

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 June 6; 10(16): 5124-5517



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

June 6, 2022

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Retrospective Study

## Protective effects of female reproductive factors on gastric signet-ring cell carcinoma

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**Specialty type:** Gastroenterology and hepatology**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind**Peer-review report's scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Lee KS, South Korea; Sudo T, Japan**Received:** September 14, 2021**Peer-review started:** September 14, 2021**First decision:** October 18, 2021**Revised:** October 21, 2021**Accepted:** April 9, 2022**Article in press:** April 9, 2022**Published online:** June 6, 2022

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**Abstract****BACKGROUND**

The overall incidence of gastric cancer is higher in men than women worldwide. However, gastric signet-ring cell carcinoma (GSRC) is more frequently observed in younger female patients.

**AIM**

To analyze clinicopathological differences between sexes in GSRC, because of the limited evidence regarding association between sex-specific differences and survival.

**METHODS**

We reviewed medical records for 1431 patients who received treatment for GSRC at the Cancer Hospital, Chinese Academy of Medical Sciences between January 2011 and December 2018 and surveyed reproductive factors. Clinicopathological characteristics were compared between female and male patients. Cox multivariable model was used to compare the mortality risks of GSRC among men, menstrual women, and menopausal women.

**RESULTS**

Of 1431 patients, 935 patients were male and 496 were female (181 menstrual and 315 menopausal). The 5-year overall survival in male, menstrual female and menopausal female groups was 65.6%, 76.5% and 65%, respectively ( $P < 0.01$ ). Menstruation was found to be a protective factor (hazard ratio = 0.58, 95% confidence interval: 0.42–0.82).

**CONCLUSION**

The mortality risk of GSRC in menstrual women was lower than that in men. This study identified the protective effects of female reproductive factors in GSRC.

**Key Words:** Gastric carcinoma; Signet-ring cell; Female reproductive factor; Menopause

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**Core Tip:** The overall incidence of gastric cancer is higher in men than in women worldwide. However, gastric signet-ring cell carcinoma (GSRC) is more frequently observed in younger female patients. Only a few studies have focused on sex-specific differences in GSRC. This study proposed clinicopathological differences between sexes to reveal sex disparities in GSRC and confirmed that female reproductive factors provided protective effects, and the mortality risk of menstrual female patients was lower. Investigation of the mechanism of action of female reproductive factors may provide new insight into the treatment of GSRC.

**Citation:** Li Y, Zhong YX, Xu Q, Tian YT. Protective effects of female reproductive factors on gastric signet-ring cell carcinoma. *World J Clin Cases* 2022; 10(16): 5217-5229

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i16/5217.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i16.5217>

## INTRODUCTION

Gastric cancer (GC) is the fifth most common adenocarcinoma and ranks third in mortality worldwide [1]. In China, an estimated 390000 people die of GC annually, which accounts for > 50% of the global deaths and imposes a severe health burden[1-3]. Commonly, the age-standardized incidence rates of GC have shown a male predominance with the male-to-female rate of more than 2:1 in most populations around the world[1,4]. The difference, however, cannot be entirely attributed to the different prevalence of established major risk factors, such as tobacco smoking[5] and *Helicobacter pylori* infection[6] between the sexes. A study reported that incidence of intestinal GC after menopause increased with time, and the incidence 10 years after menopause was comparable to that of men[7]. An umbrella review including 616 630 women in six observational studies showed that menopausal hormonal therapy was associated with decreased risk of GC[8]. The female reproductive factors and sex hormones may have protective effects on gastric adenocarcinoma.

Gastric signet-ring cell carcinoma (GSRC) is a distinct type of GC, and its incidence has been steadily increasing in Asia, Europe, and the United States, accounting for > 30% of new gastric adenocarcinoma cases[9]. GSRC belongs to the diffused, undifferentiated, and poorly differentiated types in the Laurén classification, Nakamura's classification, and Japanese Gastric Cancer Association, respectively[10-13]. GSRC in early and advanced stages is more frequently observed in younger female patients than gastric adenocarcinoma[14]. A contradiction with the protective effect of female reproductive factors on gastric adenocarcinoma seems to exist. There is also evidence that female reproductive factors induce diffuse-type GC through estrogen activity[7].

Moreover, various reproductive factors have provided contradictory results in relation to the risk of GCs. The protective effects of female reproductive factors imply the potential role of sex hormones in carcinogenesis. Importantly, the explanation for the predominance of GSRC in young women might provide significant clues to the etiology of the tumors and pave the way for research on innovative prevention and treatment. The effect of female reproductive factors on GSRC tumorigenesis and tumor development remains unclear despite the advances in the understanding of its epidemiology and clinicopathology. The purpose of this study was to estimate the effects of female reproductive factors on the prognosis and combined modality treatment of GSRC.

## MATERIALS AND METHODS

### *Study population and follow-up duration*

Our study involved 1431 participants who were histologically confirmed with GC with signet-ring cells and underwent curative resection between January 2011 and December 2018 at the Cancer Hospital, Chinese Academy of Medical Sciences, China. Subtotal gastrectomy was performed for distal GCs, whereas total gastrectomy was conducted for proximal-third GCs. Patients with definitive signs of distant organ or peritoneal seeding metastases did not undergo gastrectomy and were referred for

evaluation for chemotherapy instead. Based on the National Comprehensive Cancer Network Clinical Practice Guidelines, standard D2 lymphadenectomy was achieved in patients with curative intention [15]. All the surgical specimens were confirmed separately and independently by at least two experienced pathologists. Disagreements were resolved by discussion, especially on the proportion of signet-ring cells. The follow-up data were prospectively collected and regularly updated by surgeons every 6 mo after surgery. The overall survival was defined from the date of gastrectomy to the date of death or the end of follow-up period (April 30, 2020).

### Measurements

The demographic characteristics included age and body mass index (BMI). We considered age as an ordinal variable (< 50, 50–60, and ≥ 60 years) to approximate tertiles. We defined BMI based on the standard cutoff points established by the Work Group on Obesity in China in categories of underweight and normal: ≤ 24 kg/m<sup>2</sup>, overweight and obese: > 24.0 kg/m<sup>2</sup>[16]. Health-related lifestyle indicators, including alcohol consumption (yes: Any alcoholic beverage consumption in the last 12 mo, or no: No alcohol consumption in the last 12 mo) and smoking (yes: Any regular tobacco consumption, or no: Never smoked), were excluded from the analysis based on the variable selection outcome of best-subset selection approach and the uneven distribution. We categorized the proportion of signet-ring cells as ≤ 10%, 10%–50%, 50%–90%, and > 90%, but we used the proportion of signet-ring cells as a dichotomous variable (≤ 50% and > 50%) in the adjustments for confounding variables and to ensure that each level had a sufficient number of observations. Clinicopathological characteristics, such as BMI, proportion of signet-ring cells, T stage, N stage, adjuvant chemotherapy, neoadjuvant chemotherapy, nerve invasion, and lymphatic vessel invasion were subjected to analysis since they were closely associated with the survival of GC patients with signet-ring cell carcinoma based on *a priori* knowledge.

### Statistical analysis

The continuous variables were expressed as mean ± SD, while categorical variables were expressed as number of observations and percentages (%). Differences in the potential covariates between the sex groups were assessed by Wilcoxon–Mann–Whitney test for continuous variables and the  $\chi^2$  test for categorical variables. The proportional hazards assumption was estimated, and the Cox multivariable model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the sex factors and survival of GC patients with signet-ring cell carcinoma. The model was adjusted for following potential covariates: BMI, proportion of signet-ring cells, T stage, N stage, adjuvant chemotherapy, neoadjuvant chemotherapy, nerve invasion, and lymphatic vessel invasion. Subgroup analyses were conducted by (1) BMI; (2) Signet-ring cells proportion; (3) Adjuvant chemotherapy; (4) Neoadjuvant chemotherapy; (5) Nerve invasion; and (6) Lymphatic vessel invasion to explore if the impact of the sex difference was stronger in certain groups. Interaction terms between exposures and these covariates were added into the multivariable model, and Wald tests were used to examine whether the interaction terms were statistically significant. The survival curves were estimated by the Kaplan–Meier method. In the present analysis, two-sided  $P < 0.05$  was considered to indicate statistically significant differences. All statistical analyses (and figures created) were performed with Stata 15.0 (StataCorp LLC: College Station, TX, United States).

## RESULTS

### Clinicopathological features of GSRC in male and female patients

Table 1 displays the distributions of the demographic and potential risk factors by sex difference. Of the 1431 GC patients with signet-ring cell carcinoma, 935 (65.3%) were male, and 496 (34.7%) were female. Overall, over one-third of the participants were aged ≥ 60 (42.0%) years, with a mean age of 56.3 (SD: 11.3) years. There were no significant differences between the sex groups in terms of histological differentiation, N stage, and adjuvant or neoadjuvant chemotherapy ( $P > 0.05$ ). The female subjects were more likely to be: younger, nonsmokers and nondrinkers; with diffuse Lauren type, T1 stage and metastasis; without nerve and lymphovascular invasion; and have middle and lower tumor location, lower BMI, higher signet-ring cells proportion, and more lymph nodes removed ( $P < 0.05$ ).

The Cox proportional hazards regression model results are presented in Table 2. Overall, the menstrual women had a significantly lower risk of mortality (HR = 0.58, 95%CI: 0.42–0.82) than male patients in the multivariable model. We did not observe this protective effect in menopausal women (HR = 0.91, 95%CI: 0.72–1.14).

### Subgroup analysis in the different sex groups with GSRC

Other variables associated with the overall survival included BMI, T stage, N stage, adjuvant or neoadjuvant chemotherapy, and lymphovascular invasion. The results of the subgroup analyses (Table 3) showed that the impact of menstruation was more significant in the female participants with lower levels of signet-ring cells (HR = 0.56, 95%CI: 0.38–0.82,  $P$ -interaction = 0.038), nerve invasion (yes

**Table 1 Characteristics of 1431 gastric cancer patients with signet ring cells**

Characteristics	Overall (n = 1431, %)	Male (n = 935, 65.3%)	Female (n = 496, 34.7%)	P value <sup>1</sup>
Age (yr)				
mean ± SD	56.3 ± 11.3	57.5 ± 10.7	54.2 ± 12.1	< 0.01
< 50	386 (27.0)	213 (55.2)	173 (44.8)	< 0.01
≥ 50, < 60	444 (31.0)	303 (68.2)	141 (31.8)	
≥ 60	601 (42.0)	419 (69.7)	182 (30.3)	
BMI (kg/m <sup>2</sup> )				
mean ± SD	23.8 ± 3.4	24.3 ± 3.4	22.9 ± 3.3	< 0.01
> 24	659 (46.1)	501 (76.0)	158 (24.0)	< 0.01
≤ 24	772 (54.0)	434 (56.2)	338 (43.8)	
Smoke				
No	822 (57.4)	346 (42.1)	476 (57.9)	< 0.01
Yes	609 (42.6)	589 (96.7)	20 (3.3)	
Drink				
No	821 (57.4)	354 (43.1)	467 (56.9)	< 0.01
Yes	610 (42.6)	581 (95.3)	29 (4.8)	
Tumor site <sup>2</sup>				
Upper	334 (23.3)	271 (81.1)	63 (18.9)	< 0.01
Middle	345 (24.1)	205 (59.4)	140 (40.6)	
Lower	662 (46.3)	416 (62.8)	246 (37.2)	
Others	90 (6.3)	43 (47.8)	47 (52.2)	
Histology differentiation				
Well-/moderately differentiated	29 (2.1)	22 (75.9)	7 (24.1)	0.23
Poorly/undifferentiated	1326 (97.9)	864 (65.2)	462 (34.8)	
Signet-ring cell proportion (%)				
≤ 10	155 (10.8)	117 (75.5)	38 (24.5)	0.02
> 10, ≤ 50	954 (66.7)	616 (74.6)	338 (35.4)	
> 50, ≤ 90	235 (16.4)	143 (60.9)	92 (39.2)	
> 90	87 (6.1)	59 (67.8)	28 (32.2)	
Lauren type				
Intestinal	73 (5.1)	61 (83.6)	12 (16.4)	< 0.01
Diffused	910 (63.6)	557 (61.2)	353 (38.8)	
Mixed	353 (24.7)	261 (73.9)	92 (26.1)	
Unknown	95 (6.6)	56 (59.0)	39 (41.0)	
T stage				
T1	411 (28.7)	246 (59.9)	165 (40.2)	0.02
T2	172 (12.0)	119 (69.2)	53 (30.8)	
T3	322 (22.5)	227 (70.5)	95 (29.5)	
T4	526 (36.8)	343 (65.3)	183 (34.8)	
N stage				
N0	573 (40.0)	365 (63.7)	208 (36.3)	0.54
N1	192 (13.4)	130 (67.7)	62 (32.3)	

N2	219 (15.3)	150 (68.5)	69 (31.5)	
N3	447 (31.2)	290 (64.9)	157 (35.1)	
Metastasis				< 0.01
No	1348 (94.2)	892 (66.2)	456 (33.8)	
Yes	83 (5.8)	43 (51.8)	40 (48.2)	
Adjuvant chemotherapy				0.51
No	924 (64.6)	598 (64.7)	326 (35.3)	
Yes	507 (35.4)	337 (66.5)	170 (33.5)	
Neoadjuvant chemotherapy				0.72
No	1315 (91.9)	861 (65.5)	454 (34.5)	
Yes	116 (8.1)	74 (63.8)	42 (36.2)	
Nerve invasion				0.02
No	313 (21.9)	184 (58.8)	129 (41.2)	
Yes	714 (49.9)	477 (66.8)	237 (33.2)	
Unknown	404 (28.2)	274 (67.8)	130 (32.2)	
Lymphovascular invasion				0.02
No	416 (29.1)	249 (59.9)	167 (40.1)	
Yes	554 (38.7)	373 (67.3)	181 (32.7)	
Unknown	461 (32.2)	313 (67.9)	148 (32.1)	
HER-2				0.28
Negative	1082 (85.3)	702 (64.9)	380 (35.1)	
Positive	187 (14.7)	129 (69.0)	58 (31.0)	
Lymph nodes removed				< 0.01
≤ 16	171 (12.0)	131 (76.6)	40 (23.4)	
> 16, ≤ 30	585 (40.9)	395 (67.5)	190 (32.5)	
> 30	675 (47.2)	409 (60.6)	266 (39.7)	

<sup>1</sup>The *P* values for age and BMI (continuous variables) were calculated from Wilcoxon–Mann–Whitney test; The *P* value for other categorical variables were calculated from  $\chi^2$  test.

<sup>2</sup>Tumor site was divided by upper (cardia, fundus, gastroesophageal junction), middle (body, lesser/greater curvature), lower (antrum, pylorus) and other (gastric remnant, anastomosis, linitis plastica) parts of the stomach.

*P* < 0.05 indicates statistical significance. Row percentage was reported for the overall sample. BMI: Body mass index; HER-2: Human epidermal growth factor receptor 2.

*vs* no, HR = 0.60, 95%CI: 0.40–0.89, *P*-interaction = 0.029), or lymphovascular invasion (yes *vs* no, HR = 0.49, 95%CI: 0.30–0.80, *P*-interaction < 0.001), or without adjuvant chemotherapy (HR = 0.38, 95%CI: 0.22–0.65, *P*-interaction < 0.001) or neoadjuvant chemotherapy (HR = 0.53, 95%CI: 0.36–0.77, *P*-interaction < 0.001). There was a reversal effect across the strata of BMI for menopausal women (crossover interactions).

### Comparison of overall survival in GSRC between the sexes

The survival curves in [Figure 1](#) depict the survival probability based on the sex difference. Menstrual female patients had a significantly better overall survival than the male and menopausal female groups (*P* < 0.01). Survival analysis showed better prognosis of menstrual female patients in the non-adjuvant chemotherapy group (*P* < 0.01) and the inadequate survival advantages of menstrual female patients in the adjuvant chemotherapy group (*P* = 0.73) ([Figure 2](#)). We compared overall survival between the sexes with different levels of signet-ring cells ([Figure 3](#)). Menstrual female patients had a survival advantage compared with male and menopausal female groups; however, this advantage was not significant in the GSRC group with > 50% signet-ring cells ([Supplementary Figure 1](#)).

**Table 2** Multivariate analysis for mortality risk in gastric cancer patients with signet ring cells

Variable	HR (95%CI) <sup>1</sup>	P value
Sex disparity		
Male	Ref	
Menstrual female	0.58 (0.42-0.82)	< 0.01
Menopausal female	0.91 (0.72-1.14)	0.42
BMI (kg/m <sup>2</sup> )		
> 24	Ref	
≤ 24	1.24 (1.02-1.51)	0.03
Signet-ring cell proportion (%)		
≤ 10	Ref	
> 10, ≤ 50	0.97 (0.72-1.32)	0.86
> 50, ≤ 90	0.79 (0.53-1.17)	0.25
> 90	1.03 (0.63-1.70)	0.90
T stage		
T1	Ref	
T2	1.58 (0.87-2.88)	0.13
T3	4.20 (2.57-6.84)	< 0.01
T4	5.96 (3.67-9.69)	< 0.01
N stage		
N0	Ref	
N1	1.30 (0.87-1.93)	0.195
N2	1.92 (1.34-2.75)	< 0.01
N3	3.29 (2.38-4.55)	< 0.01
Adjuvant chemotherapy		
No	Ref	
Yes	0.75 (0.62-0.91)	< 0.01
Neoadjuvant chemotherapy		
No	Ref	
Yes	2.34 (1.79-3.04)	< 0.01
Nerve invasion		
No	Ref	
Yes	1.50 (0.93-2.43)	0.10
Unknown	1.47 (0.88-2.46)	0.14
Lymphovascular invasion		
No	Ref	
Yes	1.39 (1.02-1.90)	0.04
Unknown	1.26 (0.89-1.80)	0.19

<sup>1</sup>The Cox model included gender, BMI, signet-ring cell proportion, T stage, N stage, adjuvant chemotherapy, neoadjuvant chemotherapy, nerve invasion, and lymphovascular invasion.

*P* < 0.05 indicates statistical significance. BMI: Body mass index.

Table 3 Associations of sex and risk of mortality among gastric cancer patients with signet-ring cells by subgroups

Variable	Male		Menstrual female		Menopausal female		P-interaction <sup>3</sup>
	n <sup>1</sup> (%)	HR (95%CI) <sup>2</sup>	n <sup>1</sup> (%)	HR (95%CI) <sup>2</sup>	n <sup>1</sup> (%)	HR (95%CI) <sup>2</sup>	
BMI (kg/m <sup>2</sup> )							0.014
> 24	501 (53.6)	Ref	41 (22.7)	0.56 (0.27–1.16)	117 (37.1)	1.04 (0.72–1.50)	
≤ 24	434 (46.4)	Ref	140 (77.4)	0.58 (0.39–0.85)	198 (62.9)	0.84 (0.62–1.12)	
Signet-ring cell proportion (%)							0.038
≤ 50	733 (78.4)	Ref	129 (71.3)	0.56 (0.38–0.82)	247 (78.4)	0.94 (0.74–1.21)	
> 50	202 (21.6)	Ref	52 (28.7)	0.73 (0.33–1.61)	68 (21.6)	0.74 (0.40–1.35)	
Adjuvant chemotherapy							< 0.001
No	598 (64.0)	Ref	119 (65.8)	0.38 (0.22–0.65)	207 (65.7)	1.01 (0.75–1.36)	
Yes	337 (36.0)	Ref	62 (34.3)	0.83 (0.53–1.29)	108 (34.3)	0.80 (0.56–1.16)	
Neoadjuvant chemotherapy							< 0.001
No	861 (92.1)	Ref	165 (91.2)	0.53 (0.36–0.77)	289 (91.8)	0.80 (0.35–1.82)	
Yes	74 (7.9)	Ref	16 (8.8)	0.97 (0.76–1.25)	26 (8.3)	0.65 (0.33–1.26)	
Nerve invasion							0.029 <sup>4</sup>
No	184 (19.7)	Ref	54 (29.8)	0.36 (0.07–1.86)	75 (23.8)	0.78 (0.27–2.27)	
Yes	477 (51.0)	Ref	87 (48.1)	0.60 (0.40–0.89)	150 (47.6)	0.91 (0.69–1.21)	
Unknown	274 (29.3)	Ref	40 (22.1)	0.65 (0.31–1.39)	90 (28.6)	0.95 (0.60–1.49)	
Lymphovascular invasion							< 0.00 <sup>4</sup>
No	249 (26.6)	Ref	70 (38.7)	0.89 (0.40–1.95)	97 (30.8)	1.13 (0.61–2.11)	
Yes	373 (39.9)	Ref	56 (30.9)	0.49 (0.30–0.80)	125 (39.7.2)	0.81 (0.59–1.10)	
Unknown	313 (33.5)	Ref	55 (30.4)	0.68 (0.37–1.23)	93 (29.5)	1.23 (0.80–1.91)	

<sup>1</sup>Column percentage was reported for the overall sample; percentage can differ slightly from 100% because of rounding.

<sup>2</sup>The Cox proportional hazards model included gender, BMI, signet-ring cell proportion, T stage, N stage, adjuvant chemotherapy, neoadjuvant chemotherapy, nerve invasion, and lymphovascular invasion.

<sup>3</sup>Wald test was used to examine the interaction term between sex (male, menstrual female, and menopausal female) and BMI, signet-ring cell proportion, adjuvant chemotherapy, neoadjuvant chemotherapy, nerve invasion, and lymphovascular invasion.

<sup>4</sup>The P value shows the outcome of interaction test between sex difference and nerve invasion (no *vs* yes) and lymphovascular invasion (no *vs* yes).

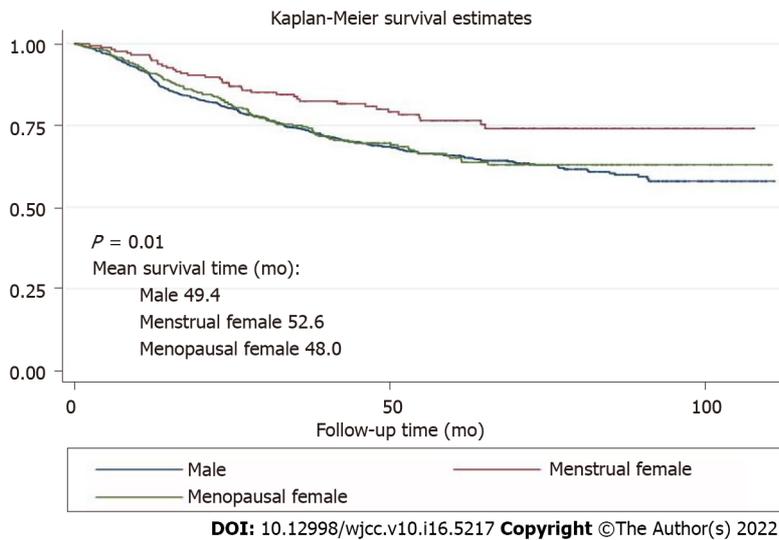
BMI: Body mass index. *P* < 0.05 indicates statistical significance.

## DISCUSSION

Although the incidence of GC has been decreasing, this disease remains the third cause of cancer mortality worldwide and in China. The proportion of GSRC in all GC cases has been increasing recently, especially in the young and female populations. There are obvious differences on morbidity of GSRC between the sexes. To find a new treatment and improve the overall survival of GSRC, this study has clinical significance to investigate the disparities of reproductive factors between male and female GSRC patients.

In this study, we focused on the influence of the sex-specific differences on the prognosis of GSRC. Our results showed that there was a stronger positive association with overall survival in menstrual female patients with GSRC, compared to that of the male or menopause female patients. The findings of the present large patient-based retrospective study may provide valuable insights into pathways for reducing GSRC mortality in the future.

The multivariate analysis results in our study showed that being a menstrual woman was a protective factor (HR = 0.58, 95%CI: 0.42–0.82) against GSRC. A similar effect was previously reported in various types of GCs[17,18]. In a study with 758 patients, Kim *et al*[7] proposed that female reproductive hormones might be a potentially protective factor against intestinal-type GC, and the incidence of intestinal-type GC after the menopause increased and became comparable to that in men. A Japanese study revealed that the risk of GC was lower in menstrual women (HR = 0.33, 95%CI: 0.23–0.49). Protective effects were observed in differentiated histological types (HR = 0.25, 95%CI: 0.11–0.55) and undifferentiated histological types (HR = 0.39, 95%CI: 0.23–0.63)[19]. The aforementioned consistent



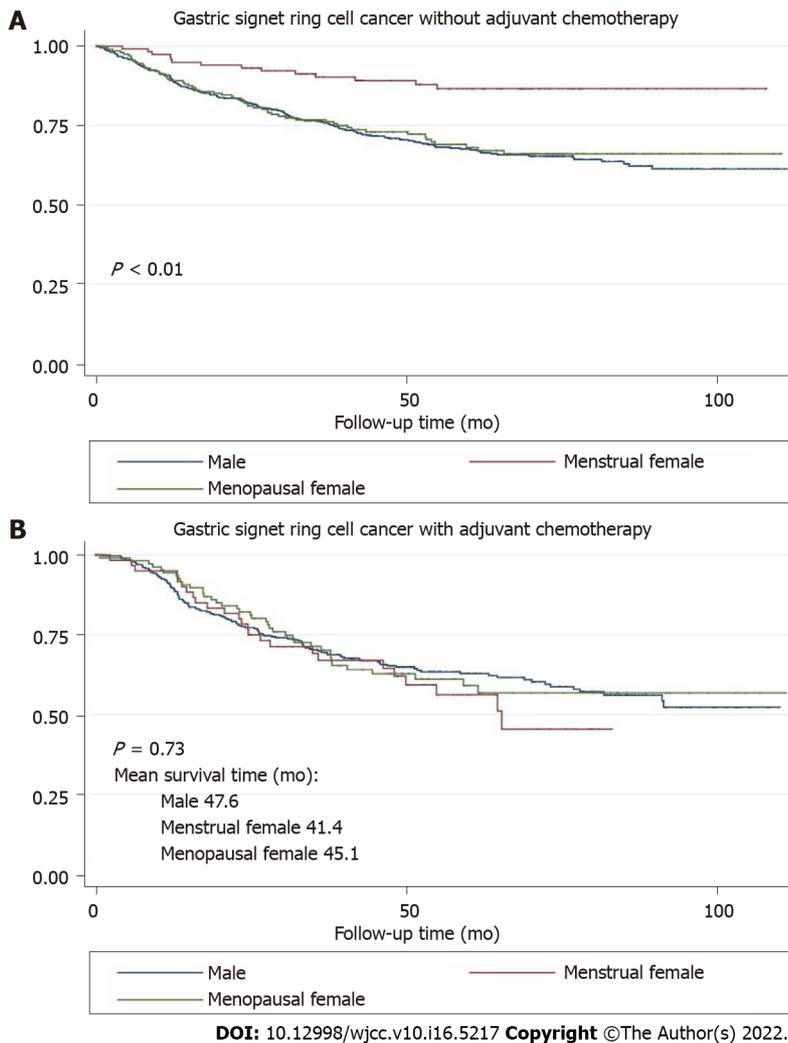
**Figure 1** Overall survival among male, menstrual female and menopausal female groups.

results demonstrate the effects of female reproductive factors in reducing the risks of different GCs. In a large Chinese prospective study with female subjects, the risks of GC increased with age of menopausal women (HR = 0.80 per 5-year increase in the menopausal age, 95%CI: 0.66–0.97)[20]. A similar finding was also obtained in a cohort study including 1 million women whose risks of GC in the menopausal age were considerably higher than those in the menstrual age (RR = 1.46, 95%CI: 1.07–2.0 and RR = 1.59, 95%CI: 1.15–2.20, respectively) from the United Kingdom[21]. Our results indicate that the effect of female reproductive factors on GSRC development is steady and robust.

Here, we hypothesize that sex hormones or their receptors, such as estrogen and estrogen receptor (ER), are the key inducers of the protective effects of female reproductive factors against GSRC. The influence of estrogen has been studied by other researchers, but the results were controversial[22]. Estrogens regulate the tissue growth, differentiation, and function, which is mediated by ER- $\alpha$  and ER- $\beta$ . The oncological importance of estrogen and ER in carcinomas occurring in the breast and ovaries has been investigated but not in GCs. The expression of ER in the stomach is a basis on which to explore the relationship between sex hormones and survival of GC. Some researchers have demonstrated the expression of ER in gastric tissues, which provides a basis for the probable functions of estrogen in this respect[23–25]. Hess *et al*[26] established that ERs and female sex hormones were expressed in the male reproductive tract and may have some functions. The protective effect of estrogen was discovered also in men who received hormonal therapy for prostate cancer; notably, the results showed a decrease risk of GC[27].

ER has several types, including ER $\alpha$ , ER $\beta$  and ER $\gamma$ . The biological actions of estrogen are mediated through two specific ERs, ER $\alpha$  and ER $\beta$ , which belong to the nuclear receptor superfamily[28]. Zhao *et al* [25] and Matsuyama *et al*[29] reported that both ER $\alpha$ , ER $\beta$  were expressed in poorly differentiated adenocarcinoma specifically in gastric signet-ring cell adenocarcinomas with characteristics of sex hormone dependency. Different effects of these two ER types were found in various studies. For example, Kameda *et al*[27] proposed that ER $\alpha$  expressed in diffuse-type GC promoted the proliferation of ER $\alpha$ -positive GC cells. The suggested mechanism was that the activation of the ER $\alpha$  pathway stimulated cancer cell proliferation by activating the hedgehog pathway in a ligand-dependent but dose-independent manner *via* Shh induction of diffuse-type GC. ER $\beta$  is homologous to ER $\alpha$ , particularly in the DNA-binding domain, but it is structurally and functionally different. ER $\beta$  manifested strong cytoplasmic staining with anti-ER $\beta$  antibody in addition to the stained nuclei[29]. This result provides evidence for the potential of GSRC treatment targets. Recently, using genomic analysis, Kang *et al*[29] identified ER $\gamma$  as a potential tumor suppressor in GC. The molecular mechanisms of its action suggest that the activation of ER $\gamma$  by the antagonizing Wnt signaling through DY131 could suppress GC cell growth and tumorigenesis. Studies on tumorigenesis regulated by estrogens or estrogen receptors are rare but will be urgently needed in the future.

Since chemoresistance is a distinct feature of GSRC, we noticed that the adjuvant chemotherapy was a protective factor in multivariate analysis. Then, we performed further subgroup analysis on adjuvant chemotherapy effects. Interestingly, protective effects exerted by female reproductive factors were observed only in the nonadjuvant chemotherapy group (HR = 0.38, 95%CI: 0.22–0.56) and the non-neoadjuvant chemotherapy group (HR = 0.53, 95%CI: 0.36–0.77). However, female reproductive factors lost their advantages and did not improve the survival after chemotherapy. It is possible that these conditions of poor survival and chemoresistance are mediated by female reproductive factors, such as ER $\alpha$  and ER $\beta$ , with unknown mechanism. Recently, Wang *et al*[30] proposed that the loss of ER $\beta$  in

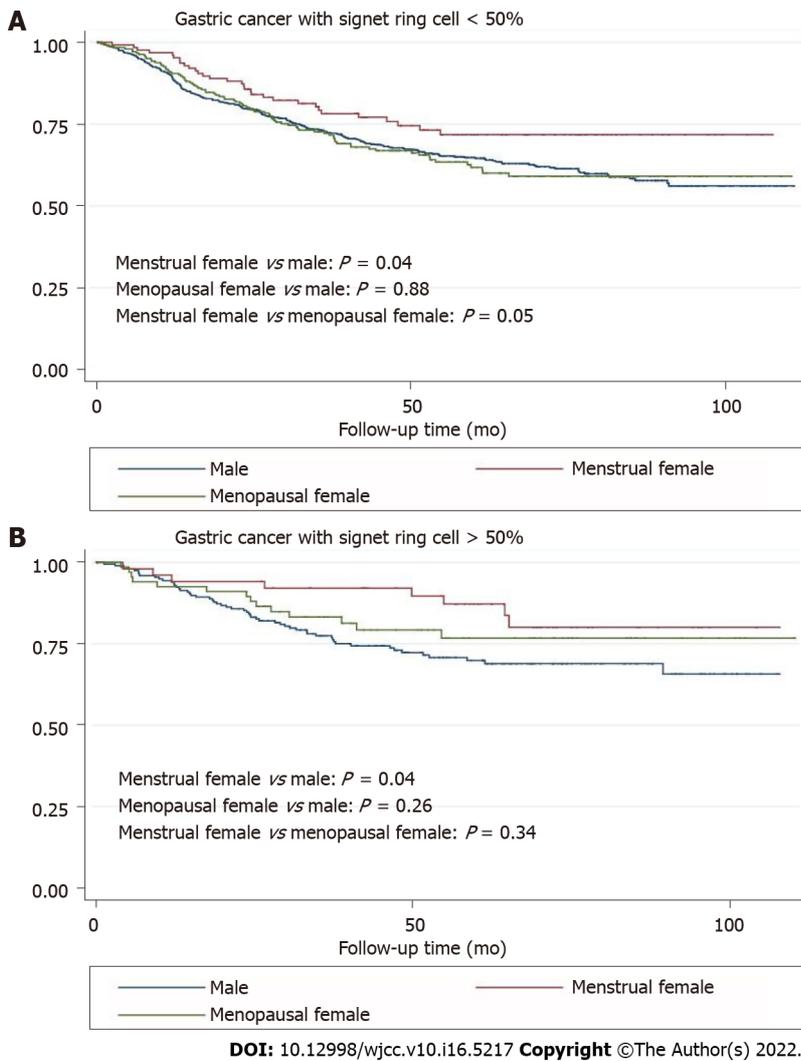


**Figure 2** Overall survival among male, menstrual female and menopausal female groups in subgroups without adjuvant chemotherapy (A) and with adjuvant chemotherapy (B).

GSRC cells might increase the potential for malignant invasion into the deep tissues easier through the mTOR signaling pathway. Therefore, ER $\beta$  might inhibit the malignancy of GSRC and can thus become a potential target in its adjuvant treatment. The investigation of Wang did not discuss the connection between ER $\beta$  and chemotherapy. We noticed that the prognostic trends are similar in all three studied groups. However, in the subgroup analysis of adjuvant chemotherapy, the mean survival time in the menstrual female group (41.4 mo) was the shortest compared to those of the male (47.6 mo) and menopausal female (45.1 mo) groups. We considered that the probable reason was the proportion of signet-ring cells in GCs. However, no association was identified between the signet-ring cell proportion and influence of female reproductive factors on the prognosis of subjects who received chemotherapy. The results of recent studies confirm the difficulties to understand the possible mechanism between sex hormones and chemoresistance in GSRC. However, more research on this topic needs to be undertaken to clearly elucidate the association between ER and chemotherapy outcomes.

We investigated the effects of female reproductive factors on the prognosis of the GSRC with various proportions of signet-ring cells. Being a menstrual female was a protective factor (HR = 0.56, 95%CI: 0.38–0.82) and was associated with better overall survival than that of menopausal women and men with GSRC cells < 50%. However, menstrual women lost their GSRC-associated advantages over menopausal women at a proportion of the signet-ring cells > 50%. We supposed that ER $\beta$  downregulation or ectopic expression in the cytoplasm could lead to a worse prognosis of GSRC with a higher proportion of signet-ring cells. Nevertheless, the probable mechanism remains unclear. Future studies on the topic are therefore highly recommended.

This is the first large population study focused on the relationship between female reproductive factors and GSRC with an 8-year follow-up. Our results highlight the significant effect of female reproductive factors on GSRC prognosis. The clinical importance of our present findings is critical as they have outlined the prognostic role of female reproductive factors in GSRC. Therefore, further strong evidence is provided which will increase the GSRC treatment effectiveness. In this study, we have also



**Figure 3 Overall survivals among male, menstrual female and menopausal female groups in subgroups with proportion of signet ring cells < 50% (A) and > 50% (B).**

investigated the effect of female reproductive factors on survival in a multidimensional aspect with robust statistics such as multivariable Cox proportional hazards model and different subgroups, which could considerably diminish the impact of confounders and explore the potential effect in a specific group.

Despite the aforementioned strengths of our study, several limitations have to be acknowledged. First, the data concerning the expression levels of ER and progesterone receptor (PR) were unavailable. Thus, we cannot conduct further analysis on the effects of ER and PR on GSRC prognosis and other molecular mechanisms. Further investigations are needed to clarify the biological role of estrogen or ER in the carcinogenesis and chemoresistance of GSRC. Second, future studies with a more specific measure of signet-ring cells in GC and more comprehensive long-term outcomes (*e.g.*, the recurrence or chemoresistance, could offer more information) will be needed to verify the conclusion in this study.

## CONCLUSION

Sex differences, especially female reproductive factors, might be protective against GSRC and serve as a significant prognostic factor. Further studies including more comprehensive measures will be essential to elucidate the mechanism of action of female reproductive factors on GSRC.

## ARTICLE HIGHLIGHTS

### Research background

Gastric signet-ring cell carcinoma (GSRC) is a distinct type of gastric cancer (GC), and its incidence has been steadily increasing. GSRC in early and advanced stages is more frequently observed in younger female patients than in gastric adenocarcinomas.

### Research motivation

The effect of female reproductive factors on GSRC tumorigenesis and tumor development remains unclear.

### Research objectives

The purpose of this study was to estimate the effects of female reproductive factors on the prognosis of GSRC.

### Research methods

Our study involved 1431 participants who were histologically confirmed with GC with signet-ring cells and underwent curative resections between January 2011 and December 2018 at the Cancer Hospital, Chinese Academy of Medical Sciences, China. Cox multivariable model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between sex factors and survival of GC patients with signet-ring cell carcinoma. Subgroup analyses were conducted by: (1) Body mass index; (2) Signet-ring cell proportion; (3) Adjuvant chemotherapy; (4) Neoadjuvant chemotherapy; (5) Nerve invasion; and (6) Lymphatic vessel invasion to explore if the impact of the sex difference was stronger in certain groups.

### Research results

The menstrual female subjects had a significantly lower risk of mortality (HR = 0.58, 95%CI: 0.42–0.82) than male participants in the multivariable model. The effect appeared to be more substantial among certain subgroup analyses.

### Research conclusions

There was a stronger positive association with overall survival in menstrual female patients with GSRC, compared to in male or menopause female patients.

### Research perspectives

Future studies with a more specific measure of signet-ring cells in GC and more comprehensive long-term outcomes (*e.g.*, the recurrence or chemoresistance, could offer more information) will be needed to verify the conclusion in this study.

## FOOTNOTES

**Author contributions:** All of the authors contributed to this work; Li Y and Tian YT designed the research study and performed the research; Li Y collected the data, performed the statistical analysis, and drafted the manuscript; Li Y, Zhong YX, Xu Q, and Tian YT participated in discussion and manuscript revision; All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

**Supported by** National Natural Science Foundation of China, No. 82072734.

**Institutional review board statement:** Ethical approval was obtained through the Chinese Academy of Medical Science (Beijing, China).

**Informed consent statement:** All participants gave written informed consent.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** All data included in this study are available on reasonable request from the corresponding author.

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**S-Editor:** Ma YJ

**L-Editor:** Kerr C

**P-Editor:** Ma YJ

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