acceptable in both the training and validation cohorts, external validation is warranted to confirm the reliability and generalizability of the nomogram model. A prospective multicenter study with a large sample size is necessary to confirm the present findings. Finally, gastric SRCC with distant metastasis was excluded from the analysis because patients with metastatic disease are mainly treated with palliative systemic therapy and are likely to show a distinct prognostic pattern.[28] Thus, another study is necessary to examine this particular subgroup of patients.

In summary, we investigated the clinicopathological characteristics of non-metastatic gastric SRCC and identified predictors of LTS using the SEER database. Young age, other race (not black or white population), female gender, married status, small tumor size, lower tumor infiltration, and negative lymph node involvement were independent predictors of LTS in non-metastatic gastric SRCC. These seven parameters were used to construct a nomogram-based prediction model of LTS, which showed acceptable performance in both training and validation cohorts.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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