

Influence of marital status on small intestinal adenocarcinoma survival: an analysis of the Surveillance, Epidemiology, and End Results (SEER) database

Zhihui Chen^{1,*}Ji Cui^{1,*}Weigang Dai^{1,*}Hong Yang²Yulong He¹Xinming Song¹

¹Department of Gastrointestinal Surgery Centre, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China;

²Department of Operating Room, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China

*These authors contributed equally to this work

Aim: No studies have been published on the relationship between marital status and outcomes in small intestinal cancers. The present study was conducted to explore the influence of marital status on small intestinal adenocarcinoma survival based on the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Data from eligible patients diagnosed with small intestinal adenocarcinoma between 2004 and 2015 were extracted from the SEER database. Patients were categorized into married group (including common law) and unmarried group (including single [never married], widowed, divorced, separated, and unmarried or domestic partner). The primary endpoints were 5-year overall survival (OS) and 5-year cancer-specific survival (CSS). A survival curve was generated by the Kaplan–Meier method, and the survival rate differences were estimated by a log-rank test. A multivariate Cox proportional hazard model was used to evaluate the independent risk factors for survival.

Results: A total of 6,747 small intestinal adenocarcinoma patients were enrolled, including 3,862 married and 2,885 unmarried patients. The 5-year OS and 5-year CSS were significantly greater in married patients than in unmarried patients (27.1 vs 18.8% for OS and 45.7 vs 39.3% for CSS, both $P < 0.001$). After adjusting for age, insurance status, tumor primary site, TNM stage, tumor grade, tumor histology, and surgery, the multivariate Cox proportional hazards model showed that marriage is an independent protective factor for OS (HR = 0.789, 95% CI: 0.745–0.836, $P < 0.001$) and CSS (HR = 0.794, 95% CI: 0.736–0.857, $P < 0.001$).

Conclusion: Married small intestinal adenocarcinoma patients have better OS and CSS than unmarried patients. Psychological and economic supports from the spouses of married patients may contribute to improvements in survival.

Keywords: small bowel, adenocarcinomas, marriage, prognosis

Introduction

Small intestine cancers are uncommon malignancies of the digestive system. In 2018, an estimated 10,470 new small intestine cancer cases and 1,450 deaths will occur in USA.¹ Adenocarcinoma, the second most common histological subtype, accounts for 36.9% of small intestine cancers.² Other common histological subtypes included carcinoids, lymphomas, and stromal tumors.^{2–5}

Due to the relative rarity of small intestinal cancers, few large-scale population-based studies have been conducted. The Surveillance, Epidemiology, and End Results (SEER) database includes almost all cancer incidence, prevalence, tumor pathology,

Correspondence: Xinming Song
Department of Gastrointestinal Surgery
Centre, The First Affiliated Hospital, Sun
Yat-sen University, No 58, Zhongshan
2nd Road, Guangzhou 510080, China
Tel +86 20 8775 5766
Email songxm@mail.sysu.edu.cn

and demographic data, such as age, gender, ethnicity, marital status, and prognosis.⁶ Some known prognostic factors, such as race, tumor location, TNM stage, and number of retrieved lymph nodes, have been proposed by studies based on the SEER database.^{2,7–9} The protective effect of marriage on survival was inconsistent. Marital status was reported to be associated with survival in some cancers, such as renal cell carcinoma,¹⁰ head and neck cancers,¹¹ squamous cell carcinoma of the penis,¹² and rectal cancer.¹³ However, other studies could not find any protective effect of marriage on patients' outcome.^{14,15} Previous study by Kato et al¹⁶ found that single females showed increased risks for small intestine cancers. However, no study has been published to evaluate the relationship between marital status and outcome in small intestinal cancers. Therefore, the present study was conducted to explore the influence of marital status on small intestinal adenocarcinoma survival based on the SEER database.

Methods

Patients

The SEER database (<http://seer.cancer.gov>) is the largest publicly available dataset and consists of 18 tumor registries covering ~26% of the US population. The de-identified data held by the SEER database were authorized to obtain in May 2018. The following inclusion criteria were adopted: 1) tumor histological type: mucinous adenocarcinoma (SEER histology codes 8480 and 8481), signet ring cell (SEER histology code 8490), and other carcinoma adenocarcinoma (SEER histology codes 8140, 8144, 8210, 8211, 8220, 8221, 8255, 8260, 8261, 8262, 8263, 8574, and 8576); 2) marital status known; and 3) survival data known.

Tumor location was categorized by the following SEER cancer site codes: C17.0-duodenum, C17.1-jejunum, C17.2-ileum, C17.3-Meckel's diverticulum, C17.8-overlapping lesion of small intestine, and c17.9-small intestine, not otherwise specified (NOS). Race classifications were "white" (race/ethnicity code, 1), "black" (race/ethnicity code, 2), and "others" (the remaining codes). The American Joint Committee on Cancer (AJCC) seventh TNM staging system was used.

Statistical analysis

Comparisons of categorical variables between married and unmarried patients were performed using the chi-squared test, and continuous variables were compared using the Student's *t*-test. The primary endpoints were 5-year overall survival (OS) and 5-year cancer-specific survival (CSS). Survival curves were generated by the Kaplan–Meier method, and survival rate differences were estimated by a log-rank

test. Variables with statistically significant differences were entered into a multivariate Cox proportional hazard model. HRs with 95% CIs were calculated for all the prognostic factors. Statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered to be statistically significant.

Results

Patient baseline characteristics

A total of 6,747 small intestinal adenocarcinoma patients diagnosed between 2004 and 2015 were enrolled, including 3,656 (54.2%) male and 3,091 (45.8%) female patients. Of these patients, the mean age of the whole population was 67.78 ± 13.81 years (mean \pm SD). Therefore, patients were divided into the following two groups according to age: < 68 and ≥ 68 years. According to the SEER coding program, the marital status of patients with small intestinal adenocarcinoma was divided into married (including common law, $N = 3,862$) and unmarried (including single [never married], widowed, divorced, separated, and unmarried or domestic partner, $N = 2,885$).

Clinicopathological features of married and unmarried patients

As shown in Table 1, male patients were more prevalent in the married group than in the unmarried group (65.2 vs 39.5%, $P < 0.001$). The mean age of married patients was significantly younger than that of unmarried patients (66.47 ± 12.76 vs 69.54 ± 14.93 , $P < 0.001$). Additionally, more Caucasians and patients with insurance/any Medicaid were found in the married group than in the unmarried group (all $P < 0.001$). For the TNM stage, unmarried patients had a higher percentage of stage IV disease than married patients. More married patients received surgery than unmarried patients (64.0 vs 55.9%, $P < 0.001$). No significant differences were found between the married and unmarried groups regarding tumor primary site, histology, or distant metastasis (M stage).

Influence of marital status on small intestinal adenocarcinoma OS

As shown in Table 2, the 5-year OS for the whole population was 23.6%. The 5-year OS was significantly longer in married patients than in unmarried patients (27.1 vs 18.8%, $P < 0.001$, Figure 1). Younger patients (age at diagnosis < 68 years) had a significantly better 5-year OS than older patients (30.7 vs 16.1%, $P < 0.001$). Surprisingly, the 5-year OS of patients without insurance was significantly better than that of patients with insurance/Medicaid (32.4 vs 23.0%,

Table I Comparison of clinicopathological features between married and unmarried patients with small intestinal adenocarcinoma

Characteristics	Unmarried N=2,885, n (%)	Married N=3,862, n (%)	P
Gender			<0.001
Male	1,139 (39.5)	2,517 (65.2)	
Female	1,746 (60.5)	1,345 (34.8)	
Age (years), mean \pm SD	69.54 \pm 14.93	66.47 \pm 12.76	<0.001
Race			<0.001
White	2,040 (70.7)	3,095 (80.1)	
Black	673 (23.3)	474 (12.3)	
Others ^a	172 (6.0)	293 (7.6)	
Insurance			<0.001
Insured/Medicaid	2,138 (74.1)	2,891 (74.9)	
Uninsured	93 (3.2)	64 (1.7)	
Unknown	654 (22.7)	907 (23.4)	
Tumor primary site			0.066
Duodenum	1,671 (57.9)	654 (58.7)	
Jejunum	374 (13.0)	574 (14.9)	
Ileum	370 (12.8)	475 (12.3)	
Meckel's diverticulum	5 (0.2)	4 (0.1)	
Overlapping lesion of small intestine	38 (1.3)	43 (1.1)	
Small intestine, NOS	427 (14.8)	498 (12.9)	
AJCC seventh TNM stage			0.001
I	191 (6.6)	244 (6.3)	
II	362 (12.5)	489 (12.7)	
III	305 (10.6)	544 (14.1)	
IV	524 (18.2)	665 (17.2)	
Unknown/NA/blank(s)	1,503 (52.1)	1,920 (49.7)	
AJCC seventh T stage			0.008
T0	7 (0.2)	6 (0.2)	
T1	221 (7.7)	278 (7.2)	
T2	65 (2.3)	119 (3.1)	
T3	371 (12.9)	599 (15.5)	
T4	564 (19.5)	750 (19.4)	
TX/unknown/NA/blank(s)	1,657 (57.4)	2,110 (54.6)	
AJCC seventh N stage			0.047
N0	845 (29.3)	1,082 (28.0)	
N1	362 (12.5)	557 (14.4)	
N2	173 (6.0)	266 (6.9)	
NX/unknown/NA/blank(s)	1,505 (52.2)	1,957 (50.7)	
AJCC seventh M stage			0.328
M0	1,024 (35.5)	1,433 (37.1)	
M1	526 (18.2)	666 (17.2)	
Blank(s)	1,335 (46.3)	1,763 (45.6)	
Grade			0.012
Well differentiated	215 (7.5)	292 (7.6)	
Moderately differentiated	1,174 (40.7)	1,629 (42.2)	
Poorly differentiated	848 (29.4)	1,209 (31.3)	
Undifferentiated/anaplastic	34 (1.2)	40 (1.0)	
Unknown	614 (21.3)	692 (17.9)	
Histology			0.676
Other adenocarcinoma	2,542 (88.1)	3,407 (88.2)	
Mucinous adenocarcinoma	234 (8.1)	297 (7.7)	
Signet ring cell	109 (3.8)	158 (4.1)	
Surgery			<0.001
Yes	1,612 (55.9)	2,472 (64.0)	
No	1,257 (43.6)	1,367 (35.4)	
Unknown	16 (0.6)	23 (0.6)	

Note: ^aIncluding American Indian/AK native and Asian/Pacific Islander (N=448) and unknown race (N=17).

Abbreviations: AJCC, American Joint Committee on Cancer; NOS, not otherwise specified; NA, not applicable.

Table 2 Univariate and multivariate analyses of small intestinal adenocarcinoma OS

Characteristics	5-Year OS (%)	Univariate analysis		Multivariate analysis	
		Log-rank χ^2 test	P	HR (95% CI)	P
Marital status		121.810	<0.001		<0.001
Unmarried	18.8			Reference	
Married	27.1			0.789 (0.745–0.836)	
Gender		0.023	0.879		
Male	23.6				
Female	23.6				
Age (years)		387.401	<0.001		<0.001
<68	30.7			Reference	
≥68	16.1			1.515 (1.426–1.610)	
Race		0.421	0.810		
White	24.0				
Black	21.7				
Others ^a	23.3				
Insurance		7.762	0.021		0.703
Insured/Medicaid	23.0			Reference	
Uninsured	32.4			0.914 (0.740–1.128)	
Unknown	24.0			0.998 (0.926–1.076)	
Tumor primary site		325.506	<0.001		<0.001
Duodenum	18.2			Reference	
Jejunum	38.6			0.829 (0.751–0.914)	
Ileum	34.0			0.982 (0.887–1.088)	
Meckel's diverticulum	0			1.632 (0.730–3.646)	
Overlapping lesion of small intestine	28.0			0.967 (0.732–1.276)	
Small intestine, NOS	21.3			1.218 (1.114–1.331)	
AJCC seventh TNM stage		626.818	<0.001		<0.001
I	38.1			Reference	
II	41.0			1.011 (0.852–1.200)	
III	29.8			1.276 (1.080–1.508)	
IV	4.6			1.923 (1.652–2.238)	
Unknown/NA/blank(s)	22.1			1.460 (1.264–1.686)	
Grade		399.771	<0.001		<0.001
Well differentiated	35.1			Reference	
Moderately differentiated	29.8			1.096 (0.969–1.239)	
Poorly differentiated	21.6			1.438 (1.268–1.631)	
Undifferentiated/anaplastic	14.7			1.731 (1.296–2.312)	
Unknown	0.9			1.102 (0.966–1.257)	
Histology		28.093	<0.001		0.002
Other adenocarcinoma	23.8			Reference	
Mucinous adenocarcinoma	27.3			1.042 (0.933–1.164)	
Signet ring cell	12.0			1.287 (1.117–1.483)	
Surgery		2,161.604	<0.001		<0.001
Yes	36.7			Reference	
No	2.9			3.222 (2.983–3.480)	
Unknown	23.8			1.731 (1.118–2.520)	

Note: ^aIncluding American Indian/AK native and Asian/Pacific Islander (N=448) and unknown race (N=17).

Abbreviations: AJCC, American Joint Committee on Cancer; NOS, not otherwise specified; OS, overall survival; NA, not applicable.

$P<0.021$). Compared with other tumor sites, tumors located in the duodenum and Meckel's diverticulum had the lowest 5-year OS at 18.2 and 0%, respectively ($P<0.001$). For the histology subtypes, signet ring cells had worse 5-year OS than mucinous adenocarcinoma and other adenocarcinoma (12.0 vs 27.3 and 23.8%, respectively, $P<0.001$). Unevent-

fully, the 5-year OS of well-differentiated and moderately differentiated small intestinal adenocarcinoma was better than that of poorly differentiated and undifferentiated/anaplastic adenocarcinoma (35.1 and 29.8% vs 21.6 and 14.7%, respectively, $P<0.001$). A total of 4,084 of the 6,747 (60.5%) patients received surgery, and the 5-year OS was

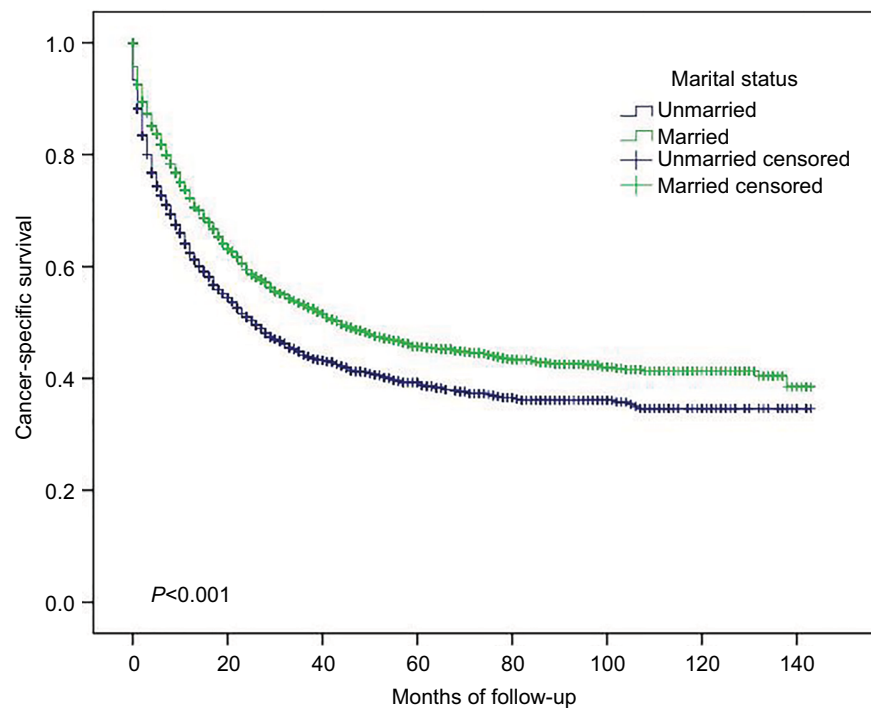


Figure 1 Overall survival in small intestinal adenocarcinoma according to marital status.

better in patients undergoing surgery than in patients without surgery (36.7 vs 2.9%, $P<0.001$). Finally, TNM stage was significantly correlated with OS. The 5-year OS was 38.1, 41.0, 29.8, and 4.6% for stages I, II, III, and IV, respectively ($P<0.001$).

Influence of marital status on small intestinal adenocarcinoma CSS

As shown in Table 3, the 5-year CSS for the whole population was 43.0%. The 5-year CSS was significantly greater in married patients than in unmarried patients (45.7 vs 39.3%, $P<0.001$, Figure 2). Patients whose age at diagnosis were <68 years had significantly better 5-year CSS than older patients (46.7 vs 39.5%, $P<0.001$). Gender, race, and insurance had no influence on 5-year CSS. Tumors located in the duodenum and Meckel's diverticulum had lower 5-year CSS than tumors located in the jejunum, ileum, and small intestine NOS (35.6 and 0% vs 53.5, 57.0, and 57.0%, respectively, $P<0.001$). For histology subtypes, signet ring cells had worse 5-year CSS than mucinous adenocarcinoma and other adenocarcinoma (24.6 vs 48.6 and 43.3%, respectively, $P<0.001$). Additionally, the 5-year CSS of well-differentiated and moderately differentiated small intestinal adenocarcinoma was better than that of poorly differentiated and undifferentiated/anaplastic adenocarcinoma (61.9 and 51.3% vs 38.1 and 34.4%, respectively, $P<0.001$). Patients

undergoing surgery had better 5-year CSS than those without surgery (57.2 vs 10.9%, $P<0.001$). Finally, TNM stage was significantly correlated with CSS. The 5-year CSS was 68.3, 65.4, 44.5, and 11.1%, respectively, for stages I, II, III, and IV ($P<0.001$).

Multivariate analysis

Variables that had a significant association with survival in univariate analysis ($P<0.05$) were enrolled in the multivariate Cox proportional hazards model. As shown in Tables 2 and 3, marital status, age, tumor primary site, TNM stage, grade, histology, and surgery were independent prognostic factors for OS and CSS. Compared with unmarried patients, married patients had an HR of 0.789 (95% CI: 0.745–0.836, $P<0.001$, Table 2) for OS and 0.794 (95% CI: 0.736–0.857, $P<0.001$, Table 3) for CSS.

Subgroup analysis

As shown in Table 4, widowed patients had worse survival (5-year CSS 36.6%) than married (5-year CSS 45.7%), never married (5-year CSS 39.9%), divorced (5-year CSS 43.1%), and separated (5-year CSS 47.7%) patients (similar results were found regarding OS, data not shown). For TNM stages I, II, III, and IV patients, married patients had better OS and CSS than unmarried patients ($P<0.001$, data not shown). Married patients had better CSS than unmarried patients no

Table 3 Univariate and multivariate analyses of small intestinal adenocarcinoma CSS

Characteristics	5-Year CSS (%)	Univariate analysis		Multivariate analysis	
		Log-rank χ^2 test	P	HR (95% CI)	P
Marital status		55.054	<0.001		<0.001
Unmarried	39.3			Reference	
Married	45.7			0.794 (0.736–0.857)	
Gender		1.392	0.238		
Male	43.3				
Female	42.7				
Age (years)		63.046	<0.001		<0.001
<68	46.7			Reference	
≥68	39.5			1.161 (1.075–1.254)	
Race		2.885	0.236		
White	44.1				
Black	38.6				
Others ^a	41.8				
Insurance		0.861	0.650		
Insured/Medicaid	42.6				
Uninsured	43.6				
Unknown	43.6				
Tumor primary site		240.334	<0.001		0.014
Duodenum	35.6			Reference	
Jejunum	53.5			0.840 (0.741–0.951)	
Ileum	57.0			0.851 (0.740–0.978)	
Meckel's diverticulum	0			2.207 (0.913–5.333)	
Overlapping lesion of small intestine	46.5			0.897 (0.624–1.287)	
Small intestine, NOS	48.7			0.967 (0.853–1.096)	
AJCC seventh TNM stage		689.047	<0.001		<0.001
I	68.3			Reference	
II	65.4			1.144 (0.880–1.489)	
III	44.5			1.887 (1.475–2.413)	
IV	11.1			3.191 (2.540–4.008)	
Unknown/NA/blank(s)	42.4			1.995 (1.604–2.482)	
Grade		360.890	<0.001		<0.001
Well differentiated	61.9			Reference	
Moderately differentiated	51.3			1.194 (1.002–1.423)	
Poorly differentiated	38.1			1.749 (1.464–2.090)	
Undifferentiated/anaplastic	34.4			2.030 (1.387–2.971)	
Unknown	22.0			1.290 (1.072–1.552)	
Histology		24.234	<0.001		0.010
Other adenocarcinoma	43.3			Reference	
Mucinous adenocarcinoma	48.6			1.070 (0.924–1.240)	
Signet ring cell	24.6			1.312 (1.096–1.571)	
Surgery		1,546.559	<0.001		<0.001
Yes	57.2			Reference	
No	10.9			3.472 (3.138–3.841)	
Unknown	44.7			1.321 (0.745–2.341)	

Note: ^aIncluding American Indian/AK native and Asian/Pacific Islander (N=448) and unknown race (N=17).

Abbreviations: AJCC, American Joint Committee on Cancer; CSS, cancer-specific survival; NOS, not otherwise specified.

matter whether they received surgery or not (Figure 3, similar results were found regarding OS, data not shown).

Discussion

To the best of our knowledge, this study is the first to examine whether marital status has an effect on survival in small

intestine adenocarcinoma. Marriage has a protective effect on the outcome in small intestine adenocarcinoma, which is consistent with recent reports.^{10–13} Married patients have better 5-year OS and CSS than unmarried patients, including single (never married), widowed, divorced, separated, and unmarried or domestic partner patients. After adjusting for

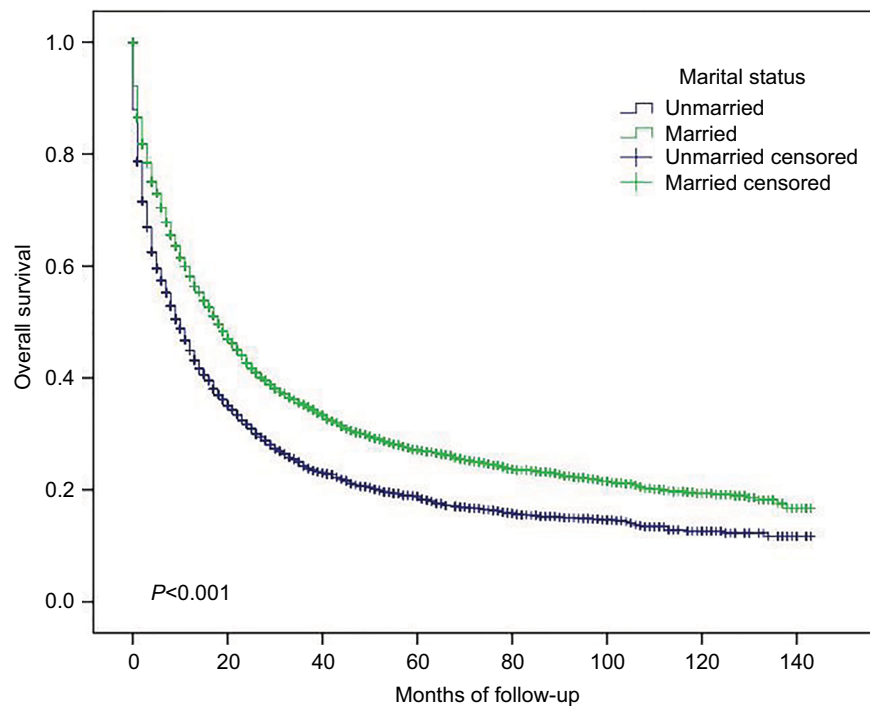


Figure 2 Cancer-specific survival in small intestinal adenocarcinoma according to marital status.

Table 4 Marital status and small intestinal adenocarcinoma CSS

Marital status	n (%)	5-Year CSS (%)	Cox univariate analysis	
			HR (95% CI)	P
Married (including common law)	3,862 (57.2)	45.7	Reference	
Unmarried				
Single (never married)	1,040 (15.4)	39.9	1.229 (1.107–1.366)	<0.001
Widowed	1,197 (17.7)	36.6	1.521 (1.376–1.682)	<0.001
Divorced	583 (8.6)	43.1	1.185 (1.035–1.356)	0.014
Separated	61 (0.9)	47.7	1.094 (0.737–1.652)	0.655
Unmarried or domestic partner	4 (0.1)	0	1.835 (0.459–7.347)	0.391

Abbreviation: CSS, cancer-specific survival.

age, insurance status, tumor primary site, TNM stage, tumor grade, tumor histology, and surgery, the multivariate Cox proportional hazards model showed that marital status was an independent prognostic factor for OS and CSS in small intestine adenocarcinoma. After stratification by TNM stage or surgery, we still found that married patients had better OS and CSS than unmarried patients.

Previous studies demonstrated that African American/black patients have later tumor stages and worse outcomes.^{17,18} The present study shows that there are more Caucasian/white patients than African American/black and other ethnicity patients in the married group. However, we could not find any OS or CSS differences between white, black, and other ethnicity patients in univariate analysis. Thus, race is not a prognostic factor for small intestine adenocarcinoma

and outcome differences between married and unmarried patients could not be explained by race disparities. Studies found that a greater percentage of uninsured patients were unmarried, which predicted poorer outcomes than those of patients with Medicaid or insurance in renal cell carcinoma and other cancers.^{10,19,20} Surprisingly, the present study found an adverse association between insurance and OS in small intestine adenocarcinoma. Patients with insurance/Medicaid had lower 5-year OS than those without insurance, although no differences were found for CSS.

Unmarried patients, lacking spousal care and support, usually live with chronic psychological distress and unhealthy lifestyle habits, such as smoking and alcohol abuse, resulting in disease progression and undertreatment.^{21–23} Unmarried patients also tend to have latter stages

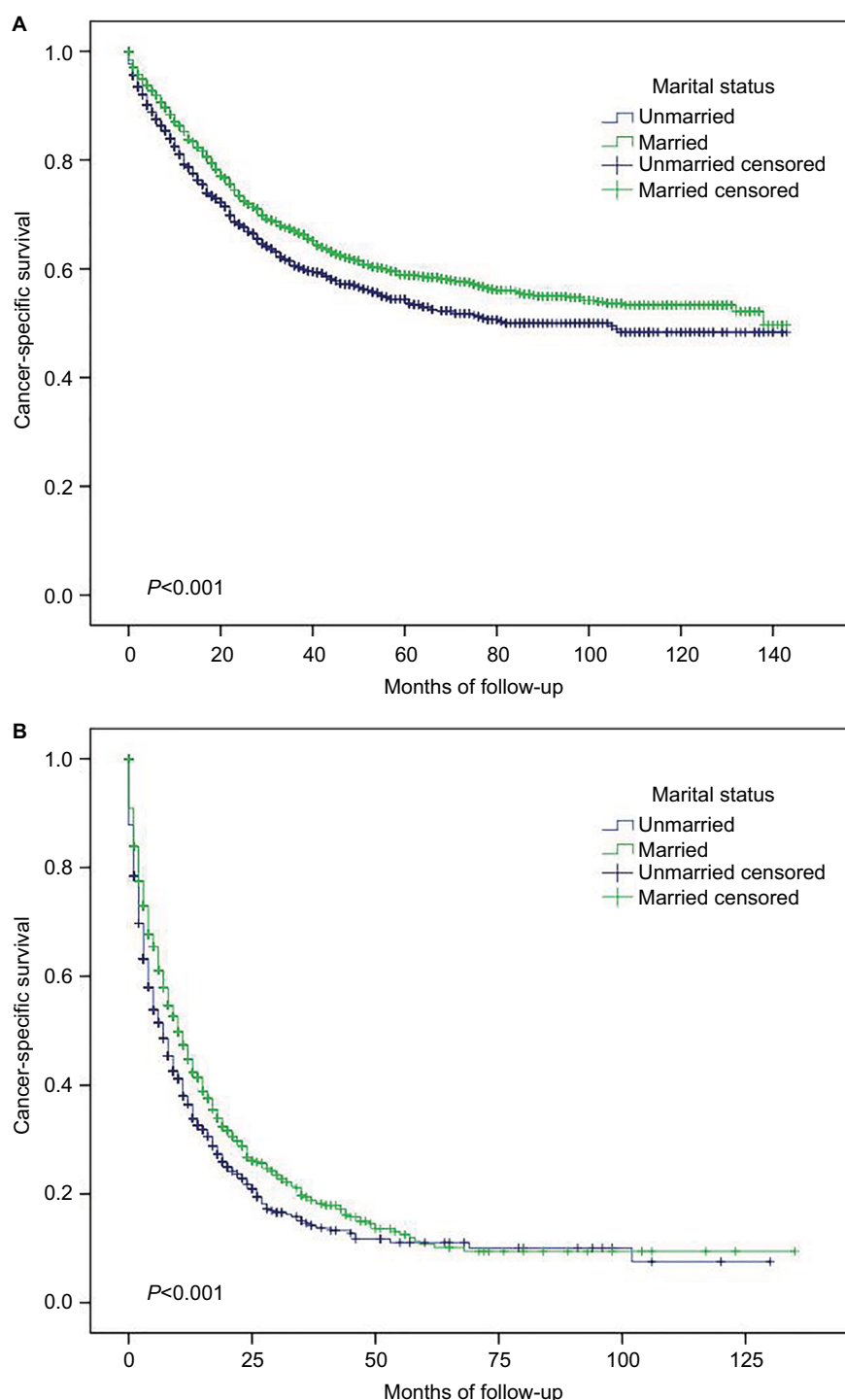


Figure 3 Subgroup analysis of cancer-specific survival in small intestinal adenocarcinoma according to marital status.

Notes: (A) Surgery, $P < 0.001$. (B) No surgery, $P < 0.001$.

of disease.¹³ Hershman et al²⁴ reported that unmarried patients were more likely to delay the initiation of adjuvant chemotherapy after breast cancer surgery, leading to higher mortality. Our results are in line with those of previous studies, as we found a higher percentage of stage IV disease in unmarried patients than in married patients

and that unmarried patients were less likely to receive surgery than married patients (55.9 vs 66.0%, $P < 0.001$). Encouragement and economic supports from the spouses of the married patients contributed to their compliance with surgery and adjuvant therapy, which may partly account for the discrepancies.^{25,26}

Our study should be interpreted with caution due to the limited nature of the SEER database. First, some clinicopathological features, such as tumor grade, TNM stage, and surgery status, had missing data. Second, lifestyle, socioeconomic status, and adjuvant therapy were not included in the database. Finally, the database recorded marital status only at diagnosis and not thereafter. All these restrictions may have led to an unreliable conclusion.

Despite the above limitations, our study indicates that marital status is an independent prognostic factor in small intestine adenocarcinoma. Married patients have better OS and CSS than unmarried patients. Psychological and economic supports from the spouses of married patients may contribute to the improved survival.

Conclusion

Married small intestinal adenocarcinoma patients have better OS and CSS than unmarried patients. Psychological and economic supports from the spouses of married patients may contribute to improvements in survival.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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