

Time-Varying Effects of Marital Status on Gastric Cancer: A Population-Based Study

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Background: Although prior studies have shown that marital status affects the prognosis of patients with gastric cancer, its time-varying effects are not well understood. We aimed to investigate the changes in marital status' impact over a 10-year follow-up time among patients with gastric cancer (GC) in the United States.

Materials and Methods: All patients with gastric cancer diagnosed between 2004 and 2008 in the Surveillance, Epidemiology, and End Results (SEER) database were retrieved. Married patients and unmarried patients (single, separated, divorced or widowed) with complete survival time were selected for comparisons. A total of 14,545 patients who had clinical data and follow-up information available were enrolled. We used Kaplan–Meier analyses and time-dependent flexible parametric models to estimate time-varying hazard ratios (HRs).

Results: Unmarried GC patients had worse overall and cancer-specific survival compared with married patients (log-rank test: $P < 0.001$ and $P < 0.001$, respectively). The time-varying analysis found that unmarried patients had a significantly higher risk of overall mortality during the 10-year follow-up time, with the lowest adjusted hazard ratio (HR) at 12 months after diagnosis (HR at 12 months, 1.08; 95% CI, 1.03–1.15). For cancer-specific mortality, the time-varying adjusted HR of unmarried patients was significantly higher initially (HR at 12 months, 1.08; 95% CI, 1.02–1.14) but decreased to null after 20 months (HR at 24 months = 1.04; 95% CI = 0.99–1.11).

Conclusion: Unmarried patients had a higher risk of cancer-specific mortality during the 20 months after gastric cancer diagnosis, which may be an appropriate time frame for intervention.

Keywords: time-varying effect, marital status, survival, gastric cancer

Introduction

Gastric cancer (GC) is the sixth most common malignant tumor worldwide and the second most frequent cause of cancer-related death after lung cancer.^{1,2} In the United States, there were 27,510 new cases of GC and 11,140 GC deaths estimated by the American Cancer Society in 2019.³

Unmarried status was shown to have significant adverse survival effects for different types of cancer.^{4–8} With regard to GC, prior studies have shown that being unmarried may also increase overall mortality and cancer-specific mortality risk in patients with GC.^{9–11} However, data on the impact of marital status across a longer follow-up time period are lacking. Studying this association has been complicated by the fact that a differential mortality hazard by marital status over time violates the proportional hazards assumption of the Cox regression model.¹²

In this study, we aimed to explore changes in the prognostic effect of marital status over a 10-year follow-up time by using the Surveillance, Epidemiology and End Results (SEER) database.

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Materials and Methods

Case Selection

Data on all gastric adenocarcinomas for each patient were obtained from the SEER database from 2004 to 2008. Patients with antecedent malignancy before gastric cancer were excluded. The SEER program covers approximately 26% of the United States population. All patients had information on marital status, 5 patients were less than 5 years old, 2222 patients were missing tumor stage, 28 patients were missing information on race, 2740 patients were missing information on tumor grade, and 46 patients were missing information on residence type. We excluded these patients in our analysis. A total of 14,545 patients fulfilled the above criteria and were included in further analyses.

Study Variables

The adjusted marital status hazard ratios were adjusted for age, sex and race, treatment, tumor characteristics and socioeconomic status. According to the SEER database, marital status was described as married (including common law), single (never married), separated, divorced, and widowed. In this study, the unmarried patients included single, separated/divorced, and widowed patients. Race/ethnicity was classified as white, black, and others. Tumor location was classified as cardia or noncardia/NOS according to the International Classification of Diseases for Oncology (third edition) (ICD-O-3). The TNM classification system was defined by the AJCC Cancer Staging Manual (the sixth edition). Residence type was determined at the county level by linkage to the 2003 US Department of Agriculture rural–urban continuum codes. Educational status and median household income were obtained from the county level of 2000 US Census American Community Survey (ACS).

Statistical Analysis

Baseline patient characteristics were compared with the *t* test or χ^2 test, as appropriate. Nonparametric analyses were performed by the Kaplan–Meier method. Median survival time was calculated by Kaplan–Meier method. Median follow-up time was calculated by reverse Kaplan–Meier method.^{13,14} Statistical significance was assessed using the log-rank test. Time-varying analyses were performed using flexible parametric models, where the logarithm of the baseline hazard function was modeled as a natural cubic spline function of log time.^{15–17} Marital status was treated as a covariate with a time-varying effect (nonproportional hazards) by including an interaction with time. For model selection, we explored

multiple degrees of freedom for the baseline mortality hazard and time-dependent effect and assessed the goodness of fit using the Akaike Information Criterion (AIC). Flexible parametric models were fitted with 6 and 3 degrees of freedom for the baseline mortality hazard and the time-dependent effect, respectively. Statistical tests were 2-sided with an α value of 0.05. We did not obtain informed consent from the patients because we analyzed deidentified cancer registry data.

Ethics Statement

Our study was carried out in accordance with the principles of the Declaration of Helsinki. The SEER was public-use data: informed consent was waived. And our study was deemed exempt from institutional review board approval by Queen Mary Hospital, The University of Hong Kong.

Results

Patient Characteristics

Among the 14,545 patients enrolled, 12,166 deaths were observed. The median survival time for enrolled patients was 13 months. The median follow-up time for enrolled patients was 122 months. The patients' baseline characteristics are shown in Table 1. The unmarried patients were, on average, 3.4 years older than the married controls ($P < 0.001$). Unmarried status was more common among female patients than among male patients ($P < 0.001$). In addition, black patients showed a higher unmarried rate than patients of other races ($P < 0.001$) (Table 1).

Unadjusted Analysis of Long-term Outcome Associated with Marital Status

Kaplan–Meier analyses and a flexible parametric model based on marital status were performed for enrolled patients (Figure 1). A statistically significant difference in both overall survival (log-rank test: $P < 0.001$) and cancer-specific survival (log-rank test: $P < 0.001$) was observed according to marital status. The 10-year overall survival rates for the unmarried group and the married group were 11.1% (95% CI, 10.3% - 12.0%) and 17.8% (95% CI, 17.0% - 18.7%), respectively.

Time-Varying Multivariable Analysis of Long-term Survival Associated with Marital Status

We used flexible parametric modeling to perform a time-varying analysis of the long-term effects of marital status at diagnosis for GC patients, adjusting for classic patient characteristics (age, sex, race), tumor characteristics (tumor

Table I Baseline Characteristics

Variable	Total	Married	Unmarried	P
Sex				<0.001
Male	9306	6500(73.2%)	2806(49.5%)	
Female	5239	2377(26.8%)	2862(50.5%)	
Age				<0.001
≤68	7520	5007(56.4%)	2513(44.3%)	
>68	7025	3870(43.6%)	3155(55.7%)	
Race				<0.001
White	10,236	6398(72.1%)	3838(67.7%)	
Black	1889	791(8.9%)	1098(19.4%)	
Others	2420	1688(19%)	732(12.9%)	
Tumor location				<0.001
Noncardia/NOS	10,125	5924(66.7%)	4201(74.1%)	
Cardia	4420	2953(33.3%)	1467(25.9%)	
Pathological grade				0.253
G1	606	356(4%)	250(4.4%)	
G2	3972	2395(27%)	1577(27.8%)	
G3	9667	5933(66.8%)	3734(65.9%)	
G4	300	193(2.2%)	107(1.9%)	
Histological type				<0.001
Adenocarcinoma	10,937	6637(74.8%)	4300(75.9%)	
Mucinous	382	206(2.3%)	176(3.1%)	
Signet	3226	2034(22.9%)	1192(21%)	
Metastasis at Dx				0.355
Yes	5360	3249(36.6%)	2111(37.2%)	
No	9126	5604(63.1%)	3522(62.1%)	
TNM stage				0.010
I	4031	2398(27%)	1633(28.8%)	
II	2068	1316(14.8%)	752(13.3%)	
III	2129	1324(14.9%)	805(14.2%)	
IV	6317	3839(43.2%)	2478(43.7%)	
Income per year, USD				0.001
≤4570	7277	4346(49%)	2931(51.7%)	
>4570	7268	4531(51%)	2737(48.3%)	
Percent that completed high school				<0.001
≤79.1%	7301	4592(51.7%)	2709(47.8%)	
>79.1%	7244	4285(48.3%)	2959(52.2%)	
Residence				0.396
Rural	1477	917(10.3%)	560(9.9%)	
Urban	13,068	7960(89.7%)	5108(90.1%)	

Notes: Age, income and percent that completed high school were divided by their median values. Income, percent that completed high school and residence were county-level data. Mean (SD) of age for unmarried patients was 65.1 (13.2) years old. Mean (SD) of age for married patients was 68.5 (15.0) years old. t-test: $P < 0.001$. Mean (SD) of income for unmarried patients was 4404.2 (1124.9) years old. Mean (SD) of income for married patients was 4312.8 (1178.4) years old. t-test: $P < 0.001$.

Abbreviation: SD, standard deviation

location, pathological grade, histological type, tumor stage) and socioeconomic conditions (household incomes, education, residence type). The findings from the time-varying hazard ratio analysis for overall mortality are shown in [Figure 2A](#).

Compared with married patients, unmarried patients had a significantly higher mortality risk at the time immediately after their first diagnosis; their risk then declined to the lowest point at 12 months after diagnosis (HR at 12 months, 1.08;

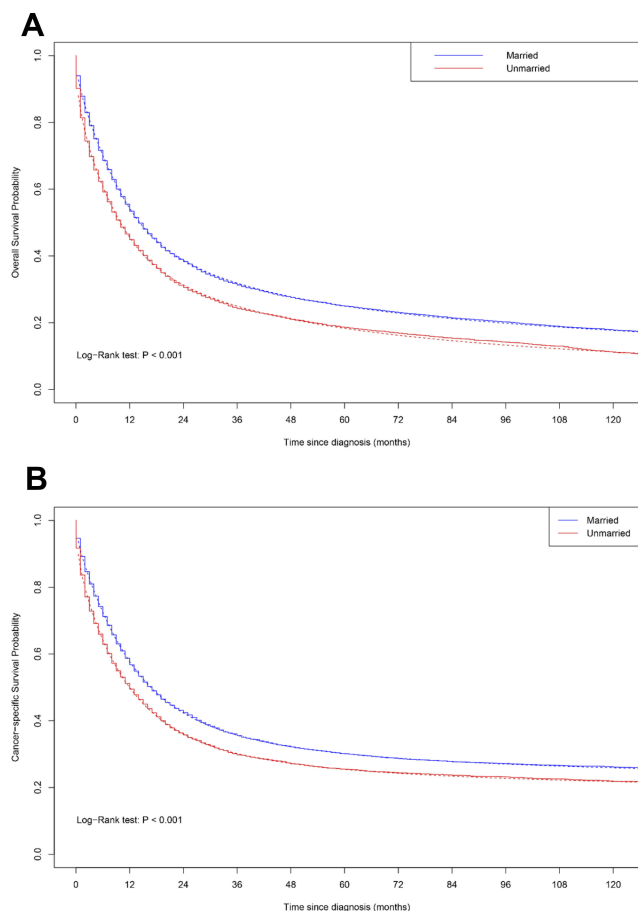


Figure 1 Overall survival and cancer-specific survival by marital status. Log-rank test: **(A)** Overall survival: married versus unmarried, $P < 0.001$; **(B)** Cancer-specific survival: married versus unmarried, $P < 0.001$. Solid lines show the Kaplan-Meier analysis, and dotted lines show the flexible parametric model.

95% CI, 1.03–1.15), and finally increased thereafter in the following 9 years of follow-up time (HR at 120 months = 1.42, 95% CI = 1.26–1.60) (Figure 2A). For cancer-specific mortality analysis, findings from the time-varying HR analysis suggested that unmarried patients were only at significantly higher mortality risk during approximately the first 20 months after GC diagnosis compared with married patients (Figure 2B) (HR at 12 months = 1.08; 95% CI, 1.02–1.14; HR at 24 months = 1.04; 95% CI, 0.99–1.11). The subgroup analyses found that the high hazard ratios for both overall and cancer-specific mortality among unmarried patients during early follow-up time were observed regardless of the component of unmarried status or tumor stage (Figures S1 and S2).

Discussion

In this study, we used data from a population-based database in the United States. Our study showed that unmarried GC patients experienced a higher risk of overall and cancer-

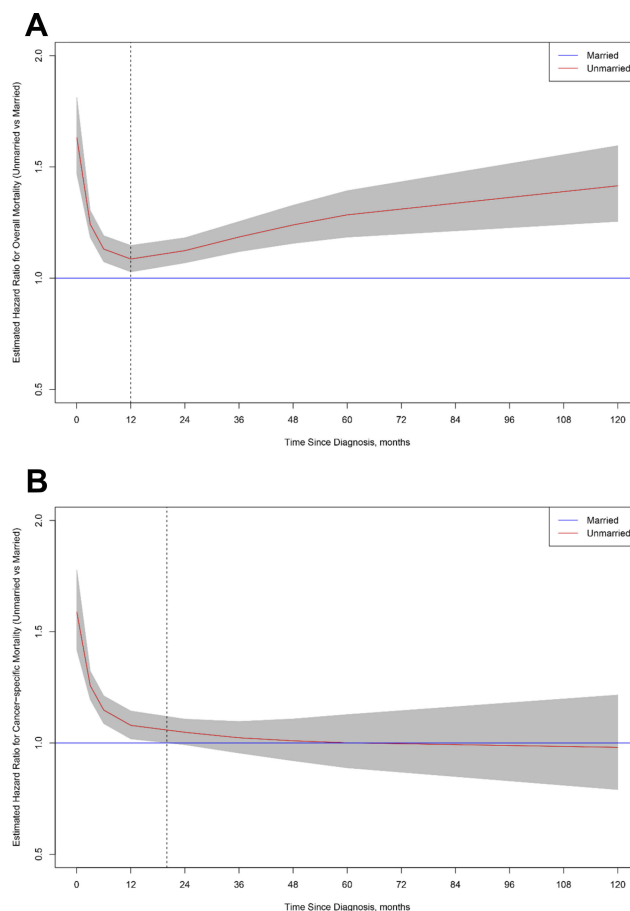


Figure 2 Estimated time-dependent hazard ratios for overall mortality and cancer-specific mortality by marital status. **(A)** Overall mortality; **(B)** Cancer-specific mortality. The married group is the reference. Shading indicates the 95% confidence interval.

specific mortality than married control GC patients throughout a 10-year follow-up period. Moreover, findings from the time-varying analysis suggested that the relative overall and cancer-specific mortality risk changes over follow-up time. Specifically, compared with married patients, the cancer-specific mortality risk for unmarried patients was significantly higher during the first 20 months after GC diagnosis, and then the risk gradually attenuated to null. To the best of our knowledge, this has not been reported previously. This 20-month period may become a “window of opportunity” for social interventions.

Until now, it has generally been accepted that there must be some factors (e.g., psychological, physiological or socio-economic factors), not marital status per se, that may be an innate reason for the effect of marriage on survival outcome. Based on this assumption, many potential underlying etiologies are proposed to explain the adverse effects of unmarried status on survival outcomes.

Because the cancer-specific mortality risk of unmarried patients mainly happens in the early follow-up period, medical access and adherence may be important factors for the relationship between marital status and survival outcomes. Unmarried patients showed more advanced stage than married patients when first diagnosed,^{6,10,18} which may reflect worse access to care for unmarried than married patients. Although there is limited evidence in cancer, unmarried patients display a higher risk of medication nonadherence than married patients in numerous other chronic diseases.^{19–21} Depression strongly affects medical nonadherence²² and may also be a mediator of the association between marital status and medical adherence.⁶ Efforts to improve medical access and adherence among unmarried patients may be effective. If we assume that improved social support could improve outcomes in unmarried patients, the first 20 months after diagnosis may be an appropriate time for interventions.

Mental health is also commonly thought to play a role in the relationship between marital status and survival outcomes. Patients with cancers have a higher prevalence of mental disorders in comparison with the normal controls.^{23,24} These psychological conditions have been associated with worse survival outcomes in multiple studies.^{25–27} Single patients or patients with family disruption are more likely to experience depression, anxiety and psychological distress than married patients,^{28,29} which may be a reason for the poor outcome of cancer patients. Screening for mental health disorders and early structural intervention, if needed, among unmarried patients with cancers may be a feasible management approach.^{30,31} A previous meta-analysis that only included randomized controlled trials indicated that psychosocial interventions have survival benefits during the short-term period after cancer diagnosis,³² which is consistent with the novel concept of the “window of opportunity” in our study. Additionally, other benefits, such as improvement of quality of life, have been demonstrated for mental health interventions and should not be ignored.³³

Physiologically, unmarried patients have been demonstrated to be at higher risk of cardiovascular diseases³⁴ and dementia.³⁵ Comorbidities have included chronic conditions that affect long-term survival in multiple cancers,³⁶ although the cancer type and severity may be determinants of the magnitude and presence of this effect.^{37–39} Moreover, some stress-related endocrine and immunological changes among unmarried patients may also play a role in their survival.^{40,41}

Financial hardship and increased medical costs have commonly been reported in the cancer survivor’s family in

the United States.^{42,43} These factors are commonly thought to be a mediator in the relationship between marital status and survival outcomes. However, until now, no sufficient evidence has supported financial hardship as a mediator of the association between marital status and survival outcomes.⁵ Consistent with previous research,^{4,5} only minimal changes in the HRs for death among unmarried patients between models adjusted and not adjusted for socioeconomic conditions in the multivariate models in our study (data not shown).

The risk of overall mortality, although decreased during the first 12 months, was persistently significantly higher in unmarried patients than in married patients. However, the higher risk of overall mortality among unmarried people is present not only in GC patients but also in the general elderly population.⁴⁴ Interventions that improve the overall survival of unmarried people in the general population may also be beneficial to cancer patients.

The strengths of this study include its population-based study design, large sample size, and extensive duration of follow-up. However, there are limitations. First, changes in marital status during the survival period were not available in the SEER databases. However, changes in marital status may not be an important reason for declining cancer-specific mortality hazard ratios for unmarried patients because the risk of overall mortality increases gradually during long-term follow-up, which is consistent with the general elderly population.⁴⁴ Second, the impact of other family caregivers in addition to the spouse was not analyzed in this study. Whether accessing alternative caregivers or getting remarried could improve outcomes for unmarried patients is still unclear.

Despite these potential limitations, our study indicates that the risk of cancer-specific mortality for unmarried GC patients was significantly higher initially but decreased to null after 20 months. Given that efforts on medical and social support may improve the outcomes of cancer patients, this time period is an appropriate opportunity for interventions.

Disclosure

The authors report no conflicts of interest in this work.

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