



A population-based competing risk survival analysis of patients with salivary duct carcinoma

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Background: Salivary duct carcinoma (SDC) is a rare malignancy with high risk of local recurrence and distant metastases of the salivary gland. This study was designed to summarize the clinical and pathological features and to further evaluate them as potential prognostic factors for SDC in the salivary gland.

Methods: Clinical data of 266 patients diagnosed with SDC between 2004 and 2015 were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The prognostic factors affecting overall survival (OS) and cancer-specific survival (CSS) were determined by Kaplan-Meier analyses and Cox proportional hazards model. The nomogram was established to predict OS and CSS for SDC. The predictive accuracy of the nomograms was measured by concordance index (C-index).

Results: The 3- and 5-year OS of SDC patients were 67.41% and 47.86%, while the 3- and 5-year CSS were 84.6% and 60.7%, respectively. The primary site, T stage and M stage were identified as independent prognostic factors for OS by the multivariate analysis, whereas N stage, M stage, the presence of multiple primary carcinomas and the treatment modalities were identified as independent prognostic factors for CSS. The C-index values of the prognostic nomogram based the risk factors affecting SDC OS and CSS were 0.703 (0.646–0.760) and 0.771 (0.691–0.851), respectively.

Conclusions: SDC is an aggressive malignancy with a high proportion of advanced stage and lymph node metastases. Patients with increasing age, submandibular gland malignancy, advanced T stage, advanced N stage, advanced M stage, high lymph node ratio (LNR) and the presence of multiple primary carcinomas tend to have unfavorable outcomes. Radiotherapy or chemotherapy improve CSS remarkably. These factors will aid in effective therapeutic treatment modalities for SDC.

Keywords: Salivary duct carcinoma (SDC); Surveillance, Epidemiology, and End Results (SEER); competing risk analyses; nomogram, prognosis

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Introduction

Salivary duct carcinoma (SDC) is a rare salivary gland malignancy, accounting for 35% of the salivary gland malignancies (1). SDC commonly occurs in the parotid gland and submandibular or minor salivary glands, among which the parotid gland is the most frequently involved site

(2,3). Histologically resembling high-grade breast ductal carcinoma, SDC exhibits aggressive clinical features with a high rate of local recurrence and distant metastases, and thereby leading to poor clinical outcome (4). Previously, the clinical and pathological characteristics of SDC and their potentials as prognostic factors have been investigated (5-8).

The most commonly identified prognostic factors of SDC include age, gender, tumor grade, tumor size, lymph node metastasis and clinical stage (9-12). Some other factors such as increasing numbers of positive lymph nodes, lymph node ratio (LNR), lymph-vascular invasion, perineural invasion and HER2/neu receptor expression were also shown to influence the prognosis of SDC (8,13,14). However, due to the rarity of this disease, most of those studies focused on single-center studies with limited sample size (1,12,15,16). Therefore, the prognostic factors for SDC still remain to be largely elucidated.

To date, two large cohort studies with 495 SDC patients from 2004 to 2013 based on the National Cancer Database (NCDB) and with 228 SDC patients from 1973 to 2008 based on the Surveillance, Epidemiology, and End Results (SEER) database have been reported (9,17). Given that NCDB does not provide data regarding cause of death, the first study based on NCDB that ignored the impact of survival from competing events might have led to misleading conclusions (9). Similarly, in the second study based on SEER that used SDC patient data without evaluating traditional the tumor, lymph node, metastasis (TNM) staging systems from a long period of time (1973 to 2008), the conclusions may also be incomprehensive since during this time the clinical and histopathological diagnostic criteria for SDC have evolved significantly (17).

In this population-based study, we analyzed the clinicopathologic characteristics and determined the prognostic factors for SDC of the salivary gland using SEER database. We also established a novel nomogram for predicting the overall survival (OS) and cancer-specific survival (CSS) of SDC patients, which could more precisely estimate the survival probability of individual SDC patients. We present the following article in accordance with the TRIPOD reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-1849>) (18).

Methods

Patients

The study cohort of SDC patients from 2004 to 2015 were obtained from the SEER database (<https://seer.cancer.gov/data/>) using SEER*Stat 8.3.6 software. Inclusion criteria were as follows. Firstly, pathological diagnosis of patients was SDC [International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site code, histology code: 8500]. Secondly, the primary site was limited to the parotid gland

and submandibular gland. Thirdly, the diagnosis year was from 2004 to 2015. Exclusion criteria included patients with unknown race, clinical stage based on the American Joint Committee on Cancer (AJCC) cancer staging or TNM system that was not clear and survival time that was less than 1 month. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since any information in the SEER database does not require explicit consent from the patients, our study was not subject to the ethical approval requirements of the institutional review board.

Study variables

From SEER data, we extracted variables including race, sex, age at diagnosis, year of diagnosis, primary tumor site, laterality, histological grade, SEER summary stage, AJCC stage, T stage, N stage, M stage, surgery procedures, lymph node dissection, regional nodes examined positively, the presence of multiple primary carcinomas, adjuvant radiotherapy, chemotherapy, and follow-up information. The TNM stage were restaged according to the 7th edition of AJCC staging system. LNR was calculated as the number of positive regional lymph nodes divided by the total number of lymph nodes examined. The LNR above or below the median level of LNR of all the SDC patients was defined as high or low, respectively. The survival time was measured as the time from the date of surgery to the last follow-up or to the death due to all causes (OS) or SDC (CSS).

Statistical analyses

Before modeling, categorical variables were grouped and the continuous variables were converted to the categorical variables to conform to the linear hypothesis. The OS and CSS estimation and survival curves were evaluated by Kaplan-Meier method and verified by log-rank test. Independent risk factors were determined by backward stepwise in Cox proportional risk (PH) regression model (19). Based on Cox PH regression results, a nomogram of all independent prognostic factors for combining 3- and 5-year OS predictions was constructed using the rms package in R software. The discrimination of nomogram was evaluated by Harrell's concordance index (C-index), which could estimate the probability between the observed and predicted OS and CSS (20). The calibration was evaluated using the calibration curve by comparing the estimated

Table 1 Demographics of SDC of salivary gland

Characteristics	Patients (n=266)	
	Number	%
Age at diagnosis	29–93 years old (mean 67.5, median 68)	
Age group, years		
<50	22	9.74
50–59	43	16.17
60–69	76	28.57
70–79	75	28.20
>80	50	22.12
Gender		
Male	189	71.05
Female	77	28.95
Race		
White	215	80.82
Black	27	10.15
Other	24	9.03
Year of diagnosis		
2004–2010	121	45.49
2011–2015	145	54.51

SDC, salivary duct carcinoma.

risk line on the plot to the risk line observed on the axis. R version 3.6.1 software (The R Foundation for Statistical Computing, Shanghai, China. <http://www.r-project.org>), along with SPSS version 22 (SPSS Inc., Chicago, IL, USA), were employed to perform statistical analyses and plot the figures. A two-tailed P value <0.05 was considered statistically significant.

Results

Demographics and clinicopathological characteristics of SDC

A total of 266 patients were diagnosed with salivary gland SDC from 2004 to 2015. The median age was 68 (range, 29–93) years old, and the majority was male (71.05%), with the highest incidence in the sixth decade of life (Figure S1). Of these patients, 215 (80.82%) patients were white, 27 (10.15%) patients were black and 24 (9.03%) patients were from other ethnics (including American Indian/AK

Native, Asian/Pacific Islander). Among diagnosed cases, 121 (45.49%) patients were diagnosed from 2004 to 2010, and 145 (54.51%) patients were diagnosed from 2011 and 2015 (Table 1).

The most predominant primary site was the parotid gland (231 patients, 86.84%), followed by the submandibular gland (35 patients, 13.16%). According to the SEER summary stage, 63 (23.68%) patients were at localized stage, 92 (34.59%) patients were at regional stage, and 111 (41.73%) patients were at distant metastasis stage. Based on the 7th edition of AJCC TNM stage, the disease progressions were as follows: 54 (20.30%) T1 patients, 56 (21.05%) T2 patients, 77 (28.95%) T3 patients, 72 (27.07%) T4 patients, and 7 (2.63%) Tx patients. For lymph node metastasis, 100 (37.59%) patients were at N0 stage, 160 (60.15%) patients were at N0+ stages, and 6 (2.26%) were Nx patients. In terms of distant metastasis, most of the patients (90.97%) were at the M0 stage, while 24 (9.02%) patients were at the M1 or Mx stage. As a whole, 64 (24.06%) patients were at the early clinical stage (AJCC stage I and II) and 161 (73.68%) patients were at the advanced clinical stage (AJCC stage III and IVA-C), suggesting that SDC is an aggressive malignancy in the salivary gland. The distribution of histological grade in the cohort was also centralized in a higher grade, among which 38.72% and 27.82% had grade III and grade IV disease, respectively. Finally, among multiple primary carcinomas collected, 175 (65.79%) patients had the SDC and 91 (34.21%) patients harbored other types of carcinomas, which led to competing risks for patient survival (Table 2).

Treatment and outcome

The majority of SDC patients (255 patients, 95.86%) were treated surgically, while 9 patients were not recommended for surgery and 2 patients were recommended but refused. Among the 255 patients who received the surgery, neck dissection was performed in the majority of the patients (228, 89.80%). In 220 patients who underwent the neck dissection, examined lymph node data were available, which show that 151 patients had positive lymph nodes with the median number of 5 (range, 1–75). The number of positive regional lymph nodes against the total number of regional lymph nodes examined in the 220 patients are plotted in Figure 1A. The median LNR value was 0.167. In terms of the overall treatment modalities, 60 patients were treated surgically only, 130 patients received the adjuvant radiotherapy after surgery, and 59 patients received adjuvant

Table 2 Clinicopathological characteristics of SDC of salivary gland

Characteristics	Patients (n=266)	
	Number	%
Primary site		
Parotid gland	231	86.84
Submandibular gland	35	13.16
Laterality		
Left	117	43.98
Right	149	56.02
Summary stage		
Localized	63	23.68
Regional	92	34.59
Distant	111	41.73
AJCC stage		
I	37	13.91
II	27	10.15
III	35	13.16
IVA	125	46.99
IVB	10	3.76
IVC	26	9.77
Unknow	6	2.26
T stage		
T1	54	20.30
T2	56	21.05
T3	77	28.95
T4	72	27.07
TX	7	2.63
N stage		
N0	100	37.59
N1	32	12.03
N2	123	46.24
N3	5	1.88
NX	6	2.26
M stage		
M0	242	90.97
M1	20	7.52
MX	4	1.50

Table 2 (continued)**Table 2** (continued)

Characteristics	Patients (n=266)	
	Number	%
Grade		
Well differentiated	6	2.26
Moderately differentiated	23	8.65
Poorly differentiated	103	38.72
Undifferentiated	74	27.82
Unknow	60	22.56
Multiple primary carcinomas		
Presence	91	34.21
Absence	175	65.79

SDC, salivary duct carcinoma; AJCC, American Joint Committee on Cancer.

radiotherapy and chemotherapy. A few patients received no treatment or just received the adjuvant chemoradiotherapy or chemotherapy (*Table 3*). More specifically, among 64 early-stage (stage I & II) SDC patients, only 19 (29.69%) patients were treated surgically only, and 39 (60.94%) patients received radiotherapy after surgery. Among a total of 196 late-stage (stage III & IV) SDC patients, 38 (19.39%) patients underwent surgery alone; 88 (44.90%) patients were offered radiotherapy after surgery, 55 (28.06%) patients received adjuvant radiotherapy and chemotherapy after surgery (*Figure S2*).

The median follow-up duration for all patients was 34.5 (range, 2–143) months. A total of 119 (44.74%) patients died, among which 59 patients died of salivary gland malignancies and 60 patients died of other causes, including other malignant tumors and other types of systemic disease. The 3- and 5-year OS were 67.41% and 47.86%, respectively, while the 3- and 5-year CSS were 84.6% and 60.7%, respectively (*Figure 1B*).

Prognostic factors

For OS analysis, patients with missing or uncertain values of clinical variables were excluded, and finally a total of 198 patients were included.

The univariate analysis revealed that SEER summary stage, T stage, N stage, M stage, AJCC clinical stage, surgery and LNR were negatively associated with OS.

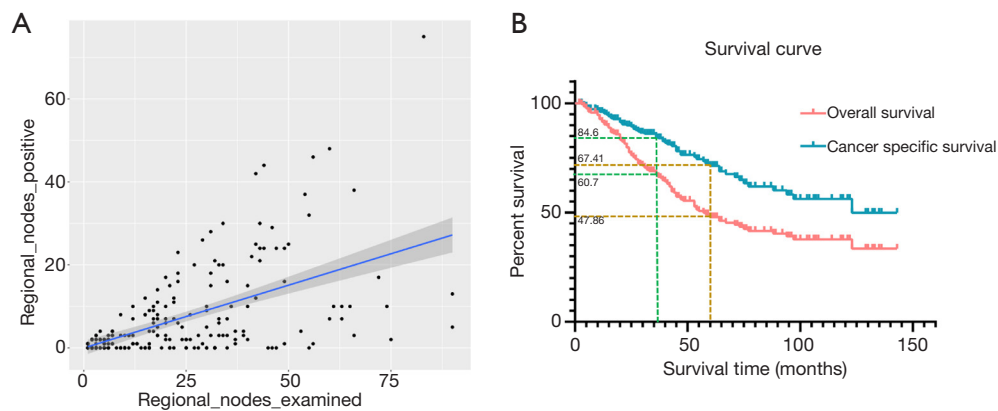


Figure 1 Lymph nodes positive and survival of SDC patients. (A) Positive regional lymph nodes are plotted against the total number of regional lymph nodes in SDC who underwent neck dissection; (B) Kaplan-Meier estimate for OS and CSS. SDC, salivary duct carcinoma; OS, overall survival; CSS, cancer-specific survival.

On the contrary, the OS rate was not influenced by the following clinical characteristics: age, gender, race, year of diagnosis, primary site, laterality, histological grade, the presence of multiple primary carcinomas, neck dissection and treatment modalities. The Kaplan-Meier analysis and log-rank test further visualized and validated the results (Figures 2 and Figure S3). The multivariate analysis identified the primary site, T stage and M stage as the negative prognostic factors. The results of the univariate and multivariate analysis for OS are shown in Table 4.

For CSS analysis, univariate analysis proved that the following factors had the significant influence on patients' survival: age at diagnosis, SEER summary stage, T stage, N stage, M stage and the presence of multiple primary carcinomas. The Kaplan-Meier curves further verified the results, and AJCC stage was also determined as a prognostic factor negatively affecting CSS (Figure 3 and Figure S4). Multivariate analysis showed that the independent prognostic factors for CSS were N stage, M stage, the presence of multiple primary carcinomas and treatment modalities. The results of the univariate and multivariate analyses for CSS are summarized in Table 5.

The survival difference among patients treated with surgery alone and patients treated with surgery and adjuvant treatment was also evaluated. On univariate and multivariate analysis for OS, no significant difference was noted between patients treated surgically alone and patients who received surgery, adjuvant radiation and chemotherapy. Similar results were also observed when these treatment modalities were compared after stratified by AJCC stage of the malignancy (Figure S5). On univariate analysis for CSS,

no significant difference was noted among patients treated with different modalities. However, on multivariate analysis for CSS, it was surprising that the prognosis of patients who received adjuvant radiation [hazard ratio (HR), 0.256; $P=0.004$] or adjuvant chemo-radiotherapy (HR, 0.217; $P=0.007$) was better than the prognosis of patients treated with surgery only. This indicates that adjuvant radiation and chemotherapy improved the survival of SDC patients.

Nomogram

To visualize the multivariate results and improve the clinical practicality, the risk factors affecting OS and CSS included in the multivariate COX model were employed to construct a prognostic nomogram. Based on the total score identified, the nomograms can provide the likelihood of 3- and 5-year OS and CSS for individual SDC patient (Figure 4). The C-index value of the nomogram for OS and CSS was 0.703 (0.646–0.760) and 0.771 (0.691–0.851), respectively. The calibration curve showed that the predictive curve fitted well with the actual observation curve, which indicated that there was a good agreement between the predicted 3- and 5-year OS and CSS in the nomogram and the actual 3- and 5-year OS and CSS in clinical practice (Figure 5).

Discussion

To our knowledge, the data collected in the present study represent the latest update from the SEER database on SDC of the salivary gland. Our results show that patient age, tumor size and lymph node metastasis negatively affect

Table 3 Treatment and outcome of SDC of salivary gland

Characteristics	Patients (n=266)	
	Number	%
Surgery		
Surgery	255	95.86
Not recommended	9	3.38
Recommended but refused	2	0.75
Neck dissection		
Yes	228	85.71
None	38	14.29
Regional nodes examined		
Yes	220	82.71
No	37	13.91
Unknow	9	3.38
Regional nodes positive (n=220)		
Positive	151	68.64
Negative	69	31.36
LNR	Median 0.167, range [0–1]	
Treatment modality		
No treatment	5	1.88
Surgery only	60	22.56
Chemotherapy only	2	0.75
Surgery + radiotherapy	130	48.87
Surgery + chemotherapy	6	2.26
Radiotherapy + chemotherapy	4	1.50
Surgery + radiotherapy + chemotherapy	59	22.18
Follow-up duration	Range 2–143 months, median 34.5 months	
Survival status		
Alive	147	55.26
Died of salivary gland	59	22.18
Died of other causes	60	22.56

SDC, salivary duct carcinoma; LNR, lymph node ratio.

the prognosis of SDC. In addition, we also identified that the SEER summary stage, AJCC stage, LNR, primary site and the presence of multiple primary carcinomas are the important factors indicating poor prognosis for SDC,

whereas histologic grade is not a prognostic factor, which might need further investigation in a large validation cohort. Overall, our study provided more clinical and survival aspects of SDC in comparison with the previous SEER study on SDC, including the 7th edition of TNM staging systems, LNR and presence of multiple primary carcinomas.

Previously, a study using NCDB to analyze the treatment patterns and the outcome data for patients with SDC in a large population-based sample (n=495), showed that advanced stage, increasing age and male gender are associated with inferior OS (9). However, the NCDB used in the study did not provide data regarding the cause of death. As the non-cancer events contribute to a proportion of patient deaths, the competing risk events need to be taken into account in the survival analysis to reach a more objective conclusion. In our study, 59 (22.18%) patients died of SDC while 60 (22.56%) patients died of other causes. Accordingly, the 5-year OS and CSS were calculated as 47.86% and 60.7%, respectively, which was consistent with that from the previous studies (3,4,21).

In agreement with the existing literature indicating that most SDC patients were the men aged 50 or older (2,17,22), and that the majority of tumors occurred in the parotid gland with advanced T stage (3,6,23) (i.e., T3 or T4) and regional lymph node metastasis (N0+) (24), our analyses showed that SDC was most frequently seen in male patients within the sixth decade of life, and that 56.20% of tumors were at the advanced T stage and 60.15% of tumors were clinical N0+ disease. Accordingly, only 24.06% of patients presented at early clinical stage (AJCC stage I and II), whereas most of patients (73.68%) presented at late clinical stage (AJCC stage III and IVA-C). Taken together, it suggests that SDC is an aggressive malignancy with advanced stage and high rate of lymph node metastasis.

In our study, the majority of SDC patients (95.86%) underwent surgical resection and a high proportion (89.80%) of them underwent neck dissection. This is in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for high grade salivary malignancies (25). In comparison with previous studies concerning the survival benefit of adjuvant therapy for SDC, our study verified the role of radiotherapy and chemotherapy in improving the prognosis in patients with SDC, which might provide new support for the establishment of therapeutic guidelines for this disease (9,15,17). However, more clinical trials are needed to further investigate the survival benefits of the addition of

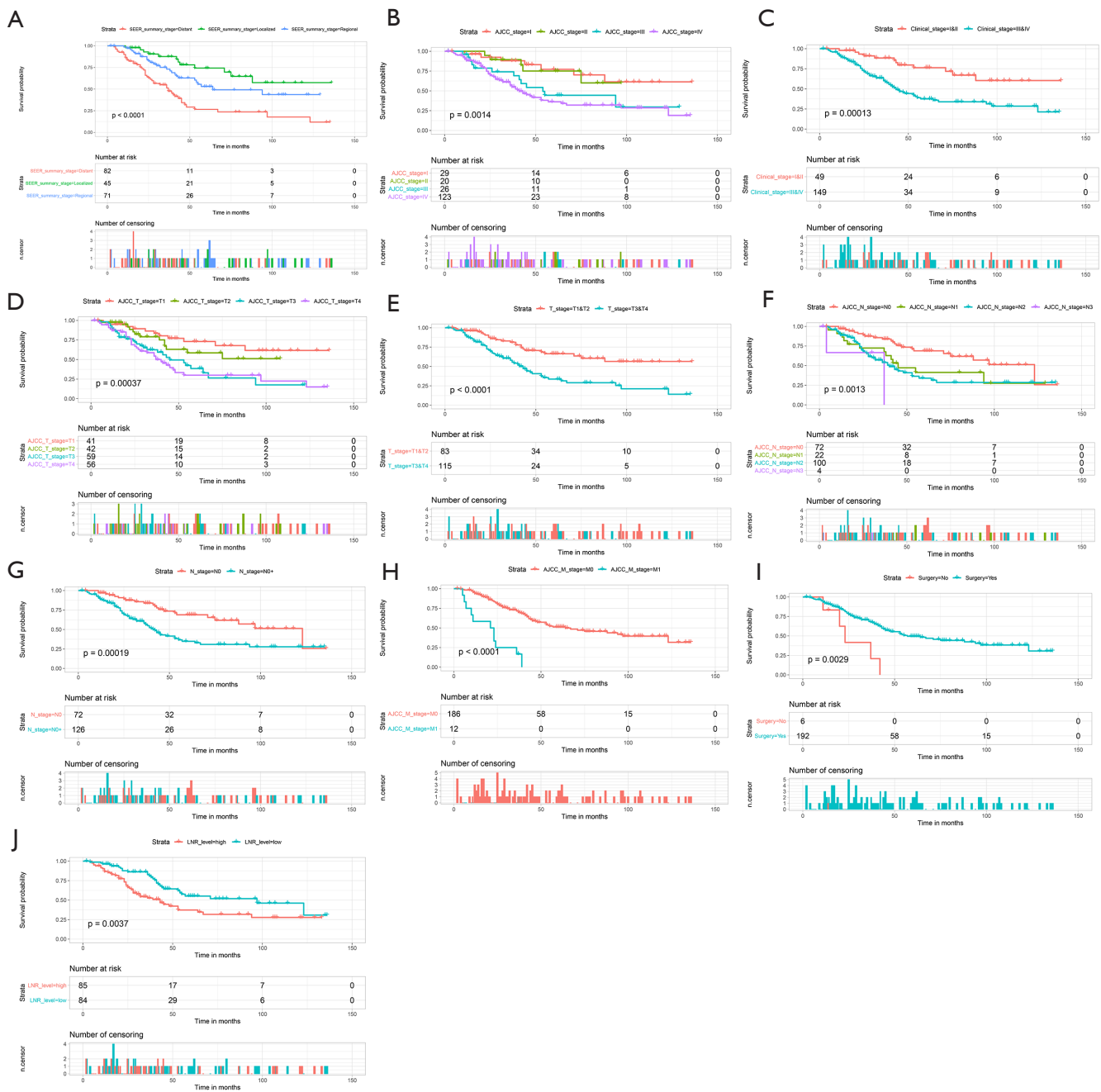


Figure 2 Kaplan-Meier curves for OS of SDC patients stratified by (A) SEER summary stage, (B,C) AJCC stage, (D,E) AJCC T stage, (F,G) AJCC N stage, (H) M stage, (I) surgery and (J) LNR level. OS, overall survival; SDC, salivary duct carcinoma; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio.

radiation and chemotherapy.

To date, the commonly identified prognostic factors of SDC are as follows: age, gender, tumor grade, tumor size, lymph node metastasis and clinical stage (9-12). The prognostic factors determined in our study were similar to

those expected based on prior studies. Furthermore, our multivariate analysis also showed that SDC originated at submandibular gland exhibited worse OS than that in the parotid gland, and that high LNR was a significant predictor of worse OS. Consistently, a retrospective study of the role

Table 4 Univariate and multivariate survival analysis on OS for patients with SDC

Variables	Univariate survival analysis		Multivariate survival analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years				
<68	Reference			
≥68	1.252 (0.820–1.911)	0.298		
Gender				
Female	Reference			
Male	1.159 (0.727–1.847)	0.536		
Race				
Black	Reference	0.643		
White	1.478 (0.496–4.407)	0.484		
Other	1.490 (0.648–3.426)	0.348		
Year of diagnosis				
2004–2010	Reference			
2011–2015	0.872 (0.553–1.376)	0.557		
Primary site				
Parotid gland	Reference		Reference	
Submandibular gland	1.498 (0.856–2.622)	0.157	1.849 (1.032–3.314)	0.039*
Laterality				
Left	Reference			
Right	0.985 (0.644–1.506)	0.985		
Summary stage		<0.001*		
Localized	Reference			
Regional	1.781 (0.902–3.519)	0.097		
Distant	3.963 (2.093–7.503)	<0.001		
T stage		0.001*		<0.001*
T1	Reference		Reference	
T2	1.516 (0.678–3.391)	0.311	1.345 (0.597–3.03)	0.475
T3	3.062 (1.520–6.171)	0.002	3.148 (1.556–6.365)	0.001
T4	3.405 (1.718–6.749)	<0.001	3.417 (1.713–6.81)	<0.001
N stage		<0.001*		
N0	Reference			
N1	2.088 (1.051–4.148)	0.035		
N2	2.510 (1.512–4.165)	<0.001		
N3	5.092 (1.181–21.963)	0.029		

Table 4 (continued)

Table 4 (continued)

Variables	Univariate survival analysis		Multivariate survival analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
M stage				
M0	Reference		Reference	
M1	5.780 (2.987–11.183)	<0.001*	5.816 (2.953–11.45)	<0.001*
AJCC stage group		0.003*		
I	Reference			
II	1.086 (0.344–3.424)	0.889		
III	2.657 (1.058–6.671)	0.038		
IV	3.379 (1.541–7.410)	0.002		
Grade		0.650		
Well differentiated	Reference			
Moderately differentiated	0.802 (0.241–2.672)	0.720		
Poorly differentiated	0.961 (0.346–2.670)	0.939		
Undifferentiated	0.714 (0.250–2.045)	0.531		
Multiple primary carcinomas				
Presence	Reference			
Absence	1.019 (0.657–1.580)	0.932		
Surgery				
No	Reference			
Yes	0.275 (0.110–0.687)	0.006		
Treatment modality		0.253		
Surgery only	Reference			
Surgery + radiotherapy	0.486 (0.235–1.002)	0.051		
Surgery + radiotherapy + chemotherapy	0.524 (0.213–1.290)	0.159		
No treatment or other	0.578 (0.074–4.505)	0.601		
Neck dissection				
No	Reference			
Yes	1.213 (0.643–2.286)	0.551		
Regional nodes positive		0.017*		
Low	Reference			
High	1.952 (1.222–3.119)	0.05		
None	1.256 (0.652–2.419)	0.495		

The number with * indicates statistical significance. OS, overall survival; SDC, salivary duct carcinoma; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.

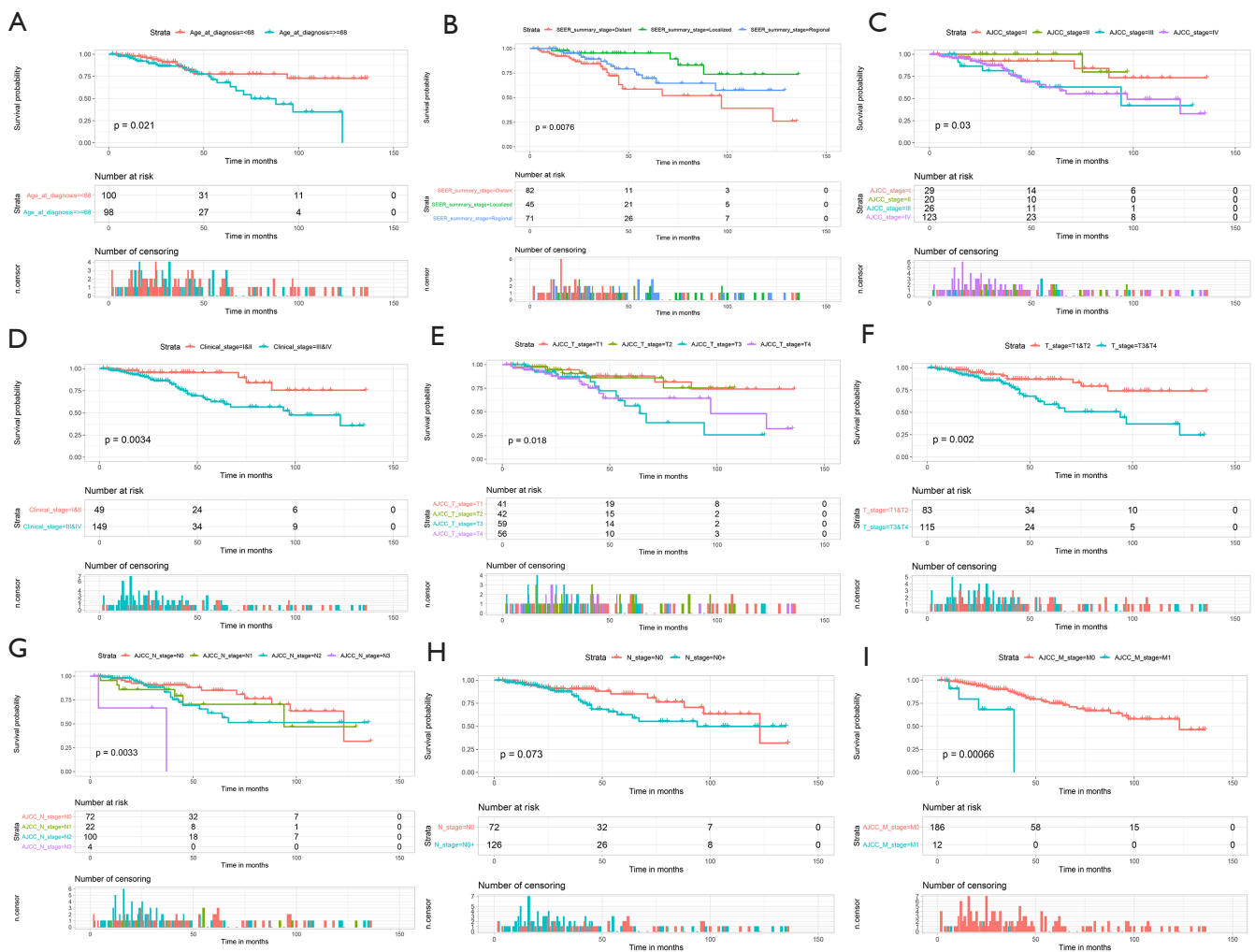


Figure 3 Kaplan-Meier curves for CSS of SDC patients stratified by (A) age at diagnosis, (B) SEER summary stage, (C,D) AJCC stage, (E,F) AJCC T stage, (G,H) AJCC N stage and (I) M stage. CSS, cancer-specific survival; SDC, salivary duct carcinoma; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

of LNR in salivary gland cancer demonstrated a significant heterogeneity in prognosis by LNR (26). Therefore, LNR classification might be considered as a complementary system to TNM staging for SDC. Complementary to the previous prognostic findings on SDC, our analyses also demonstrated that the presence of multiple primary carcinomas was an independent factor for CSS for SDC patients.

There are several limitations that need to be elucidated for the present study. Though the SEER database provides a population-based cohort for the survival analysis of the rare malignancy, some inherent weaknesses still exist.

Prior studies have shown that certain pathologic features (e.g., perineural invasion, lymph-vascular invasion, extra parenchymal extension and positive surgical margins) and some genomic alterations (e.g., HER2/neu, p53 and ERbeta) are associated with OS in single institution studies (27-30). However, these factors were not available for the analysis based on the SEER database. Moreover, given that the SEER study is a retrospective collection of clinicopathological and follow-up information of cancer patients, only patients with complete information of involved variables were included in our study, which brought about selection bias. The exclusion of patients

Table 5 Univariate and multivariate survival analysis on CSS for patients with SDC

Variables	Univariate survival analysis		Multivariate survival analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years				
<68	Reference		Reference	
≥68	2.113 (1.105–4.038)	0.024*	1.897 (1.897–3.941)	0.086
Gender				
Female	Reference		Reference	
Male	1.507 (0.773–3.098)	0.265	2.022 (0.888–4.604)	0.094
Race				
Black	Reference	0.876		
White	0.760 (0.260–2.159)	0.607		
Other	0.781 (0.194–3.148)	0.729		
Year of diagnosis				
2004–2010	Reference			
2011–2015	0.872 (0.553–1.376)	0.557		
Primary site				
Parotid gland	Reference			
Submandibular gland	1.092 (0.452–2.805)	0.854		
Laterality				
Left	Reference			
Right	0.918 (0.491–1.716)	0.789		
Summary stage		0.013*		
Localized	Reference			
Regional	2.505 (0.909–6.908)	0.076		
Distant	4.257 (1.582–11.455)	0.004		
T stage		0.028*		0.053
T1	Reference		Reference	
T2	1.171 (0.356–3.855)	0.795	1.171 (0.794–2.817)	0.722
T3	3.430 (1.901–8.981)	0.012	2.453 (0.815–7.380)	0.110
T4	2.794 (1.065–7.332)	0.037	3.036 (1.077–8.559)	0.036
N stage		0.017*		0.025*
N0	Reference		Reference	
N1	1.655 (0.628–4.362)	0.308	2.472 (2.472–7.633)	0.116
N2	1.750 (0.857–3.575)	0.125	1.959 (0.843–4.551)	0.118
N3	11.582 (2.495–53.842)	0.029	11.948 (2.206–64.725)	0.004

Table 5 (continued)

Table 5 (continued)

Variables	Univariate survival analysis		Multivariate survival analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
M stage				
M0	Reference		Reference	
M1	5.408 (1.816–16.100)	0.002*	10.713 (3.171–36.198)	0.001*
AJCC stage group		0.061		
I	Reference			
II	0.411 (0.046–3.687)	0.427		
III	3.112 (0.932–10.390)	0.065		
IV	2.849 (1.541–7.410)	0.052		
Grade		0.893		
Well differentiated	Reference			
Moderately differentiated	0.674 (0.112–4.055)	0.667		
Poorly differentiated	0.922 (0.216–3.935)	0.912		
Undifferentiated	0.737 (0.166–3.278)	0.689		
Multiple primary carcinomas				
Presence	Reference		Reference	
Absence	1.992 (1.063–3.733)	0.031*	2.256 (1.142–4.459)	0.019*
Surgery				
No	Reference			
Yes	0.561 (0.076–4.164)	0.572		
Treatment modality		0.253		0.018*
Surgery only	Reference		Reference	
Surgery + radiotherapy	0.486 (0.235–1.002)	0.051	0.256 (0.071–0.640)	0.004*
Surgery + radiotherapy + chemotherapy	0.524 (0.213–1.290)	0.159	0.217 (0.102–0.663)	0.007*
No treatment or other	0.578 (0.074–4.505)	0.601	0.013 (0.102–1.383)	0.091
Neck dissection				
No	Reference			
Yes	1.032 (0.431–2.469)	0.943		
Regional nodes positive		0.673		
Low	Reference			
High	1.291 (0.644–2.588)	0.471		
None	1.397 (0.596–3.276)	0.442		

The number with * indicates statistical significance. CSS, cancer-specific survival; SDC, salivary duct carcinoma; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.

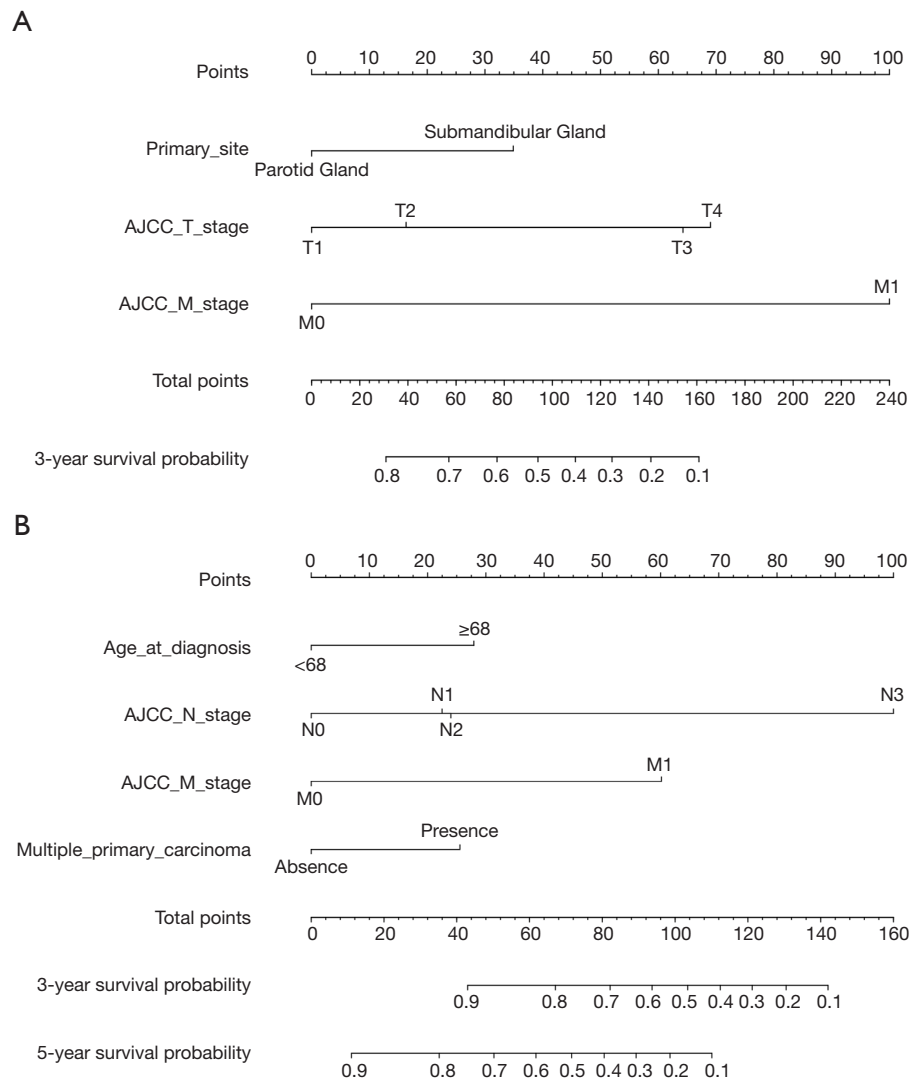


Figure 4 Nomograms for predicting 3- and 5-year OS (A) and CSS (B) of SDC patients. OS, overall survival; CSS, cancer-specific survival; SDC, salivary duct carcinoma; AJCC, American Joint Committee on Cancer.

with incomplete or missing data would also decrease the sample capacity thus reducing statistical power of our study, especially for the patients with SDC, which is a rare histological type of salivary gland cancer. Moreover, the details of adjuvant chemoradiotherapy and treatment responses could not be acquired from the SEER database, thus posing an impediment for us to evaluate the treatment regimens and facilitate the escalation of treatment modalities for SDC patients. Finally, due to the limited sample size, the reliability of our constructed nomogram could not be validated because of the lack of an independent validation cohort. Despite these limitations, our study has

provided us additional information complementary to the existing criteria characterizing this rare malignancy of SDC.

Conclusions

SDC is a clinically aggressive malignancy with a high rate of tumors at the advanced stage and with regional lymph node metastases. Age at diagnosis, primary site, AJCC staging systems, LNR, the presence of multiple primary carcinomas and treatment modalities were identified as prognostic factors for SDC. A radical surgery remains the mainstay of the treatment for SDC. The use of radiotherapy or

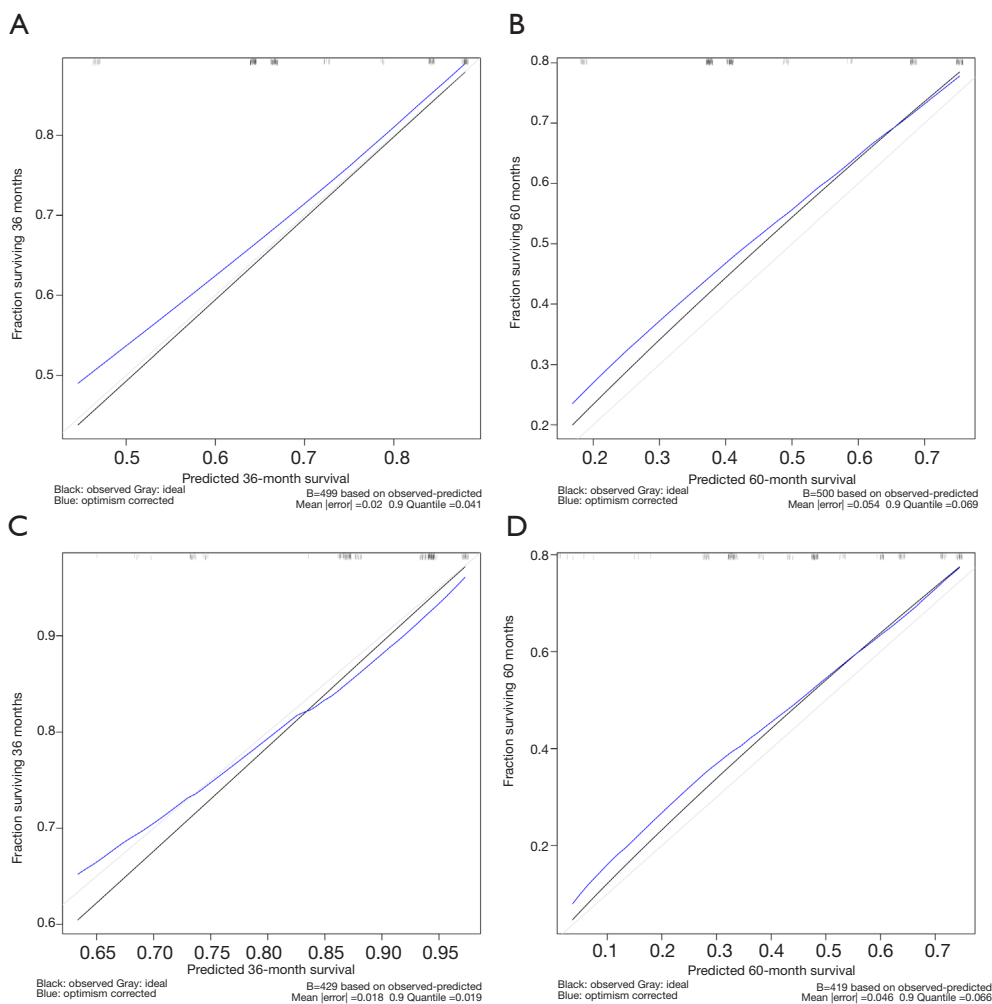


Figure 5 Calibration curves for 3-, and 5-year OS prediction (A,B) and CSS prediction (C,D) in the SDC patients. OS, overall survival; CSS, cancer-specific survival; SDC, salivary duct carcinoma.

chemotherapy was found to improve CSS remarkably. The established competing risk nomogram would facilitate the prognostic estimation of SDC patients, which needs to be further validated in more prospective studies with large sample sizes in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-1849>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since any information in the SEER database does not require explicit consent from the patients, our study was not subject to the ethical approval requirements of the institutional review board.

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