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ABOUT COVER

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AIMS AND SCOPE

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

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including islet cell adenoma, liver cell adenoma, adenomatous polyposis coli, appendiceal neoplasms, bile duct neoplasms, biliary tract neoplasms, hepatocellular carcinoma, islet cell carcinoma, pancreatic ductal carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, hereditary nonpolyposis colorectal neoplasms, common bile duct neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Adenosquamous carcinoma may have an inferior prognosis to signet ring cell carcinoma in patients with stages I and II gastric cancer

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Author contributions: Chu YX drafted the manuscript; Gong HY performed data extraction; Hu QY performed statistical analysis; and Song QB supervised the study.

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Abstract

BACKGROUND

Primary gastric adenosquamous carcinoma (ASC) is an exceedingly rare histological subtype. Gastric signet ring cell carcinoma (SRC) is a unique subtype with distinct tumor biology and clinical features. The prognosis of gastric ASC *vs* SRC has not been well established to date. We hypothesized that further knowledge about these distinct cancers would improve the clinical management of such patients.

AIM

To investigate the clinicopathological characteristics and prognosis of gastric ASC *vs* SRC.

METHODS

A cohort of gastric cancer patients was retrospectively collected from the Surveillance, epidemiology, and end results program database. The 1:4 propensity score matching was performed among this cohort. The clinicopathological features and prognosis of gastric ASC were compared with gastric SRC by descriptive statistics. Kaplan-Meier method was utilized to calculate the median survival of the two groups of patients. Cox proportional hazard regression models were used to identify prognostic factors.

RESULTS

Totally 6063 patients with gastric ASC or SRC were identified. A cohort of 465 patients was recruited to the matched population, including 370 patients with SRC and 95 patients with ASC. Gastric ASC showed an inferior prognosis to SRC after propensity score matching. In the post-matching cohort, the median cancer specific survival was 13.0 (9.7-16.3) mo in the ASC group *vs* 20.0 (15.7-24.3) mo in the SRC group, and the median overall survival had a similar trend ($P < 0.05$). ASC and higher tumor-node-metastasis stage were independently associated

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with a poor survival, while radiotherapy and surgery were independent protective factors for improved prognosis. Subgroup survival analysis revealed that the prognosis of ASC was inferior to SRC only in stages I and II patients.

CONCLUSION
ASC may have an inferior prognosis to SRC in patients with stages I and II gastric cancer. Our study supports radiotherapy and surgery for the future management of this clinically rare entity.

Key words: Adenosquamous carcinoma; Signet ring cell carcinoma; Surveillance, Epidemiology, and End results; Propensity score matching; Prognosis; Survival

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Core tip: The prognosis of gastric adenosquamous carcinoma (ASC) *vs* signet ring cell carcinoma (SRC) has not been well established to date. Our study used both propensity score matching method and multivariate Cox regression analysis to adjust the potential bias caused by the imbalanced distribution of confounding factors. We found that ASC may have an inferior prognosis to SRC in patients with stages I and II gastric cancer. Radiotherapy and surgery were proved to be independent protective factors for improving their prognosis.

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INTRODUCTION

Gastric cancer (GC) is still the second leading cause of cancer-related mortality worldwide[1]. It is also the fifth most frequently diagnosed cancer and was responsible for over 1000000 new cases in 2018 and an estimated 783000 deaths globally[2]. GC has increasingly been recognized as a heterogeneous disease, each histologic subtype of GC differs in its biology, especially in its metabolic profiles[3], so histology is very important in individualized evaluation of patients with GC. Among the various histologic types of GC, signet ring cell carcinoma (SRC) is a unique subtype with distinct tumor biology and clinical features, so it should be analyzed separately[4]. By contrast, adenosquamous carcinoma (ASC) in GC is relatively rare. ASC accounts for only 0.2%-0.4% of all gastric carcinomas[5]. According to the World Health Organization international histological classification of tumors, SRC is defined as a tumor with only intracellular mucin pools[6]. Comparatively, the diagnosis of ASC requires coexistence of both adenocarcinoma and squamous cell carcinoma in the primary tumor, and squamous component should exceed 25% of the primary tumor[7].

Previous studies revealed that primary gastric ASC exhibited early tumor progression and a worse prognosis than some typical gastric carcinomas[8]. There have been two major proposed mechanisms to explain the poor prognosis of ASC in GC. First, this rare subtype may have more extensive tumor depth and higher frequencies of lymphatic and vascular permeations of the carcinoma cells[9]. Second, adenocarcinoma predominate histology may be associated with a higher risk of metastatic disease compared to squamous carcinoma predominate histology[10]. Due to the rare incidence, most of the literature about gastric ASC is described in case reports. The study on gastric ASC with large series is still lacking. The prognosis of ASC *vs* SRC has not been well established to date. Actually, a variety of issues about gastric ASC are still unresolved.

In this study, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to extract a large cohort of patients to investigate the survival differences between ASC and SRC. Cancer-specific survival (CSS) and overall survival (OS) were comprehensively compared between the two groups of patients. We sought to clarify the clinicopathological characteristics and prognosis of gastric ASC *vs* SRC based on a large population analysis. Our study may intensify the current knowledge about these

tumors and provide additional guidance for their management.

MATERIALS AND METHODS

Patient selection

All the data in this study were extracted from SEER 18 registries Custom Data (with additional treatment fields). The SEER database comprises 18 cancer registries and covers approximately 30% of the United States population. The patients were selected using SEER Stat version 8.3.5 software directly. The patient information in SEER database is completely de-identified and publicly available, so this study was exempt from ethical approval from human study subcommittee. We initiated the following inclusion criteria to select eligible patients: (1) All patients were diagnosed from 2004 to 2015; (2) Primary site was the stomach; (3) Behavior recode for analysis was malignant; (4) Primary gastric cancer was the first or only cancer diagnosis; (5) Histological types were confined only to SRC (ICD-03, 8490/3) and ASC (ICD-03, 8560/3); and (6) The follow-up data were complete. The diagnosis was not gained from any death certificate or autopsy. Those patients with unknown information about table variables were excluded.

Data collection

The following variables were extracted for each patient: Age at diagnosis, gender, race, marital status, tumor size, tumor-node-metastasis (TNM) stage, tumor depth, LN metastasis, distant metastasis, radiation, surgery, histological type, survival months, CSS, and OS. CSS was defined as the time from the date of diagnosis to the date of death caused by gastric cancer. OS was defined as the duration from diagnosis to death from any cause. In our study, CSS was the primary endpoint, and OS was the secondary endpoint.

Statistical analysis

The patients were divided into patients with gastric SRC *vs* those with ASC. Given that the two cohorts dichotomized above were not randomized, unbalanced variables might engender selection bias, so we utilized a 1:4 propensity-score matching (PSM) method to control the non-random assignment of patients. A logistic regression model that predicts the likelihood of being assigned to ASC was constructed and set as the propensity score. The propensity scores were calculated according to unbalanced covariates. The PSM adopted nearest-neighbor matching algorithm. The caliper width was 0.01. No replacement was allowed, and all patients were matched only once. The baseline characteristics were compared in both matched and unmatched cohorts by chi-square tests. The survival curves of each histologic group were compared by Kaplan-Meier plots with log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to identify prognostic factors in the post-matching cohort. Variables with $P < 0.05$ in univariate analysis were further adjusted through multivariate analysis. PSM was conducted with R version 3.5.3. Statistical analyses were completed with SPSS statistical software, version 25.0 (SPSS, Chicago, IL, United States). A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics before PSM

Preliminarily, 10646 patients with gastric ASC or SRC were collected, but 4583 cases were excluded because of any missing data or unknown of table variables. Finally, a total of 6063 eligible patients were included in this study. Among the unmatched cohort, 5968 (98.4%) patients had SRC and 95 (1.6%) patients had ASC. The distributions of age, gender, race, marital status, LN metastasis, and radiation were significantly different between the two groups ($P < 0.05$). Compared with those SRC patients, the ASC patients were more likely to have age > 60 years old (66.3% *vs* 52.7%), be male (74.7% *vs* 52.7%) while less female (25.3% *vs* 47.3%), had a relatively higher proportion of white population (77.9% *vs* 69.5%), and be married (77.9% *vs* 61.7%). As for LN metastasis, the ASC patients showed more N1 (48.4% *vs* 34.9%) and N2 (16.8% *vs* 15.5%). With respect to radiation, more ASC patients received radiotherapy (35.8% *vs* 23.7%). No differences were observed in terms of tumor size, TNM stage, tumor depth, distant metastasis, or surgery ($P > 0.05$). The patients' characteristics before PSM are summarized in Table 1.

Table 1 Patient characteristics dichotomized by histological type before propensity score matching, *n* (%)

Characteristic	SRC *n* = 5968 (98.4)	ASC *n* = 95 (1.6)	Total *n* = 6063 (100)	*P* value
Age (yr)				0.008
≤ 60	2823 (47.3)	32 (33.7)	2855 (47.1)	
> 60	3145 (52.7)	63 (66.3)	3208 (52.9)	
Gender				< 0.001
Male	3146 (52.7)	71 (74.7)	3217 (53.1)	
Female	2822 (47.3)	24 (25.3)	2846 (46.9)	
Race				0.045
White	4147 (69.5)	74 (77.9)	4221 (69.6)	
Black	725 (12.1)	13 (13.7)	738 (12.2)	
Others	1096 (18.4)	8 (8.4)	1104 (18.2)	
Marital status				0.001
Not married	2287 (38.3)	21 (22.1)	2308 (38.1)	
Married	3681 (61.7)	74 (77.9)	3755 (61.9)	
Tumor size (mm)				0.220
≤ 50	2271 (38.1)	42 (44.2)	2313 (38.1)	
> 50	3697 (61.9)	53 (55.8)	3750 (61.9)	
TNM Stage				0.299
I	1595 (26.7)	21 (22.1)	1616 (26.7)	
II	888 (14.9)	20 (21.1)	908 (15.0)	
III	1129 (18.9)	15 (15.8)	1144 (18.9)	
IV	2356 (39.5)	39 (41.1)	2395 (39.5)	
Tumor depth				0.139
T1	1398 (23.4)	16 (16.8)	1414 (23.3)	
T2	2177 (36.5)	45 (47.4)	2222 (36.6)	
T3	1384 (23.2)	18 (18.9)	1402 (23.1)	
T4	1009 (16.9)	16 (16.8)	1025 (16.9)	
LN metastasis				0.011
N0	2472 (41.4)	31 (32.6)	2503 (41.3)	
N1	2080 (34.9)	46 (48.4)	2126 (35.1)	
N2	926 (15.5)	16 (16.8)	942 (15.5)	
N3	490 (8.2)	2 (2.1)	492 (8.1)	
Distant metastasis				0.966
No	4197 (70.3)	67 (70.5)	4264 (70.3)	
Yes	1771 (29.7)	28 (29.5)	1799 (29.7)	
Radiotherapy				0.006
No	4553 (76.3)	61 (64.2)	4614 (76.1)	
Yes	1415 (23.7)	34 (35.8)	1449 (23.9)	
Surgery				0.231
No	2047 (34.3)	27 (28.4)	2074 (34.2)	
Yes	3921 (65.7)	68 (71.6)	3989 (65.8)	

SRC: Signet ring cell carcinoma; ASC: Adenosquamous carcinoma; TNM: Tumor-node-metastasis; LN: Lymph node.

Patient characteristics after PSM

A 1:4 PSM was initiated. The logit of propensity score for histological type was derived from other covariates. Totally 465 patients were matched, including 95 ASC patients and 370 SRC patients. After the PSM, all covariates were well balanced with no significant differences between the two groups ($P > 0.05$). The patients' characteristics categorized by histology after PSM are displayed in Table 2.

Table 2 Patient characteristics dichotomized by histological type after propensity score matching, *n* (%)

Characteristic	SRC	ASC	Total	*P* value
	n = 370 (79.6)	*n* = 95 (20.4)	*n* = 465 (100)	
Age (yr)				0.754
≤ 60	131 (35.4)	32 (33.7)	163 (35.1)	
> 60	239 (64.6)	63 (66.3)	302 (64.9)	
Gender				0.809
Male	272 (73.5)	71 (74.7)	343 (73.8)	
Female	98 (26.5)	24 (25.3)	122 (26.2)	
Race				0.845
White	290 (78.4)	74 (77.9)	364 (78.3)	
Black	44 (11.9)	13 (13.7)	57 (12.3)	
Others	36 (9.7)	8 (8.4)	44 (9.5)	
Marital status				0.901
Not married	84 (22.7)	21 (22.1)	105 (22.6)	
Married	286 (77.3)	74 (77.9)	360 (77.4)	
Tumor size (mm)				0.828
≤ 50	159 (43.0)	42 (44.2)	201 (43.2)	
> 50	211 (57.0)	53 (55.8)	264 (56.8)	
Stage				0.365
I	94 (25.4)	21 (22.1)	115 (24.7)	
II	55 (14.9)	20 (21.1)	75 (16.1)	
III	77 (20.8)	15 (15.8)	92 (19.8)	
IV	144 (38.9)	39 (41.1)	183 (39.4)	
Tumor depth				0.598
T1	77 (20.8)	16 (16.8)	93 (20.0)	
T2	156 (42.2)	45 (47.4)	201 (43.2)	
T3	84 (22.7)	18 (18.9)	102 (21.9)	
T4	53 (14.3)	16 (16.8)	69 (14.8)	
LN metastasis				0.151
N0	151 (40.8)	31 (32.6)	182 (39.1)	
N1	134 (36.2)	46 (48.4)	180 (38.7)	
N2	69 (18.6)	16 (16.8)	85 (18.3)	
N3	16 (4.3)	2 (2.1)	18 (3.9)	
Distant metastasis				0.840
No	257 (69.5)	67 (70.5)	324 (69.7)	
Yes	113 (30.5)	28 (29.5)	141 (30.3)	
Radiotherapy				0.786
No	232 (62.7)	61 (64.2)	293 (63.0)	
Yes	138 (37.3)	34 (35.8)	172 (37.0)	
Surgery				0.883
No	108 (29.2)	27 (28.4)	135 (29.0)	
Yes	262 (70.8)	68 (71.6)	330 (71.0)	

SRC: Signet ring cell carcinoma; ASC: Adenosquamous carcinoma; TNM: Tumor-node-metastasis; LN: Lymph node.

Comparison of the prognosis between gastric SRC and ASC before PSM

As for the 6063 patients finally enrolled, 4560 patients were dead at the end of the last follow-up. Moreover, 4160 patients were dead from gastric cancer specifically. The prognosis of gastric SRC *vs* ASC before PSM was compared. The Kaplan-Meier plots showed that the prognosis of SRC was comparable to that of ASC in both CSS and OS curves (Figure 1, $P > 0.05$). The median CSS of the SRC group was 16.0 (15.2-16.8) mo, while that of the ASC group was 13.0 (9.7-16.3) mo ($P = 0.101$; Table 3). Similarly, the

median OS of the SRC group was not significantly different from that of the ASC group (P = 0.084; Table 3). Hence, the results indicated the prognosis was not statistically different between gastric SRC and ASC before PSM.

Comparison of the prognosis in matched groups

We initiated a 1:4 (ASC:SRC) matched case-control analysis by PSM, in order to adjust the baseline characteristic differences between the two groups. The PSM analysis resulted in a balanced cohort including the ASC group (n = 95) and the SRC group (n = 370). As for the cohort after PSM, statistically significant differences appeared in both CSS and OS, dejecting the ASC group compared with the SRC group (P < 0.05 for both endpoints; Figure 2). Furthermore, the median CSS was 13.0 (9.7-16.3) mo in ASC *vs* 20.0 (15.7-24.3) mo in SRC group (P = 0.027; Table 3). In parallel, the median OS of the ASC group was also inferior to that of the SRC group (Table 3, P = 0.017). The survival curves of CSS and OS after PSM are exhibited in Figure 2. Obviously, the ASC patients had an inferior prognosis to SRC patients in matched groups.

Identify predictors of survival

The Cox proportional hazard models were constructed to evaluate the impact of clinicopathological factors on CSS of the post-matching cohort (Table 4). In univariate analysis, the variables significantly associated with CSS were histological type, marital status, tumor size, TNM stage, tumor depth, distant metastasis, radiation, and surgery (P < 0.05). ASC was found to be a risk factor for poor prognosis [hazard ratio (HR) = 1.343, 95%CI = 1.029-1.752, P < 0.05]. All the significant variables mentioned above were subsequently included to the multivariate Cox regression analysis. Multivariable analysis confirmed some of the prognostic factors identified in univariate analysis. After adjusting for other confounding predictors, histological type and TNM stage were proved to be independent risk factors for poor survival (HR > 1, P < 0.05), while radiotherapy and surgery were independent protective factors for favorable prognosis (HR < 1, P < 0.05). Anyway, ASC was still associated with an inferior prognosis to SRC (HR = 1.316, 95%CI = 1.004-1.726, P < 0.05). The detailed results are available in Table 4.

Subgroup survival analysis

Given that TNM stage is also independently associated with the patients' survival after PSM, we performed a subgroup analysis to highlight the impact of histological type on the prognosis of patients. The Kaplan-Meier plots revealed that the CSS of gastric ASC was worse than that of gastric SRC in both stages I (P < 0.001) and II (P < 0.05) patients. However, no significant survival difference was found for ASC *vs* SRC in either stage III or IV (P > 0.05). Thus, the prognosis of ASC was inferior to SRC only in stages I and II patients. The survival curves of CSS stratified by TNM stage are illustrated in Figure 3.

DISCUSSION

Primary gastric ASC is an extremely rare subtype[11]. The clinicopathological characteristics and prognosis of gastric ASC are still poorly understood. Based on a large cohort from the SEER database, we utilized PSM analysis to evaluate the prognosis of ASC *vs* SRC for patients with gastric cancer. Moreover, we also used Cox proportional hazard regression models to identify prognostic factors for the post-matching population. The overall results suggest that ASC had an inferior survival to SRC in patients with gastric cancer. ASC and higher TNM stages were independently associated with a poor prognosis.

The clinicopathological features and prognosis of gastric ASC have been reviewed by several previous studies. Based on the National Cancer Database analysis, a recent original research has reported the clinical features and outcomes of gastric squamous cell carcinoma (SCC) and ASC. They collected 61215 patients with primary gastric cancer. ASC only accounted for 0.5%. The median OS was 9.9 mo in ASC *vs* 13.2 mo in adenocarcinoma. On multivariate analysis, ASC histology was still associated with a worse survival compared to adenocarcinoma[12]. Furthermore, another study reported the clinical features and outcomes of 167 gastric ASC cases. Only 109 cases with R0 resection were recruited in survival analysis. Their results revealed that the median OS time was 17 mo for patients with gastric ASC receiving R0 resection. They also found that the prognosis of gastric ASC was significantly poorer than that of gastric adenocarcinoma[13]. Quan *et al*[14] also reported that the median OS of gastric ASC was 12 mo, and 87.5% of the patients survived for less than 24 mo after diagnosis. In our present study, we compared the survival outcomes of gastric ASC with SRC. As for our matched cohort, the median OS was 12.0 (9.5-14.5) mo in ASC *vs* 19.0 (14.9-23.1)

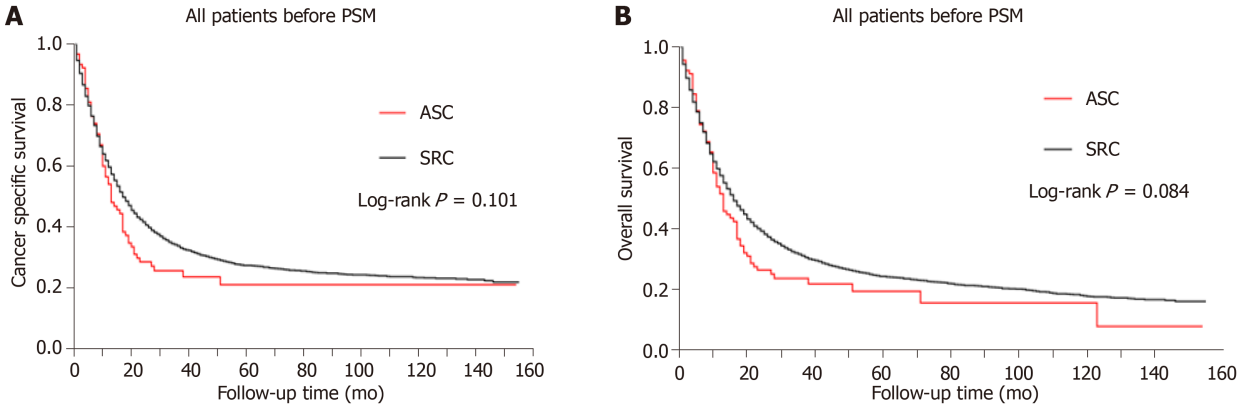

Figure 1 Kaplan-Meier survival curves by histology before propensity score matching. A: Cancer-specific Survival ($P > 0.05$); B: Overall Survival ($P > 0.05$). ASC: Adenosquamous carcinoma; SRC: Signet ring cell carcinoma.

mo in SRC group. In parallel, the median CSS of ASC was also significantly worse than that of SRC. Consistently, the prognosis of ASC was inferior to that of SRC after PSM analysis.

When it comes to the prognostic factors for gastric ASC, we found that the histological type ASC and higher TNM stage were independent risk factors for poor survival (HR > 1, $P < 0.05$), while radiotherapy (HR = 0.587; 95%CI: 0.444-0.776, $P < 0.001$) and surgery were independent protective factors for favorable prognosis (HR < 1, $P < 0.05$). So far, surgery remains the optimal treatment for gastric cancer without distant metastasis[15]. So the survival advantage of gastrectomy has been further confirmed by our study. Additionally, radiotherapy has been reported to be an effective adjuvant treatment for improving the OS in patients with gastric cancer after resection[16]. Considering that squamous cell carcinoma is generally sensitive to radiation therapy, the squamous component of gastric ASC may specifically benefit from radiotherapy[17]. Therefore, our study has provided evidence to support radiotherapy for patients with gastric ASC.

In addition to histological type, other confounders such as tumor TNM stage may also account for the potentially important survival differences. In order to further adjust the confounding factors, we performed subgroup survival analysis by TNM stage. Our results revealed that the CSS of gastric ASC was significantly worse than that of SRC in stages I and II patients, whereas no significant survival difference was found for stages III and IV patients. A recent study revealed that half of gastric ASC cases were diagnosed at advanced stages, and most patients had lymph node metastasis[18]. These results suggest that gastric ASC has an aggressive clinical course compared with conventional gastric cancer. The prognosis of stages I and II ASC patients should be concerned.

In terms of the prognosis for patients with gastric SRC, a recent review has indicated that early SRC had a better clinical outcome, but advanced SRC was generally considered to have a worse prognosis. Therapeutic strategies are still controversial for these patients[19]. Consistently, our study also revealed that stages I and II SRC patients had better survival curves than ASC patients. Their median CSS was 20.0 (15.7-24.3) mo, and median OS was 19.0 (14.9-23.1) mo. Our Cox proportional hazard regression models identified radiotherapy and surgery as independent protective factors for improving their prognosis (HR < 1, $P < 0.05$). Hence, our results may improve the therapeutic recommendations for these patients.

There are several limitations in our study. First, the retrospective nature of the current study could not exclude the possibility of selection bias. Although we could balance known covariates by PSM analysis, there may be unmeasured confounders not addressed in propensity matching. Hence, the results of our study should be interpreted cautiously. Second, the constituent ratio of adenocarcinoma and SCC components varied among different primary tumors. The prognostic value of constituent ratio on the survival of gastric ASC could not be evaluated. Third, there were limited data about cancer recurrence and subsequent involved sites in SEER database, so the patterns of recurrence and corresponding impact on the prognosis of patients remain unclear. In spite of the limitations stated above, SEER registry data usually have high completeness and are representative of the real-world patient population. Thus, the results of our study are still considerably convincing.

The major strength of our study is that we used both PSM method and multivariate Cox regression analysis to adjust the potential bias caused by the imbalanced

Table 3 Comparison of median survival of the patients before and after propensity score matching

	Patients, *n*	Median CSS 95%CI, mo	Median OS 95%CI, mo
Before PSM			
SRC	5968	16.0 (15.2-16.8)	15.0 (14.3-15.7)
ASC	95	13.0 (9.7-16.3)	12.0 (9.5-14.5)
P value		0.101	0.084
After PSM			
SRC	370	20.0 (15.7-24.3)	19.0 (14.9-23.1)
ASC	95	13.0 (9.7-16.3)	12.0 (9.5-14.5)
P value		0.027	0.017

CSS: Cancer-specific survival; OS: Overall survival; PSM: Propensity-score matching; SRC: Signet ring cell carcinoma; ASC: Adenosquamous carcinoma.

distribution of confounding factors. This doubly robust estimation combines two approaches to evaluate the causal effect of exposures on outcomes, which will encourage researchers to more fully interpret their findings on both scales[20].

In summary, gastric ASC differs significantly from gastric SRC in terms of clinicopathological characteristics. ASC may have an inferior prognosis to SRC in patients with stages I and II gastric cancer, so greater attention should be paid to these patients. Histological type ASC and higher TNM stage are associated a poor survival, but radiotherapy and surgery are independent protective factors for improving their prognosis. Our study supports radiotherapy and surgery for the future management of this clinically rare entity.

Table 4 Cox regression analysis of cancer-specific survival (*n* = 465)

Characteristic	Univariate Cox		Multivariate Cox	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Histological type				
SRC	Reference		Reference	
ASC	1.343 (1.029-1.752)	0.030	1.316 (1.004-1.726)	0.047
Age (yr)				
≤ 60	Reference		NI	
> 60	1.027 (0.819-1.288)	0.815		
Gender				
Male	Reference		NI	
Female	0.952 (0.740-1.223)	0.698		
Race				
White	Reference		NI	
Black	1.199 (0.870-1.652)	0.268		
Others	0.883 (0.597-1.304)	0.531		
Marital status				
Not married	Reference		Reference	
Married	0.768 (0.593-0.994)	0.045	0.709 (0.540-0.932)	0.014
Tumor size (mm)				
≤ 50	Reference		Reference	
> 50	1.994 (1.587-2.503)	<0.001	1.217 (0.947-1.564)	0.125
Stage				
I	Reference		Reference	
II	1.482 (0.993-2.212)	0.054	1.564 (1.021-2.394)	0.040
III	2.472 (1.714-3.564)	< 0.001	2.460 (1.601-3.780)	< 0.001
IV	5.179 (3.739-7.175)	< 0.001	2.884 (1.665-4.997)	< 0.001
Tumor depth				
T1	Reference		Reference	
T2	0.962(0.705-1.312)	0.805	1.296 (0.923-1.821)	0.135
T3	1.478(1.051-2.077)	0.025	1.482 (0.986-2.228)	0.058
T4	1.801 (1.243-2.609)	0.002	1.070 (0.699-1.638)	0.757
LN metastasis				
N0	Reference		NI	
N1	0.978(0.760-1.258)	0.863		
N2	1.218 (0.901-1.647)	0.200		
N3	1.642 (0.985-2.737)	0.057		
Distant metastasis				
No	Reference		Reference	
Yes	4.303 (3.397-5.451)	< 0.001	1.278 (0.778-2.100)	0.333
Radiotherapy				
No	Reference		Reference	
Yes	0.484(0.383-0.612)	< 0.001	0.587 (0.444-0.776)	< 0.001
Surgery				
No	Reference		Reference	
Yes	0.244(0.192-0.311)	< 0.001	0.450 (0.319-0.635)	< 0.001

HR: Hazard ratio; NI: Not included; LN: Lymph node; SRC: Signet ring cell carcinoma; ASC: Adenosquamous carcinoma; TNM: Tumor-node-metastasis.

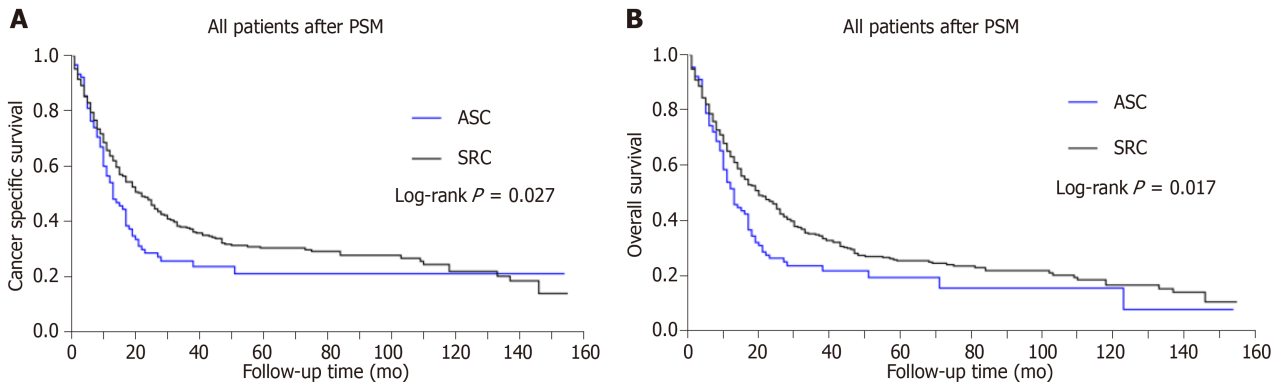

Figure 2 Kaplan-Meier survival curves by histology after propensity score matching. A: Cancer-specific Survival ($P < 0.05$); B: Overall Survival ($P < 0.05$). ASC: Adenosquamous carcinoma; SRC: Signet ring cell carcinoma.

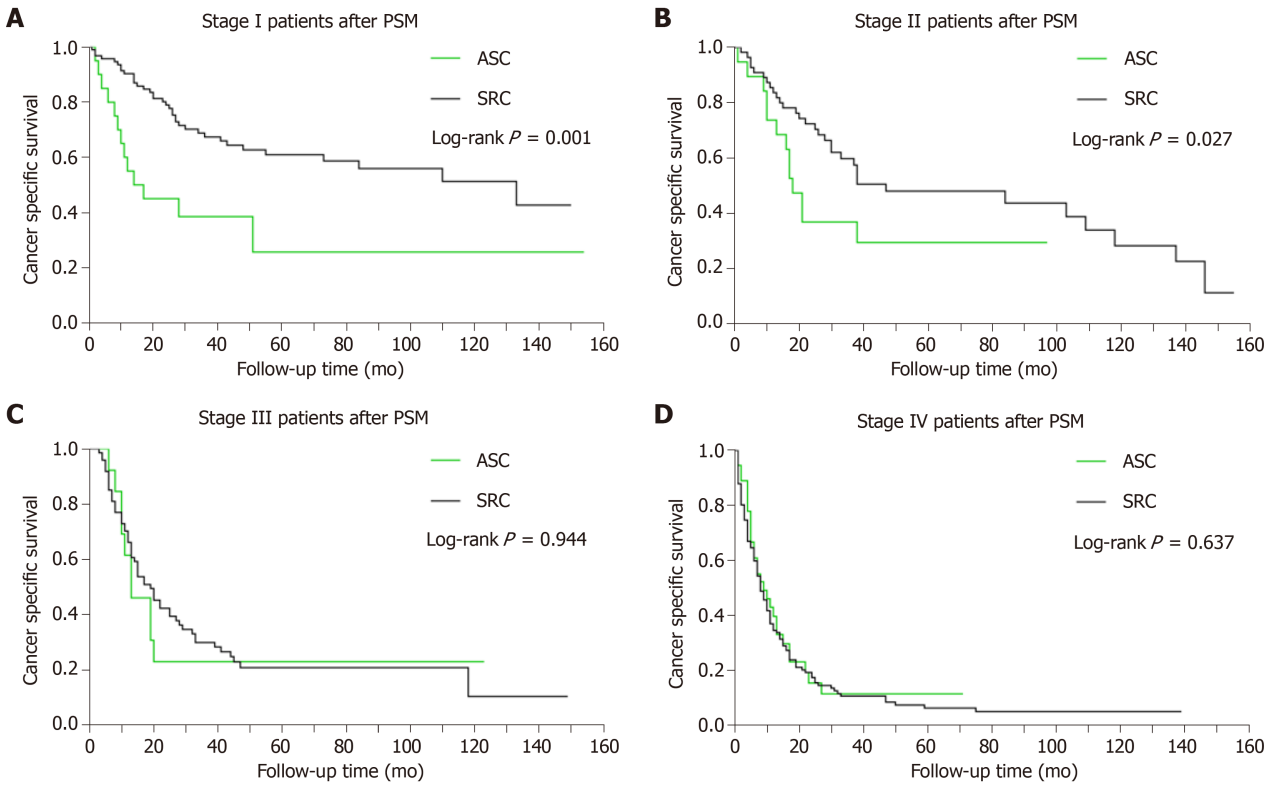

Figure 3 Kaplan-Meier plots of adenosquamous carcinoma *vs* signet ring cell carcinoma stratified by TNM stage. A: Stage I ($P < 0.05$); B: Stage II ($P < 0.05$); C: Stage III ($P > 0.05$); D: Stage IV ($P > 0.05$). ASC: Adenosquamous carcinoma; SRC: Signet ring cell carcinoma.

ARTICLE HIGHLIGHTS

Research background

Adenosquamous carcinoma (ASC) is a rare entity in gastric cancer, which exhibits early tumor progression and a poorer prognosis than other typical gastric adenocarcinoma. Gastric signet ring cell carcinoma (SRC) is a unique subtype with distinct tumor biology and clinical features. We hypothesized that further knowledge about these distinct cancers would improve the clinical management of such patients.

Research motivation

Given the relative rarity of these two subtypes in gastric cancer, the study on gastric ASC with large series is still lacking. The clinicopathological characteristics and prognosis of ASC *vs* SRC has not been well established to date. The current study adopted a large cohort of such patients from the Surveillance, Epidemiology, and End Results (SEER) database. Study on the clinicopathological features, treatment, and prognosis of such patients may bring deeper knowledge on these tumors and provide additional assistance for their treatment.

Research objectives
The goal of our study was to evaluate the clinicopathological characteristics and prognosis of ASC *vs* SRC based on a large cohort from the SEER database. Achieving this objective may provide additional assistance for their management.

Research methods
We conducted a retrospective study using a large cohort from the SEER database. The clinicopathological features of patients with ASC *vs* SRC were comprehensively compared by chi-square tests. We used both propensity-score matching (PSM) method and multivariate Cox regression analysis to adjust the potential bias caused by the imbalanced distribution of confounding factors. Clinical outcomes including cancer-specific survival (CSS) and overall survival (OS) were also compared by the Kaplan-Meier method. The prognostic factors were identified.

Research results
A total of 6063 eligible patients were collected. After PSM, 370 patients with SRC and 95 patients with ASC were analyzed. In the post-matching cohort, gastric ASC showed an inferior prognosis to SRC in both CSS and OS. ASC and higher TNM stage were independently associated with a poor survival (HR > 1, $P < 0.05$), while radiotherapy (HR = 0.587; 95%CI: 0.444-0.776, $P < 0.001$) and surgery were independent protective factors for favorable prognosis (HR < 1, $P < 0.05$). Subgroup survival analysis revealed that the inferior prognosis was most significant in stages I and II patients.

Research conclusions
ASC may have an inferior prognosis to SRC in patients with stages I and II gastric cancer, so greater attention should be paid to these patients. Our study supports radiotherapy and surgery for the future management of this clinically rare entity. Improved clinical and biological understanding of ASC *vs* SRC may lead to more individualized therapy for such patients.

Research perspectives
Our study shows that gastric ASC has an inferior prognosis to SRC in stages I and II patients. Precautions should be taken to such patients. Radiotherapy and surgery have the potential to improve their clinical outcomes. Future long-term prospective studies are warranted to validate our findings.

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