Differential prognostic implications of gastric adenocarcinoma based on Lauren's classification: a Surveillance, Epidemiology, and End Results (SEER)-based cohort study

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Background: Our study aims to analyze the association between Lauren's classification and gastric adenocarcinoma prognosis using comprehensive statistical analyses.

Methods: According to the selection criteria, patients were included from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate Cox regression, propensity score matching, and a multivariate competing risk model were used to investigate the association between Lauren's classification and prognosis. Subgroup analysis was used to investigate the role of confounding factors on the association between Lauren types and prognosis.

Results: After exclusion, a total of 20,218 patients from the SEER database were included, with 14,374 intestinal types and 5,844 diffuse types. The univariate Cox regression analysis revealed that the diffuse type had a poorer cancer-specific survival (CSS) rate [hazard ratio (HR), 1.44; 95% confidence interval (CI), 1.38–1.50]. After adjusting for confounding variables, the diffuse type also showed a higher risk of cancer-specific death (HR, 1.20; 95% CI, 1.15–1.20). Sensitivity analysis showed that after propensity score matching, the diffuse type had a poorer CSS rate (HR, 1.23; 95% CI, 1.10–1.36), and the competing risk model further validated these results [subdistribution HR (SHR), 1.32; 95% CI, 1.23–1.41]. Moreover, subgroup analysis demonstrated stable results in the subgroups, except for patients with T1 stage (HR, 1.06; 95% CI, 0.87–1.28) and a tumor size <2 cm (HR, 1.00; 95% CI, 0.83–1.21).

Conclusions: Diffuse-type gastric adenocarcinoma had an overall poorer prognosis compared to the intestinal type. However, in patients with T1 stage and tumor size <2 cm, the diffuse type had a comparable survival rate with the intestinal type.

Keywords: Gastric adenocarcinoma; Lauren's classification; Surveillance, Epidemiology, and End Results (SEER); survival

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Introduction

Gastric adenocarcinoma is the main type of gastric cancer (GC), accounting for approximately 95% of all cases (1). Although numerous novel therapies have been developed in recent decades, surgical resection remains the only curative therapy for this malignancy (2). However, due to a lack of effective methodologies to diagnose this malignancy at an early stage, most patients are diagnosed at advanced stages and do not meet surgical resection indications (3). Hence, most gastric adenocarcinoma patients' prognosis remains poor, with a 5-year survival rate of less than 25% (2).

Lauren's classification is the most commonly used histological subtype criteria for predicting prognosis and establishing a treatment strategy in gastric adenocarcinoma (4-7). Lauren's classification divides gastric adenocarcinoma into two histological subtypes: an intestinal type and a diffuse type (8). Previous reports have shown that diffuse-type gastric adenocarcinoma exhibits a comparable strong association with *Helicobacter pylori* (*H. pylori*) infection compared with intestinal type via different mechanisms (9). Intestinal-type lesions derive from premalignant lesions through an initial *H. pylori*-induced chronic gastritis and subsequent atrophic and metaplastic gastritis (10). Diffuse-type lesions also originate from *H. pylori*-induced chronic inflammation with overpassing multiple steps including atrophic gastritis and intestinal metaplasia (11,12). According to the British Society of Gastroenterology's latest guidelines, complete (R0) endoscopic resection is recommended to patients with intestinal-type intramucosal gastric adenocarcinoma but is not suitable for those with the diffuse type (13). However, recent studies have shown significant variations in patients' clinical outcomes with the same histological subtype. For instance, numerous studies have demonstrated that diffuse-type lesions are associated with younger age, a higher risk of lymph node metastasis (LNM), and a worse prognosis than intestinal-type lesions (14-18). However, several recent studies reported that diffuse-type gastric adenocarcinoma, such as signet ring cell (SRC), showed a similar or even better prognosis than other histologic subtypes at an early stage (19-22). Although the sample sizes of these studies were relatively small and, stage-stratified analyses were lacking. Also, only a few studies considered the interaction between confounding factors and Lauren's classification. Therefore, more studies are needed to confirm Lauren's classification's clinical role and provide adequate prognostic information to facilitate personalized medicine.

In this study, we investigated the association between Lauren's classification and cause-specific prognosis. Multivariate regression was performed to adjust confounding factors to reveal the independent association between Lauren's classification and cause-specific prognosis. Subgroup and sensitivity analyses were performed to validate the independent association. This study may provide evidence for therapeutic decision-making and follow-up strategies for different histologic types of gastric adenocarcinoma. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7953).

Methods

Patients

This is a retrospective cohort study. All patients with gastric adenocarcinoma were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database using SEER*Stat software (version 8.6.1; www.seer.cancer.gov). Informed consent or ethical approval was not required since the SEER database only contains de-identified data and is publically available. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The International Classification of Diseases for Oncology (ICD-O, third edition) was used to identify intestinal- or diffuse-type gastric adenocarcinoma patients. Intestinal-type gastric adenocarcinoma includes carcinoma [not otherwise specified (NOS); M8010], adenocarcinoma (NOS; M8140), tubular (M8211), and intestinal-type (M8144). Meanwhile, the diffuse type includes SRC (M8490), diffuse carcinoma (M8145), and linitis plastica (M8142) (23).

A total of 78,303 patients diagnosed with GC between 2004 and 2015 were included in this study since data before 2004 lacked detailed information concerning cancer staging. The exclusion criteria were as follows: (I) GC was not the first diagnosed primary tumor (N=14,344); (II) GC with unknown surgery status, unknown histological information, or no tumor (N=34,579); (III) GC with other pathological types (not intestinal or diffuse type, N=7,572); (IV) gastric adenocarcinoma with no complete dates of follow-up (N=1,142); and (V) gastric adenocarcinoma with an unknown reason for death (N=448). After exclusion, 20,218 patients with gastric adenocarcinoma were included for analysis.

Variables and outcomes

The clinicopathological variables extracted from the SEER database included age, sex, race, year of diagnosis, primary site, pathology grade, tumor (T) stage, node (N) stage, metastasis (M) stage, regional nodes examined, regional nodes positive, operation, radiation, chemotherapy, insurance, and marital status. Age was recorded as a continuous variable in the univariable and multivariable analyses, and as a binary variable (classified into two groups: <70 years and ≥70 years) in subgroups and interactions analyses. Sex was recorded as male or female. The year of diagnosis was classified into three groups (2004–2007, 2008–2011, 2012–2015) according to the univariable analysis coefficient. The primary site was classified into nine different sites: cardia, fundus, lesser curve, greater curve, gastric body, antrum, pylorus, NOS, and overlapping lesion in the univariable and multivariable analyses, and five sites according to the mucosal origin, including cardia, oxyntic mucosa, antral mucosa, stomach NOS and overlapping lesions in subgroups, interactions and sensitivity analyses. The pathological grade was recorded as moderately or well-differentiated, poorly differentiated or undifferentiated, and unknown. T stage was recorded as T1 (mucosa or submucosa), T2a (muscularis propria), T2b (subserosa), T2 NOS (muscularis propria or subserosa, NOS), T3 (penetrates serosa), T4 (adjacent structures), and TX (unknown). N stage was recorded as N0 (no lymph nodes positive), N1 (1–6 nodes positive), N2 (7–15 nodes positive), N3 (>15 nodes positive), and NX (unknown). M stage was recorded as M0 (no distant metastasis) and M1 (distant metastasis). The operation was recorded as an endoscopy and surgery. Radiation therapy and chemotherapy were recorded as none/unknown and yes, respectively. Tumor size was classified into five groups according to the diameter: T ≤2 cm, T ≤3 cm, T ≤5 cm, T >5 cm, and unknown. The race was recorded as White, Asian or Pacific Islander, Black, American Indian/Alaska Native, and unknown. Insurance was recorded as insured, Medicaid, uninsured, and unknown. Marital status was recorded as married, divorced or separated, widowed, single (never married), unmarried or domestic partner, and unknown. The primary outcome was cancer-specific survival (CSS). Survival time was defined as the time from diagnosis to the date of death or the date of last contact (or November 2016). CSS referred to death caused by gastric adenocarcinoma. In the competing risk model, mortality was recorded as death related to gastric adenocarcinoma and death related to other causes. Patients who were still alive at the date of the last follow-up were censored.

Statistical analyses

For descriptive statistics, categorical variables were presented as frequencies and percentages, while continuous variables were presented with Gaussian distribution as means and standard deviations and as medians and interquartile ranges with non-normal distribution. Different patient groups were compared with the chi-square test for categorical variables, the Student's t-test for continuous variables with Gaussian distribution, and the nonparametric Kruskal-Wallis rank-sum test for continuous variables with non-normally distributed data or ordinal categorical variables. CSS curves were produced using the Kaplan-Meier method, and a log-rank test was used for comparison. Univariable Cox regression was performed to investigate the effect size of potential risk factors for CSS, with results presented as a hazard ratio (HR) with 95% confidence interval (CI). Multivariate Cox regression was further conducted to investigate Lauren's classification and CSS's association with two models adjusting for confounding variables. The model I confounders was selected based on their associations with the outcomes of a change in effect estimate of more than 10% (data not shown). All baseline parameters and clinical characteristics were included for adjustment as confounders in model II.

Furthermore, a sensitivity analysis was performed to validate Lauren's classification and CSS's association using two models. Propensity score matching (PSM) was performed to match the potential confounders selected in the multivariate Cox regression model. According to histology in a multivariate logistic regression model, propensity scores were calculated for every patient with gastric adenocarcinoma. Diffuse-type patients were matched with intestinal-type patients at a ratio of 1:1. Further univariable and multivariate Cox regression analyses, Kaplan-Meier curves, and log-rank tests were conducted among the new cohort with well-balanced clinical characteristics.

Additionally, for the competing risk model analysis, death unrelated to gastric adenocarcinoma was simultaneously modeled as a competing risk. Patients who were still alive were censored. Gray's test was applied to compare the two histologic types' CSS, and results were presented by subdistribution HRs (SHRs) and 95% CIs. Interaction

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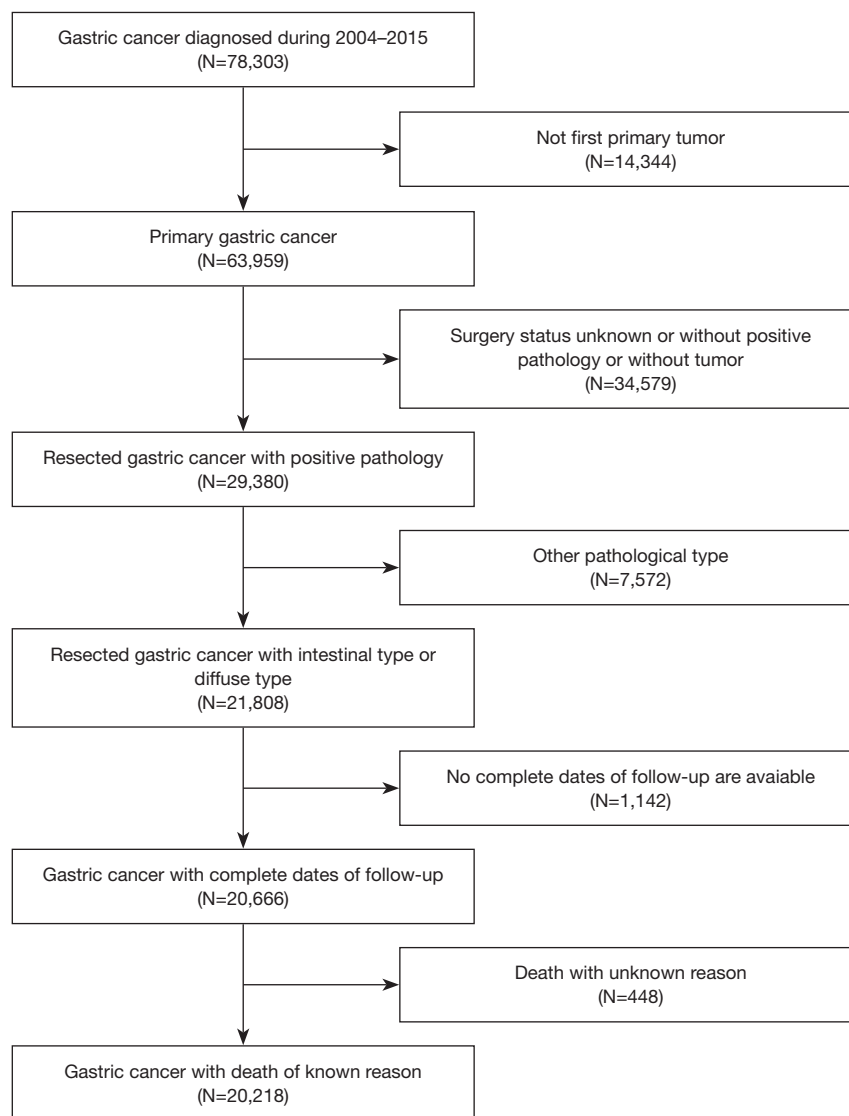
Figure 1 Flow chart of study participants

and stratified analyses were also conducted according to the risk factors selected from model I described above. To minimize selection bias, we included as many cases as possible, including cases containing missing data in non-grouped variables. The missing data in each item were listed and calculated in the regression formula as a separate group. Based on the univariable Cox regression results, we combined the missing data groups to groups with similar effect coefficients when performing survival and subgroup analyses. All the analyses were performed using EmpowerStats (https://www.empowerstats.com) and R statistical software (version 4.0.2, The R Foundation). A two-sided P<0.05 was considered statistically significant.

Results

Clinical characteristics of patients with gastric adenocarcinoma

After exclusion, a total 20,218 patients were finally included in this study, consisting of 14,374 intestinal-type patients (71.1%) and 5,844 diffuse-type patients (28.9%) (*Figure 1*). The clinical characteristics of patients with these two histologic types are outlined in *Table 1*. Results showed that intestinal-type patients had a better survival rate than diffuse-type patients, with a median survival time of 27 months (interquartile range, 12–62 months) for the intestinal type and 20 months (interquartile range, 9–48 months)

**Table 1** Baseline characteristics of the participants

Variables	All patients (N=20,218)	Intestinal (N=14,374)	Diffuse (N=5,844)	P value
Age (years)	65.6±13.4	67.5±12.6	60.9±14.0	<0.001
Sex				<0.001
Male	12,746 (63.0%)	9,739 (67.8%)	3,007 (51.5%)	
Female	7,472 (37.0%)	4,635 (32.2%)	2,837 (48.5%)	
Year of diagnosis				0.606
2004–2007	7,174 (35.5%)	5,073 (35.3%)	2,101 (36.0%)	
2008–2011	6,635 (32.8%)	4,720 (32.8%)	1,915 (32.8%)	
2011–2015	6,409 (31.7%)	4,581 (31.9%)	1,828 (31.3%)	
Primary site				<0.001
Cardia	5,657 (28.0%)	4,939 (34.4%)	718 (12.3%)	
Fundus of stomach	576 (2.8%)	412 (2.9%)	164 (2.8%)	
Lesser curvature of stomach	2,140 (10.6%)	1,404 (9.8%)	736 (12.6%)	
Greater curvature of stomach	883 (4.4%)	589 (4.1%)	294 (5.0%)	
Body of stomach	1,800 (8.9%)	1,135 (7.9%)	665 (11.4%)	
Gastric antrum	5,075 (25.1%)	3,429 (23.9%)	1,646 (28.2%)	
Pylorus	786 (3.9%)	551 (3.8%)	235 (4.0%)	
Stomach, NOS	1,823 (9.0%)	1,134 (7.9%)	689 (11.8%)	
Overlapping lesion of stomach	1,478 (7.3%)	781 (5.4%)	697 (11.9%)	
Grade				<0.001
Moderately differentiated or well differentiated	6,142 (30.4%)	5,989 (41.7%)	153 (2.6%)	
Poorly differentiated or undifferentiated	12,711 (62.9%)	7,455 (51.9%)	5,256 (89.9%)	
Unknown	1,365 (6.8%)	930 (6.5%)	435 (7.4%)	
T stage				<0.001
T1	4,824 (23.9%)	3,778 (26.3%)	1,046 (17.9%)	
T2a	2,183 (10.8%)	1,687 (11.7%)	496 (8.5%)	
T2b	6,417 (31.7%)	4,673 (32.5%)	1,744 (29.8%)	
T2, NOS	134 (0.7%)	105 (0.7%)	29 (0.5%)	
T3	4,507 (22.3%)	2,764 (19.2%)	1,743 (29.8%)	
T4	1,750 (8.7%)	1,059 (7.4%)	691 (11.8%)	
TX	403 (2.0%)	308 (2.1%)	95 (1.6%)	
N stage				<0.001
N0	8,155 (40.3%)	6,274 (43.6%)	1,881 (32.2%)	
N1	7,332 (36.3%)	5,401 (37.6%)	1,931 (33.0%)	
N2	3,124 (15.5%)	1,853 (12.9%)	1,271 (21.7%)	
N3	1,253 (6.2%)	594 (4.1%)	659 (11.3%)	
NX	354 (1.8%)	252 (1.8%)	102 (1.7%)	

Table 1 (*continued*)

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Table 1 (*continued*)

Variables	All patients (N=20,218)	Intestinal (N=14,374)	Diffuse (N=5,844)	P value
M stage				<0.001
M0	17,483 (86.5%)	12,652 (88.0%)	4,831 (82.7%)	
M1	2,378 (11.8%)	1,457 (10.1%)	921 (15.8%)	
MX	357 (1.8%)	265 (1.8%)	92 (1.6%)	
Operation				<0.001
Surgery	19,272 (95.3%)	13,534 (94.2%)	5,738 (98.2%)	
Endoscopy	946 (4.7%)	840 (5.8%)	106 (1.8%)	
Radiation				<0.001
None/unknown	13,531 (66.9%)	9,728 (67.7%)	3,803 (65.1%)	
Yes	6,687 (33.1%)	4,646 (32.3%)	2,041 (34.9%)	
Chemotherapy				<0.001
No/unknown	9,931 (49.1%)	7,508 (52.2%)	2,423 (41.5%)	
Yes	10,287 (50.9%)	6,866 (47.8%)	3,421 (58.5%)	
Tumor size (cm)				<0.001
T ≤2	3,553 (17.6%)	2,683 (18.7%)	870 (14.9%)	
2< T ≤3	2,551 (12.6%)	1,860 (12.9%)	691 (11.8%)	
3< T ≤5	4,724 (23.4%)	3,584 (24.9%)	1,140 (19.5%)	
T >5	6,512 (32.2%)	4,229 (29.4%)	2,283 (39.1%)	
Unknown	2,878 (14.2%)	2,018 (14.0%)	860 (14.7%)	
Race				<0.001
White	13,649 (67.5%)	9,790 (68.1%)	3,859 (66.0%)	
Asian or Pacific Islander	3,714 (18.4%)	2,538 (17.7%)	1,176 (20.1%)	
Black	2,615 (12.9%)	1,894 (13.2%)	721 (12.3%)	
American Indian/Alaska Native	177 (0.9%)	114 (0.8%)	63 (1.1%)	
Unknown	63 (0.3%)	38 (0.3%)	25 (0.4%)	
Insurance				<0.001
Insured	11,626 (57.5%)	8,378 (58.3%)	3,248 (55.6%)	
Medicaid	2,425 (12.0%)	1,697 (11.8%)	728 (12.5%)	
Uninsured	459 (2.3%)	295 (2.1%)	164 (2.8%)	
Unknown	5,708 (28.2%)	4,004 (27.9%)	1,704 (29.2%)	
Marital status				<0.001
Married	12,309 (60.9%)	8,736 (60.8%)	3,573 (61.1%)	
Divorced or separated	1,826 (9.0%)	1,275 (8.9%)	551 (9.4%)	
Widowed	2,659 (13.2%)	2,036 (14.2%)	623 (10.7%)	
Single (never married)	2,619 (13.0%)	1,752 (12.2%)	867 (14.8%)	
Unmarried or domestic partner	18 (0.1%)	14 (0.1%)	4 (0.1%)	
Unknown	787 (3.9%)	561 (3.9%)	226 (3.9%)	
Survival months, median (interquartile range)	25.0 (11.0–58.0)	27.0 (12.0–62.0)	20.0 (9.0–48.0)	<0.001

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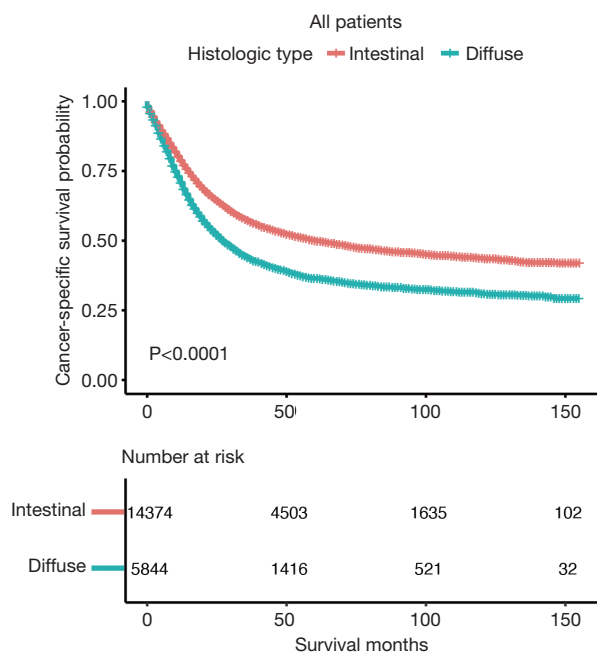
Figure 2 Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification.

for the diffuse type. The results also showed that patients with diffuse-type were younger females, and lesions were mostly located in gastric antrum with a larger size and poorer differentiation grade than the intestinal type. Also, patients with diffuse-type exhibited a lower proportion of T1 stage, N0 stage, and M0 stage lesions and a higher proportion of radiation therapy and chemotherapy than intestinal type patients.

CSS in intestinal and diffuse types

The CSS of gastric adenocarcinoma was initially compared using Kaplan-Meier curves. The results showed that in the total cohort, intestinal-type gastric adenocarcinoma had a significantly higher CSS rate than the diffuse type (*Figure 2*, P<0.0001). To identify the prognostic factors and analyze the potential risk factors for poor CSS of gastric adenocarcinoma, univariable and multivariate Cox regression analyses were carried out. According to the univariate Cox analysis, age at diagnosis (P<0.0001), sex (P=0.0248), year of diagnosis (P<0.0001), primary site (P<0.0001), grade of differentiation (P<0.0001), histologic type (P<0.0001), T stage (P<0.0001), N stage (P<0.0001), M stage (P<0.0001), operation (P<0.0001), chemotherapy (P<0.0001), tumor size (P<0.0001), race (P<0.0001),

insurance (P<0.0001), and marital status (P<0.0001) were significantly associated with CSS (*Table 2*).

The univariate Cox regression analysis demonstrated that diffuse-type gastric adenocarcinoma had a poorer CSS rate than intestinal-type gastric adenocarcinoma (*Table 3*; HR, 1.44; 95% CI, 1.38–1.50, P<0.001). After adjusting for confounding variables including the age of diagnosis, primary site, the grade of differentiation, T stage, N stage, M stage, and tumor size (model I), the diffuse-type group still exhibited a significantly higher risk of cancer-specific death than the intestinal-type group (HR, 1.19; 95% CI, 1.14–1.25, P<0.001). Notably, after adjusting all the potential confounding variables (model II), the diffuse-type group also showed a significantly higher risk of cancer-specific death than the intestinal-type group (HR, 1.20; 95% CI, 1.15–1.20, P<0.001).

Comparison of CSS in intestinal and diffuse types in subgroups

We further performed a subgroup analysis to estimate the role of potential confounding factors on the association between Lauren's classification and CSS rate. As shown in *Figure 3*, the subgroup analysis revealed a highly consistent pattern. In the T1-stage subgroup, the effect of the diffuse-type group was similar to that of the intestinal-type group (HR, 1.06; 95% CI, 0.87–1.28), while in the T2–TX subgroup, the diffuse-type group showed a higher risk of cancer-specific death than the intestinal-type group (HR, 1.24; 95% CI, 1.19–1.31; P for interaction =0.107). In the subgroup with tumor-size <2 cm, the diffuse-type group showed a comparable risk of cancer-specific death with the intestinal-type group (HR, 1.00; 95% CI, 0.83–1.21), but in the subgroup with tumor-size >2 cm, the diffuse-type group exhibited a poorer CSS (HR, 1.22; 95% CI, 1.16–1.28; P for interaction =0.035). In all other subgroups, including the age of diagnosis, sex, N stage, M stage, the grade of differentiation, year of diagnosis and primary sites, Lauren's classification and CSS's association were consistent.

Survival analysis of patients with intestinal-type and diffuse-type gastric adenocarcinoma

To further investigate the association between Lauren's classification and CSS, we first compared the Kaplan-Meier curves of the intestinal and diffuse types in the subgroups based on the subgroups analysis results. For gastric adenocarcinoma with a different differentiation status,

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Table 2 Univariable Cox regression analysis for cancer-specific survival in patients with gastric cancer

Variables	HR (95% CI)	P value
Age	1.00 (1.00, 1.01)	<0.0001
Sex		
Male	Reference	
Female	1.05 (1.01, 1.09)	0.0248
Year of diagnosis		
2004–2007	Reference	
2008–2011	0.85 (0.82, 0.89)	<0.0001
2011–2015	0.71 (0.68, 0.75)	<0.0001
Primary site		
Cardia	Reference	
Fundus of stomach	1.10 (0.97, 1.24)	0.1449
Lesser curvature of stomach	0.92 (0.85, 0.99)	0.0238
Greater curvature of stomach	1.10 (1.00, 1.22)	0.0547
Body of stomach	1.00 (0.92, 1.08)	0.9686
Gastric antrum	1.02 (0.97, 1.08)	0.4569
Pylorus	1.29 (1.16, 1.42)	<0.0001
Stomach, NOS	1.42 (1.32, 1.53)	<0.0001
Overlapping lesion of stomach	1.72 (1.59, 1.85)	<0.0001
Grade		
Moderately differentiated or well differentiated	Reference	
Poorly differentiated or undifferentiated	1.85 (1.76, 1.94)	<0.0001
Unknown	1.08 (0.98, 1.19)	0.1143
Histologic type		
Intestinal	Reference	
Diffuse	1.44 (1.38, 1.50)	<0.0001
T stage		
T1	Reference	
T2a	1.96 (1.78, 2.16)	<0.0001
T2b	4.04 (3.75, 4.34)	<0.0001
T2, NOS	2.27 (1.68, 3.07)	<0.0001
T3	6.08 (5.64, 6.55)	<0.0001
T4	9.06 (8.33, 9.86)	<0.0001
TX	5.34 (4.63, 6.14)	<0.0001
N stage		
N0	Reference	
N1	2.62 (2.49, 2.76)	<0.0001
N2	4.25 (4.01, 4.51)	<0.0001
N3	6.12 (5.68, 6.59)	<0.0001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	HR (95% CI)	P value
NX	3.80 (3.31, 4.36)	<0.0001
M stage		
M0	Reference	
M1	3.80 (3.62, 4.00)	<0.0001
MX	1.69 (1.47, 1.93)	<0.0001
Operation		
Surgery	Reference	
Endoscopy	0.77 (0.69, 0.85)	<0.0001
Radiation		
None/unknown	Reference	
Yes	0.97 (0.93, 1.02)	0.2129
Chemotherapy		
No/unknown	Reference	
Yes	1.20 (1.16, 1.25)	<0.0001
Tumor size (cm)		
T ≤2	Reference	
2< T ≤3	1.96 (1.79, 2.14)	<0.0001
3< T ≤5	2.80 (2.59, 3.03)	<0.0001
T >5	3.90 (3.62, 4.20)	<0.0001
Unknown	2.68 (2.46, 2.92)	<0.0001
Race		
White	Reference	
Asian or Pacific Islander	0.76 (0.72, 0.81)	<0.0001
Black	1.00 (0.95, 1.06)	0.9010
American Indian/Alaska Native	1.35 (1.12, 1.63)	0.0018
Unknown	0.14 (0.06, 0.33)	<0.0001
Insurance		
Insured	Reference	
Medicaid	1.14 (1.07, 1.22)	<0.0001
Uninsured	1.23 (1.07, 1.40)	0.0034
Unknown	1.26 (1.20, 1.31)	<0.0001
Marital status		
Married	Reference	
Divorced or separated	1.11 (1.03, 1.19)	0.0041
Widowed	1.26 (1.19, 1.34)	<0.0001
Single (never married)	1.14 (1.08, 1.21)	<0.0001
Unmarried or domestic partner	0.79 (0.35, 1.75)	0.5540
Unknown	0.92 (0.82, 1.02)	0.1272

NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval.

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Table 3 Multivariable Cox regression models evaluating the association between Lauren's classification and cancer-specific survival

Lauren's classification	Crude		Model I		Model II	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Intestinal	Reference		Reference		Reference	
Diffuse	1.44 (1.38, 1.50)	<0.001	1.19 (1.14, 1.25)	<0.001	1.20 (1.15, 1.26)	<0.001

Adjustment I: age; primary site; grade; T stage; N stage; M stage; tumor size. Adjustment II: age; sex; year; primary site; grade; T stage; N stage; M stage; operation; chemotherapy; tumor size; race; insurance; marital status. HR, hazard ratio; CI, confidence interval.

the CSS rate was also significantly higher in intestinal-type gastric adenocarcinoma (*Figure 4A,B*). In the T1 stage gastric adenocarcinoma, the diffuse type showed a comparable CSS rate compared with the intestinal type, while in the T2–TX stage, the intestinal type exhibited a higher CSS rate than the diffuse type (*Figure 4C,D*). In gastric adenocarcinoma with different M stages, the intestinal type also showed a higher CSS rate than the diffuse type (*Figure 4E,F*). In gastric adenocarcinoma with size <2 cm, the diffuse type showed a comparable CSS rate compared with the intestinal type, while in patients with size >2 cm, the intestinal type showed a higher CSS rate than the diffuse type (*Figure 4G,H*). In gastric adenocarcinoma with different primary sites, the intestinal type showed a significantly higher CSS rate than the diffuse type in each site (Figure S1).
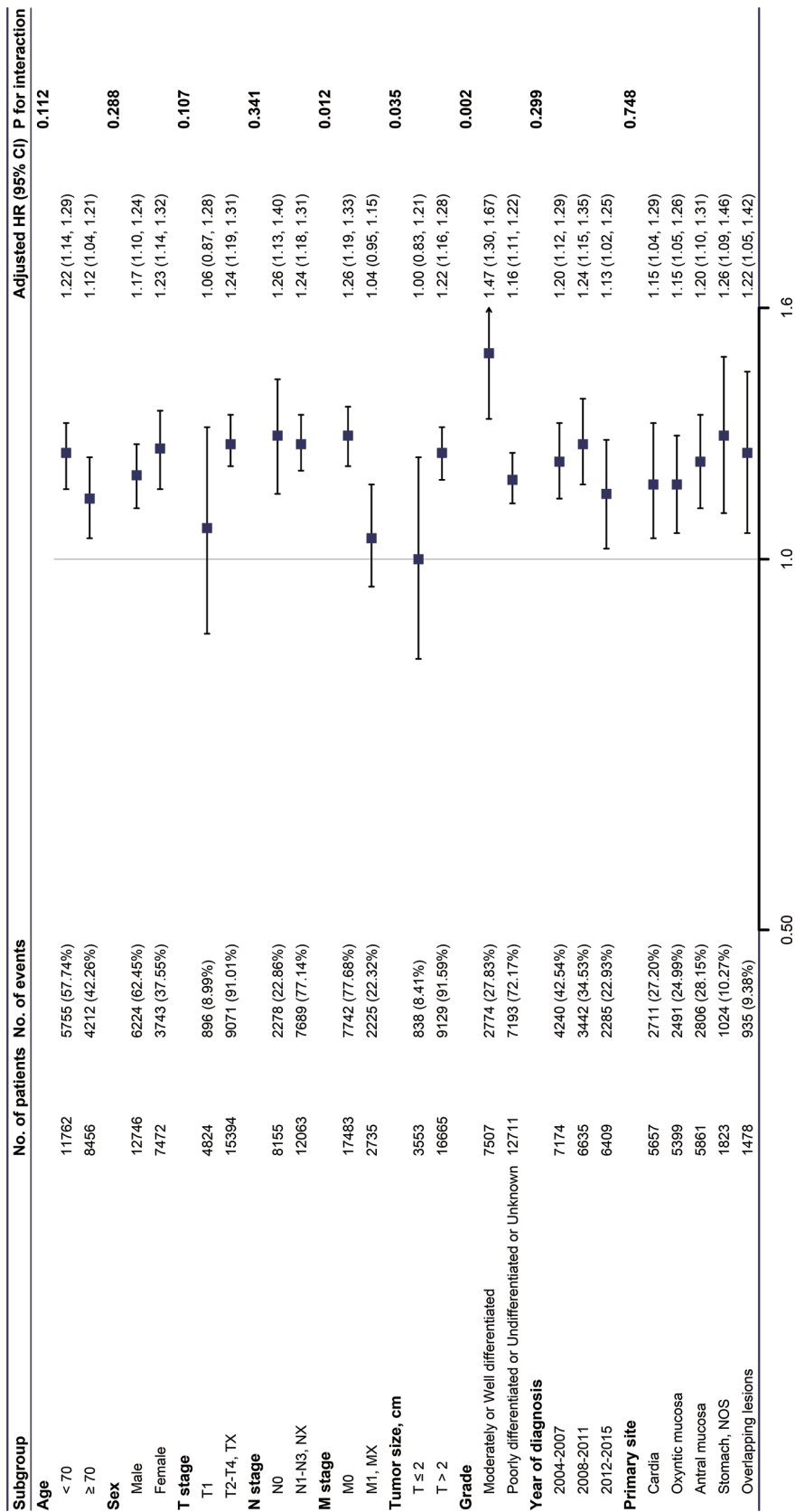
Sensitivity analysis

We matched 1,311 intestinal-type patients with 1,311 diffuse-type patients with 1:1 PSM based on the significant confounding variables mentioned in model I. As shown in Table S1, the clinical characteristics were comparable and balanced between the intestinal and diffuse types, apart from sex and radiation condition. We performed Kaplan-Meier curve analysis after PSM and found a positive association between diffuse-type gastric adenocarcinoma and a poorer CSS rate (Figure S2; P=0.00014). Univariable Cox regression analysis was performed to investigate the association between Lauren's classification and CSS in the matched cohort. In the univariable analysis, diffuse-type gastric adenocarcinoma had a poorer CSS rate than intestinal-type gastric adenocarcinoma (Table S2; HR, 1.23; 95% CI, 1.10–1.36). Notably, the risk effect remained stable after adjusting for sex with multivariable analysis (Table S3; model I; HR, 1.22; 95% CI, 1.10–1.36) or adjusting for both sex and radiation in model II (HR, 1.22; 95% CI, 1.10–1.36). The competing risk model further validated

that the diffuse type was associated with a worse risk of death than the intestinal type, and the result was statistically significant (Table S4; SHR, 1.32; 95% CI, 1.23–1.41).
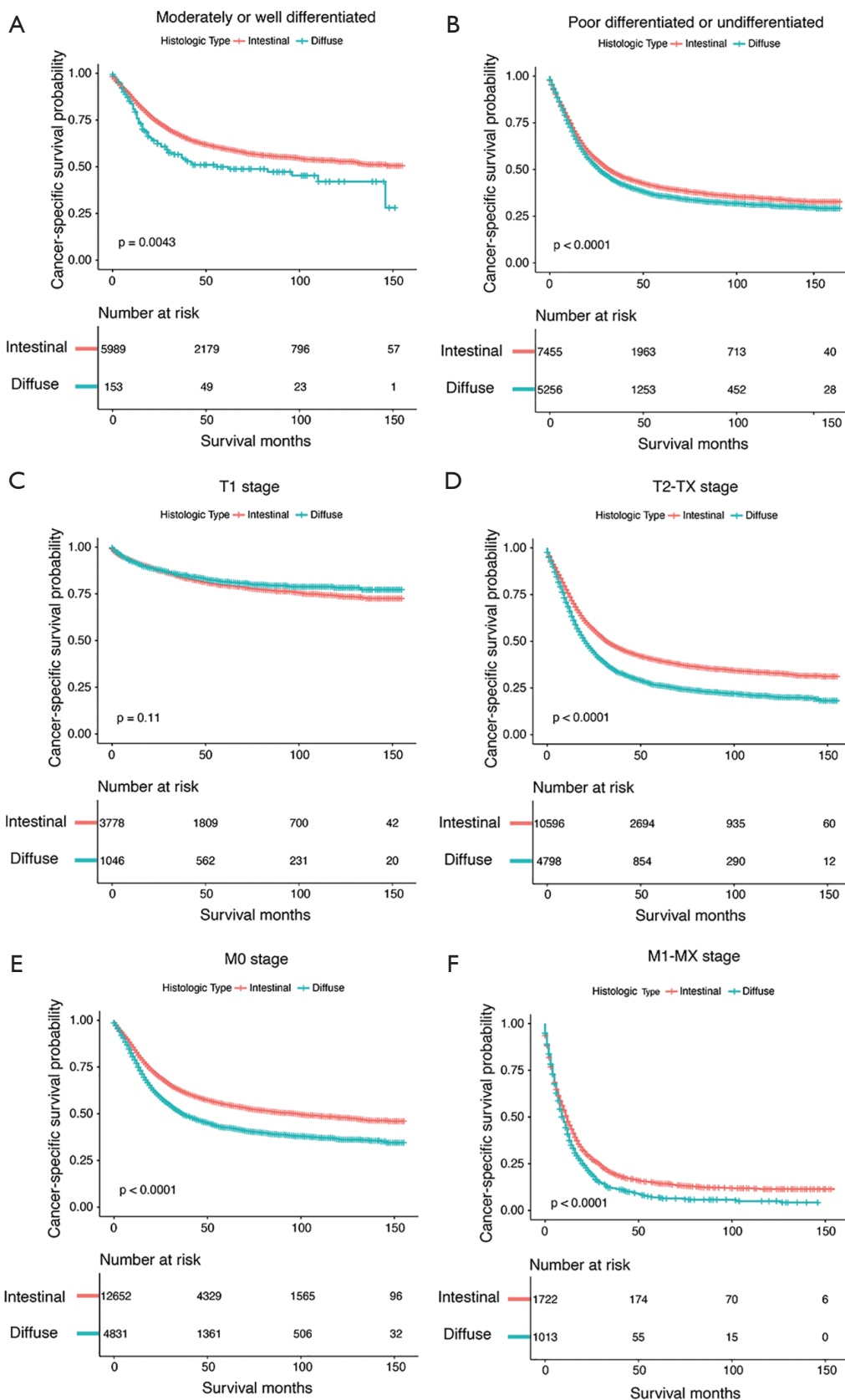
We also classified the primary site into five categories according to the mucosal origin, including cardia, oxyntic mucosa, antral mucosa, stomach NOS and overlapping lesions to perform further analysis. The results of univariable Cox regression analysis showed that lesions from cardia, oxyntic mucosa, and antral mucosal showed a marginally different impact on CSS of gastric adenocarcinoma (Table S5, cardia, HR, reference; oxyntic mucosa, HR, 0.99, 95% CI, 0.94–1.05; antral mucosa, HR, 1.05, 95% CI, 1.00–1.11). The results of multivariable Cox regression models showed that the association of Lauren's classification and CSS was stable (Table S6, HR, 1.19; 95% CI, 1.13–1.24, P<0.001) with adjusting the age of diagnosis, primary site (five sites), grade of differentiation, T stage, N stage, M stage and tumor size (model III), which was comparable to nine sites (HR, 1.19; 95% CI, 1.14–1.25, P<0.001). After adjusting all the potential confounding variables (five sites, model IV), the diffuse-type group also showed a significantly higher risk of cancer-specific death than the intestinal-type group (HR, 1.20; 95% CI, 1.15–1.26, P<0.001). Besides, the subgroup analysis revealed a highly consistent pattern with these results. In the subgroups with different mucosal origins, the diffuse-type group showed more inferior CSS (*Figure 3*, HR >1.00; P for interaction =0.299) compared with the intestinal type. These results demonstrated that mucosal origin had marginal effects on the association between Lauren's classification and CSS of gastric adenocarcinoma.
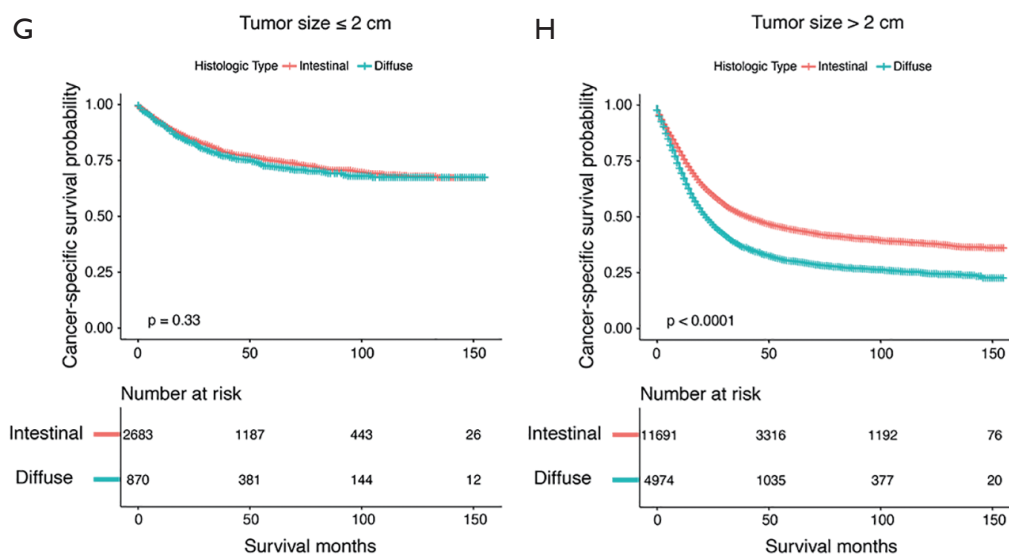
Discussion

In the present study, we comprehensively analyzed the difference in prognosis between diffuse-type and intestinal-type gastric adenocarcinoma. This study contained the largest number of patients with gastric adenocarcinoma

Subgroup	No. of patients	No. of events	Adjusted HR (95% CI)	P for interaction
Age				0.112
<70	11762	5755 (57.74%)	1.22 (1.14, 1.29)	
≥70	8456	4212 (42.26%)	1.12 (1.04, 1.21)	
Sex				0.288
Male	12746	6224 (62.45%)	1.17 (1.10, 1.24)	
Female	7472	3743 (37.55%)	1.23 (1.14, 1.32)	
T stage				0.107
T1	4824	896 (8.99%)	1.06 (0.87, 1.28)	
T2-T4, TX	15394	9071 (91.01%)	1.24 (1.19, 1.31)	
N stage				0.341
N0	8155	2278 (22.86%)	1.26 (1.13, 1.40)	
N1-N3, NX	12063	7689 (77.14%)	1.24 (1.18, 1.31)	
M stage				0.012
M0	17483	7742 (77.68%)	1.26 (1.19, 1.33)	
M1, MX	2735	2225 (22.32%)	1.04 (0.95, 1.15)	
Tumor size, cm				0.035
T ≤ 2	3553	838 (8.41%)	1.00 (0.83, 1.21)	
T > 2	16665	9129 (91.59%)	1.22 (1.16, 1.28)	
Grade				0.002
Moderately or Well differentiated	7507	2774 (27.83%)	1.47 (1.30, 1.67)	
Poorly differentiated or Undifferentiated or Unknown	12711	7193 (72.17%)	1.16 (1.11, 1.22)	
Year of diagnosis				0.299
2004-2007	7174	4240 (42.54%)	1.20 (1.12, 1.29)	
2008-2011	6635	3442 (34.53%)	1.24 (1.15, 1.35)	
2012-2015	6409	2285 (22.93%)	1.13 (1.02, 1.25)	
Primary site				0.748
Cardia	5657	2711 (27.20%)	1.15 (1.04, 1.29)	
Oxyntic mucosa	5399	2491 (24.99%)	1.15 (1.05, 1.26)	
Antral mucosa	5861	2806 (28.15%)	1.20 (1.10, 1.31)	
Stomach, NOS	1823	1024 (10.27%)	1.26 (1.09, 1.46)	
Overlapping lesions	1478	935 (9.38%)	1.22 (1.05, 1.42)	

Figure 3 Subgroup analyses of the effect of Lauren's classification on cancer-specific survival. Adjusted, if not be stratified, for age; sex; year; primary site; grade; T stage; N stage; M stage; operation; chemotherapy; tumor size; race; insurance and marital status.

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Figure 4 Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in subgroups. Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in the (A) moderately or well differentiated subgroup; (B) poorly differentiated or undifferentiated subgroup; (C) T1 stage subgroup; (D) T2–TX stage subgroup; (E) M0 stage subgroup; (F) M1–MX stage subgroup; (G) tumor size ≤2 cm subgroup; (H) tumor size >2 cm subgroup.

(N=20,218). Our results revealed that after adjusting potential confounders, diffuse-type gastric adenocarcinoma showed an overall poorer prognosis than the intestinal type, yet in patients with T1 stage and tumor size <2 cm, the prognosis of the diffuse type was similar to that of the intestinal type. This indicated that diffuse-type gastric adenocarcinoma was an independent risk factor associated with a poorer prognosis, except for patients with T1 stage and tumor size of less than 2 cm.

According to previous reports, diffuse-type gastric adenocarcinoma is associated with younger female patients and exhibits a shorter survival and worse prognosis than the intestinal type (14-18). Our results showed that patients with diffuse-type were younger females with shorter CSS, which is consistent with previous studies. Our results also showed that the diffuse type of gastric adenocarcinoma was significantly associated with advanced stages compared with the intestinal type. This is also consistent with a previous report that revealed that diffuse type was an independent predictor of peritoneal metastases using staging laparoscopy (24).

Although Lauren's classification has been proposed for over 50 years, this classification's clinical value remains controversial. Various studies have investigated the association between Lauren's classification and prognosis of gastric adenocarcinoma with significantly varying results.

A recent meta-analysis showed that diffuse-type gastric adenocarcinoma had a poorer prognosis than patients with the intestinal type (14). However, the sample sizes of the included studies were relatively small, and the adjusted confounders in each study were quite different from the others, which may reduce the reliability and confidence of the pooled results. Furthermore, among all 73 included studies, only six included a sample size of more than 2,000 cases. Notably, our findings were consistent with the six studies with large sample sizes, which showed that patients with the diffuse type had a worse prognosis than patients with the intestinal type (HR: 1.085–1.498). The crude HR we calculated in the present study was 1.44 (95% CI, 1.38–1.50), and the adjusted HR was 1.19 (95% CI, 1.14–1.25) and 1.20 (95% CI, 1.15–1.26) in model I and model II, respectively. These crude and adjusted HRs were in the range of HRs reported in the six studies above. The variance of the adjusted confounders may have caused the minor difference in the HRs. One of the six studies (sample size: 9,325 cases) also used the SEER database to analyze the association between Lauren's classification and prognosis of gastric adenocarcinoma and found that the diffuse type had a worse prognosis, with an HR of 1.347 (95% CI, 1.264–1.434) (25). The confounders they adjusted for included age, sex, race, socioeconomic status, site, summary stage, differentiation, surgery, chemotherapy,

radiation therapy, hospital size, academic institution, and year of diagnosis. However, tumor size, race, and marital status, which were documented to influence gastric adenocarcinoma prognosis (26-28), were not included in their study. In the present study, we used strict statistical adjustment to minimize residual confounders, and thus our results might be more reliable. To further validate our findings, we performed sensitivity analyses, including conducting PSM and establishing a competing risk model. Our sensitivity analyses showed that the diffuse type had a worse prognosis [HR (PSM), 1.23; 95% CI, 1.10–1.36; SHR, 1.32; 95% CI, 1.23–1.41], which bolstered the strength of our results. Our previous reports have suggested that different stomach parts express different glands and exhibit various clinicopathological features (29). However, few studies reported the impact of the mucosal origin on Lauren's classification in GCs. Here, the results based on the mucosal origins showed that the diffuse-type group showed a significantly higher risk of cancer-specific death than the intestinal-type group in different mucosa origins.

Interestingly, we also noticed that several studies suggested that patients with diffuse-type gastric adenocarcinoma had a similar or even a better prognosis than those with the intestinal type (30-37). However, these studies' sample sizes were relatively small, and only Kaplan-Meier analyses with log-rank tests were performed, which could not rule out the influence of potential confounders. Recently, two studies based on the SEER database suggested that the diffuse type showed a comparable or better prognosis than the intestinal type. The first study by Tang *et al.* revealed that diffuse-type early gastric cancer (EGC) had a better prognosis than intestinal-type EGC by using PSM for adjusting confounders. However, after matching, only 2,672 cases were included in their study, which might weaken the whole sample's representativeness (23). Herein, we performed multivariate regression first and then conducted PSM, and established a competing risk model to perform sensitivity analysis. The comprehensive statistical analyses fully adjusted for residual confounders, thus making the results more reliable. Another study by Li *et al.* only included EGC and performed the comprehensive statistical analysis, including multivariate regression and PSM, to adjust for confounders (38). They found that diffuse-type EGC may have a comparable prognosis to intestinal-type EGC. Notably, this is consistent with our findings. Our subgroup analysis showed that in patients with T1 stage and tumor size <2 cm, the diffuse type had a comparable survival rate with the intestinal type. The British Society

of Gastroenterology's latest guidelines recommended that complete (R0) endoscopic resection is only suitable for patients with the intestinal type and is not suitable for those with the diffuse type (13). However, our results may provide evidence that endoscopic submucosal dissection is suitable for intestinal-type patients and diffuse-type patients when the tumor is at the T1 stage and the tumor size is smaller than 2 cm.

However, this study has several limitations that should be noted. Firstly, we did not rule out all the cases containing missing data, which might have influenced the results' strength. To minimize selection bias, we included as many cases as possible. The missing data in each item were listed and calculated in the regression formula as a separate group. Based on the univariable Cox regression results, we combined the missing data groups to groups with similar effect coefficients when performing survival and subgroup analyses. Secondly, lymphatic vessel involvement and mixed type information was not available in the SEER database. As noted previously, lymphatic vessel involvement is considered a significant prognostic factor for EGC instead of N stage, and thus may have potential influence when performing subgroup analysis. Further studies should include lymphatic vessel involvement as a potential confounder to evaluate the association between Lauren's classification and prognosis of EGC. The association between the mixed type and prognosis of gastric adenocarcinoma is still controversial; however, we cannot investigate this important topic due to limited information. In the future, the characteristics and clinical value of the mixed type should be fully investigated.

Conclusions

In this study, we found that diffuse-type gastric adenocarcinoma had an overall poorer prognosis than the intestinal type. However, in patients with T1 stage and tumor size of less than 2 cm, the diffuse type had a comparable survival rate with the intestinal type. This study may deepen our understanding of Lauren's classification and provide evidence that endoscopic submucosal dissection is suitable for intestinal-type patients and diffuse-type patients when the tumor is at T1 stage, the tumor size is smaller than 2 cm.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-7953

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-7953

Peer Review File: Available at http://dx.doi.org/10.21037/atm-20-7953

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7953). 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). Informed consent or ethical approval was not required since SEER database only contain deidentified data and is available to the public.

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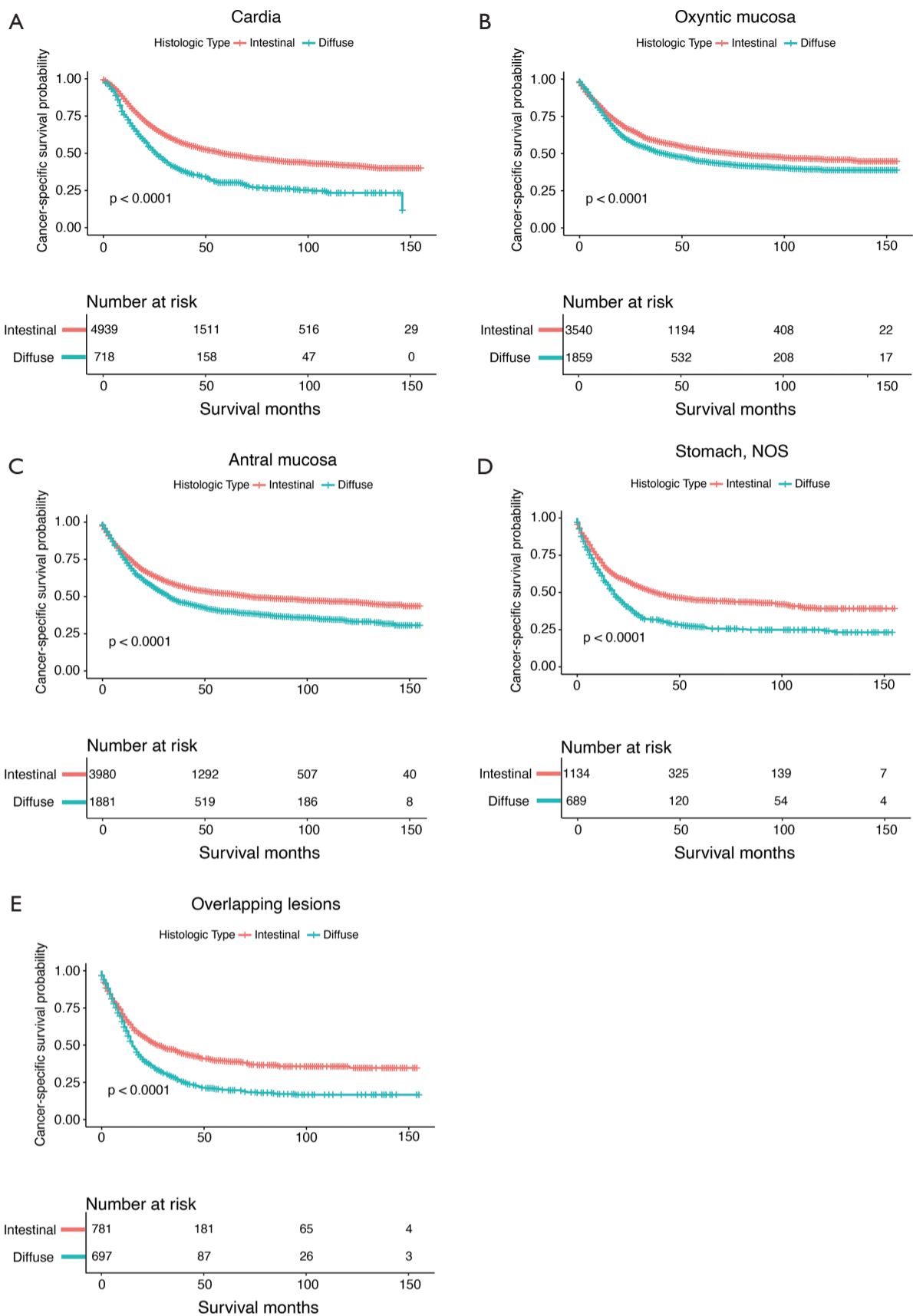
Figure S1 Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in subgroups of primate sites. (A) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in cardia subgroup; (B) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in oxyntic mucosa subgroup; (C) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in antral mucosa subgroup; (D) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in stomach, NOS subgroup; (E) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification in overlapping lesions subgroup. NOS, not otherwise specified.
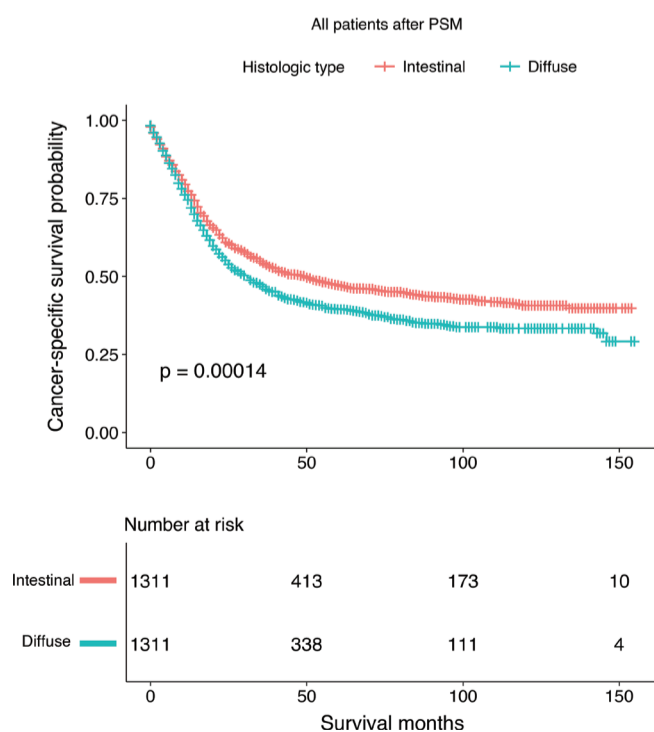
Figure S2 Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification after propensity score matching.

Table S1 Baseline characteristics of the participants before and after propensity score matching

Variables	Before PSM				After PSM			
	All patients (N=20,218)	Intestinal (N=14,374)	Diffuse (N=5,844)	P value	All patients (N=2,622)	Intestinal (N=1,311)	Diffuse (N=1,311)	P value
Age (years)	65.6±13.4	67.5±12.6	60.9±14.0	<0.001	66.2±11.0	66.15±11.01	66.15±11.01	1.0000
Sex				<0.001				<0.0001
Male	12,746 (63.0%)	9,739 (67.8%)	3,007 (51.5%)		1,599 (61.0%)	861 (65.7%)	738 (56.3%)	
Female	7,472 (37.0%)	4,635 (32.2%)	2,837 (48.5%)		1,023 (39.0%)	450 (34.3%)	573 (43.7%)	
Year				0.606				0.0686
2004–2007	7,174 (35.5%)	5,073 (35.3%)	2,101 (36.0%)		945 (36.0%)	500 (38.1%)	445 (33.9%)	
2008–2011	6,635 (32.8%)	4,720 (32.8%)	1,915 (32.8%)		879 (33.5%)	419 (32%)	460 (35.1%)	
2011–2015	6,409 (31.7%)	4,581 (31.9%)	1,828 (31.3%)		798 (30.4%)	392 (29.9%)	406 (31%)	
Primary site				<0.001				1.0000
Cardia	5,657 (28.0%)	4,939 (34.4%)	718 (12.3%)		684 (26.1%)	342 (26.1%)	342 (26.1%)	
Fundus of stomach	576 (2.8%)	412 (2.9%)	164 (2.8%)		18 (0.7%)	9 (0.7%)	9 (0.7%)	
Lesser curvature of stomach	2,140 (10.6%)	1,404 (9.8%)	736 (12.6%)		300 (11.4%)	150 (11.4%)	150 (11.4%)	
Greater curvature of stomach	883 (4.4%)	589 (4.1%)	294 (5.0%)		54 (2.1%)	27 (2.1%)	27 (2.1%)	
Body of stomach	1,800 (8.9%)	1,135 (7.9%)	665 (11.4%)		198 (7.6%)	99 (7.6%)	99 (7.6%)	
Gastric antrum	5,075 (25.1%)	3,429 (23.9%)	1,646 (28.2%)		950 (36.2%)	475 (36.2%)	475 (36.2%)	
Pylorus	786 (3.9%)	551 (3.8%)	235 (4.0%)		46 (1.8%)	23 (1.8%)	23 (1.8%)	
Stomach, NOS	1,823 (9.0%)	1,134 (7.9%)	689 (11.8%)		174 (6.6%)	87 (6.6%)	87 (6.6%)	
Overlapping lesion of stomach	1,478 (7.3%)	781 (5.4%)	697 (11.9%)		198 (7.6%)	99 (7.6%)	99 (7.6%)	
Grade				<0.001				1.0000
Moderately differentiated or well differentiated	6,142 (30.4%)	5,989 (41.7%)	153 (2.6%)		76 (2.9%)	38 (2.9%)	38 (2.9%)	
Poorly differentiated or undifferentiated	12,711 (62.9%)	7,455 (51.9%)	5,256 (89.9%)		2,478 (94.5%)	1,239 (94.5%)	1,239 (94.5%)	
Unknown	1,365 (6.8%)	930 (6.5%)	435 (7.4%)		68 (2.6%)	34 (2.6%)	34 (2.6%)	
T stage				<0.001				1.0000
T1	4,824 (23.9%)	3,778 (26.3%)	1,046 (17.9%)		590 (22.5%)	295 (22.5%)	295 (22.5%)	
T2a	2,183 (10.8%)	1,687 (11.7%)	496 (8.5%)		140 (5.3%)	70 (5.3%)	70 (5.3%)	
T2b	6,417 (31.7%)	4,673 (32.5%)	1,744 (29.8%)		1,042 (39.7%)	521 (39.7%)	521 (39.7%)	
T2, NOS	134 (0.7%)	105 (0.7%)	29 (0.5%)		0 (0)	0 (0%)	0 (0%)	
T3	4,507 (22.3%)	2,764 (19.2%)	1,743 (29.8%)		700 (26.7%)	350 (26.7%)	350 (26.7%)	
T4	1,750 (8.7%)	1,059 (7.4%)	691 (11.8%)		140 (5.3%)	70 (5.3%)	70 (5.3%)	
TX	403 (2.0%)	308 (2.1%)	95 (1.6%)		10 (0.4%)	5 (0.4%)	5 (0.4%)	
N stage				<0.001				1.0000
N0	8,155 (40.3%)	6,274 (43.6%)	1,881 (32.2%)		872 (33.3%)	436 (33.3%)	436 (33.3%)	
N1	7,332 (36.3%)	5,401 (37.6%)	1,931 (33.0%)		1,096 (41.8%)	548 (41.8%)	548 (41.8%)	
N2	3,124 (15.5%)	1,853 (12.9%)	1,271 (21.7%)		516 (19.7%)	258 (19.7%)	258 (19.7%)	
N3	1,253 (6.2%)	594 (4.1%)	659 (11.3%)		130 (5.0%)	65 (5%)	65 (5%)	
NX	354 (1.8%)	252 (1.8%)	102 (1.7%)		8 (0.3%)	4 (0.3%)	4 (0.3%)	
M stage				<0.001				1.0000
M0	17,483 (86.5%)	12,652 (88.0%)	4,831 (82.7%)		2,490 (95.0%)	1,245 (95%)	1,245 (95%)	
M1	2,378 (11.8%)	1,457 (10.1%)	921 (15.8%)		126 (4.8%)	63 (4.8%)	63 (4.8%)	
MX	357 (1.8%)	265 (1.8%)	92 (1.6%)		6 (0.2%)	3 (0.2%)	3 (0.2%)	
Operation				<0.001				0.0723
Surgery	19,272 (95.3%)	13,534 (94.2%)	5,738 (98.2%)		2,584 (98.6%)	1,286 (98.1%)	1,298 (99%)	
Endoscopy	946 (4.7%)	840 (5.8%)	106 (1.8%)		38 (1.4%)	25 (1.9%)	13 (1%)	
Radiation				<0.001				0.0347
None/unknown	13,531 (66.9%)	9,728 (67.7%)	3,803 (65.1%)		1,638 (62.5%)	830 (63.3%)	808 (61.6%)	
Yes	6,687 (33.1%)	4,646 (32.3%)	2,041 (34.9%)		984 (37.5%)	481 (36.7%)	503 (38.4%)	
Chemotherapy				<0.001				0.3678
No/unknown	9,931 (49.1%)	7,508 (52.2%)	2,423 (41.5%)		1,220 (46.5%)	622 (47.4%)	598 (45.6%)	
Yes	10,287 (50.9%)	6,866 (47.8%)	3,421 (58.5%)		1,402 (53.5%)	689 (52.6%)	713 (54.4%)	
Tumor size (cm)				<0.001				1.0000
T ≤2	3,553 (17.6%)	2,683 (18.7%)	870 (14.9%)		434 (16.6%)	217 (16.6%)	217 (16.6%)	
2< T ≤3	2,551 (12.6%)	1,860 (12.9%)	691 (11.8%)		256 (9.8%)	128 (9.8%)	128 (9.8%)	
3< T ≤5	4,724 (23.4%)	3,584 (24.9%)	1,140 (19.5%)		594 (22.7%)	297 (22.7%)	297 (22.7%)	
T >5	6,512 (32.2%)	4,229 (29.4%)	2,283 (39.1%)		1,118 (42.6%)	559 (42.6%)	559 (42.6%)	
Unknown	2,878 (14.2%)	2,018 (14.0%)	860 (14.7%)		220 (8.4%)	110 (8.4%)	110 (8.4%)	
Race				<0.001				0.1424
White	13,649 (67.5%)	9,790 (68.1%)	3,859 (66.0%)		1,723 (65.7%)	843 (64.3%)	880 (67.1%)	
Asian or Pacific Islander	3,714 (18.4%)	2,538 (17.7%)	1,176 (20.1%)		565 (21.5%)	279 (21.3%)	286 (21.8%)	
Black	2,615 (12.9%)	1,894 (13.2%)	721 (12.3%)		309 (11.8%)	175 (13.3%)	134 (10.2%)	
American Indian/Alaska Native	177 (0.9%)	114 (0.8%)	63 (1.1%)		17 (0.6%)	9 (0.7%)	8 (0.6%)	
Unknown	63 (0.3%)	38 (0.3%)	25 (0.4%)		8 (0.3%)	5 (0.4%)	3 (0.2%)	
Insurance				<0.001				0.0531
Insured	11,626 (57.5%)	8,378 (58.3%)	3,248 (55.6%)		1,512 (57.7%)	730 (55.7%)	782 (59.6%)	
Medicaid	2,425 (12.0%)	1,697 (11.8%)	728 (12.5%)		308 (11.7%)	155 (11.8%)	153 (11.7%)	
Uninsured	459 (2.3%)	295 (2.1%)	164 (2.8%)		53 (2.0%)	34 (2.6%)	19 (1.4%)	
Unknown	5,708 (28.2%)	4,004 (27.9%)	1,704 (29.2%)		749 (28.6%)	392 (29.9%)	357 (27.2%)	
Marital status				<0.001				0.9833
Married	12,309 (60.9%)	8,736 (60.8%)	3,573 (61.1%)		1,654 (63.1%)	829 (63.2%)	825 (62.9%)	
Divorced or separated	1,826 (9.0%)	1,275 (8.9%)	551 (9.4%)		229 (8.7%)	110 (8.4%)	119 (9.1%)	
Widowed	2,659 (13.2%)	2,036 (14.2%)	623 (10.7%)		343 (13.1%)	170 (13%)	173 (13.2%)	
Single (never married)	2,619 (13.0%)	1,752 (12.2%)	867 (14.8%)		303 (11.6%)	153 (11.7%)	150 (11.4%)	
Unmarried or domestic partner	18 (0.1%)	14 (0.1%)	4 (0.1%)		2 (0.1%)	1 (0.1%)	1 (0.1%)	
Unknown	787 (3.9%)	561 (3.9%)	226 (3.9%)		91 (3.5%)	48 (3.7%)	43 (3.3%)	
Survival months, median (interquartile range)	25.0 (11.0–58.0)	27.0 (12.0–62.0)	20.0 (9.0–48.0)	<0.001	24.0 (11.0–57.0)	26.0 (11.0–65.0)	22.0 (10.0–51.0)	0.002

PSM, propensity score matching; NOS, not otherwise specified.

Table S2 Univariable Cox regression analysis for cancer-specific survival in patients with gastric adenocarcinoma

Variable	β/HR (95% CI)	P value
Age	1.01 (1.01, 1.02)	<0.0001
Sex		
Male	Reference	
Female	1.05 (0.94, 1.17)	0.3632
Year		
2004–2007	Reference	
2008–2011	0.91 (0.81, 1.03)	0.1258
2011–2015	0.76 (0.66, 0.88)	0.0002
Primary site		
Cardia	Reference	
Fundus of stomach	0.84 (0.45, 1.56)	0.5742
Lesser curvature of stomach	0.74 (0.61, 0.89)	0.0020
Greater curvature of stomach	0.54 (0.35, 0.84)	0.0058
Body of stomach	0.85 (0.68, 1.06)	0.1506
Gastric antrum	0.80 (0.70, 0.92)	0.0015
Pylorus	1.20 (0.83, 1.73)	0.3284
Stomach, NOS	1.13 (0.91, 1.41)	0.2618
Overlapping lesion of stomach	1.42 (1.16, 1.73)	0.0005
Grade		
Moderately differentiated or well differentiated	Reference	
Poorly differentiated or undifferentiated	2.23 (1.48, 3.37)	0.0001
Unknown	0.92 (0.50, 1.68)	0.7780
Histologic type		
Intestinal	Reference	
Diffuse	1.23 (1.10, 1.36)	0.0002
T stage		
T1	Reference	
T2a	2.07 (1.46, 2.93)	<0.0001
T2b	4.77 (3.88, 5.86)	<0.0001
T3	6.49 (5.25, 8.01)	<0.0001
T4	9.44 (7.27, 12.26)	<0.0001
TX	2.98 (1.10, 8.09)	0.0320
N stage		
N0	Reference	
N1	3.37 (2.89, 3.93)	<0.0001
N2	5.32 (4.49, 6.30)	<0.0001
N3	7.89 (6.25, 9.95)	<0.0001
NX	6.04 (2.68, 13.59)	<0.0001
M stage		
M0	Reference	
M1	2.79 (2.28, 3.42)	<0.0001
MX	1.60 (0.60, 4.28)	0.3454
Operation		
Surgery	Reference	
Endoscopy	0.47 (0.25, 0.88)	0.0180
Radiation		
None/unknown	Reference	
Yes	1.08 (0.97, 1.20)	0.1755
Chemotherapy		
No/unknown	Reference	
Yes	1.25 (1.13, 1.40)	<0.0001
Tumor size (cm)		
T ≤2	Reference	
2< T ≤3	2.37 (1.78, 3.17)	<0.0001
3< T ≤5	3.79 (2.98, 4.83)	<0.0001
T >5	5.92 (4.72, 7.43)	<0.0001
Unknown	2.79 (2.08, 3.75)	<0.0001
Race		
White	Reference	
Asian or Pacific Islander	0.73 (0.63, 0.84)	<0.0001
Black	1.00 (0.85, 1.18)	0.9817
American Indian/Alaska Native	2.14 (1.26, 3.63)	0.0047
Unknown	0.19 (0.03, 1.34)	0.0959
Insurance		
Insured	Reference	
Medicaid	1.25 (1.05, 1.48)	0.0110
Uninsured	1.05 (0.70, 1.58)	0.7990
Unknown	1.28 (1.14, 1.44)	<0.0001
Marital status		
Married	Reference	
Divorced or separated	1.33 (1.11, 1.60)	0.0021
Widowed	1.46 (1.26, 1.70)	<0.0001
Single (never married)	1.04 (0.87, 1.23)	0.6912
Unmarried or domestic partner	6.71 (1.67, 26.93)	0.0073
Unknown	0.77 (0.54, 1.08)	0.1274

PSM, propensity score matching; NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval.

Table S3 Multivariable Cox regression models evaluating the association between Lauren's classification and cancer-specific survival

Lauren's classification	Crude		Model I		Model II	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Intestinal	Reference		Reference		Reference	
Diffuse	1.23 (1.10, 1.36)	0.0002	1.22 (1.10, 1.36)	0.0002	1.22 (1.10, 1.36)	0.0002

Adjustment I: sex. Adjustment II: sex; radiation. HR, hazard ratio; CI, confidence interval.

Table S4 Results of competing risks regression model with all the risk factors in patients with gastric adenocarcinoma

Variables	HR (95% CI)	P value
Age	1.01 (1.01, 1.01)	<0.0001
Sex		
Male	Reference	
Female	0.97 (0.91, 1.03)	0.3042
Year of diagnosis		
2004–2007	Reference	
2008–2011	0.84 (0.76, 0.92)	0.0003
2011–2015	0.44 (0.39, 0.49)	<0.0001
Primary site		
Cardia	Reference	
Fundus of stomach	0.77 (0.65, 0.91)	0.0018
Lesser curvature of stomach	0.64 (0.58, 0.70)	<0.0001
Greater curvature of stomach	0.71 (0.61, 0.82)	<0.0001
Body of stomach	0.72 (0.65, 0.80)	<0.0001
Gastric antrum	0.71 (0.66, 0.77)	<0.0001
Pylorus	0.82 (0.71, 0.95)	0.0065
Stomach, NOS	0.82 (0.73, 0.91)	0.0003
Overlapping lesion of stomach	0.79 (0.70, 0.89)	<0.0001
Grade		
Moderately differentiated or well differentiated	Reference	
Poorly differentiated or Undifferentiated	1.23 (1.15, 1.31)	<0.0001
Unknown	0.93 (0.83, 1.05)	0.2568
Histologic type		
Intestinal	Reference	
Diffuse	1.32 (1.23, 1.41)	<0.0001
T stage		
T1	Reference	
T2a	1.60 (1.42, 1.80)	<0.0001
T2b	2.47 (2.23, 2.74)	<0.0001
T2, NOS	1.76 (1.25, 2.47)	0.0011
T3	3.21 (2.89, 3.58)	<0.0001
T4	4.38 (3.82, 5.02)	<0.0001
TX	2.74 (2.21, 3.39)	<0.0001
N stage		
N0	Reference	
N1	1.67 (1.57, 1.79)	<0.0001
N2	2.42 (2.22, 2.63)	<0.0001
N3	3.34 (2.91, 3.83)	<0.0001
NX	1.33 (1.05, 1.67)	0.0161
M stage		
M0	Reference	
M1	2.98 (2.66, 3.34)	<0.0001
MX	1.31 (1.04, 1.64)	0.0209
Operation		
Surgery	Reference	
Endoscopy	1.29 (1.12, 1.50)	0.0005
Radiation		
None/unknown	Reference	
Yes	0.91 (0.85, 0.98)	0.0146
Chemotherapy		
No/unknown	Reference	
Yes	1.00 (0.92, 1.08)	0.9243
Tumor size (cm)		
T ≤2	Reference	
2< T ≤3	1.25 (1.12, 1.39)	<0.0001
3< T ≤5	1.25 (1.13, 1.38)	<0.0001
T >5	1.28 (1.16, 1.40)	<0.0001
Unknown	1.41 (1.27, 1.57)	<0.0001
Race		
White	Reference	
Asian or Pacific Islander	0.79 (0.74, 0.85)	<0.0001
Black	1.00 (0.91, 1.08)	0.9193
American Indian/Alaska Native	1.51 (1.09, 2.09)	0.0122
Unknown	0.14 (0.06, 0.34)	<0.0001
Insurance		
Insured	Reference	
Medicaid	0.99 (0.91, 1.08)	0.8124
Uninsured	0.93 (0.78, 1.11)	0.4342
Unknown	1.01 (0.91, 1.11)	0.8773
Marital status		
Married	Reference	
Divorced or separated	1.08 (0.99, 1.19)	0.0979
Widowed	1.05 (0.96, 1.14)	0.3263
Single (never married)	1.05 (0.96, 1.14)	0.2666
Unmarried or domestic partner	0.69 (0.21, 2.28)	0.5484
Unknown	0.96 (0.83, 1.11)	0.5745

NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval.

Table S5 Univariable Cox regression analysis for cancer-specific survival in patients with gastric cancer

Variables	HR (95% CI)	P value
Primary site		
Cardia	Reference	
Oxyntic mucosa	0.99 (0.94, 1.05)	0.7774
Antral mucosa	1.05 (1.00, 1.11)	0.0493
Stomach, NOS	1.42 (1.32, 1.53)	<0.0001
Overlapping lesions	1.72 (1.59, 1.85)	<0.0001

NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval.

Table S6 Multivariable Cox regression models evaluating the association between Lauren's classification and cancer-specific survival

Lauren's classification	Crude		Model III		Model IV	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Intestinal	Reference		Reference		Reference	
Diffuse	1.44 (1.38, 1.50)	<0.001	1.19 (1.13, 1.24)	<0.001	1.20 (1.15, 1.26)	<0.001

Adjustment III: age; primary site (5 sites); grade; T stage; N stage; M stage; tumor size. Adjustment IV: age; sex; year; primary site (5 sites); grade; T stage; N stage; M stage; operation; chemotherapy; tumor size; race; insurance; marital status. NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval.