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Sex disparity, prediagnosis lifestyle factors, and long-term survival of gastric cancer: a multi-center cohort study from China

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Abstract

Background This multi-center cohort study aimed to investigate whether sex and prediagnosis lifestyle affect the prognosis of gastric cancer.

Methods Patients with gastric cancer were from four gastric cancer cohorts of the National Cancer Center of China, The First Hospital of Lanzhou University, Lanzhou University Second Hospital, and Gansu Provincial Cancer Hospital. Prediagnosis lifestyle factors in our study included body mass index (BMI) at diagnosis, usual BMI, weight loss, the history of Helicobacter pylori (Hp) infection, and the status of smoking and drinking.

Results Four gastric cancer cohorts with 29,779 gastric cancer patients were included. In total patients, female patients had a better prognosis than male patients (HR = 0.938, 95%CI: 0.881–0.999, $P = 0.046$). For prediagnosis lifestyle factors, BMI at diagnosis, usual BMI and the amount of smoking were statistically associated with the prognosis of gastric cancer patients. Female patients with smoking history had a poorer survival than non-smoking females (HR = 0.782, 95%CI: 0.616–0.993, $P = 0.044$). Tobacco consumption > 40 cigarettes per day (HR = 1.182, 95%CI: 1.035–1.350, $P = 0.013$) was independent adverse prognostic factors in male patients. Obesity paradox was observed only in male patients (BMI < 18.5, HR = 1.145, 95%CI: 1.019–1.286, $P = 0.023$; BMI: 23–27.4, HR = 0.875, 95%CI: 0.824–0.930, $P < 0.001$; BMI ≥ 27.5, HR = 0.807, 95%CI: 0.735–0.886, $P < 0.001$).

Introduction

Gastric cancer, the fifth most prevalent cancer worldwide and the fourth leading cause of cancer-related deaths, is twice as common in males as in females [1, 2]. However, it remains to be discussed whether sex disparity exists in the prognosis of gastric cancer. In most studies, female patients had a better prognosis than male patients [3–12], whereas several other studies showed no independent sex-related associations with overall survival (OS) [13–16]. Three studies even showed that males with gastric cancer had a better prognosis [17–19].

Extensive evidence indicates that prediagnosis lifestyle factors such as cigarette smoking [20–22], alcohol

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Conclusions Sex and some prediagnosis lifestyle factors, including BMI at diagnosis, usual BMI and the amount of smoking, were associated with the prognosis of gastric cancer.

Keywords Gastric cancer, Sex disparity, Prediagnosis lifestyle factors, Prognosis, Gastrectomy

consumption [21, 22], BMI [23–25], and Hp infection [26–28] might significantly affect the prognosis of gastric cancer. To date, evidence for the association between prediagnosis lifestyle factors and prognosis in gastric cancer patients has been inconsistent. The prediagnosis lifestyle habits of males and females are quite different. And it is possible that this difference between male and female gastric cancer patients might modify the relationship between sex and the prognosis of gastric cancer.

Thus, we conducted a multi-center cohort study using four gastric cancer cohorts from the National Cancer Center of China, The First Hospital of Lanzhou University, Lanzhou University Second Hospital, and Gansu Provincial Cancer Hospital to clarify the effects of sex and prediagnosis lifestyle on the prognosis of gastric cancer patients. The findings of our study might assist clinicians in identifying high-risk groups with risk factors, forecasting prognoses, and devising personalized treatment strategies.

Methods

Study population and data source

In this multi-center cohort study, gastric cancer patients from four gastric cancer cohorts of the National Cancer Center of China, The First Hospital of Lanzhou University, Lanzhou University Second Hospital, and Gansu Provincial Cancer Hospital between January 2000 and December 2020 were included in the study. The four cohorts accommodated 30,034 gastric cancer patients. The prospective database of four cohorts tracks data on patient anthropometrics, demographics, clinical history, past medical history, smoking and alcohol consumption, family history, diagnostic tests, tumor characteristics, therapeutic interventions, complications, pathologic data, and outcomes. Except for outcomes, the rest of the data belong to the clinicopathological factors of gastric cancer. All data were backed up by source documents and the accuracy of the data entered into the database was periodically reviewed. The main exclusion criteria was patients with incomplete gender or age information. All patients met the inclusion criteria except for the 255 patients with missing data. Finally, a total of 29,779 gastric cancer patients were included. Data comparison among four gastric cancer cohorts was shown in Table S1.

After the analyses of all included gastric cancer patients, we further analyzed two detailed subgroups to avoid the risk of error in survival outcomes due to different treatment methods: gastrectomy patients, and no surgery patients.

Data elements

BMI was calculated as weight (kg) of gastric cancer patients divided by the square of height (m^2). The weight in the formula when calculating BMI at diagnosis was the weight at diagnosis, whereas usual BMI was calculated by the weight of gastric cancer patients before they lost weight, also known as the usual weight. The term "usual weight" refers to an individual's average weight over a period of time when they are not experiencing significant weight gain or loss. It serves as a baseline for tracking weight changes and assessing health status, which was recorded in the prospective database based on patient-reported. Patient-reported is part of the standard medical approach in completing a history of lifestyle. Patients were stratified according to the Asian criteria of BMI classification: underweight (<18.5 kg/m^2), healthy weight (≥18.5 to <23 kg/m^2), overweight (≥23 to <27.5 kg/m^2) and obese (≥27.5 kg/m^2).

Lifestyle variables were one aspect of clinicopathological factors, which was recorded in the prospective database based on patient-reported. Lifestyle variables associated with smoking included smoking history (never and smokers), duration of smoking (short-term,1–10; mid-term,11–20; and long-term, > 20 years), and number of cigarettes per day (≤20, 21–39, and ≥40). For alcohol drinking, drinking history (never and drinkers), duration of drinking (short-term,1–10; mid-term,11–20; and long-term, > 20 years), and amount of alcohol consumed per day (light drinkers, 1–50 ml; moderate drinkers, 51–100 ml; and heavy drinkers, ≥ 100 ml) were included. Subjects who smoke or drink regularly more than one year before the present admission were regarded as smokers or drinkers, respectively.

Upper endoscopy is performed as one of the initial diagnostic tests in gastric cancer patients. Some patients completed the rapid urease test, which could detect the presence of Hp within half an hour, with an accuracy rate of 90%.

Follow-up and survival information

The follow-up was performed through outpatient clinical visits, telephone contact, and death registries. Last follow-up was performed in August 31st, 2022. The median and interquartile range (IQR) follow-up time were 38.10 months, 16.53 months (IQR1), and 74.13 months (IQR3), respectively. The main long-term outcome was overall

survival (OS), which was defined as the total time from the diagnosis of gastric cancer to the date of death or the last date the patient was confirmed alive.

Missing data

Patients with incomplete important clinicopathological and prognostic information were excluded in the study. We assumed the data to be missing at random, and pairwise deletion was employed to handle the missing data.

Statistical analysis

All statistical analyses were done using R (version 4.2.1) and SPSS (version 26). Comparisons between two groups were examined using the t test for continuous variables and chi-square test for categorical variables. Survival analysis was performed via Kaplan-Meier estimates and compared using the log-rank test. The cox regression analysis was performed to identify the relationship between prognostic factors and survival. Independent risk factors with a p-value of less than 0.10 in the univariate analysis and some clinically meaningful variables were adopted for the multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the risk of death. A p-value of less than 0.05 was considered statistically significant and all the tests were two-sided.

Results

Baseline characteristics

The baseline characteristics of the gastric cancer patients from four gastric cancer cohorts were presented in Table 1. The number of female patients was much less than that of male patients (25.72% vs. 74.28%, $P<0.001$). In comparison to male patients, female patients were younger in age (aged ≤ 50 years, 30.2% vs. 17.5%, $P<0.001$). Female gastric cancer patients showed a higher percentage of distal (73.5% vs. 57.7%, $P<0.001$), diffuse (27.2% vs. 16.3%, $P<0.001$), signet-ring cell carcinoma (39.3% vs. 24.7%, $P<0.001$), HER-2 negative (52.2% vs. 46.7%, $P<0.001$), and linitis plastica (4.2% vs. 2.1%, $P<0.001$). The stage of gastric cancer was more advanced in female patients than that of male patients (T4, 47.6% vs. 45.2%; N3, 30.1% vs. 27.7%; M1, 14.4% vs. 11.8%; TNM IV, 14.4% vs. 11.9%). Male patients tended to develop vascular invasion (35.9% vs. 33.3%, $P<0.001$). There was no significant difference in treatment between male and female patients (gastrectomy: 76.6% vs. 76.8%, $P=0.75$; perioperative therapy: 75.36% vs. 74.61%, $P=0.506$).

The prediagnosis lifestyle of male patients differed greatly from that of female patients. Overweight and obese patients were more likely to be male, in terms of BMI at diagnosis (overweight, 39.6% vs. 33.2%; obese, 10.6% vs. 9.1%). Of the total male patients, 44% had smoking history and 34.9% had drinking history. In contrast to male patients, only 4.6% female patients had smoking history ($P<0.001$) and 3.8% had drinking history ($P<0.001$). In addition, the amount of smoking and drinking were higher in male patients than in female patients, and they also had a longer duration of tobacco and alcohol (tobacco consumption > 40 cigarettes per day: 10.7% vs. 5.0%, $P<0.001$; alcohol consumption > 100 ml per day: 56.6% > 32.9%, $P<0.001$; smoking years ≥ 20 year: 61.8% vs. 43.9%, $P<0.001$; drinking years ≥ 20 year: 60.7% vs. 59.5%, $P<0.001$).

After stratification by type of gastrectomy, baseline characteristics of gastric cancer patients differ slightly. In gastrectomy patient subgroup (Table S2), the proportion of patients with the most advanced gastric cancer was less than that in the total patients (TNM IV: 3.2% vs. 12.5%). For postoperative complications, male patients were more likely to suffer from complications after surgery than female patients (4.1% vs. 3.4%, $P=0.014$). Regards to other baseline characteristics, the gastrectomy patients showed similar trends with total patients, except for the duration of drinking. Female patients had a longer duration of alcohol consumption than males (drinking years ≥ 20 year: 63.1% vs. 60.9%, $P<0.001$). The proportion of the most advanced gastric cancer patients in no surgery patient subgroup (Table S3) was much more than that in the total patients (TNM IV: 82.5% vs. 12.5%). Compared with the total patients, most baseline characteristics showed similar trends. However, there was no significant difference in the amount of alcohol consumption between male and female patients ($P=0.449$).

Overall survival (OS)

Figure 1 showed the Kaplan-Meier curves for OS of different genders in total gastric cancer patients. The median OS (Table S4) of total patients was as follows: overall, 46.99 months; male patients, 46.43 months; and female patients, 48.65 months. And female patients had a better OS than males ($P=0.017$). Figure 2 showed the Kaplan-Meier curves for OS of different BMI at diagnosis in total gastric cancer patients. Except obese patients, the OS of female patients was better than that in male patients (BMI < 18.5, median OS: 34.55 vs. 31.81 months, $P=0.032$; BMI: 18.5–22.9, median OS: 45.01 vs. 41.71 months, $P=0.005$; BMI: 23–27.4, median OS: 68.33 vs. 60.07 months, $P=0.01$; BMI ≥ 27.5, median OS: 65.52 vs. 70.04 months, $P=0.484$). When usual BMI were taken into account (Figure S1), only the healthy weight patients had sex disparity in OS (BMI: 18.5–22.9, median OS: 46.97 vs. 42.97 months, $P=0.004$).

For non-smoking patients (Fig. 3), male patients had a worse OS than female patients (median OS: 43.58 vs. 48.72 months, $P<0.001$). However, there was no significant difference in OS between male and female patients among smoking patients (median OS: 41.71 vs. 45.01

Table 1 Characteristics of gastric cancer patients of four cohorts

Characteristics		Overall (*N* = 29779)		Male (*N* = 22120)		Female (*N* = 7659)		*P* value
		N	%	*N*	%	*N*	%	
Sex								
	Male	22,120	74.3%					
	Female	7659	25.7%					
Age at diagnosis (years)								
	18–34	884	3.0%	410	1.9%	474	6.2%	< 0.001
	35–50	5282	17.7%	3446	15.6%	1836	24.0%	
	51–64	14,259	47.9%	11,000	49.7%	3259	42.6%	
	≥ 65	9354	31.4%	7264	32.8%	2090	27.3%	
Smoking history								
	Yes	9938	33.9%	9592	44.0%	346	4.6%	< 0.001
	Never	19,403	66.1%	12,221	56.0%	7182	95.4%	
Smoking years								
	Short-term (1–10 year)	832	9.6%	772	9.2%	60	21.1%	< 0.001
	Mid-term (11–20 year)	2527	29.2%	2427	29.0%	100	35.1%	
	Long-term (20 yr+)	5292	61.2%	5167	61.8%	125	43.9%	
No. of cigarettes (per day)								
	≤ 20 (≤ 1 pack)	7317	83.0%	7058	82.7%	259	92.5%	< 0.001
	21–39	567	6.4%	560	6.6%	7	2.5%	
	≥ 40 (≥ 2 packs)	929	10.5%	915	10.7%	14	5.0%	
Drinking history								
	Yes	7877	26.9%	7590	34.9%	287	3.8%	< 0.001
	Never	21,402	73.1%	14,173	65.1%	7229	96.2%	
Drinking years								
	Short-term (1–10 year)	713	13.2%	679	12.9%	34	21.5%	0.003
	Mid-term (11–20 year)	1417	26.2%	1387	26.4%	30	19.0%	
	Long-term (20 yr+)	3287	60.7%	3193	60.7%	94	59.5%	
Amount of alcohol consumption								
	Light drinkers (1–50 ml)	878	17.2%	844	17.0%	34	23.8%	< 0.001
	Moderate drinkers (51–100 ml)	1371	26.9%	1309	26.4%	62	43.4%	
	Heavy drinkers (100 ml+)	2855	55.9%	2808	56.6%	47	32.9%	
BMI(kg/m^2) at diagnosis								
	< 18.5	2318	8.6%	1531	7.7%	787	11.4%	< 0.001
	18.5–22.9	11,582	43.2%	8400	42.1%	3182	46.3%	
	23–27.4	10,179	37.9%	7893	39.6%	2286	33.2%	
	≥ 27.5	2747	10.2%	2123	10.6%	624	9.1%	
Usual BMI(kg/m^2)								
	< 18.5	1187	5.0%	775	4.4%	412	6.7%	< 0.001
	18.5–22.9	8776	36.6%	6267	35.3%	2509	40.5%	
	23–27.4	10,367	43.3%	7957	44.8%	2410	38.9%	
	≥ 27.5	3618	15.1%	2757	15.5%	861	13.9%	
Weight loss as % of usual weight								
	None	15,261	58.0%	11,335	58.1%	3926	57.7%	< 0.001
	0–10	7606	28.9%	5769	29.5%	1837	27.0%	
	> 10	3464	13.2%	2419	12.4%	1045	15.3%	
H Pylori infection								
	Negative	1525	46.8%	1144	46.3%	381	48.4%	0.292
	Positive	1735	53.2%	1329	53.7%	406	51.6%	
Primary tumor location								
	Proximal	9006	32.4%	7516	36.4%	1490	20.9%	< 0.001
	Distal	17,155	61.7%	11,923	57.7%	5232	73.5%	
	Total	1622	5.8%	1224	5.9%	398	5.6%	
Lauren type								

Table 1 (continued)

Characteristics		Overall (*N* = 29779)		Male (*N* = 22120)		Female (*N* = 7659)		*P* value
		N	%	*N*	%	*N*	%	
	Intestinal	4327	19.3%	3572	21.5%	755	13.1%	< 0.001
	Diffuse	4280	19.1%	2710	16.3%	1570	27.2%	
	Mixed	3059	13.7%	2403	14.5%	656	11.4%	
	Unknown	10,704	47.8%	7912	47.7%	2792	48.4%	
Signet ring cell								
	Yes	5708	28.5%	3667	24.7%	2041	39.3%	< 0.001
	No	14,345	71.5%	11,191	75.3%	3154	60.7%	
Type of gastrectomy								
	Gastrectomy	22,685	76.6%	16,841	76.6%	5844	76.8%	0.75
	No surgery	6922	23.4%	5152	23.4%	1770	23.2%	
Surgical Margin								
	Negative	20,580	97.1%	15,318	97.2%	5262	96.9%	0.183
	Positive	608	2.9%	438	2.8%	170	3.1%	
Pathologic T stage								
	T0 + Tis	165	0.8%	126	0.8%	39	0.7%	< 0.001
	T1	4093	19.3%	2891	18.3%	1202	22.1%	
	T2	2351	11.1%	1792	11.3%	559	10.3%	
	T3	4905	23.1%	3854	24.4%	1051	19.3%	
	T4	9737	45.8%	7151	45.2%	2586	47.6%	
Pathologic N stage								
	N0	7964	36.8%	5930	36.8%	2034	36.7%	0.001
	N1	3640	16.8%	2757	17.1%	883	15.9%	
	N2	3903	18.0%	2949	18.3%	954	17.2%	
	N3	6139	28.4%	4469	27.7%	1670	30.1%	
Pathologic M stage								
	M0	20,299	87.5%	15,166	88.2%	5133	85.6%	< 0.001
	M1	2899	12.5%	2036	11.8%	863	14.4%	
Pathologic TNM stage								
	0	163	0.7%	126	0.7%	37	0.6%	< 0.001
	I	4866	21.0%	3573	20.9%	1293	21.6%	
	II	4846	21.0%	3636	21.2%	1210	20.2%	
	III	10,348	44.8%	7757	45.3%	2591	43.2%	
	IV	2899	12.5%	2036	11.9%	863	14.4%	
HER-2								
	Negative	7272	48.0%	5309	46.7%	1963	52.2%	< 0.001
	+	4585	30.3%	3414	30.0%	1171	31.1%	
	++	2158	14.3%	1725	15.2%	433	11.5%	
	+++	1126	7.4%	929	8.2%	197	5.2%	
Linitis plastica								
	Yes	639	2.7%	378	2.1%	261	4.2%	< 0.001
	No	23,424	97.3%	17,482	97.9%	5942	95.8%	
Grade								
	Poorly	9854	46.0%	6648	41.6%	3206	59.0%	< 0.001
	Poorly-Moderately	5648	26.4%	4528	28.3%	1120	20.6%	
	Moderately	4467	20.8%	3650	22.8%	817	15.0%	
	Well-Moderately	712	3.3%	582	3.6%	130	2.4%	
	Well	731	3.4%	575	3.6%	156	2.9%	
	Undifferentiated	17	0.1%	13	0.1%	4	0.1%	
Nerve invasion								
	Yes	6569	34.7%	4896	34.8%	1673	34.3%	0.621
	No	12,375	65.3%	9173	65.2%	3202	65.7%	
Vascular invasion								

Table 1 (continued)

Characteristics		Overall (*N* = 29779)		Male (*N* = 22120)		Female (*N* = 7659)		*P* value
		N	%	*N*	%	*N*	%	
	Yes	8170	35.2%	6172	35.9%	1998	33.3%	< 0.001
	No	15,040	64.8%	11,034	64.1%	4006	66.7%	
ELNs								
	< 30	13,032	65.9%	9771	66.5%	3261	64.3%	0.005
	≥ 30	6734	34.6%	4923	33.5%	1811	35.7%	
Perioperative therapy								
	Yes	12,102	75.2%	9034	75.4%	3068	74.6%	0.506
	No	3997	24.8%	2953	24.6%	1044	25.4%	
Postoperative complications								
	Yes	886	3.8%	689	4.0%	197	3.3%	0.016
	No	22,324	96.2%	16,517	96.0%	5807	96.7%	

months, $P=0.532$). With regard to alcohol drinking (Fig. 4), the result was similar. The female patients without drinking history had a better OS than male patients who never drank (median OS: 49.27 vs. 44.70 months, $P<0.001$), but there was no gender difference in OS among drinking patients (median OS: 41.17 vs. 51.3 months, $P=0.778$).

Among patients who were diagnosed at an early pTNM stage (pTNM I and II, Fig. S2), females showed better OS than males (median OS: not reached vs. 211.25 months, $P<0.001$; median OS: 148.53 vs. 111.27 months, $P=0.012$, respectively). For later pTNM stage (pTNM III and IV), there was no significant difference between female and male patients in OS (median OS: 38.70 vs. 37.49 months, $P=0.671$; median OS: 16.20 vs. 14.63 months, $P=0.265$, respectively).

The history of Hp infection also affected the OS of gastric cancer patients differently between different sex (Fig. S3). Female patients showed a better survival than males in non-Hp infection group (median OS: 123.81 vs. 85.00 months, $P=0.039$), but this result was not observed in patients with Hp infection (median OS: 71.50 vs. 89.02 months, $P=0.396$).

After patients were divided into two subgroups based on whether they had surgery, there was a significant difference in the effect of sex on OS (Fig. S4). In the gastrectomy patient group, the OS of female patients was significantly better than that of male patients (median OS: 79.05 vs. 72.76 months, $P<0.001$). However, for no surgery patients, male gastric cancer patients had a better OS than female patients (median OS: 20.10 vs. 17.76 months, $P=0.044$).

Survival outcomes in univariate and multivariate analyses

Univariate analysis (Table 2) showed female patients had better survival than male patients (HR = 0.955, 95%CI: 0.92–0.992, $P=0.017$). The history of Hp infection had no effect on the survival of male and female patients respectively (male patients: HR = 1.056, 95%CI: 0.922–1.209, $P=0.432$; female patients: HR = 0.782, 95%CI: 0.61–1.001, $P=0.051$). Variables with a P-value of less than 0.10 in the univariate analysis or considered clinically relevant were involved in the multivariate analysis, including sex, age at diagnosis, smoking history, the duration of smoking, the amount of smoking, drinking history, the duration of drinking, the amount of alcohol consumption, BMI at diagnosis, usual BMI, weight loss, tumour location, type of gastrectomy, the grade of tumour, signet ring cell and pTNM stage.

The results of univariate analysis among the gastrectomy patients were showed in Table S5. For no surgery patients (Table S6), there was no significant difference on survival among female patients with different BMI at diagnosis (female patients: BMI < 18.5, reference; BMI: 18.5–22.9, $P=0.851$; BMI: 23–27.4, $P=0.190$; BMI ≥ 27.5, $P=0.075$). Usual BMI did not affect the survival in no surgery patients (BMI < 18.5, reference; BMI: 18.5–22.9, $P=0.670$; BMI: 23–27.4, $P=0.398$; BMI ≥ 27.5, $P=0.073$).

Multivariable analysis (Table 3) showed female patients had a better prognosis than male patients in the total patients (HR = 0.938, 95%CI: 0.881–0.999, $P=0.046$). Alcohol consumption was not associated with prognosis, regardless of the patient's gender. Smoking history had no relationship with the prognosis in total patient group ($P=0.461$). After gender stratification, smoking history was associated with poor survival only in female patient group (HR = 0.782, 95%CI: 0.616–0.993, $P=0.044$). Smoking history was not associated with the OS in male patient group ($P=0.761$). However, smoking more than 40 cigarettes per day was associated with worse prognosis than others in total and male patient groups (total patients: HR = 1.166, 95%CI: 1.021–1.330, $P=0.023$; male patients: HR = 1.182, 95%CI: 1.035–1.350, $P=0.013$). This indicates that smoking habits affected the prognosis of gastric cancer patients.

BMI at diagnosis was an independent prognostic factor in total patient group. Overweight and obesity were associated with good survival but underweight was the

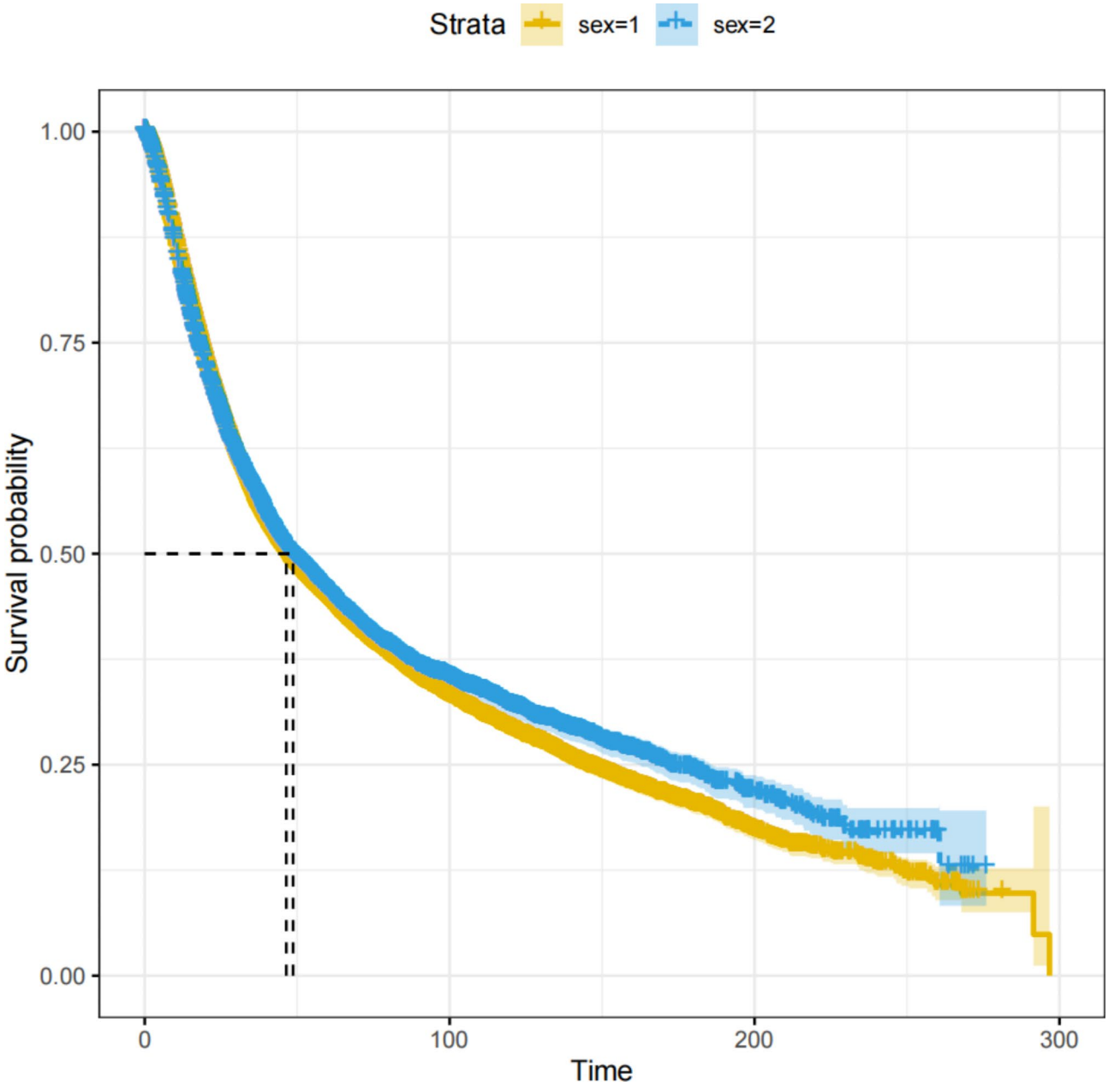

Fig. 1 The Kaplan-Meier curves for OS of different genders in total gastric cancer patients

opposite (BMI < 18.5, HR = 1.161, 95%CI: 1.055–1.277, $P = 0.002$; BMI: 18.5–22.9, reference; BMI: 23–27.4, HR = 0.880, 95%CI: 0.834–0.928, $P < 0.001$; BMI ≥ 27.5, HR = 0.821, 95%CI: 0.756–0.890, $P < 0.001$). After accounting for sex factor, the effect of BMI at diagnosis on prognosis was only observed in male patient group. Overweight and obese male patients had a better prognosis than others, and underweight male patients showed the worst prognosis (BMI < 18.5, HR = 1.145, 95%CI: 1.019–1.286, $P = 0.023$; BMI: 18.5–22.9, reference; BMI: 23–27.4, HR = 0.875, 95%CI: 0.824–0.930, $P < 0.001$; BMI ≥ 27.5, HR = 0.807, 95%CI: 0.735–0.886, $P < 0.001$).

Usual BMI was statistically associated with the prognosis in the total patient group. Overweight and obese patients before diagnosis of gastric cancer seemed to have a better prognosis than others (BMI: 23–27.4, HR = 0.894, 95%CI: 0.844–0.947, $P < 0.001$; BMI ≥ 27.5, HR = 0.878, 95%CI: 0.813–0.948, $P = 0.001$). However, unlike the effect of BMI at diagnosis, underweight before developing gastric cancer was not associated with prognosis ($P = 0.062$). Once sex factor was taken into account, usual BMI had effect on the OS only in male patient group (BMI < 18.5, $P = 0.173$; BMI: 18.5–22.9, reference;

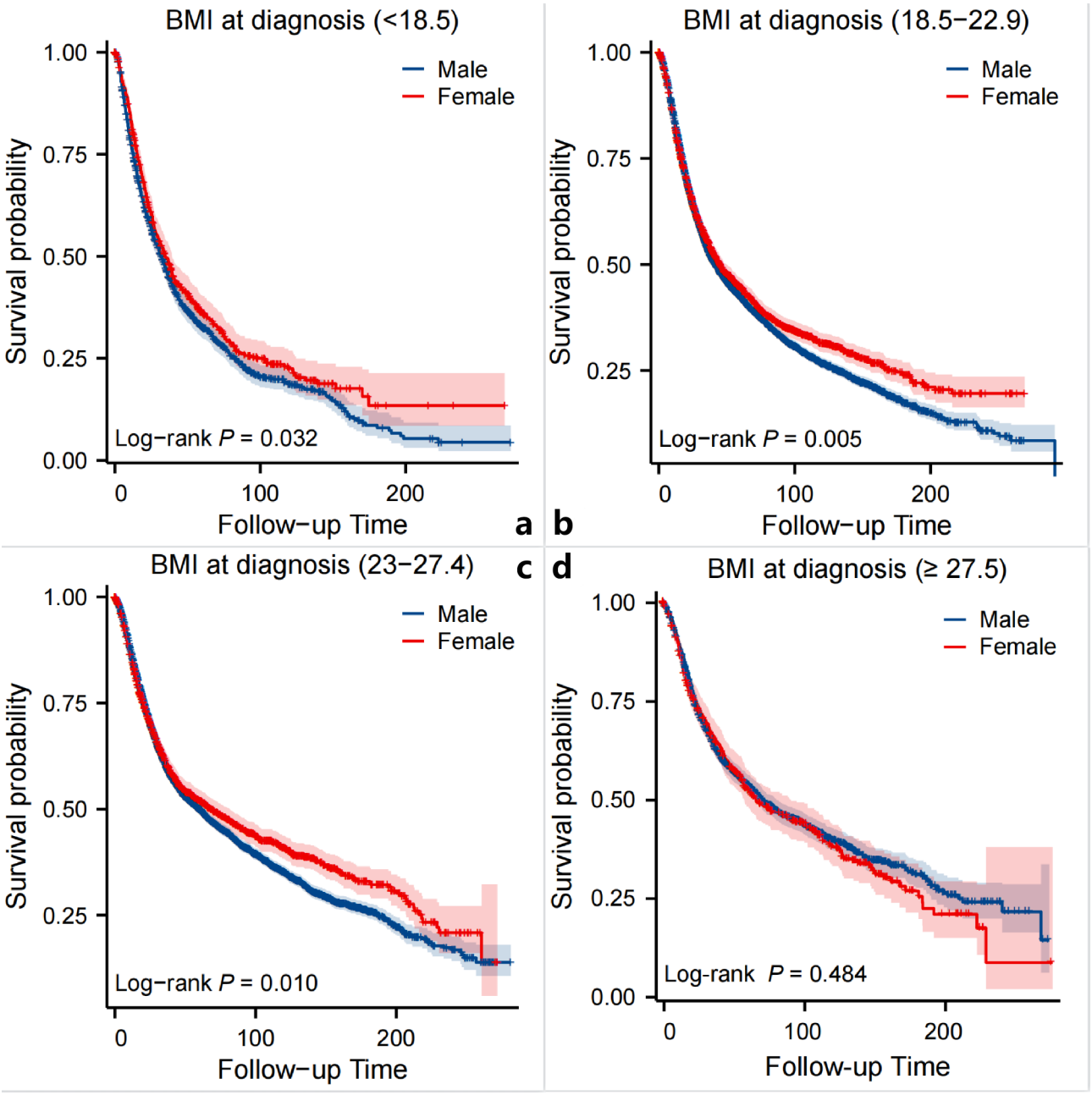

Fig. 2 The Kaplan-Meier curves for OS of different BMI at diagnosis in total gastric cancer patients. **a** Underweight patients, **b** Healthy weight patients, **c** Overweight patients, **d** Obese patients

BMI: 23–27.4, HR=0.878, 95%CI: 0.821–0.938, $P<0.001$; BMI≥27.5, HR=0.856, 95%CI: 0.784–0.935, $P=0.001$).

As Table 3 shown, weight loss was associated with poor prognosis only when the weight lost more than 10% of usual weight in total gastric cancer patients (HR=1.288, 95%CI: 1.194–1.390, $P<0.001$). When male and female patients were studied separately, the results remained the same as before (male patients: HR=1.433, 95%CI: 1.203–1.708, $P<0.001$; female patients: HR=1.291, 95%CI: 1.118–1.491, $P<0.001$, respectively).

In the gastrectomy patient subgroup (Table S7), female patients showed a better prognosis than male patients (HR=0.897, 95%CI: 0.822–0.978, $P=0.014$). Most prediagnosis lifestyle factors showed similar trends compared to the total patients. Smoking more than 40 cigarettes per day was not an independent predictor for poor survival for gastrectomy patients ($P=0.841$), which was inconsistent with the result presented in total patients. After stratification by sex, it was still not a poor independent prognostic factor in either male or female patients (male

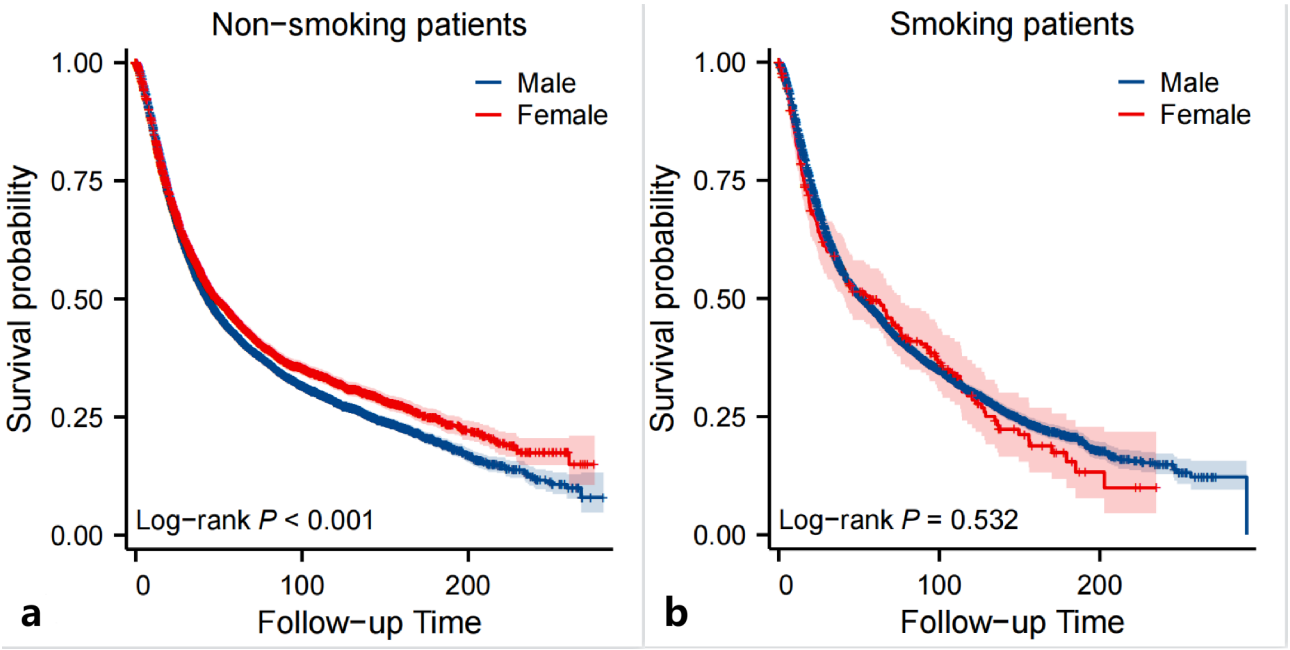

Fig. 3 The Kaplan-Meier survival curves for OS of patients with a history of smoking. **a** Non-smoking patients, **b** Smoking patients

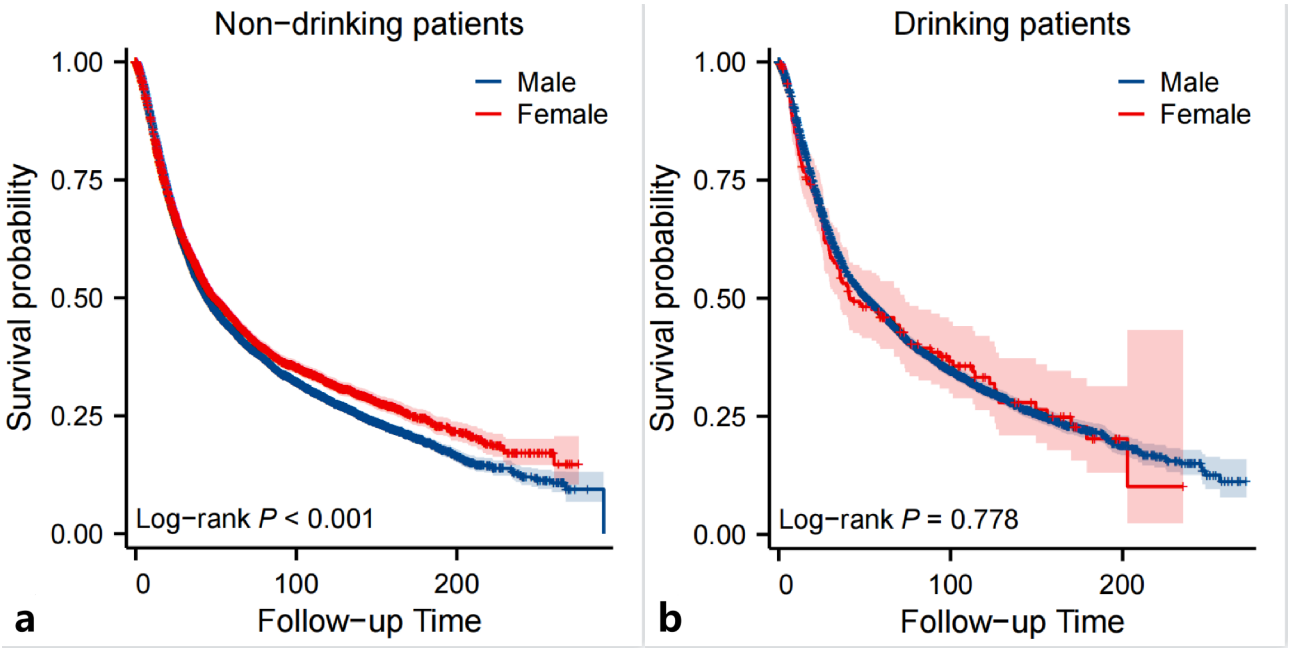

Fig. 4 The Kaplan-Meier survival curves for OS of patients with a history of drinking. **a** Non-drinking patients, **b** Drinking patients

patients: P=0.847; female patients: P=0.738). In the no surgery patient subgroup (Table S8), there was no sex disparity in the prognosis (P=0.589). In addition, pre-diagnosis lifestyle factors were not associated with the prognosis of gastric cancer patients without surgery.

Discussion

This multi-center cohort study systematically investigated the prognostic effect of sex disparity and pre-diagnosis lifestyle factors in gastric cancer, including BMI at diagnosis, usual BMI, weight loss, the history of Hp infection, and the status of smoking and drinking. To the best of our knowledge, our analysis represents the largest evaluation of this issue for gastric cancer patients in China, with the number of 29,779 gastric cancer patients

Table 2 Univariate analysis of gastric cancer patients of four cohorts

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
Sex													
	Male	1											
	Female	0.955	0.92	0.992	0.017								
Age at diagnosis (years)													
	18–34	1				1				1			
	35–50	0.919	0.826	1.024	0.125	0.928	0.794	1.084	0.345	0.964	0.828	1.121	0.631
	51–64	0.923	0.833	1.023	0.126	0.983	0.846	1.142	0.824	0.849	0.734	0.981	0.027
	≥65	1.262	1.138	1.399	< 0.001	1.371	1.18	1.594	< 0.001	1.083	0.935	1.255	0.288
Smoking history													
	Yes	1				1				1			
	Never	1.053	1.017	1.09	0.004	1.092	1.05	1.134	< 0.001	0.947	0.812	1.105	0.49
Smoking years													
	Short-term (1–10 year)	1				1				1			
	Mid-term (11–20 year)	0.912	0.812	1.023	0.116	0.929	0.824	1.047	0.225	0.686	0.423	1.114	0.128
	Long-term (20 yr+)	1.061	0.954	1.179	0.275	1.077	0.965	1.202	0.184	0.826	0.532	1.283	0.396
No. of cigarettes (per day)													
	≤ 20 (≤ 1 pack)	1				1				1			
	21–39	1	0.887	1.127	1	0.983	0.871	1.109	0.781	6.381	2.317	17.574	< 0.001
	≥40 (≥ 2 packs)	0.992	0.899	1.095	0.879	0.997	0.903	1.101	0.956	0.314	0.077	1.27	0.104
Drinking history													
	Yes	1				1				1			
	Never	1.049	1.011	1.09	0.012	1.077	1.034	1.121	< 0.001	0.975	0.816	1.166	0.783
Drinking years													
	Short-term (1–10 year)	1				1				1			
	Mid-term (11–20 year)	0.93	0.814	1.062	0.285	0.941	0.821	1.078	0.382	0.88	0.438	1.769	0.719
	Long-term (20 yr+)	1.059	0.939	1.193	0.351	1.08	0.956	1.221	0.217	0.574	0.316	1.044	0.069
Amount of alcohol consumption													
	Light drinkers (1–50 ml)	1				1				1			
	Moderate drinkers (51–100 ml)	0.899	0.795	1.018	0.093	0.907	0.8	1.029	0.13	0.623	0.319	1.218	0.167
	Heavy drinkers (100 ml+)	0.937	0.842	1.043	0.236	0.933	0.837	1.04	0.212	1.151	0.625	2.12	0.651
BMI(kg/m^2) at diagnosis													
	< 18.5	1				1				1			
	18.5–22.9	0.777	0.732	0.825	< 0.001	0.761	0.708	0.818	< 0.001	0.805	0.723	0.896	< 0.001
	23–27.4	0.625	0.588	0.665	< 0.001	0.612	0.569	0.659	< 0.001	0.643	0.573	0.72	< 0.001
	≥27.5	0.571	0.528	0.618	< 0.001	0.54	0.492	0.592	< 0.001	0.656	0.564	0.763	< 0.001
Usual BMI(kg/m^2)													
	< 18.5	1				1				1			

Table 2 (continued)

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
	18.5–22.9	0.831	0.766	0.903	< 0.001	0.836	0.756	0.923	< 0.001	0.817	0.706	0.945	< 0.001
	23–27.4	0.731	0.674	0.794	< 0.001	0.725	0.657	0.801	< 0.001	0.739	0.638	0.856	< 0.001
	≥ 27.5	0.737	0.674	0.807	< 0.001	0.719	0.645	0.801	< 0.001	0.784	0.664	0.927	0.004
Weight loss as % of usual weight													
	None	1				1				1			
	0–10	1.295	1.244	1.348	< 0.001	1.303	1.245	1.364	< 0.001	1.263	1.164	1.371	< 0.001
	> 10	1.864	1.776	1.956	< 0.001	1.903	1.798	2.014	< 0.001	1.771	1.615	1.942	< 0.001
H Pylori infection													
	Negative	1				1				1			
	Positive	0.982	0.872	1.105	0.763	1.056	0.922	1.209	0.432	0.782	0.61	1.001	0.051
Primary tumor location													
	Proximal	1				1				1			
	Distal	0.852	0.822	0.884	< 0.001	0.847	0.813	0.882	< 0.001	0.904	0.833	0.981	0.016
	Total	1.577	1.468	1.693	< 0.001	1.534	1.413	1.665	< 0.001	1.76	1.52	2.038	< 0.001
Lauren type													
	Intestinal	1				1				1			
	Diffuse	1.598	1.487	1.717	< 0.001	1.601	1.474	1.738	< 0.001	1.847	1.567	2.177	< 0.001
	Mixed	1.282	1.182	1.391	< 0.001	1.271	1.163	1.39	< 0.001	1.397	1.146	1.703	0.001
	Unknown	1.54	1.449	1.637	< 0.001	1.471	1.376	1.573	< 0.001	1.982	1.702	2.308	< 0.001
Signet ring cell													
	Yes	1				1				1			
	No	0.779	0.743	0.816	< 0.001	0.765	0.723	0.809	< 0.001	0.784	0.717	0.856	< 0.001
Type of gastrectomy													
	Gastrectomy	1				1				1			
	No surgery	3.368	3.251	3.488	< 0.001	3.255	3.125	3.391	< 0.001	3.674	3.426	3.94	< 0.001
Surgical Margin													
	Negative	1				1				1			
	Positive	2.144	1.935	2.374	< 0.001	2.043	1.81	2.307	< 0.001	2.457	2.031	2.974	< 0.001
Pathologic T stage													
	T0 + Tis												
	T1	1				1				1			
	T2	1.889	1.672	2.135	< 0.001	1.751	1.526	2.009	< 0.001	2.316	1.776	3.019	< 0.001
	T3	4.613	4.183	5.086	< 0.001	4.079	3.654	4.553	< 0.001	6.64	5.371	8.209	< 0.001
	T4	6.028	5.498	6.609	< 0.001	5.412	4.878	6.005	< 0.001	8.261	6.774	10.073	< 0.001
Pathologic N stage													
	N0	1				1				1			
	N1	1.789	1.666	1.922	< 0.001	1.794	1.654	1.945	< 0.001	1.742	1.496	2.029	< 0.001

Table 2 (continued)

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
	N2	2.769	2.595	2.955	< 0.001	2.717	2.523	2.927	< 0.001	2.905	2.534	3.331	< 0.001
	N3	4.514	4.263	4.779	< 0.001	4.35	4.074	4.645	< 0.001	5.026	4.468	5.655	< 0.001
Pathologic M stage													
	M0	1				1				1			
	M1	3.803	3.62	3.995	< 0.001	3.666	3.459	3.887	< 0.001	4.146	3.783	4.547	< 0.001
Pathologic TNM stage													
	0												
	I	1				1				1			
	II	2.693	2.456	2.954	< 0.001	2.472	2.231	2.74	< 0.001	3.709	2.998	4.588	< 0.001
	III	6.22	5.73	6.752	< 0.001	5.544	5.063	6.071	< 0.001	9.374	7.726	11.372	< 0.001
	IV	15.702	14.349	17.183	< 0.001	13.828	12.494	15.304	< 0.001	24.271	19.796	29.758	< 0.001
HER-2													
	Negative	1				1				1			
	+	0.82	0.773	0.871	< 0.001	0.836	0.781	0.895	< 0.001	0.769	0.681	0.869	< 0.001
	++	0.802	0.741	0.868	< 0.001	0.809	0.74	0.884	< 0.001	0.76	0.638	0.907	< 0.001
	+++	0.961	0.873	1.058	0.415	0.953	0.856	1.061	0.377	1.009	0.81	1.256	0.936
Linitis plastica													
	Yes	1				1				1			
	No	0.433	0.395	0.475	< 0.001	0.482	0.427	0.545	< 0.001	0.371	0.322	0.427	< 0.001
Grade													
	Poorly	1				1				1			
	Poorly-Moderately	0.881	0.838	0.926	< 0.001	0.885	0.837	0.937	< 0.001	0.815	0.732	0.908	< 0.001
	Moderately	0.736	0.696	0.777	< 0.001	0.74	0.696	0.787	< 0.001	0.668	0.588	0.758	< 0.001
	Well-Moderately	0.527	0.459	0.605	< 0.001	0.52	0.446	0.606	< 0.001	0.521	0.375	0.726	< 0.001
	Well	0.37	0.314	0.436	< 0.001	0.365	0.304	0.438	< 0.001	0.388	0.265	0.567	< 0.001
	Undifferentiated	1.019	0.509	2.039	0.957	1.313	0.625	2.756	0.472				
Nerve invasion													
	Yes	1				1				1			
	No	0.474	0.452	0.497	< 0.001	0.494	0.468	0.522	< 0.001	0.423	0.384	0.466	< 0.001
Vascular invasion													
	Yes	1				1				1			
	No	0.533	0.511	0.555	< 0.001	0.521	0.497	0.547	< 0.001	0.574	0.528	0.624	< 0.001
ELNs													
	< 30	1				1				1			
	≥ 30	1.045	0.996	1.096	0.074	1.066	1.008	1.127	0.025	0.991	0.899	1.092	0.85
Perioperative therapy													
	Yes	1				1				1			

Table 2 (continued)

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
	No	0.772	0.73	0.817	< 0.001	0.785	0.736	0.838	< 0.001	0.751	0.667	0.844	< 0.001
Postoperative complications													
	Yes	1				1				1			
	No	0.714	0.646	0.79	< 0.001	0.723	0.646	0.81	< 0.001	0.691	0.555	0.86	0.001

in four gastric cancer cohorts. To avoid the risk of error in survival outcomes due to different treatment methods, we further analyzed two detailed subgroups: gastrectomy patients, and no surgery patients. In this study, we found that female patients with gastric cancer had better prognosis than male patients. Smoking history only affected the prognosis of female patients, while BMI at diagnosis, usual BMI and the amount of smoking were only independent prognostic factors for male patients.

Gastric cancer is closely related to sex. Statistically, the incidence of gastric cancer in males is almost twice as high as in females [2]. The effect of sex factor on the prognosis of gastric cancer has also been extensively studied, but several controversies about the result still remained. In most studies, female patients had a better prognosis than males [3–12]. However, several other studies showed that sex had no prognostic effect on OS [13–16]. Three studies even demonstrated that males with gastric cancer had a better prognosis than female patients [17–19]. Our study showed that female patients had a slightly better prognosis than male patients. Some studies believed the difference in prognosis between females and males could be related to the type of gastric cancer [11, 29, 30]. They found proximal and cardiac gastric cancer were more likely to be males, which was consistent with our research, and patients with these types of gastric cancer had a poorer prognosis than patients with distal and non-cardiac gastric cancer. One study suggested androgen receptors (AR) might play an important role in the prognosis of gastric cancer [12]. AR could play the role of oncoprotein when accepted the action of androgens, including regulation of cell proliferation and tumour growth. These reactions might be a major cause of poor prognosis in male patients. In addition, AR could provide conditions for the occurrence and progression of tumors by activating cyclin-dependent kinases (CDKs) and the vascular endothelial growth factor (VEGF) gene. The expression of tumour suppressor genes p53 and p27 could be inhibited by the AR, leading to differentiation and proliferation of gastric cancer cells. Another study found AR-positive cells were only absent from samples of female gastric cancer patients with T1 and T2 stage, which might be the reason why we found that females had better OS than males in patients with early pTNM stage in our study [31]. Anyway, our study clearly demonstrates statistically significant and clinically relevant sex differences in tumor characteristics and survival among gastric cancer patients. Therefore, the consideration of sex disparity in cancer prevention education and treatment decisions is necessary.

Our study suggested that weight loss > 10% was significantly related to the prognosis of gastric cancer in both male and female patients. One previous study noted that this result might be related to the comparatively

aggressive potential of the tumor in patients who lost weight, wherein the physical condition of being underweight did not cause a progression of the tumor, but rather the progression of the tumors brought about the weight loss [32]. In our study, we found underweight before developing gastric cancer was not associated with the prognosis of gastric cancer, which partly supported this opinion. Weight loss may be due to dysphagia, odynophagia, anorexia or cancer cachexia as gastric cancer progresses to more advanced stages [33, 34]. The more advanced stages the gastric cancer patients were, the greater surgical manipulation they required, and the higher risk for bleeding that requires a transfusion they had [32]. In additions, human adipose tissue may have the function of preserving nutrients and increase the chance of survival, thus it has a negative effect on survival when weight lost [24, 35, 36].

Although overweight and obesity are considered an important risk factor for the development of cancer, their presence appears to be a paradoxical protective factor for survival in patients [35]. Our study showed this phenomenon known as the obesity paradox, and was consistent with most previous research [23, 24, 33, 37–39]. To our surprise, after stratified by gender, this phenomenon was only observed in male patients. No study has yet concluded that the obesity paradox has sex disparity in gastric cancer patients. However, one study found that only male patients seemed to contribute to the obesity paradox observed in patients with acute coronary syndromes [40]. Another study showed that obesity was associated with improved prognosis of metastatic melanoma, driven by strong associations observed only in male patients treated with targeted or immune therapy [41]. And they believed it was due to different hormone levels in obese patients between the sexes. However, in the recent study, some researchers have suggested that obesity or adipose tissue is not associated with the prognosis of cancer [42, 43]. Though BMI is widely-used to measure obesity, it may misclassify body composition (fat versus muscle). The real factor associated with the prognosis was skeletal muscle mass rather than fat. However, BMI still holds significant predictive value for the prognosis of gastric cancer patients according to the results of our study. The consideration of BMI in treatment decisions is conducive to the individualization of gastric cancer patients.

The effect of smoking on the prognosis of gastric cancer has long been investigated. Most previous studies demonstrated that cigarette consumption might bring an adverse effect on the prognosis [20, 22, 44–49], but there were also some studies that showed no relationship between smoking and the prognosis [50–52]. One study even found an unexpected association between smoking and better survival in gastric cancer patients [21]. Consistent with most previous studies, our study suggested that smoking was associated with a poor prognosis for gastric cancer. In one study, cigarette smoke exposure could increase TxA2 release [20]. TxA2 mediated diverse biologic effects, such as platelet activation, cell contraction and angiogenesis, which might facilitate tumor growth and metastasis in smokers. In addition, nicotine is one of the main ingredients in cigarettes. Although nicotine was not carcinogenic by itself, it induced proliferation and angiogenesis in several preclinical models [53–55]. Moreover, smoking had an adverse impact on the pulmonary, circulatory, and immunologic systems, and on wound healing, which might reduce the effect of gastrectomy or other treatments [56, 57]. However, the impact of cigarette consumption was different between the sexes. Female patients with smoking history had a worse prognosis than non-smokers, regardless of how much they smoked in our study. Among male patients, smoking only had adverse effects if they smoked more than 40 cigarettes per day. Although the exact mechanism was unclear, the reason could be that females were more susceptible to the adverse effects of smoking as a result of biological differences, such as immunological or hormonal determinants [58–65]. As such, prediagnosis smoking habits might contribute to the development of cancer also appear to exert an influence on cancer outcomes. Quitting smoking promptly is critical not only for cancer prevention but also for improving overall outcomes.

There are many available studies regarding the prognostic effect of drinking on gastric cancer, but the results were inconsistent. Some studies believed alcohol consumption was associated with poor prognosis [21, 44, 66, 67], but others showed drinking had few impacts in the survival of gastric cancer patients [22, 48, 50, 51, 68]. Our study showed there was no significant association between drinking and long-term prognosis, regardless of the amount and duration of alcohol consumption. As such, the association between alcohol consumption and the prognosis of gastric cancer still needs further study.

The history of Hp infection has always been a high-risk factor for gastric cancer [2]. However, its effect on prognosis has not yet been established. There were many studies that believed Hp infection would develop the progress or lead to the recurrence of gastric cancer, which brought poor prognosis for gastric cancer patients [28, 69–72]. One study found Hp infection was significantly associated with heparanase expression, which might promote the invasion and metastasis of gastric cancer and cause a poorer prognosis in the end [73]. In another study, the effects of Hp infection on gastric cancer were as follows: it caused DNA damage and affected the repair of the tumor microenvironment (TME) to the damage, activated the oncogenic signaling pathways to promote cancer growth, and modulated the immune environment

Table 3 Multivariate analysis of all gastric cancer patients of four cohorts

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
Sex													
	Male	1											
	Female	0.938	0.881	0.999	0.046								
Age at diagnosis (years)													
	18–34	1				1				1			
	35–50	0.884	0.753	1.038	0.131	0.871	0.695	1.091	0.229	0.906	0.719	1.143	0.406
	51–64	0.932	0.798	1.089	0.375	0.942	0.757	1.172	0.592	0.933	0.744	1.17	0.549
	≥65	1.306	1.116	1.527	0.001	1.35	1.084	1.682	0.007	1.208	0.956	1.526	0.114
Smoking history													
	Yes	1				1				1			
	Never	0.976	0.917	1.04	0.461	1.01	0.946	1.079	0.761	0.782	0.616	0.993	0.044
Smoking years													
	Short-term (1–10 year)	1				1				1			
	Mid-term (11–20 year)	1.051	0.9	1.228	0.527	1.053	0.897	1.235	0.531	1.485	0.685	3.218	0.317
	Long-term (20 yr+)	1.064	0.919	1.232	0.408	1.068	0.919	1.243	0.391	1.386	0.64	3	0.408
No. of cigarettes (per day)													
	≤20 (≤1 pack)	1				1				1			
	21–39	0.941	0.8	1.108	0.467	0.913	0.79	1.098	0.395	4.656	0.959	22.601	0.056
	≥40 (≥2 packs)	1.166	1.021	1.33	0.023	1.182	1.035	1.35	0.013	0.301	0.065	1.382	0.123
Drinking history													
	Yes	1				1				1			
	Never	0.96	0.9	1.025	0.221	0.945	0.884	1.01	0.095	1.189	0.89	1.587	0.242
Drinking years													
	Short-term (1–10 year)	1				1				1			
	Mid-term (11–20 year)	1.026	0.86	1.224	0.777	1.021	0.853	1.221	0.823	1.306	0.301	5.677	0.721
	Long-term (20 yr+)	1.143	0.974	1.341	0.102	1.156	0.982	1.361	0.081	0.394	0.096	1.617	0.196
Amount of alcohol consumption													
	Light drinkers (1–50 ml)	1				1				1			
	Moderate drinkers (51–100 ml)	0.966	0.827	1.128	0.659	0.97	0.828	1.136	0.704	0.967	0.202	4.626	0.967
	Heavy drinkers (100 ml+)	1.053	0.917	1.209	0.463	1.043	0.907	1.199	0.558	4.211	0.706	25.113	0.115
BMI(kg/m^2) at diagnosis													
	<18.5	1.161	1.055	1.277	0.002	1.145	1.019	1.286	0.023	1.167	0.917	1.484	0.21
	18.5–22.9	1				1				1			
	23–27.4	0.88	0.834	0.928	<0.001	0.875	0.824	0.93	<0.001	0.95	0.843	1.07	0.398
	≥27.5	0.821	0.756	0.89	<0.001	0.807	0.735	0.886	<0.001	0.976	0.834	1.143	0.765
Usual BMI(kg/m^2)													
	<18.5	1.134	0.994	1.293	0.062	1.116	0.953	1.306	0.173	1.167	0.917	1.484	0.21

Table 3 (continued)

Characteristics		Total				Male				Female			
		HR	95%CI		*P* value	HR	95%CI		*P* value	HR	95%CI		*P* value
			low	high			low	high			low	high	
	18.5–22.9	1				1				1			
	23–27.4	0.894	0.844	0.947	< 0.001	0.878	0.821	0.938	< 0.001	0.95	0.843	1.07	0.398
	≥ 27.5	0.878	0.813	0.948	0.001	0.856	0.784	0.935	0.001	0.976	0.834	1.143	0.765
Weight loss as % of usual weight													
	None	1				1				1			
	0–10	1.037	0.98	1.098	0.208	1.086	0.96	1.228	0.19	1.116	0.99	1.256	0.071
	> 10	1.288	1.194	1.39	< 0.001	1.433	1.203	1.708	< 0.001	1.291	1.118	1.491	0.001
Location													
	Proximal	1				1				1			
	Distal	0.85	0.806	0.896	< 0.001	0.857	0.808	0.91	< 0.001	0.815	0.725	0.916	0.001
	Total	1.277	1.137	1.434	< 0.001	1.287	1.126	1.471	< 0.001	1.204	0.951	1.525	0.123
Type of gastrectomy													
	Gastrectomy	1				1				1			
	No surgery	1.402	1.133	1.734	0.002	1.398	1.095	1.785	0.007	1.552	1.006	2.396	0.047
Grade													
	Poorly	1				1				1			
	Poorly-Moderately	0.9	0.848	0.956	0.001	0.927	0.867	0.992	0.029	0.806	0.701	0.926	0.002
	Moderately	0.822	0.765	0.883	< 0.001	0.859	0.793	0.929	< 0.001	0.675	0.569	0.801	< 0.001
	Well-Moderately	0.698	0.578	0.843	< 0.001	0.686	0.557	0.845	< 0.001	0.721	0.465	1.116	0.142
	Well	0.748	0.605	0.924	0.007	0.682	0.539	0.862	0.001	1.123	0.682	1.851	0.647
	Undifferentiated	1.499	0.672	3.344	0.323	1.801	0.807	4.019	0.151				
Signet ring cell													
	Yes	1				1				1			
	No	0.859	0.81	0.91	< 0.001	0.857	0.801	0.917	< 0.001	0.861	0.77	0.962	0.008
Pathologic TNM stage													
	0												
	I	1				1				1			
	II	2.461	2.211	2.74	< 0.001	2.21	1.963	2.488	< 0.001	3.854	2.978	4.989	< 0.001
	III	5.77	5.238	6.356	< 0.001	5.012	4.506	5.574	< 0.001	9.901	7.808	12.556	< 0.001
	IV	12.824	10.962	15.003	< 0.001	10.499	8.676	12.585	< 0.001	23.921	17.371	32.94	< 0.001

within the TME [74]. However, more studies have found the opposite that Hp positive status was associated with better outcome [26, 27, 75–86]. Those studies suggested that although Hp infection increased the risk of gastric cancer, the histological type of gastric cancer induced by Hp was associated with a better prognosis [75, 77, 86]. And they believed the immune change caused by Hp infection was beneficial to the prognosis of gastric cancer patients [26, 78, 82]. In addition, some studies found that there was no relationship between Hp infection and the prognosis of gastric cancer [87–89], which were consistent with our research.

One of the main strengths of this study is the large number of patients included, which allows the identification of sex differences with clinical relevance and statistical significance. Another strength is we analyzed three groups included total patients, gastrectomy, and no surgery groups, which avoids the risk of error in survival outcomes due to different treatment methods. However, when interpreting the findings of this study, several potential limitations need to be considered. Firstly, many patients may change their lifestyle after the diagnosis of gastric cancer, such as stopping or limiting their tobacco and alcohol consumption. This may lead to differences in survival due to lifestyle changes after diagnosis, which has a potential confounding effect on the result of our study. Secondly, the incorrect collection of smoking and drinking history in patients with gastric cancer may occur when lifestyle factors were collected in an indirect manner due to recall bias. Thirdly, the sample of no surgery patients was relatively small. Therefore, the results might not be used as a reference for patients who cannot undergo surgery.

Conclusions

In conclusion, our study contributes to a better understanding of the effects of sex disparity and prediagnosis lifestyle factors on the long-term prognosis of gastric cancer. Female gastric cancer patients had a better prognosis than male patients. For prediagnosis lifestyle factors, BMI at diagnosis, usual BMI and the amount of smoking were statistically associated with the prognosis of gastric cancer patients, but drinking and the history of Hp infection were not related to survival outcomes. Female patients with smoking history were at increased risk of poorer survival than who never smoke. Male patients who smoked more than 40 cigarettes per day had a worse prognosis than other male patients. Obesity paradox was only observed in male patients. Further investigation is needed to elucidate mechanisms targeting the complex effects of sex and prediagnosis lifestyle factors on prognosis.

Supplementary Information

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Supplementary Material 1

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All authors made substantial contributions to the intellectual content of this paper.

Author contributions

Luan X.Y. : Writing-original draft, Data curation; Zhao L.L. : Writing-original draft, Visualization; Zhang F. : Resources; Wang W.Q. : Formal analysis; Jiao F.Z. : Resources; Zhou X.D. : Resources; Niu P.H. : Formal analysis; Han X. : Data curation; Zhang X.J. : Writing-review & editing; Zhao D.B. : Writing-review & editing, Supervision; He M.Y. : Resources, Supervision; Guan Q.L. : Resources, Supervision; Li Y.M. : Resources, Supervision; and Chen Y.T. : Conceptualization, Resources, Methodology, Writing-review & editing, Supervision. All authors discussed the findings and approved the final version of the manuscript.

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Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethical approval and consent to participate

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. This study was approved by the ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17–156/1412), and waived the requirement for an informed consent due to the anonymous nature of the data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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