Original Research Article

Cancer Control
Volume 28: 1–12

DOI: 10.1177/10732748211066309
journals.sagepub.com/home/ccx
SAGE

Effect of Marital Status on the Survival of Patients With Adenocarcinoma of the Esophagogastric Junction: A Population-Based, Propensity-Matched Study

Sihan Wang, PhD[1], Liubo Chen, MD[2], Dongdong Chen, MM[1], Jian Chao, MM[3], Yangliu Shao, MM[4], Kejun Tang, PhD[5], and Wenteng Chen, PhD[6,7]

Abstract

Background: Marital status has been reported as an independent prognostic factor in various types of malignancies. However, the association between marital status and outcomes of patients with adenocarcinoma of the esophagogastric junction (AEG) has not been fully explored. To this end, we aimed to investigate the effect of marital status on survival of AGE patients.

Methods: The Surveillance Epidemiology and End Results (SEER) database (2010–2015) was used to extract eligible patients with Siewert type II AEG. Meanwhile, propensity score matching was performed to match 1576 unmarried patients with 1576 married patients. Kaplan–Meier method with log-rank test was used to plot survival curves, univariate and multivariate Cox regression analyses were adopted to investigate the association of marital status with overall survival (OS) and cancer-specific survival (CSS) in AEG patients before and after matching.

Results: Multivariate analysis in the unmatched cohort revealed that marital status was an independent prognostic factor in patients with Siewert type II AEG. Unmarried patients had poorer OS (hazard ratio [HR]: 1.22, 95% confidence interval [CI]: 1.12–1.29, $P < .001$) and poorer CSS (HR: 1.19, 95% CI: 1.10–1.29, $P < .001$) than married patients before matching. Additionally, widowed patients had the poorest OS (HR: 1.26, 95% CI: 1.11–1.44, $P < .001$) and CSS (HR: 1.29, 95% CI: 1.12–1.48, $P < .001$) compared with married patients. Furthermore, unmarried status remained as an independent prognostic for both OS (HR: 1.20, 95% CI: 1.10–1.31, $P < .001$) and CSS (HR: 1.18, 95% CI: 1.08–1.30, $P < .001$) in 1:1 propensity score-matched analysis. Subgroup analysis further revealed that OS and CSS rates were significantly higher in married patients than unmarried ones in most subgroups stratified by different variables.

Conclusions: This population-based study identified that marital status was an independent prognostic indicator for AEG patients. Married AEG patients had better prognosis than their unmarried counterparts.

[1]Cancer Institute (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education, Key Laboratory of Molecular Biology in Medical Sciences), the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[2]Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[3]Department of Electrocardigram, Ningbo Medical Center Lihuili Hospital, Ningbo, Zhejiang, China
[4]Department of Hematology, Chinese PLA General Hospital, Beijing, China
[5]Department of Surgery, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China
[6]College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang, China

Sihan Wang, Liubo Chen, Dongdong Chen, and Jian Chao contributed equally to this work.

Corresponding Authors:
Wenteng Chen, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang, China.
Email: wentengchen@zju.edu.cn

Liubo Chen, The Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Rd, Hangzhou, Zhejiang 310009, China.
Email: liubochen@zju.edu.cn

Keywords
marital status, adenocarcinoma of the esophagogastric junction, prognosis, SEER

Introduction

Adenocarcinoma of the esophagogastric junction (EGJ) is situated at the transition zone between the esophagus and the stomach. The EGJ tumor can be categorized into three subtypes based on the anatomical location according to Siewert: Siewert type I (5 to 1 cm above the EGJ), type II (1 cm above to 2 cm below the EGJ), and type III (2 to 5 cm below the EGJ).[1,2] Among the three subtypes, Siewert type II is commonly regarded as the true cardia carcinoma, which originates from the esophagogastric junction.[2,3] The incidence of adenocarcinoma of the esophagogastric junction (AEG) has risen drastically in both Western and Asian countries over the last few decades.[4-6]

For anti-tumor treatment, surgery remains the primary curative treatment for AEG. Other treatment includes chemotherapy, radiotherapy and newly emerged immune therapy. Neoadjuvant chemoradiotherapy has been reported to improve long-term overall survival (OS) and progression-free survival in patients with esophageal and junctional cancer, followed by surgical resection.[7] Apart from the above therapeutic regimens, endoscopic submucosal dissection (ESD) is a potentially useful, safe, and curative treatment for superficial EGJ cancers.[8] Several studies have reported that en bloc resection rates of ESD for EGJ cancers could reach 90–100%.[9-12] Despite the continuous advancement in the diagnosis and treatment of AEG, the overall prognosis of AEG patients remains dismal due to high rates of local recurrence and distant metastasis.

Several clinicopathological features have been widely identified to be associated with poor prognosis of patients, including tumor grade, tumor stage at diagnosis, and the performance of surgery or adjuvant therapy. Apart from oncological factors and treatment regimens, psychosocial factors are also associated with the outcome of AEG patients, which have already been demonstrated in several types of cancers.[13-16] To be specific, previous studies have shown that marital status has significant influence on the outcomes of patients with various types of cancers, including colorectal,[16] gastric,[17] pancreatic,[15] and breast cancers.[18] By analyzing 18 196 patients with gastric cancer selected from Surveillance, Epidemiology, and End Results (SEER) database, a population-based research reported that unmarried patients were at a higher risk of cancer-specific mortality compared with the married group.[17] Additionally, among the unmarried group, widowed patients were at the highest risk of cancer-specific mortality.[17] According to a report by Zhai et al, marriage had a protective effect against cause-specific mortality in breast cancer.[18] However, few studies have examined the impact of marital status on the survival of AEG patients, and the potential association between marital status and AEG survival is still unclear. Thus, we conducted this study to systematically explore the correlation between marital status and survival of AEG patients based on the data provided by SEER cancer registry program.

Methods

Data Sources and Study Population

Our analysis was based on the data obtained from the SEER database. The SEER Program is sponsored by the National Cancer Institute, which assembles and reports data on cancer incidence, treatment, and survival from 18 population-based cancer registries covering approximately 28% of the United States population.[19] We enrolled a total of 11 556 patients diagnosed with Type II AEG between 2010 and 2015 in line with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition, 2010). Since the detailed information on the Siewert classification for AEG (type I, II or III) was not directly available in the SEER database, we used the two conditions ('TNM 7/CS v0204+ Schema' encoded 28 (EsophagusGEJunction) and "Primary Site – Labelled" encoded 160 (Cardia, NOS)) to specifically identify Siewert type II AEG.[20,21] The exclusion criteria for the candidates of our study were as follows: (1) patients younger than 18 years old; (2) patients with in situ adenocarcinoma or other type of histology; (3) patients with multiple primary tumors; (4) patients only clinically diagnosed; (5) patients without certain important clinicopathological information, such as AJCC stage, age at diagnosis, race, and marital status; (6) patients with follow-up time less than 6 months; (7) patients without prognostic data. The rest of subjects were enrolled as the eligible cohort of the study. The detailed description of the inclusion/exclusion criteria were shown in Supplemental Figure 1. Since SEER database is publicly available and re-identified, approval was waived by the local ethics committee. Written informed consent was not required in this retrospective study.

Statistical Analysis

Eligible patients were divided into the married group and unmarried group (including divorced/separated, single, and widowed) based on the marital status at diagnosis. Descriptive statistics were performed to investigate the baseline characteristics of patients. Clinicopathological parameters were analyzed and compared by Chi-square (χ^2) test. Survival curves were generated by Kaplan–Meier method (both OS and cancer-specific survival (CSS), and the possible differences were analyzed by log-rank test. Univariate Cox proportional hazard analysis was used to explore possible prognostic

factors, and variables with P values <.05 were further incorporated into the multivariate Cox proportional hazard model. Results were shown in hazard ratio (HR) and 95% confidence interval (CI).

The major methodological challenges of retrospective studies include systematic differences in baseline covariates and cohort selection bias.[22] Thus, we employed propensity score matching (PSM) to balance baseline covariates between married patients and unmarried patients.[23] Propensity scores (PSs) were calculated using a multivariable logistic regression model to balance two groups (married/unmarried). In this model, marital status was used as the dependent variable and all other recorded variables in Table 1 were used as covariates. We then matched married and unmarried patients who had very similar PSs. Subsequently, 1:1 PS-matching was conducted using the nearest-neighbor algorithm with a caliper

Table 1. Clinicopathological characteristics of patients before matching.

	Total (N = 4968)	Married (N = 3320)	Unmarried (N = 1648)	*P*
Age				.03
≤65	2691 (54.17)	1762 (53.07)	929 (56.37)	
>65	2277 (45.83)	1558 (46.93)	719 (43.63)	
Race				<.001
Black	269 (5.41)	132 (3.98)	137 (8.31)	
White	4341 (87.38)	2931 (88.28)	1410 (85.56)	
Other	358 (7.21)	257 (7.74)	101 (6.13)	
Sex				<.001
Male	3987 (80.25)	2821 (84.97)	1166 (70.75)	
Female	981 (19.75)	499 (15.03)	482 (29.25)	
Tumor grade				.221
Well differentiated	282 (5.68)	188 (5.66)	94 (5.7)	
Moderately differentiated	1610 (32.41)	1055 (31.78)	555 (33.68)	
Poorly differentiated/undifferentiated	2396 (48.23)	1635 (49.25)	761 (46.18)	
Unknown	680 (13.69)	442 (13.31)	238 (14.44)	
Tumor size (cm)				.031
≤2	813 (16.36)	557 (16.78)	256 (15.53)	
2.1–5	1683 (33.88)	1145 (34.49)	538 (32.65)	
>5	886 (17.83)	604 (18.19)	282 (17.11)	
Unknown	1586 (31.92)	1014 (30.54)	572 (34.71)	
TNM stage				.057
I	970 (19.52)	630 (18.98)	340 (20.63)	
II	932 (18.76)	602 (18.13)	330 (20.02)	
III	1635 (32.91)	1130 (34.04)	505 (30.64)	
IV	1431 (28.8)	958 (28.86)	473 (28.7)	
Surgery				<.001
No	2425 (48.81)	1526 (45.96)	899 (54.55)	
Endoscopic resection	280 (5.64)	190 (5.72)	90 (5.46)	
Surgery	2249 (45.27)	1595 (48.04)	654 (39.68)	
Unknown	14 (.28)	9 (.27)	5 (.3)	
Radiation				.752
Yes	2646 (53.26)	1774 (53.43)	872 (52.91)	
No/unknown	2322 (46.74)	1546 (46.57)	776 (47.09)	
Chemotherapy				<.001
Yes	3856 (77.62)	2635 (79.37)	1221 (74.09)	
No/unknown	1112 (22.38)	685 (20.63)	427 (25.91)	
Cause of death				<.001
Alive	1855 (37.34)	1318 (39.7)	537 (32.58)	
Dead from cancer	2794 (56.24)	1808 (54.46)	986 (59.83)	
Dead not from cancer	288 (5.80)	175 (5.27)	113 (6.86)	
Unknown	31 (.62)	19 (.57)	12 (.73)	
Follow-up time (months) median (IQR)	19 (11, 34)	20 (12, 35)	17 (10, 30)	<.001

Abbreviation: IQR, interquartile range.

width of .1. Standardized mean difference (SMD) was calculated before and after matching and SMD values <.1 indicated that variables were well balanced between 2 groups. After matching, we similarly plotted Kaplan–Meier curves to compare the OS and CSS between married and unmarried patients. Univariate Cox proportional hazard analysis was also performed to identify prognostic factors in the matched cohort.

SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R software for Mac version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used to analyze data and to plot figures. Results were considered to be statistically significant if a two-sided *P* value was less than .05.

Results

Characteristics of Patients

We enrolled 4968 eligible Siewert Type II AEG patients diagnosed from 2010 to 2015 from the SEER database according to the inclusion and exclusion criteria. Patients were further divided into the married group (n = 3320, 66.83%) and unmarried group (n = 1648, 33.17%). The detailed process of screening was shown in Supplemental Figure 1. The baseline clinicopathological features of patients in two groups of marital status were summarized in Table 1. The median age was 64 years old (interquartile range (IQR): 56–72), and the median follow-up time was 19 months (IQR: 11–34). There was a significant difference in age ($P = .03$), race ($P < .001$), sex ($P < .001$), tumor size ($P = .031$), rate of receiving surgery ($P < .001$), and chemotherapy ($P = .001$) between married and unmarried groups. Unmarried AEG patients had higher proportion of younger patients (56.37% vs 53.07%, higher proportion of females (29.25% vs 15.03%), lower rate of surgery (39.68% vs 48.04%), and lower rate of chemotherapy (74.09% vs 79.37%) compared to the married group.

Prognostic Factors for Patients With AEG Before Matching

Kaplan–Meier curves were used to evaluate OS and CSS rates of AEG patients. As shown in Figure 1(A) and 1(B), unmarried status was associated with significantly worse

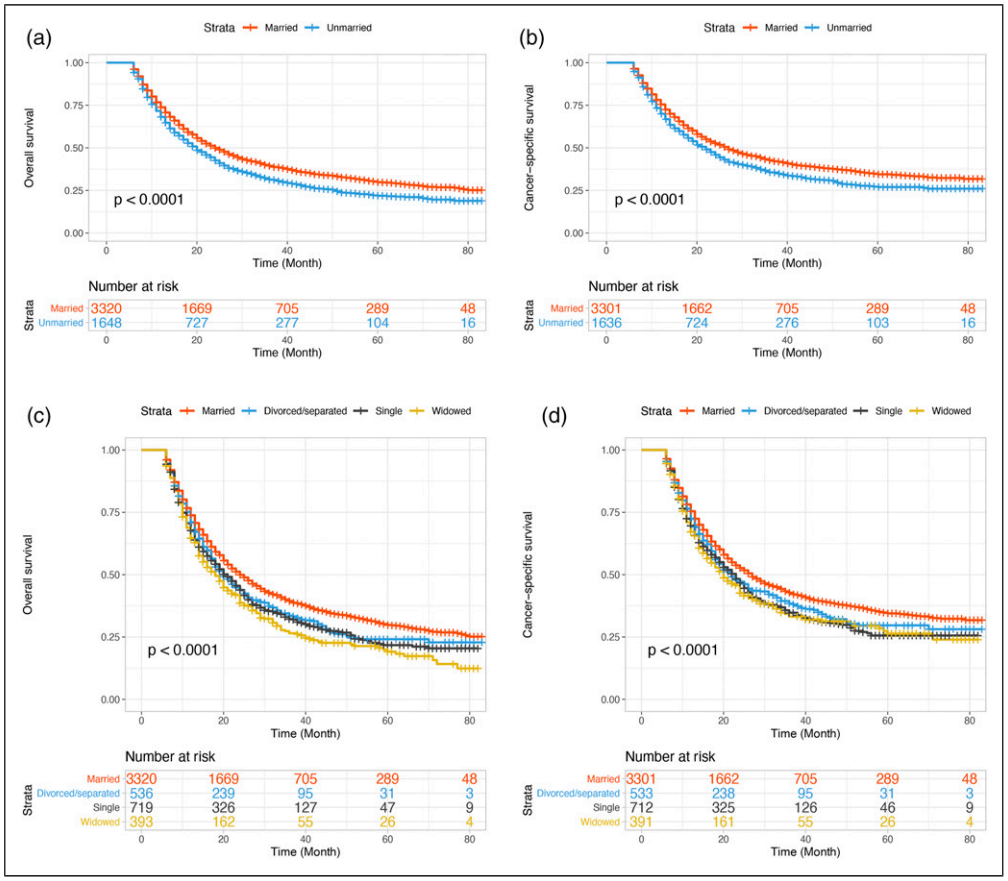

Figure 1. Kaplan–Meier curves of overall survival (OS) and cancer-specific survival (CSS) in AEG patients according to marital status before matching. (A) OS curves between married and unmarried patients. (B) CSS curves between married and unmarried patients. (C) OS curves among married, single, widowed, and divorced/separated patients. (D) CSS curves among married, single, widowed, and divorced/separated patients.

prognosis compared to married status ($P < .0001$). To further explore whether different unmarried status could cause worse prognosis than married status respectively, we partitioned the unmarried group into three subgroups: divorced/separated, single, and widowed patients. As shown in Figure 1(C), compared with married patients, divorced/separated patients, and single patients had significantly decreased OS rates. Widowed patients had the poorest prognosis. Similarly, compared with married patients, divorced patients and single patients also had significantly decreased CSS rates, while widowed patients had the poorest CSS rate (Figure 1(D)).

To investigate possible prognostic factors in AEG patients, we performed univariate and multivariate Cox regression analyses. Variables with P value <.05 in the univariate analysis were further incorporated into the multivariate analysis. For marital status, unmarried patients had significantly poorer OS (HR: 1.24, 95% CI: 1.10–1.38, $P < .001$ for divorced/separated patients; HR: 1.18, 95% CI: 1.07–1.31, $P = .001$ for single patients; HR: 1.26, 95% CI: 1.11–1.44, $P < .001$ for widowed patients) and CSS (HR: 1.18, 95% CI: 1.05–1.33, $P = .006$ for divorced/separated patients; HR: 1.15, 95% CI: 1.03–1.27, $P = .010$ for single patients; HR: 1.29, 95% CI: 1.12–1.48, $P < .001$ for widowed patients) than married patients. In addition, multivariate Cox analysis revealed that tumor grade, TNM stage, surgery, and chemotherapy were independent prognostic factors for OS and CSS. And age was significantly associated with OS, but not CSS. The detailed description of each prognostic factor was displayed in Table 2.

Prognostic Value of Marital Status Stratified by Different Clinicopathological Features Before Matching

To examine the credibility of our conclusions, we further performed subgroup analysis by dividing patients into the married and unmarried groups. As shown in Figure 2, unmarried status was associated with significantly unfavorable OS and CSS than married status in most subgroups. Although no significance was reached for some subgroup analyses, such as the analyses of patients of black and other races for OS and CSS possibly due to the small sample size, there were trends indicating that unmarried status contributed to poorer OS and CSS in these subgroups.

Prognostic Significance of Marital Status for Patients With AEG After Matching

To further verify the finding that married AEG patients had favorable prognosis and to minimize selection bias in this study, PSM analysis was carried out. By using a 1:1 PSM method with a caliper width of .1, we matched 1576 unmarried patients with 1576 married patients. As shown in Table 3, all the baseline variables were well matched (all SMD <.1). As shown in Table 4, after PSM analysis, unmarried patients still showed poorer OS (HR: 1.20, 95% CI: 1.10–1.31, $P < .001$) and CSS (HR: 1.18, 95% CI: 1.08–1.30, $P < .001$) in the univariate Cox model. Kaplan–Meier curves were also used to evaluate OS rate and CSS rate of AEG patients with different marital status after matching. As shown in Figure 3(A) and 3(B), unmarried patients still suffered worse prognosis compared to married patients after matching ($P < .001$). Furthermore, compared with married patients, divorced patients and single patients had significantly decreased OS and CSS rates, and widowed patients had the poorest prognosis according to our results after matching (Figure 3(C) and 3(D)). Subgroup analysis was similarly carried out after matching. As shown in Figure 4, most of the subgroup analyses showed that unmarried patients had unfavorable OS and CSS than married patients stratified by different variables. Our results showed the similar effects of marital status on OS and CSS both before and after PSM, further confirming that marital status was an independent prognostic factor for AEG patients.

Discussion

This population-based study showed that AEG patients who were unmarried at diagnosis had a significantly higher death risk of all causes compared to the married ones. Moreover, different types of unmarried statuses, including single, widowed, and divorced/separated statuses, all contributed to poorer prognosis than married status. Among the unmarried patients, widowed patients had the poorest prognosis.

Although mounting evidence indicates the adverse effects of unmarried status compared to married status on cancer prognosis,[13-15,17,24] the mechanism is not fully understood. The first possible underlying reason why married patients with AEG had better prognosis is that married patients generally have better economic status, which might support them to have easier access to better and earlier medical service and treatment.[25-28] Additionally, in this study, we found that married AEG patients were more likely to undergo surgery and endoscopic resection than their counterparts, which indicated that the worse prognosis of unmarried patients can partly be attributed to undertreatment. Similarly, some related researches show that married patients would have better prognosis because they could be diagnosed and undergo treatment at an early stage.[29,30] This partly explains why unmarried patients have poorer prognosis than married ones. Another possible reason for the prognostic value of marital status in AEG patients is that married patients could have encouragement and emotional support from their spouses. Unmarried patients lack the support and care from their spouses, thus they often suffer from mental stress, pressure, and even depression. As a result, they are more likely to be indulged in bad habits such as smoking and alcohol abuse, which could cause the development of tumor.[31,32] Spouse support plays an important role in helping married patients

Table 2. Cox regression model to assess factors associated with overall survival (OS) and cancer-specific survival (CSS) before matching

	OS				CSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age								
≤65	Reference	—	Reference	—	Reference	—	—	—
>65	1.13 (1.05–1.21)	<.001	1.19 (1.11–1.29)	<.001	1.06 (.98–1.14)	.138		
Race								
Black	Reference	—	—	—	Reference	—	—	—
White	.89 (.77–1.04)	.144	—	—	.91 (.78–1.07)	.268	—	—
Other	.85 (.70–1.04)	.105	—	—	.87 (.71–1.08)	.199	—	—
Sex								
Male	Reference	—	—	—	Reference	—	—	—
Female	.94 (.86–1.03)	0.2	—	—	.91 (.85–1.02)	.133	—	—
Marital status								
Married	Reference	—	Reference	—	Reference	—	Reference	—
Divorced/separated	1.17 (1.05–1.31)	.006	1.24 (1.10–1.38)	<.001	1.15 (1.02–1.30)	.023	1.18 (1.05–1.33)	.006
Single	1.22 (1.11–1.35)	<.001	1.18 (1.07–1.31)	.001	1.24 (1.11–1.37)	<.001	1.15 (1.03–1.27)	.010
Widowed	1.39 (1.22–1.57)	<.001	1.26 (1.11–1.44)	<.001	1.29 (1.12–1.47)	<.001	1.29 (1.12–1.48)	<.001
Tumor grade								
Well differentiated	Reference	—	Reference	—	Reference	—	Reference	—
Moderately differentiated	1.66 (1.36–2.01)	<.001	1.23 (1.01–1.50)	.037	1.94 (1.55–2.41)	<.001	1.36 (1.09–1.70)	.007
Poorly differentiated/ undifferentiated	2.37 (1.96–2.87)	<.001	1.58 (1.30–1.92)	<.001	2.82 (2.27–3.51)	<.001	1.74 (1.40–2.17)	<.001
Unknown	2.00 (1.63–2.47)	<.001	1.20 (.98–1.48)	.083	2.26 (1.79–2.86)	<.001	1.29 (1.02–1.63)	.034
Tumor size (cm)								
≤2	Reference	—	Reference	—	Reference	—	Reference	—
2.1–5	1.90 (1.68–2.15)	<.001	1.28 (1.12–1.46)	<.001	2.25 (1.96–2.59)	<.001	1.40 (1.21–1.62)	<.001
>5	2.27 (1.98–2.59)	<.001	1.34 (1.16–1.55)	<.001	2.74 (2.36–3.19)	<.001	1.45 (1.24–1.70)	<.001
unknown	2.55 (2.25–2.89)	<.001	1.26 (1.10–1.43)	<.001	3.06 (2.66–3.51)	<.001	1.38 (1.19–1.59)	<.001
TNM stage								
I	Reference	—	Reference	—	Reference	—	Reference	—
II	1.83 (1.60–2.10)	<.001	1.54 (1.32–1.79)	<.001	2.13 (1.82–2.49)	<.001	1.66 (1.39–1.97)	<.001
III	2.39 (2.12–2.71)	<.001	2.18 (1.89–2.53)	<.001	3.05 (2.65–3.52)	<.001	2.53 (2.15–2.98)	<.001
IV	5.57 (4.93–6.29)	<.001	2.86 (2.46–3.32)	<.001	7.41 (6.44–8.52)	<.001	3.33 (2.82–3.93)	<.001
Surgery								
No	Reference	—	Reference	—	Reference	—	Reference	—
Surgery	.29 (.27–.31)	<.001	.36 (.33–.40)	<.001	.28 (.25–.30)	<.001	.35 (.32–.39)	<.001
Endoscopic resection	.16 (.13–.20)	<.001	.34 (.27–.44)	<.001	.10 (.07–.13)	<.001	.25 (.18–.35)	<.001
Unknown	1.05 (.61–1.82)	.85	1.42 (.82–2.46)	.210	1.03 (.57–1.87)	.913	1.39 (.77–2.53)	.276
Radiation								
No/unknown	Reference	—	—	—	Reference	—	—	—
Yes	1.02 (.95–1.10)	.528	—	—	1.00 (.93–1.08)	.938	—	—
Chemotherapy								
No/unknown	Reference	—	Reference	—	Reference	—	Reference	—
Yes	.55 (.50–.60)	<.001	.87 (.78–.97)	.013	.48 (.43–.53)	<.001	.87 (.77–.98)	.019

Abbreviations: 95% CI, 95% confidence intervals; HR, hazard ratio.

receive medical care and encourage them to have an optimistic attitude towards disease.

Sociopsychological factors, including marital status, can impact the development and prognosis of oncological diseases by regulating the endocrine and immune systems. It has been previously reported that reduced social support and mental stress could activate specific immunosuppression signaling transduction pathways, leading to tumor growth and progression.[33-35] Levy et al[36] reported that decreased social support was related with reduced activity of natural killer

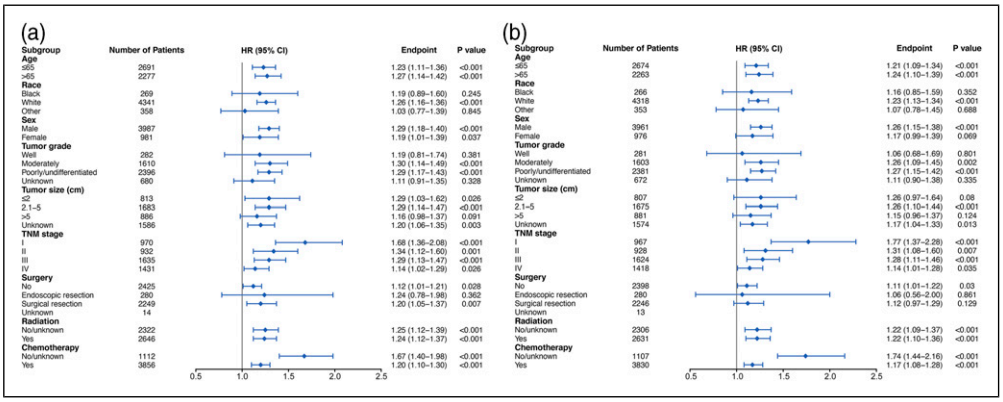

Figure 2. Forest plot summarizing the hazard ratio (HR) for unmarried status vs married status of the (A) overall survival and (B) cancer-specific survival rates of AEG patients in the subgroups according to different clinicopathological factors in the unmatched cohort. The *X*-axis displays the HR and 95% confidence interval (CI) of each subgroup, ticks are arranged at .5, 1.0, 1.5, 2.0, and 2.5.

Table 3. Clinicopathological Characteristics Between Married and Unmarried Patients Before and After Propensity Score Matching.

	Before Matching			After Matching		
Variable	Married (N = 3320)	Unmarried (N = 1648)	SMD	Married (N = 1576)	Unmarried (N = 1576)	SMD
Age			.066			.037
≤65	1762 (53.07)	929 (56.37)	—	918 (58.25)	889 (56.41)	—
>65	1558 (46.93)	719 (43.63)	—	658 (41.75)	687 (43.59)	—
Race			.188			.049
Black	132 (3.98)	137 (8.31)		105 (6.66)	114 (7.23)	
White	2931 (88.28)	1410 (85.56)		1355 (85.98)	1364 (86.55)	
Other	257 (7.74)	101 (6.13)		116 (7.36)	98 (6.22)	
Sex			.348			.009
Male	2821 (84.97)	1166 (70.75)		1168 (74.11)	1162 (73.73)	
Female	499 (15.03)	482 (29.25)		408 (25.89)	414 (26.27)	
Tumor grade			.063			.048
Well differentiated	188 (5.66)	94 (5.7)		97 (6.15)	88 (5.58)	
Moderately differentiated	1055 (31.78)	555 (33.68)		498 (31.6)	529 (33.57)	
Poorly differentiated/undifferentiated	1635 (49.25)	761 (46.18)		760 (48.22)	735 (46.64)	
Unknown	442 (13.31)	238 (14.44)		221 (14.02)	224 (14.21)	
Tumor size (cm)			.089			.028
≤2	557 (16.78)	256 (15.53)		255 (16.18)	248 (15.74)	
2.1–5	1145 (34.49)	538 (32.65)		501 (31.79)	521 (33.06)	
>5	604 (18.19)	282 (17.11)		280 (17.77)	274 (17.39)	
Unknown	1014 (30.54)	572 (34.71)		540 (34.26)	533 (33.82)	
TNM stage			.083			.031
I	630 (18.98)	340 (20.63)		329 (20.88)	314 (19.92)	
II	602 (18.13)	330 (20.02)		298 (18.91)	313 (19.86)	
III	1130 (34.04)	505 (30.64)		495 (31.41)	492 (31.22)	
IV	958 (28.86)	473 (28.7)		454 (28.81)	457 (29)	
Surgery			.176			.034
No	1526 (45.96)	899 (54.55)		830 (52.66)	842 (53.43)	
Endoscopic resection	190 (5.72)	90 (5.46)		95 (6.03)	88 (5.58)	
Surgery	1595 (48.04)	654 (39.68)		648 (41.12)	641 (40.67)	
Unknown	9 (.27)	5 (.3)		3 (.19)	5 (.32)	

(continued)

Table 3. (continued)

Variable	Before Matching			After Matching		
	Married (N = 3320)	Unmarried (N = 1648)	SMD	Married (N = 1576)	Unmarried (N = 1576)	SMD
Radiation			.010			.013
Yes	1774 (53.43)	872 (52.91)		825 (52.35)	835 (52.98)	
No/unknown	1546 (46.57)	776 (47.09)		751 (47.65)	741 (47.02)	
Chemotherapy			.125			.003
Yes	2635 (79.37)	1221 (74.09)		1186 (75.25)	1188 (75.38)	
No/unknown	685 (20.63)	427 (25.91)		390 (24.75)	388 (24.62)	

Abbreviation: SMD, standardized mean difference.

Table 4. Univariate Cox regression model to assess factors associated with overall survival (OS) and cancer-specific survival (CSS) after matching.

	OS		CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
≤65	Reference		Reference	
>65	1.18 (1.08–1.29)	<.001	1.11 (1.01–1.21)	.035
Race				
Black	Reference		Reference	
White	.91 (.77–1.08)	.288	.92 (.77–1.10)	.38
Other	.83 (.66–1.06)	.133	.86 (.67–1.11)	.25
Sex				
Male	Reference		Reference	
Female	.87 (.79–.96)	.007	.86 (.77–.96)	.005
Marital status				
Married	Reference		Reference	
Unmarried	1.20 (1.10–1.31)	<.001	1.18 (1.08–1.30)	<.001
Tumor grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.74 (1.37–2.20)	<.001	2.14 (1.62–2.81)	<.001
Poorly differentiated/undifferentiated	2.47 (1.96–3.11)	<.001	3.02 (2.32–3.98)	<.001
Unknown	2.03 (1.58–2.61)	<.001	2.39 (1.78–3.19)	<.001
Tumor size (cm)				
≤2	Reference		Reference	
2.1–5	2.01 (1.72–2.35)	<.001	2.46 (2.05–2.95)	<.001
>5	2.45 (2.06–2.90)	<.001	3.07 (2.53–3.72)	<.001
unknown	2.62 (2.25–3.06)	<.001	3.26 (2.73–3.90)	<.001
TNM stage				
I	Reference		Reference	
II	1.90 (1.62–2.24)	<.001	2.17 (1.80–2.61)	<.001
III	2.33 (2.00–2.70)	<.001	2.90 (2.45–3.44)	<.001
IV	5.36 (4.63–6.21)	<.001	6.99 (5.91–8.26)	<.001
Surgery				
No	Reference		Reference	
Surgery	.28 (.26–.31)	<.001	.26 (.24–.29)	<.001
Endoscopic resection	.15 (.12–.20)	<.001	.09 (.06–.14)	<.001
Unknown	2.03 (1.01–4.08)	.046	2.42 (1.15–5.09)	.020

(continued)

Table 4. (continued)

	OS		CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Radiation				
No/unknown	Reference		Reference	
Yes	1.02 (.93–1.11)	.675	1.01 (.92–1.11)	.85
Chemotherapy				
No/unknown	Reference		Reference	
Yes	.58 (.52–.65)	<.001	.51 (.45–.58)	<.001

Abbreviations: 95% CI, 95% confidence intervals; HR, hazard ratio.

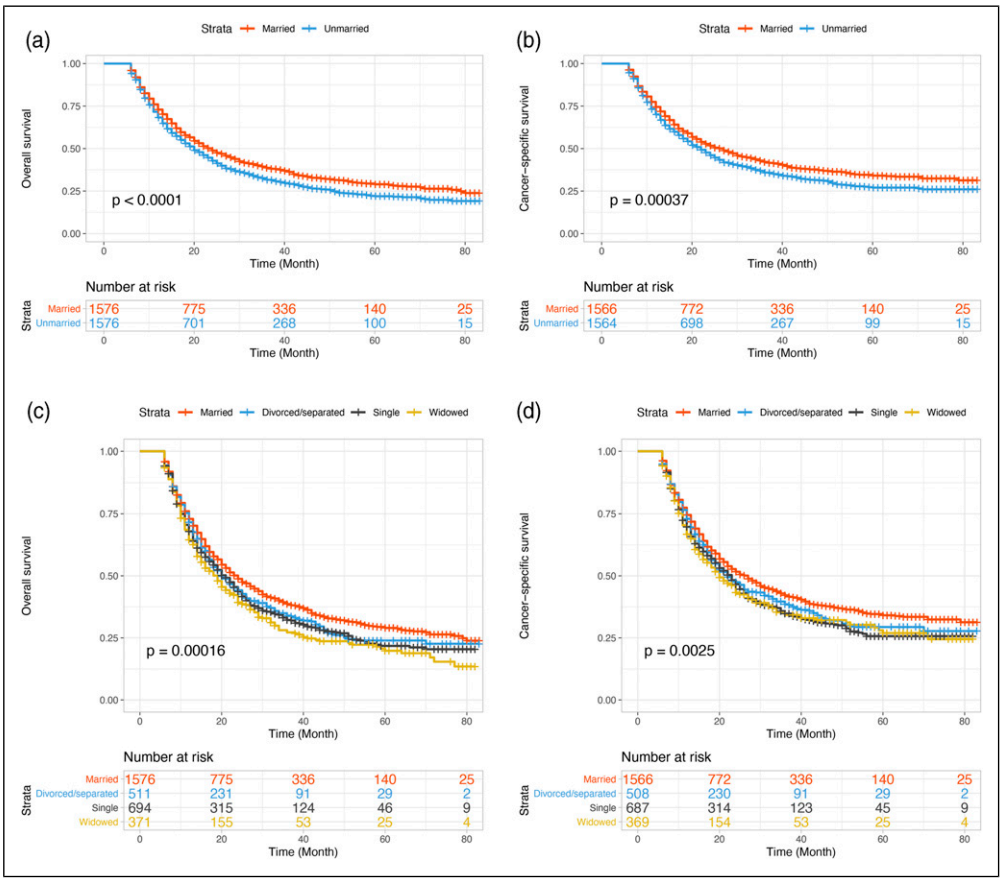

Figure 3. Kaplan–Meier curves of overall survival (OS) and cancer-specific survival (CSS) in AEG patients according to marital status after matching. (A) OS curves between married and unmarried patients. (B) CSS curves between married and unmarried patients. (C) OS curves among married, single, widowed and divorced/separated patients. (D) CSS curves among married, single, widowed and divorced/separated patients.

cells.[36] Social support and reduced stress are associated with the level of cortisol. Cortisol is one of the steroid hormones produced in the adrenal glands, the secretion of cortisol is controlled by the hypothalamus, the pituitary gland, and the adrenal gland (the hypothalamic–pituitary–adrenal (HPA) axis) in response to stress.[37-39] It has been reported that the HPA axis is activated to suppress T–cell-mediated immune responses in the depressed group.[40]

The influence of sociopsychological factors on the prognosis of cancer patients has gained increasing attention. Positive sociopsychological factors can alleviate the pain and stress of cancer patients, thus increasing their treatment

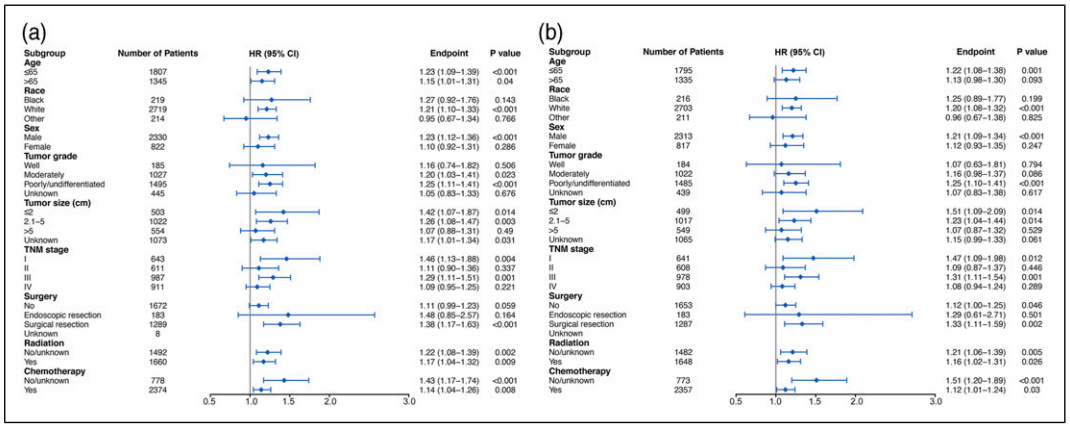

Figure 4. Forest plot summarizing the hazard ratio (HR) for unmarried status vs married status of the (A) overall survival and (B) cancer-specific survival rates of AEG patients in the subgroups according to different clinicopathological factors in the matched cohort. The *X*-axis displays the HR and 95% confidence interval (CI) of each subgroup, ticks are arranged at .5, 1.0, 1.5, 2 and 3.0.

compliance and outcome. Therefore, it is of great significance to fully understand the relationship between psychosocial factors and prognosis of tumor patients. Therefore, it is necessary to monitor the psychological changes of tumor patients and to provide more psychological care and social support for unmarried patients.

Our present findings must be interpreted in view of several limitations. First, some information related to both marital status and prognosis of AEG patients was unavailable in the SEER database, such as socioeconomic status, quality of marriage, reproductive history and subsequent therapy. However, these prognostic factors could have a major impact on the survival of AEG patients. For instance, occupation and education levels are independent prognostic factors for the survival of breast cancer patients.[41-43] Moreover, higher education level is associated with improved survival of patients with prostate cancer, esophageal cancer, and non-small cell lung cancer.[44-46] Despite the inaccessible information on AEG patients in the SEER database, we could rationally assume that these socioeconomic factors could influence the survival of AEG patients. Second, we only analyzed marital status at diagnosis. Marital status is not followed up after diagnosis in the SEER database, which may change after diagnosis and during anti-cancer treatment.

Conclusion

In summary, we found that married AEG patients had higher 5-year OS and CSS rates than those of unmarried ones. Widowed patients were at the highest risk of cancer-specific mortality. In addition, our study sheds light on the mechanisms of how marital status affects both OS and CSS in AEG patients with data from the large population-based SEER database. Interestingly, our results indicate that undertreatment might be one of the causes for the prognostic significance of marriage on patients, since unmarried patients were less likely to undergo surgery or chemotherapy. The underlying mechanism of the relationship between marital status and prognosis of AEG patients might be much more complicated and comprehensive. Further studies should be carried out to clarify the specific mechanisms. Finally, according to our research, greater social and psychological support should be provided to unmarried patients.

Acknowledgments

The authors are grateful for the efforts of the SEER program in creating the SEER database.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Statement

Since SEER database is publicly available and re-identified, approval was waived by the local ethics committee (the Second Affiliated Hospital, Zhejiang University School of Medicine) in this retrospective study. Written informed consent is not required in this retrospective analysis.

ORCID iDs

Liubo Chen https://orcid.org/0000-0002-5582-7203
Kejun Tang https://orcid.org/0000-0002-9461-3646

Supplemental Material

Supplemental material for this article is available online.

References

1. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg*. 1998;85(11):1457-1459.

2. Rüdiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg*. 2000;232(3):353-361.
3. von Rahden BHA, Feith M, Stein HJ. Carcinoma of the cardia: classification as esophageal or gastric cancer?. *Int J Colorectal Dis*. 2005;20(2):89-93.
4. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin*. 2002;11(2): 235-256.
5. Carr JS, Zafar SF, Saba N, Khuri FR, El-Rayes BF. Risk factors for rising incidence of esophageal and gastric cardia adenocarcinoma. *J Gastrointest Cancer*. 2013;44(2):143-151.
6. Zhao J, Zhao J, Du F, et al. Cardia and non-cardia gastric cancer have similar stage-for-stage prognoses after R0 resection: a large-scale, multicenter study in China. *J Gastrointest Surg*. 2016;20(4):700-707.
7. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16(9): 1090-1098.
8. Nagami Y, Machida H, Shiba, et al. Clinical efficacy of endoscopic submucosal dissection for adenocarcinomas of the esophagogastric junction. *Endosc Int Open*. 2014;2(1):E15-E20.
9. Hirasawa K, Kokawa A, Oka H, et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc*. 2010; 72(5):960-966.
10. Imai K, Kakushima N, Tanaka M, et al. Validation of the application of the Japanese curative criteria for superficial adenocarcinoma at the esophagogastric junction treated by endoscopic submucosal dissection: a long-term analysis. *Surg Endosc*. 2013; 27(7):2436-2445.
11. Omae M, Fujisaki J, Horiuchi Y, et al. Safety, efficacy, and long-term outcomes for endoscopic submucosal dissection of early esophagogastric junction cancer. *Gastric Cancer*. 2013;16(2): 147-154.
12. Yoshinaga S, Gotoda T, Kusano C, Oda I, Nakamura K, Takayanagi R. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. *Gastrointest Endosc*. 2008;67(2):202-209.
13. Aizer AA, Chen M-H, McCarthy EP, et al. Marital status and survival in patients with cancer. *J Clin Oncol*. 2013;31(31): 3869-3876.
14. He X-K, Lin Z-H, Qian Y, Xia D, Jin P, Sun L-M. Marital status and survival in patients with primary liver cancer. *Oncotarget*. 2017;8(39):64954-64963.
15. Wang X-D, Qian J-J, Bai D-S, Li Z-N, Jiang G-Q, Yao J. Marital status independently predicts pancreatic cancer survival in patients treated with surgical resection: an analysis of the SEER database. *Oncotarget*. 2016;7(17):24880-24887.
16. Wang X, Cao W, Zheng C, Hu W, Liu C. Marital status and survival in patients with rectal cancer: an analysis of the Surveillance, Epidemiology and End Results (SEER) database. *Cancer Epidemiol*. 2018;54:119-124.
17. Jin JJ, Wang W, Dai FX, et al. Marital status and survival in patients with gastric cancer. *Cancer Med*. 2016;5(8): 1821-1829.
18. Zhai Z, Zhang F, Zheng Y, et al. Effects of marital status on breast cancer survival by age, race, and hormone receptor status: a population-based Study. *Cancer Med*. 2019;8(10): 4906-4917.
19. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of surveillance, epidemiology, and end results-medicare data to conduct case-control studies of cancer among the US elderly. *Am J Epidemiol*. 2011;174(7):860-870.
20. Miccio JA, Oladeru OT, Yang J, Xue Y, Choi M, Zhang Y, et al. Neoadjuvant vs. adjuvant treatment of Siewert type II gastroesophageal junction cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *J Gastrointest Oncol*. 2016;7(3):403-410.
21. Chen L, Tang K, Wang S, Chen D, Ding K. Predictors of lymph node metastasis in siewert type II T1 adenocarcinoma of the esophagogastric junction: a population-based study. *Cancer Control*. 2021;28:10732748211026668.
22. Zhao Q-Y, Luo J-C, Su Y, Zhang Y-J, Tu G-W, Luo Z. Propensity score matching with R: conventional methods and new features. *Ann Transl Med*. 2021;9(9):812.
23. Chen M, Yang Q, Xu Z, et al. Survival analysis and prediction model for pulmonary sarcomatoid carcinoma based on SEER database. *Front Oncol*. 2021;11:630885.
24. Li M, Dai C-Y, Wang Y-N, et al. Marital status is an independent prognostic factor for tracheal cancer patients: an analysis of the SEER database. *Oncotarget*. 2016;7(47): 77152-77162.
25. Aizer AA, Paly JJ, Zietman AL, et al. Multidisciplinary care and pursuit of active surveillance in low-risk prostate cancer. *J Clin Oncol*. 2012;30(25):3071-3076.
26. Patel K, Kanu M, Liu J, et al. Factors influencing breast cancer screening in low-income African Americans in Tennessee. *J Community Health*. 2014;39(5):943-950.
27. Ali AA, Xiao H, Kiros GE. Health insurance and breast-conserving surgery with radiation treatment. *Am J Manag Care*. 2014;20(6):502-516.
28. Elmore L, Deshpande A, Daly M, Margenthaler JA. Postmastectomy radiation therapy in T3 node-negative breast cancer. *J Surg Res*. 2015;199(1):90-96.
29. Doherty MK, Knox JJ. Adjuvant therapy for resected biliary tract cancer: a review. *Chin Clin Oncol*. 2016;5(5):64.
30. Yabar CS, Winter JM. Pancreatic cancer: a review. *Gastroenterol Clin N Am*. 2016;45(3):429-445.
31. Goldzweig G, Andritsch E, Hubert A, et al. How relevant is marital status and gender variables in coping with colorectal cancer? A sample of middle-aged and older cancer survivors. *Psycho Oncol*. 2009;18(8):866-874.
32. Goldzweig G, Andritsch E, Hubert A, et al. Psychological distress among male patients and male spouses: what do oncologists need to know?. *Ann Oncol*. 2010;21(4):877-883.
33. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol*. 2010;6(12):1863-1881.

34. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain Behav Immun*. 2013;30(suppl l): S41-S47.
35. Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol*. 2004;5(10): 617-625.
36. Levy SM, Herberman RB, Whiteside T, Sanzo K, Lee J, Kirkwood J. Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer cell activity in breast cancer patients. *Psychosom Med*. 1990;52(1): 73-85.
37. Sephton S, Spiegel D. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease?. *Brain Behav Immun*. 2003;17(5):321-328.
38. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev*. 2000;21(1):55-89.
39. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007;87(3): 873-904.
40. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatr*. 2003;54(3):269-282.
41. Liu Y, Zhang J, Huang R, et al. Influence of occupation and education level on breast cancer stage at diagnosis, and treatment options in China: A nationwide, multicenter 10-year epidemiological study. *Medicine*. 2017;96(15):e6641.
42. Malik R, Vera N, Dayal C, et al. Factors associated with breast cancer awareness and breast self-examination in Fiji and Kashmir India - a cross-sectional study. *BMC Cancer*. 2020;20(1):1078.
43. DeSantis C, Jemal A, Ward E. Disparities in breast cancer prognostic factors by race, insurance status, and education. *Cancer Causes Control*. 2010;21(9):1445-1450.
44. Mickeviciene A, Vanagas G, Ulys A, et al. Factors affecting health-related quality of life in prostate cancer patients. *Scand J Urol Nephrol*. 2012;46(3):180-187.
45. Brusselaers N, Mattsson F, Lindblad M, Lagergren J. Association between education level and prognosis after esophageal cancer surgery: a Swedish population-based cohort study. *PLoS One*. 2015;10(3):e0121928.
46. Di Maio M, Signoriello S, Morabito A, et al. Prognostic impact of education level of patients with advanced non-small cell lung cancer enrolled in clinical trials. *Lung Cancer*. 2012;76(3):457-464.

Abbreviations

AEG	adenocarcinoma of esophagogastric junction
AJCC	American Joint Committee on Cancer; CIconfidence interval
CSS	cancer-specific survival
EGJ	esophagogastric junction
ESD	endoscopic submucosal dissection
HPA	hypothalamic–pituitary–adrenal
HR	hazard ratio
IQR	interquartile range
OS	overall survival
PS	propensity score
PSM	propensity score matching
SMD	standardized mean difference
SEER	Surveillance, Epidemiology, and End Results