Original Article

Operable gastric adenocarcinoma with different histological subtypes: Cancer-specific survival in the United States

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Abstract

Background/Aims: Gastric signet ring cell carcinoma (GSRC), a subtype of adenocarcinoma, has been considered a histological type with poor survival. We aimed to compare the survival outcomes between patients with GSRC and patients with gastric non-signet ring cell adenocarcinoma (NGSRC) and constructed a nomogram to predict gastric adenocarcinoma-specific survival (GCSS).

Patients and Methods: We identified 10,031 patients with gastric adenocarcinoma (GA) from the surveillance, epidemiology, and end results (SEER) database and stratified them into two histological type groups: GSRC and NGSRC. We used propensity score matching and identified 4304 patients (training cohort) to assess the effect of the histological type on GCSS with Kaplan–Meier curves, and constructed a predictive nomogram. The accuracy of the nomogram was tested on the remaining 5727 patients (validation cohort) with concordance index (C-index) values, calibration curves, and receiver operating characteristic (ROC) curve analysis.

Results: We found that the histological type SRC was not associated with significantly poor survival (5-year survival rate: 46.1% vs 46.7%, $P = 0.822$). GSRC patients had similar GCSS rates compared to those with NGSRC in each tumor, node, and metastasis (TNM) stage (all $P > 0.05$). The nomogram showed that histological type was a relatively weak predictor of survival. The C-index value of the nomogram for predicting survival was 0.720, similar to that in the validation cohort (0.724).

Conclusions: Patients with GSRC had a similar prognosis to those with NGSRC. The proposed nomogram allowed a relatively accurate survival prediction for operable GA patients after gastrectomy.

Keywords: Gastric adenocarcinoma, nomogram, signet ring cell carcinoma, survival

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors in the world. According to statistics from the International Agency for Research on Cancer, in 2012, there were approximately 952,000 new cases of gastric cancer and 723,000 deaths worldwide, ranking fifth in the incidence of malignant tumors and third in mortality rate.[1] Although the incidence and mortality of gastric cancer are steadily declining and have been associated with a comparative decrease in *Helicobacter pylori* infection,[2-4] differential trends such as an increase in gastric adenocarcinoma (GA),[5,6] particularly gastric signet ring cell carcinoma (GSRC), have

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_406_19

How to cite this article: Lin CL, Zhu GW, Huang YJ, Zheng W, Yang SG, Ye JX. Operable gastric adenocarcinoma with different histological subtypes: Cancer-specific survival in the United States. Saudi J Gastroenterol 2020;26:46-52.

been observed. As Henson[7] reported, from 1937 to 2000, the incidence of SRC grew by more than 6.5% annually in the United States. Therefore, it is necessary for us to evaluate the prognosis of GSRC and generate a predictive model to aid in clinical decisions.

SRC is a subtype of adenocarcinoma that has a large vacuole and contains many mucins, pushing the nucleus to one side and resembling a signet ring. It can originate from any tissue, including the colon, breast, prostate, and gallbladder, but it is mostly associated with gastric cancer. For decades, GSRC has been reported as a type of histology with poor survival[8-10] that seriously threatens human health. A retrospective study of 198 patients performed by Aguiar[8] demonstrated that the GSRC type had the worst prognosis of all gastric cancer histology types, and Liu[9] reported that the survival rate of 1464 GSRC patients was lower than that of patients with other types of gastric cancer. A study of 59 patients who underwent resection described by Guillaume[10] indicated that GSRC patients had a worse prognosis than NGSRC patients. However, an increasing number of studies have confirmed that GSRC patients do not have a worse prognosis than patients with other histological types of gastric cancer. A study of 128 patients with GSRC enrolled to analyze prognosis, performed by Fang *et al*.[11] indicated a better result for patients with the GSRC type during the early stage, than patients with other types of gastric cancer histology. Although the survival and histological type of gastric cancer have been assessed, most of the studies have been based in single centers and examined small samples, and their results are conflicting. In this study, we compared the prognostic outcomes of GA between GSRC patients and NGSRC patients based on sufficient and complete data. Furthermore, a nomogram was generated in our study to predict the survival of GA patients. The present study was conducted to compare survival between patients with different histological types and to develop a predictive model for GA.

PATIENTS AND METHODS

Data selection

The surveillance, epidemiology, and end results (SEER) database was launched by President Richard Nixon[12] in 1973 and provides cancer data (e.g., treatment, primary site, tumor size, tumor stage, treatment regimen, pathological type, time of death, and cause of death) from the population-based registries of 18 sites that cover approximately 30% of the USA population. We used SEER*Stat software (version 8.3.5, http://seer.cancer.gov/seerstat/) to identify patients who were diagnosed with GA. To obtain enough data from the SEER database, the selection process was as follows [Figure 1]. Data regarding the histological type, sex, age, race, American Joint Committee on Cancer (AJCC, 7th Edition) stage, T stage, N stage, M stage, differentiation grade, tumor size, gastric cancer-specific death, vital status, and survival time were extracted from the SEER database (2004–2013) for further analysis. Gastric cancer-specific survival (GCSS) was defined as the time from diagnosis to death related to gastric carcinoma.

Inclusion and exclusion criteria

Inclusion criteria were as follows: the primary tumor site was limited to the stomach (C16.0–C16.9); the histology type was limited to adenocarcinoma, which was further categorized as SRC (ICD-03, 8490/3) or adenocarcinoma (ICD-03, 8140/3); the diagnosis was made between 2004 and 2013; and the diagnostic method was limited to surgery. The exclusion criterion was as follows: if the information of patient was incomplete (e.g., sex, age, race, AJCC T stage; N stage; M stage, differentiation grade, tumor size, or survival time). The time frame from 2004 to 2013 was selected because information on the AJCC TNM stage became available in 2004; meanwhile, patients diagnosed after 2013 were excluded to ensure a sufficient follow-up time. All the cases were staged based on the criteria in the 7th edition of the AJCC staging manual.

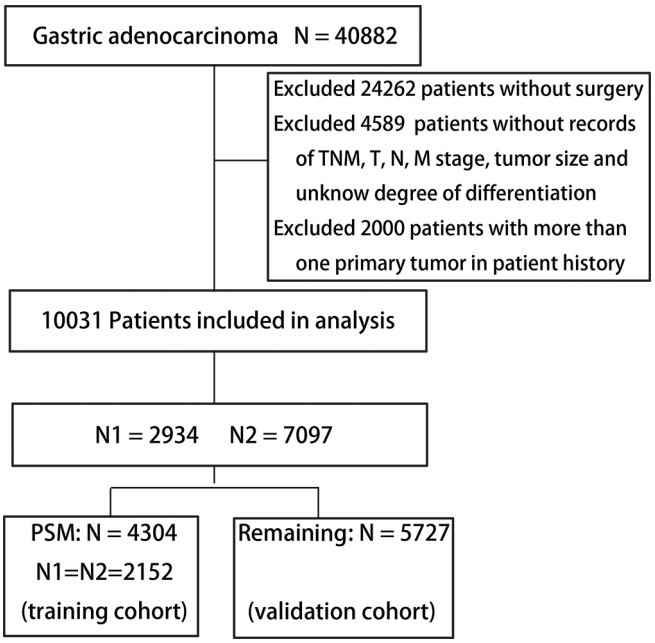

Figure 1: Flow diagram of the selection process used to obtain the study cohort. N1—GSRC: gastric signet ring cell carcinoma. N2—NGSRC: gastric non-signet ring cell carcinoma

Statistical analysis

Statistical analysis was performed with IBM SPSS 24.0. GCSS was calculated with Kaplan–Meier and log-rank methods. To reduce the differences in variables between GSRC and NGSRC, propensity score matching (PSM)[12] was conducted. Nine variables that could affect the selection of histology types were used to perform PSM through logistic regression. These variables were sex, age, race, AJCC T stage, N stage, differentiation grade, tumor size, and year of diagnosis. In the two groups, the patients were matched 1:1. After PSM, the clinical characteristics were verified by Chi-square test for significance. Univariate and multivariate analyses were performed with Cox regression to identify independent prognostic risk factors. All results are reported as the hazard ratios (HRs) and 95% confidence intervals (CIs). A *P* value <0.05 was considered statistically significant. The nomogram, concordance index (C-index), receiver operating characteristic (ROC) curve and calibration plot were generated using the RMS package[13] in R version 3.5.3 (http://www.r-project.org/).

RESULTS

Demographics

A total of 10,031 patients with GA were included: 2934 had GSRC and 7097 had NGSRC. The median follow-up periods of GSRC and NGSRC patients were 67 months and 69 months, respectively. Patient clinical characteristics and tumor-related variables before PSM are summarized in Table 1. The two histological type groups differed significantly in nearly all clinical variables.

Propensity score matching

PSM generated 2152 patient pairs whose clinical characteristics and tumor-related variables after propensity score matching are shown in Table 1. All variables were perfectly balanced between the two groups. As shown in Tables 2 and 3, the 5-year GCSS rate of GA patients with GSRC was 46.1%, and that of patients with NGSRC was 46.7%; the difference was not significant by univariate ($X^2 = 0.050$, $P = 0.824$) and multivariate (GSRC group as a ref., HR = 0.988, 95% CI 0.912–1.070; $P = 0.759$) analyses. The 1-, 2-, 3-, 4-, and 5-year GCSS rates are given in Table 2. Sex, differentiation grade, age, race, AJCC T stage, N stage, M stage, and tumor size were identified as significant risk factors for poor survival by the univariate analysis and therefore included in the multivariate Cox regression analysis. Ultimately, the multivariate Cox regression analysis revealed that tumor size, age, race, AJCC T stage and N stage (all $P < 0.001$) were independent prognostic factors (Table 3, all $P < 0.05$).

Subgroup analysis

We further analyzed the effect of histological type on the long-term (more than 5 years) GCSS rate at each TNM stage, including stage I, II, III, and IV. We found that GSRC patients had a similar long-term GCSS rate to NGSRC patients in each TNM stage [Figure 2, $P > 0.05$]. Histological

Table 1: Patient characteristics based on the histological type of gastric cancer before and after propensity score matching

Characteristics	Before matching			After matching		
	GSRC (*n*=2934)	NGSRC (*n*=7097)	*P*	GSRC (*n*=2152)	NGSRC (*n*=2152)	*P*
Sex						
Male	1517	4844	<0.001	1265	1265	1.000
Female	1417	2253		887	887	
Age						
<60	1313	1895	<0.001	761	761	1.000
>=60	1621	5202		1391	1391	
TNM stage						
Stage I-II	1407	4498	<0.001	1111	1112	0.976
Stage III-IV	1527	2599		1041	1040	
T stage						
Stage T1-2	1421	4103	<0.001	1123	1123	1.000
Stage T3-4	1513	2994		1029	1029	
N stage						
Stage N0-1	1391	4281	<0.001	1037	1038	0.976
Stage N2-3	1543	2816		1115	1114	
M stage						
Stage M0	2515	6400	<0.001	1946	1947	0.959
Stage M1	419	697		206	205	
Differentiation grade						
Un/poor differentiation	2841	4321	<0.001	2075	2075	1.000
Middle/well differentiation	93	2776		77	77	
Tumor size						
<=5 cm	1691	4598	<0.001	1290	1288	0.950
>5 cm	1243	2499		862	864	

NGSRC: Gastric non-signet ring cell carcinoma; GSRC: Gastric signet ring cell carcinoma, TNM: Tumor, node, and metastasis

Table 2: Comparison of GCSS (%) between GSRC and NGSRC patients post surgery

	GSRC (*n*=2152)	NGSRC (*n*=2152)	X^2	*P*
1-year	74.5	74.0	0.207	0.649
2-year	59.3	59.8	0.016	0.899
3-year	51.9	51.7	0.036	0.850
4-year	48.2	48.8	0.037	0.847
5-year	46.1	46.7	0.050	0.824

GCSS: Gastric cancer-specific survival, NGSRC: Gastric non-signet ring cell carcinoma, GSRC: Gastric signet ring cell carcinoma

type was further validated as not an independent prognostic factor in patients with stage I (GSRC as a reference, HR = 0.996, 95% CI 0.790–1.256, $X^2 = 0.001$, $P = 0.975$), stage II (GSRC as a reference, HR = 0.998, 95% CI 0.848–1.176, $X^2 < 0.001$, $P = 0.985$), stage III (GSRC as a reference, HR = 1.013, 95% CI 0.904–1.134, $X^2 = 0.051$, $P = 0.822$), and stage IV (GSRC as a reference, HR = 0.839, 95% CI 0.682–1.034, $X^2 = 2.892$, $P = 0.089$) [Figure 2].

Nomogram of GCSS for GA patients

The survival nomogram that incorporated all significant independent risk factors for GCSS in the training cohort is shown in Figure 3. The nomogram identified the TNM stage as the largest contributor to GCSS, followed by T stage, N stage, age, differentiation grade, race, tumor size, and histological type. Each variable was assigned a score on a point scale. The 3- and 5-year GCSS probability could be predicted by calculating the total score, locating it on the total point scale, and then drawing a line down on the GCSS scale. The C-index for GCSS prediction was 0.720 in the training cohort. The ROC curve analysis and calibration plot for the probability of 3- and 5-year GCSS showed an optimal model between the actual observation and prediction by the nomogram [Figure 4a-d].

Validation of predictive accuracy of the nomogram plot for GCSS

In the validation cohort, the C-index of the nomogram for predicting GCSS was 0.724, and the ROC curve analysis and calibration plot also showed an optimal model of probability between the observation and prediction in 3- and 5-year GCSS [Figure 4e and f].

DISCUSSION

We conducted this study to compare the prognosis of GSRC patients to that of NGSRC patients and constructed a nomogram to predict survival for patients with GA. Moreover, PSM was performed to reduce bias and to make a more reasonable comparison between the two groups.

The 1-, 3-, and 5-year GSRC-specific survival rates were 74.5%, 51.9%, and 46.1%, respectively, which were not worse than those of non-signet ring cell cancer (NSRC) ($P > 0.05$). Furthermore, we studied different prognoses between GSRC and NGSRC in each tumor stage. The results suggested that GSRC did not confer significantly worse survival. Compared with NGSRC patients, GSRC patients in different tumor stages (stages I, II, III, and IV) experienced a similar 5-year cancer-specific survival rate (all $P < 0.05$).

Table 3: Univariate and multivariate Cox analyses of the determinants of gastric cancer-specific survival of patients with gastric adenocarcinoma

Variable		No. of patients	5-year GCSS (%)	Univariate		Multivariate		
				Log-rank text X^2	*P*	HR	95% CI	*P*
Histology type	SRC	2152	46.1	0.050	0.824	1		
	NSRC	2152	46.7			0.980		
Age	<60	1522	50.1	40.447	<0.001	1	Reference	
	>=60	2782	44.5			1.509	1.382-1.647	<0.001
Race	White	3034	43.6	33.836	<0.001	1	Reference	
	Black	424	49.8			0.983	0.852-1.135	0.815
	Other	846	54.8			0.769	0.687-0.860	<0.001
TNM stage	Stage I	1182	79.1	1161.471	<0.001	1	Reference	
	Stage II	1041	49.8			1.428	1.121-1.820	0.004
	Stage III	1670	29.3			1.660	1.228-2.243	0.001
	Stage IV	411	13.9			3.137	2.312-4.256	<0.001
T stage	Stage T1	746	83.5	680.632	<0.001	1	Reference	
	Stage T2	1500	48.5			1.971	1.549-2.507	<0.001
	Stage T3	1340	34.9			2.511	1.922-3.279	<0.001
	Stage T4	718	25.2			3.198	2.418-4.228	<0.001
N Stage	Stage N0	1418	73.6	887.227	<0.001	1	Reference	
	Stage N1	657	46.3			1.472	1.223-1.771	<0.001
	Stage N2	780	38.7			1.531	1.252-1.873	<0.001
	Stage N3	1449	24.2			2.179	1.754-2.708	<0.001
M stage	Stage M0	3893	49.9	454.157	<0.001			
	Stage M1	411	13.9					
Tumor size	<=5 cm	2578	56.2	314.964	<0.001	1	Reference	
	>5 cm	1726	31.9			1.106	1.012-1.209	0.026

GCSS: Gastric cancer-specific survival, SRC: Signet ring cell, NSRC: Non-signet ring cell, HR: Hazard ratio

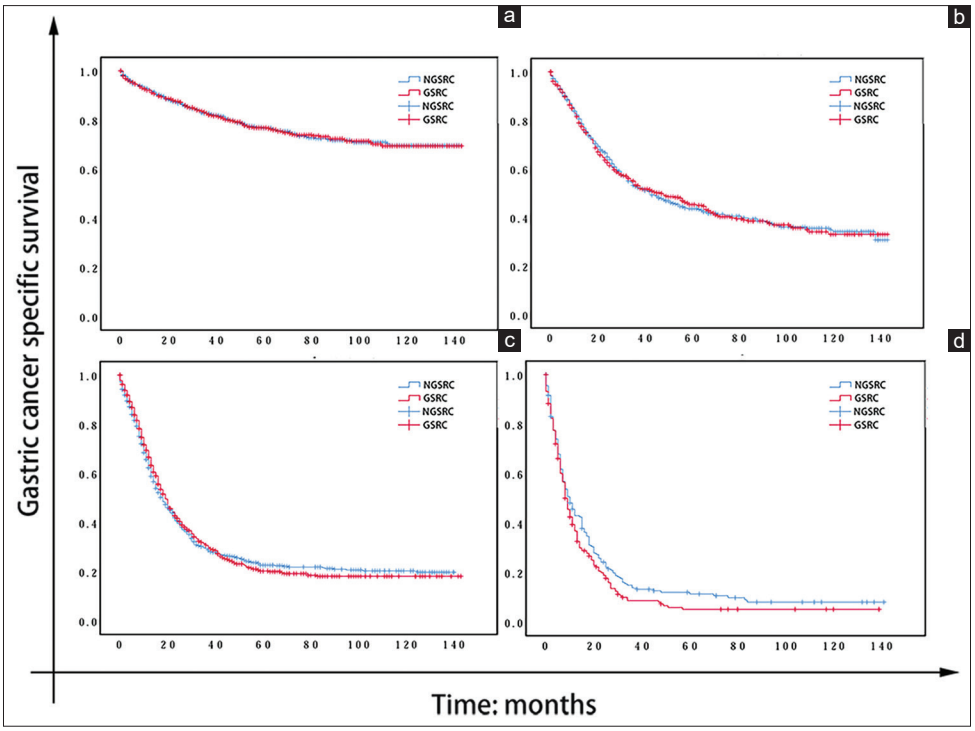

Figure 2: Survival curves for patients with gastric adenocarcinoma based on tumor stage subgroups. (a) Stage I: HR = 0.996, 95% CI 0.790–1.256; *P* = 0.975; (b) stage II: HR = 0.998, 95% CI 0.848–1.176, *P* = 0.985; (c) stage III: HR = 1.013, 95% CI 0.904–1.134, *P* = 0.822; (d) and stage IV: HR = 0.839, 95% CI 0.682–1.034, *P* = 0.089 (GSRC as a reference). NGSRC: Gastric non-signet ring cell carcinoma; GSRC: Gastric signet ring cell carcinoma, HR: Hazard ratio

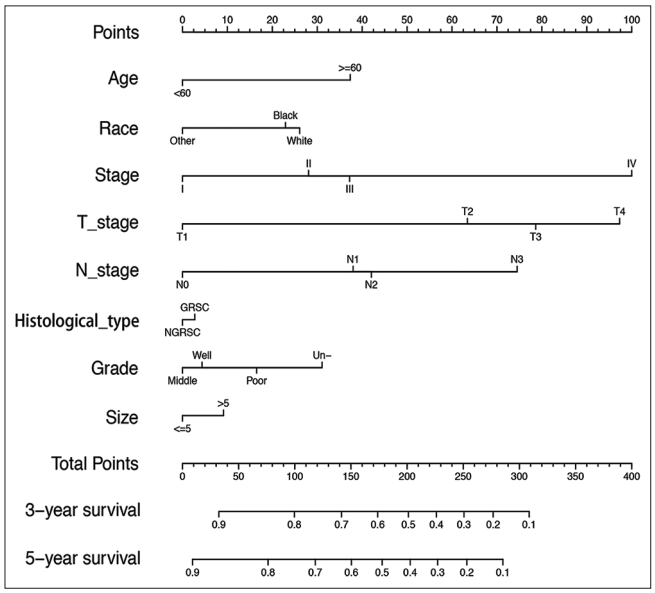

Figure 3: Gastric adenocarcinoma survival nomogram

In terms of the prognosis of GSRC, Jiang[14] reported that GSRC is associated with a better prognosis than NGSRC in the early stage of GA, but the two showed similar survival outcomes in the advanced stage. Ha[15] reported that in the early stage, GSRC had a better prognosis than NSRC. However, some studies have demonstrated that in the early stage, the survival outcomes are similar between GSRC and NGSRC.[16,17] Concerning GSRC in the advanced stage, some studies have shown similar survival outcomes to those of NGSRC.[18] Li[19] showed that GSRC had more lymph node metastasis, deeper tumor invasion, and intraperitoneal dissemination than NGSRC, leading to a worse prognosis. The same study concluded that the prognosis was comparable in the early and advanced stages and that GSRC patients had no worse survival outcomes than NGSRC patients.

In our study, before PSM, 1527 (52%) patients with GSRC were in stage III or IV, while only 2599 (37%) patients with NGSRC were in stage III or IV. This shows that GSRC patients usually present at a later stage overall, leading, in general, to a worse prognosis. If the prognosis was compared between the two groups directly without matching, the results were insignificant. In contrast to previous studies, our study showed that GSRC patients had a similar prognosis to NGSRC patients, and the major reason for this difference was maybe due to selection bias. Most of the previous studies were retrospective and vast differences existed between patients. For these reasons, PSM was used to maintain the balance in variables related to survival between the two groups in our study. Therefore, we confidently believe that patients with GSRC have a similar prognosis to those with other kinds of adenocarcinoma if the patients have the same characteristics.

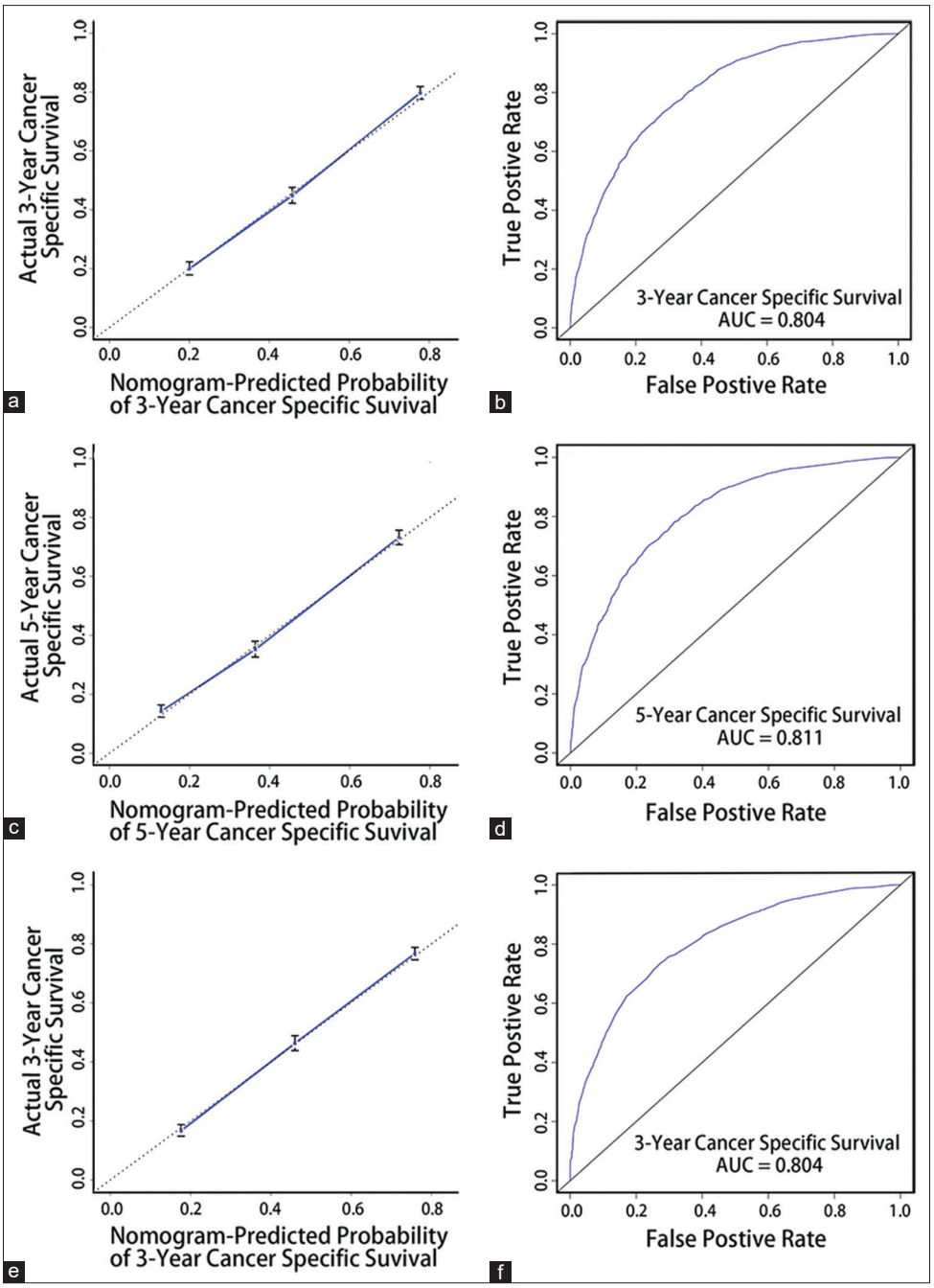

Figure 4: Calibration for predicting gastric adenocarcinoma (GA) patient survival at (a) 3 years and (c) 5 years in the training cohort and at (e) 3 years in the validation cohort. The ROC curve diagram for predicting GA patient survival at (b) 3 years and (d) 5 years in the training cohort and at (f) 3 years in the validation cohort

Currently, the AJCC TNM stage is commonly used to predict the prognosis of cancer patients. However, whether additional variables are important risk factors for individual patients is unknown. Thus, we constructed a nomogram to comprehensively consider the prognosis. Nomograms have been proven to be more accurate than the conventional AJCC TNM stage for the prediction of survival in many cancers.[20,21] Hence, a nomogram for GA patients after gastrectomy was constructed by combining the TNM stage and other important risk factors. The nomogram showed a good predictive ability for prognosis. This finding was supported by the calibration curves, ROC curve analyses, and C-index values (0.720 and 0.724 for the training cohort and validation cohort, respectively).

Nevertheless, this study has some limitations. First, information on the specific surgical procedures performed on the patients enrolled was lacking, which may have affected the prognosis. Patients with gastric cancer can undergo noncurative surgeries, including diagnostic

laparoscopy and feeding jejunostomy. To exclude these patients, this study enrolled only patients who underwent surgery and whose number of lymph nodes swept was clearly documented. On the premise of a guarantee for patients to undergo curative surgery, laparoscopic surgery or open surgery has little effect on patients.[22,23] Second, all the data were derived from the SEER database, which lacks information on chemotherapy and radiation therapy. Data obtained from the SEER registry and Medicare insurance claim documents should be combined to analyze chemotherapy and radiation therapy related information. While the Medicare program provides health insurance only for the population aged more than 65 years in the United States, these patients do not represent all American patients with gastric cancer. Therefore, in terms of GCSS, an analysis of all patients may be more accurate.

CONCLUSION

In conclusion, patients with GSRC had a similar prognosis to those with NGSRC. These findings suggest that GSRC should not be regarded as a distinct type of GA. Moreover, the nomogram constructed in our study can be used to predict the prognosis of GA patients after gastrectomy.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 81702424 and 81872364), the Fujian Provincial Health Department Young and Middle-aged Talents Training Project (No. 2018-ZQN-46), the Joint Funds for the Innovation of Science and Technology, Fujian Province (No. 2017Y9092), the Project of Science and Technology Research Program in Fujian Province (No. 2016B044), the Fujian Provincial Natural Science Foundation (No. 2018J05127), and the National Clinical Key Specialty Construction Project (General Surgery) of China.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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