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The effect of marital status on the survival of patients with colorectal neuroendocrine neoplasms: an analysis of the SEER database

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ABSTRACT

Background: increasing evidence suggests that marital status is associated with tumor prognosis. The prognostic impact of marital status on colorectal neuroendocrine neoplasms has not been studied adequately. This study explored the relationship between marital status and prognosis of colorectal neuroendocrine neoplasms.

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Methods: during 2004-2012, 7,180 colorectal neuroendocrine neoplasm patients were identified from the Surveillance, Epidemiology and End Results database. A primary comparison (married *vs* unmarried) was performed with a 1:1 propensity matching score. Secondary comparisons were performed individually between three unmarried subgroups (single, divorced/separated, widowed) and the married group. The effect of marital status according to sex and extension of disease was explored.

Results: married patients had better survival (overall survival) ($p < 0.001$) and colorectal neuroendocrine neoplasm cause-specific survival ($p = 0.001$) rates compared to unmarried patients. Multivariate analysis indicated that marital status was an independent prognostic factor and married patients had a better overall survival (HR = 1.673; 95% CI: 1.446-1.936; $p < 0.001$) and colorectal neuroendocrine neoplasm cause-specific survival (HR = 1.365; 95% CI: 1.141-1.632; $p = 0.001$). Subgroup analysis showed that married patients had the best prognosis of cause-specific survival/overall survival and widowed patients had the worst prognosis (log-rank test $p < 0.05$). Marital status plays a more important role in colorectal neuroendocrine neoplasms patients with localized disease than in those with regional or distant disease.

Conclusions: marital status is an independent prognostic factor for survival in colorectal neuroendocrine neoplasms patients. Married patients have a better prognosis with early stage disease. Single, widowed and male patients are regarded as a high-risk population.

Keywords: Colorectal neuroendocrine neoplasms. Marital status. SEER. Prognosis.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a heterogeneous group of malignancies. For functional purposes, NENs are divided into two groups on the basis of clinical behavior, histology, and proliferation rate as well differentiated (low grade to intermediate grade) neuroendocrine tumors (NETs) and poorly differentiated (high grade) neuroendocrine neoplasms (1). High-grade neuroendocrine neoplasms, also known as neuroendocrine carcinomas (NECs), have a high mitotic rate (over 20/10

HPF) and Ki-67 proliferation index (over 20%) (2,3). They are often diagnosed at an advanced stage and are quite aggressive, with a poor prognosis (4).

Previous studies have proved that marital status is an independent prognostic factor of survival in some cancers and married patients have better survival rates in colorectal cancer, gastric cancer, lung cancer and breast cancer (5-8). Marital status is an independent prognostic factor for gastric NET and unmarried patients were at high risk of cancer-related death from gastric NET (9). However, the impact of marital status on colorectal neuroendocrine neoplasm (CRNEN) survival has not been rigorously studied, with only limited knowledge.

The Surveillance, Epidemiology and End Results (SEER) database covers about 30% of the population in the United States and has been widely used to explore the relationship between marital status and the survival of cancer patients (5,8,10). The SEER database was used in this study to explore the survival rates according to marital status in colorectal neuroendocrine neoplasm patients.

MATERIALS AND METHODS

Data source

This was a retrospective study. Data from patients with a histological diagnosis of CRNEN between January 2004 and December 2012 was extracted from the SEER database (1973-2015) using the SEER*Stat software version 8.3.5. The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) morphology codes including 8013, 8041, 8240, 8241, 8244, 8246 and 8249 were used to identify CRNEN . All colorectal anatomical sites (C18.0, C18.2-C18.9, C19.9, C20.9) were included in the study, including C18.0-Cecum, C18.2-Ascending colon, C18.3-Hepatic flexure of colon, C18.4-Transverse colon, C18.5-Splenic flexure of colon, C18.6-Descending colon, C18.7-Sigmoid colon, C18.8-Overlapping lesion of colon, C18.9-Colon, NOS, C19.9-Rectosigmoid junction and C20.9-Rectum, NOS. Given that several covariates used in this study were introduced in SEER in 2004, this year was selected as the first year of the study. The available SEER data were limited to 2015, thus 2012 was set as the follow-up cutoff date to ensure that all eligible cases were followed up for at least three years.

Patients were excluded from the study cohort if they: a) had more than one primary cancer; b) age at diagnosis was < 18 years; c) marital status was unknown; d) there was an unknown cause of death; and e) the survival time was less than one month or unknown.

This study was based on the public data (the SEER database) and permission was obtained to access this data for the purpose of research only. This was not an interventional study and did not use personal identifying information. Therefore, informed consent for the study was not required. The authors have no conflicts of interest to declare.

Variables

The data was extracted from the SEER database, including sex, age, race, primary tumor site, TNM stage, tumor size, pathology grade, extent of disease, surgical treatment and marital status. Patients were divided into two groups according to age at diagnosis (≤ 60 years *vs* > 60 years). Race was divided into white, black and others. According to the SEER staging system, disease extension was categorized using the Collaborative Stage classification criteria, including localized, regional and distant. The TNM stage was determined according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition). In the SEER database, marital status was divided into married, widowed, divorced, separated, single (never married) and unmarried or domestic partner. Patients were classified as married and unmarried (including single, divorced, separated and widowed).

Outcomes

The outcomes of this study were overall survival (OS) and colorectal neuroendocrine neoplasm cause-specific survival (CSS). OS was defined as the time from diagnosis to the date of death due to any cause. CSS was derived from the time of diagnosis to the date of CRNEN cancer-specific death. Death attributed to CRNEN was regarded as an event. Patients who died from other causes or were still alive at the follow-up cutoff date were treated as censored observations. The follow-up cutoff date was December 31, 2012.

Statistical analyses

All data are expressed as frequencies. Quantitative data were transformed into qualitative data. The differences between baseline characteristics of the groups were analyzed using the Chi-squared test. OS and CSS were calculated using the Kaplan-Meier method and the differences between groups were compared using the log-rank test. Moreover, the univariate and multivariate Cox regression method was used to quantitatively determine the effect of marital status on survival. Hazard ratios (HRs) refer to mortality. Based on our expertise, we included variables that might be related to the prognosis of CRNEN in the univariate analysis and subsequently, the meaningful variables of univariate analysis ($p < 0.05$) were included in the multivariate analysis. A forest plot was used to express the results of Cox regression using GraphPad Prism 7.

To mimic the randomized controlled trials and minimize the influence of potential confounders on selection bias, a 1-to-1 propensity score matching method without replacement was performed using the nearest-neighbor method with a stringent caliper of 0.05. All statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient characteristics

In the present study, 7,180 eligible CRNEN patients diagnosed in the SEER database from 2004 to 2012 were identified. The baseline characteristics of patients stratified by marital status are summarized in table 1. Of these, 4,704 (65.5%) were married and 2,476 (34.5%) were unmarried. Before matching, significant differences were found with regard to age, race, sex, primary tumor site, tumor size, grade, disease extension and surgery ($p < 0.05$) between married and unmarried patients. After the propensity score matching, the differences between these groups were eliminated, with the exception of race.

Among married patients, male patients (2,546, 54.1%) were more frequent than female patients (2,158, 45.9%). In the localized stage group, the proportion of

married patients (3,403, 72.3%) was higher than that of unmarried patients (1,675, 67.6%). However, there was a higher proportion of advanced stage tumors in unmarried patients (14.2%) as compared to married patients (10.4%) (Table 1).

Marital status and overall survival (OS)

There were significant differences according to marital status both before and after matching (log-rank test $p < 0.001$), as shown in the OS Kaplan-Meier curve (Fig. 1A and C). Married patients had a better OS than unmarried cases. After matching, several covariates were significantly associated with OS according to the univariate log-rank test ($p < 0.05$), including age, sex, race, primary site, tumor size, tumor grade, disease extension, AJCC group and surgical treatment (Table 2). Marital status was an independent prognostic factor, even after propensity score matching in the Cox proportional hazards regression model. Married patients had a better OS than unmarried patients (hazard ratio [HR] = 1.673; confidence interval [95% CI]: 1.446-1.936; $p < 0.001$].

Marital status and colorectal neuroendocrine neoplasm cause-specific survival (CSS)

As displayed in figure 1B and D, unmarried patients had an increased risk of colorectal neuroendocrine neoplasm-caused mortality compared with married cases. There were significant differences according to marital status both before and after matching (log-rank test $p < 0.001$ *vs* log-rank test $p = 0.001$). Univariate analysis showed that sex, race, age, primary tumor site, tumor size, tumor grade, disease extension, AJCC group and surgical treatment were regarded as significant factors for CSS ($p < 0.05$) (Table 2). The Cox regression analysis still suggested that marital status was an independent prognostic factor, with a better CSS among married patients (HR = 1.365; 95% CI: 1.141-1.632; $p = 0.001$). Race was an independent prognostic factor for OS ($p = 0.001$) in CRNEN patients but not an independent prognostic factor for CSS ($p = 0.491$).

Subgroup analysis of the effect of marital status

The effect of marital status on CSS and OS in the secondary comparison determined the prognostic relationship between married and unmarried subtypes (single, divorced/separated, widowed). As shown in figure 1E and F, married patients had the best prognosis according to CSS/OS, whereas widowed patients had the worst prognosis (log-rank test $p < 0.05$).

A forest plot was used to assess the effect of marital status on CSS/OS in three 1-to-1 matched cohorts in the secondary comparison, which were: single *versus* married (n = 2,604; 1,302 *vs* 1,302); divorced/separated *versus* married (n = 1,138; 569 *vs* 569); and widowed *versus* married (n = 710; 355 *vs* 355) (Fig. 2). Single patients (CSS: HR = 1.350, 95% CI = 1.061-1.719, p = 0.015; OS: HR = 1.533, 95% CI = 1.258-1.868, p < 0.001), widowed patients (CSS: HR = 1.478, 95% CI = 1.194-1.828, p < 0.001; OS: HR = 1.430, 95% CI = 1.701-2.023, p < 0.001), except divorced/separated patients (CSS: HR = 1.305, 95% CI = 0.921-1.849, p = 0.135; OS: HR = 0.963, 95% CI = 0.732-1.268, p = 0.789), were more likely to have poorer survival outcomes as compared to married patients.

Subgroup analysis of the effect of marital status according to sex and extension of disease

The effects of marital status on survival in the male and female subgroups were assessed. Figure 2 shows the Kaplan-Meier survival analysis with regard to marital status in male and female patients. For male patients, the five-year OS and CSS were 85.7% and 88.6% for the married group *versus* 75.9% and 75.9% for the unmarried patients (log-rank test Pos < 0.001; log-rank test PCSS = 0.011). Regarding female patients, the OS and CSS of the married groups were also higher than those of unmarried patients (log-rank test Pos < 0.001; log-rank test PCSS = 0.025) (Table 3). The multivariate analysis revealed that marital status was an independent risk factor for OS and CSS according to sex ($p < 0.05$). Patients were divided into three subgroups by disease extension: localized (2,976), regional (329) and distant (446). Univariate and multivariate analysis showed that married status was an independent prognostic factor for CSS in localized disease (PCSS = 0.022), but not in regional disease (PCSS = 0.073) or distant stage disease (PCSS = 0.080) (Table 3 and Figure 3).

DISCUSSION

In this study, the relationship between marital status and survival outcomes in patients with CRNEN was explored using the SEER database. Being married had a positive effect on survival compared to any unmarried status. A better prognosis in married patients may be associated with an early tumor stage. Single, widowed and male patients are regarded as the high-risk population.

Several potential mechanisms may explain the association between marital status and survival. Firstly, patients who are married have less distress and depression (11) than unmarried patients after a diagnosis of cancer, as a partner can share the emotional burden and provide the appropriate social support (12). Chronic stress, loneliness and depression can down regulate the cellular immune response (13), stimulate tumor angiogenesis (14) and increase tumor burden and invasiveness (15,16). Secondly, patients with emotional and financial support from their spouses or children had a better compliance from doctors (17,18). Emotional support may increase well-being among cancer survivors by reducing cancer mortality (19). KB Ehrlich et al. (20) showed that pre-transplant emotional support was marginally associated with lower rates of mortality in the allogeneic hematopoietic stem cell transplantation patients. Thirdly, marital status has an influence on the diagnosis and treatment of patients (10). It has been shown that married patients have better prognosis as a result of diagnosis and therapy at an early stage (21-23), which are consistent with the results found in this study. Unmarried patients are often diagnosed at later tumor stage and they often receive insufficient treatment (24). Recent research shows that married patients are more likely to present with earlier clinically localized melanoma and never married, divorced and widowed patients are less likely to accept the appropriate treatment for lesions (25). Clinical medical workers should pay attention to the marital status of CRNEN patients. Furthermore, society should consider social support services and psychological interventions that may help to reduce the significant survival differences between married and unmarried patients with cancer.

Another interesting finding is that female patients have a better prognosis than male

patients. The extent of the protective effect of marriage depended on the sex of patients, and males had more than a 50% increased risk of a late-stage diagnosis than females (26). Recent studies have shown that females diagnosed at an early stage have a better prognosis than males in colorectal cancer (27). This is especially true for male widows with a poor prognosis; more care should be given as well as an effective treatment. Regular follow-up to help improve psychological problems may improve the prognosis of patients. We found that race had an impact on the prognosis of CRNEN patients. However, when we studied the prognostic impact of marital status on CRNEN patients, PSM was used to eliminate the influence of racial factors on the results. Therefore, the study is representative and scientific.

However, the limitations of the study should be considered. First, the criteria for the diagnosis of neuroendocrine tumors has also changed over time (9). Second, whether the marital status of patients has changed during treatment remains unknown. Third, the SEER database does not provide the quality of marriage, which can also influence the survival results (28). Fourth, some patients may be cohabiting with a partner without being married. In fact, these patients who were considered as unmarried in the SEER database would have a better prognosis and this would bias the results (24). Fifth, geographical location may also affect the outcome. This was not included in the study due to the variability in geographical location. Finally, the SEER database lacks more detailed data on treatment, comorbidities, economic situation and recurrence. Further studies are needed to confirm these findings.

AUTHOR CONTRIBUTIONS

X.X. Liu and K.S. Xiao were responsible for the conception and design of the study, interpretation of data and drafting and writing of the article.

Y. Zhao and P. Chen were responsible for the acquisition, analysis and interpretation of the data, drafted the text and also participated in the drafting of the article.

Y.J. Cai, J.J. Chen, B. Yuan and R.J. Ye were responsible for the interpretation of data and the review of the intellectual content.

All authors participated in the final approval of the article and agreed to be accountable for all aspects of the work.

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Table 1. Baseline characteristics of CRNEN patients before and after propensity score matching

	Before matching n (%)			After matching n (%)		
Characteristics	Married 4,704 (65.5)	Unmarried 2,476 (34.5)	p-value	Married 2,032 (50.0)	Unmarried 2,032 (50.0)	p-value
Age			< 0.001			0.843
< 60	3,182 (67.6)	1,537 (62.1)		1,335 (65.7)	1,341 (66.0)	
≥ 60	1,522 (32.4)	939 (37.9)		697 (34.3)	691 (34.0)	
Race			< 0.001			0.006
White	3,126 (66.5)	1,424 (57.5)		1,295 (63.7)	1,256 (61.8)	
Black	732 (15.6)	783 (31.6)		464 (22.8)	544 (26.8)	
Others	846 (18.0)	269 (10.9)		273 (13.4)	232 (11.4)	
Sex			< 0.001			0.899
Male	2.546 (54.1)	988 (39.9)		869 (42.8)	873 (43.0)	
Female	2,158 (45.9)	1,488 (60.1)		1,163 (57.2)	1,159 (57.0)	
Primary site			0.017			0.622
Colon	1,288 (27.4)	744 (30.0)		560 (27.6)	546 (26.9)	
Rectal	3,412 (72.6)	1,732 (70.0)		1,472 (72.4)	1,486 (73.1)	
Tumor size			< 0.001			0.630
< 1 cm	1,670	779 (31.5)		724 (35.6)	709 (34.9)	

	(35.5)					
1-2 cm	362 (7.7)	198 (8.0)		165 (8.1)	147 (7.2)	
2-5cm	488 (10.4)	279 (11.3)		213 (10.5)	203 (10.0)	
≥ 5 cm	284 (6.0)	216 (8.7)		122 (6.0)	134 (6.6)	
Unknown	1,900 (40.4)	1,004 (40.5)		808 (39.8)	839 (41.3)	
Grade			< 0.001			0.183
Grade I	997 (21.2)	512 (20.7)		433 (21.3)	420 (20.7)	
Grade II	226 (4.8)	116 (4.7)		85 (4.2)	74 (3.6)	
Grade III	261 (5.5)	190 (7.7)		94 (4.6)	128 (6.3)	
Grade IV	111 (2.4)	88 (3.6)		50 (2.5)	48 (2.4)	
Unknown	3,109 (66.1)	1,570 (63.4)		1,370 (67.4)	1,362 (67.0)	
Disease extension			< 0.001			0.290
Localized	3,403 (72.3)	1,675 (67.6)		1,492 (73.4)	1,484 (73.0)	
Regional	421 (8.9)	243 (9.8)		173 (8.5)	156 (7.7)	
Distant	488 (10.4)	352 (14.2)		206 (10.1)	240 (11.8)	
Unknown	392 (8.3)	206 (8.3)		161 (7.9)	152 (7.5)	
AJCC group			0.222			0.593
I/II	824 (17.5)	430 (17.4)		400 (19.7)	376 (18.5)	
III/IV	313 (6.7)	192 (7.8)		114 (5.6)	121 (6.0)	
Unknown	3,567 (75.8)	1,854 (74.9)		1,518 (74.7)	1,535 (75.5)	
Surgery			< 0.001			0.262
Performed	3,913 (83.2)	1,973 (79.7)		1,697 (83.5)	1,678 (82.6)	
Not performed				321 (15.8)	346 (17.0)	

Unknown	744 (15.8) 47 (1.0)	488 (19.7) 15 (0.6)	14 (0.7)	8 (0.4)

SEER: Surveillance, Epidemiology and End Results; CRNEN: colorectal neuroendocrine neoplasms; AJCC: American Joint Committee on Cancer.

Table 2. Univariate and multivariate analysis of the effect of marital status on survival outcomes in CRNEN

Characteristics	OS			CSS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	p	HR (95% CI)	p		HR (95% CI)	p
Age	< 0.001			< 0.001		
≤ 60		Reference			Reference	
> 60		2.440 (2.094-2.844)	< 0.001		1.778 (1.469-2.153)	< 0.001
Race	< 0.001		0.001	< 0.001		0.491
White		Reference			Reference	
Black		1.242 (1.025-1.505)	0.027		0.976 (0.736-1.295)	0.868
Others		0.654 (0.469-0.912)	0.012		0.772 (0.504-1.181)	0.233
Sex	< 0.001			0.007		
Male		Reference			Reference	
Female		0.741 (0.643-0.855)	< 0.001		0.811 (0.679-0.969)	0.021
Site	< 0.001			< 0.001		
Colon		Reference			Reference	
Rectal		0.981 (0.812-1.185)	0.841		1.058 (0.841-1.331)	0.631
Size	< 0.001		0.001	< 0.001		0.001
< 1 cm		Reference			Reference	
1-2 cm		1.277 (0.859-1.900)	0.227		1.435 (0.656-3.141)	0.366
2-5 cm		1.447 (1.029-2.035)	0.034		2.044 (1.045-4.000)	0.037
≥ 5 cm		1.993 (1.412-	<		3.200 (1.754-	0.002

		2.814)	0.001		5.839)	
Unknown		1.500 (1.128-1.995)	0.005		2.144 (1.120-4.105)	0.021
Grade	< 0.001		< 0.001	< 0.001		< 0.001
Grade I		Reference			Reference	
Grade II		1.562 (1.056-2.309)	0.026		2.788 (1.700-4.574)	< 0.001
Grade III		3.713 (2.792-4.937)	< 0.001		5.767 (3.877-8.578)	< 0.001
Grade IV		4.864 (3.532-6.697)	< 0.001		7.105 (4.656-10.843)	< 0.001
Unknown		1.270 (0.992-1.624)	0.058		1.990 (1.355-2.924)	< 0.001
Extension	< 0.001		< 0.001	< 0.001		< 0.001
Localized		Reference			Reference	
Regional		3.903 (2.875-5.300)	< 0.001		21.687 (12.923-36.393)	< 0.001
Distant		10.98 (8.292-14.542)	< 0.001		67.562 (0.986-111.37)	< 0.001
Unknown		0.847 (0.575-1.247)	0.400		2.376 (1.197-4.716)	0.013
AJCC group	< 0.001		0.404	< 0.001		0.300
I/II		Reference			Reference	
III/IV		1.264 (0.789-2.024)	0.330		0.585 (0.244-1.403)	0.230
Unknown		1.325 (0.859-2.044)	0.202		0.667 (0.283-1.283)	0.353
Surgery	< 0.001		< 0.001	< 0.001		< 0.001

Yes		Reference			Reference	
No		2.112 (1.745-2.557)	< 0.001		2.251 (1.760-2.879)	< 0.001
Unknown		0.761 (0.279-2.076)	0.594		1.053 (0.329-3.373)	0.930
Marriage	< 0.001			0.001		
Married		Reference			Reference	
Unmarried		1.673 (1.446-1.936)	< 0.001		1.365 (1.141-1.632)	0.001

OS: overall survival; CSS: cause-specific survival; SEER: Surveillance, Epidemiology and End Results; CRNEN: colorectal neuroendocrine neoplasms; AJCC: American Joint Committee on Cancer; 95% CI: 95% confidence interval; HR: hazard ratio.

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Table 3. Univariate and multivariate survival analysis of colorectal neuroendocrine neoplasm survival based on different sex and disease extension

Characteristic	5-year survival	Univariate analysis		Multivariate analysis		
		Log-rank χ^2	p-value	HR	95% CI	p-value
Overall survival						
Male		29.989	< 0.001			
Married	85.7%			Reference		
Unmarried	75.9%			1.765	1.430-2.178	< 0.001
Female		17.595	< 0.001			
Married	88.2%					
Unmarried	81.7%			1.610	1.313-1.973	< 0.001
Localized		42.986	< 0.001			
Married	97.3%			Reference		
Unmarried	91.8%			2.605	1.950-3.479	< 0.001
Regional		12.690	< 0.001			
Married	73.1%			Reference		
Unmarried	52.8%			1.578	1.116-2.231	0.010
Distant		3.950	0.047			
Married	20.0%			Reference		
Unmarried	14.4%			1.257	1.022-1.547	0.030
CSS						
Male		29.989	< 0.001			
Married	88.6%			Reference		
Unmarried	75.9%			1.765	1.430-2.178	< 0.001
Female		17.595	< 0.001			
Married	88.2%			Reference		
Unmarried	81.7%			1.610	1.313-1.973	< 0.001
Localized		4.020	0.045			
Married	99.5%			Reference		
Unmarried	98.6%			2.542	1.144-5.651	0.022
Regional		7.865	0.005			

Married	77.4%			Reference		
Unmarried	65.5%			1.465	0.966-2.222	0.073
Distant		2.325	0.127			
Married	21.1%			Reference		
Unmarried	16.3%			1.208	0.977-1.494	0.080

SEER: Surveillance, Epidemiology and End Results; 95% CI: 95% confidence interval; HR: hazard ratio; CSS: cause-specific survival; AJCC: American Joint Committee on Cancer.

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Figure 1

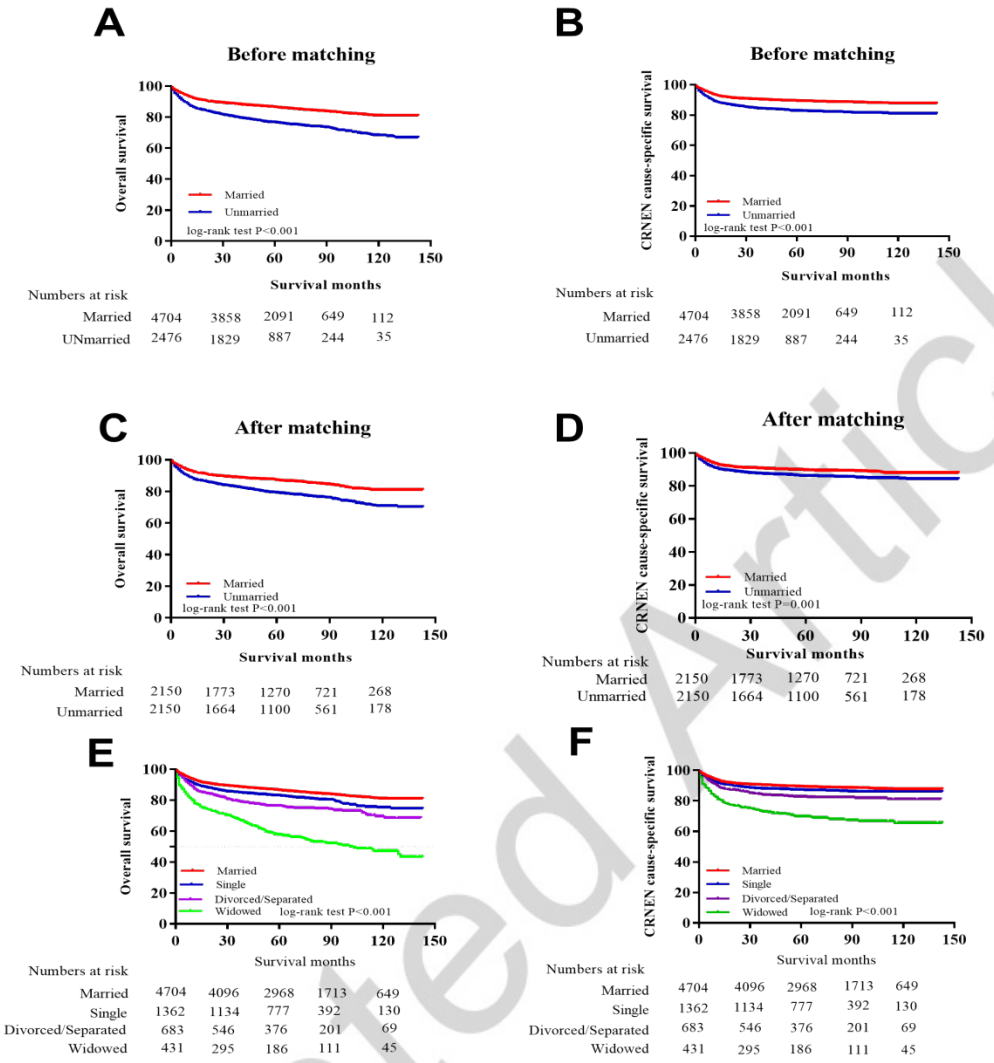

Fig. 1. Survival curves of married and unmarried patients with colorectal neuroendocrine neoplasms, before matching (A and B) and after matching (C-F). A. Overall survival (OS): Chi^2 = 123.344, p < 0.001. B. Colorectal neuroendocrine neoplasms cause-specific survival (CSS): Chi^2 = 58.051, p = 0.002. C. Overall survival (OS): Chi^2 = 46.761, p < 0.001. D. Colorectal neuroendocrine neoplasm cause-specific survival (CSS): Chi^2 = 11.498, p = 0.001. Kaplan-Meier survival curves of different marriage subgroups in CRNEN patients (n = 7,180). E. Overall survival (OS): Chi^2 = 301.5, p < 0.001. F. Colorectal neuroendocrine neoplasm cause-specific survival (CSS): Chi^2 = 158.8, p < 0.001.

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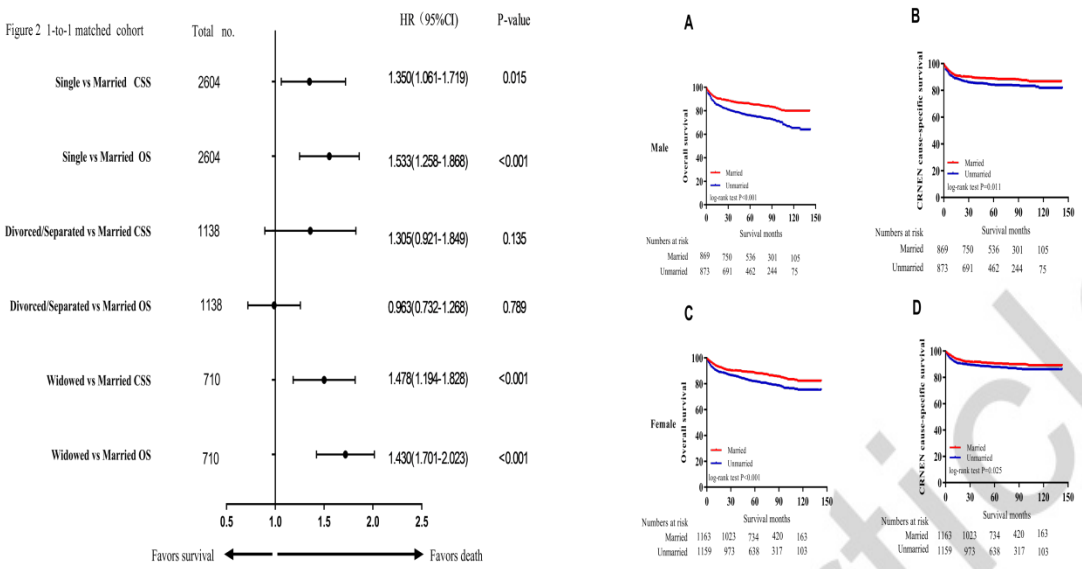

Fig. 2. A. Male, overall survival (OS): Chi^2 = 29.989, p < 0.001. B. Male, colorectal neuroendocrine neoplasm cause-specific survival (CSS): Chi^2 = 6.492, p = 0.011. C. Female, OS: Chi^2 = 17.595, p < 0.001. D. Female, CSS: Chi^2 = 5.017, p = 0.025.

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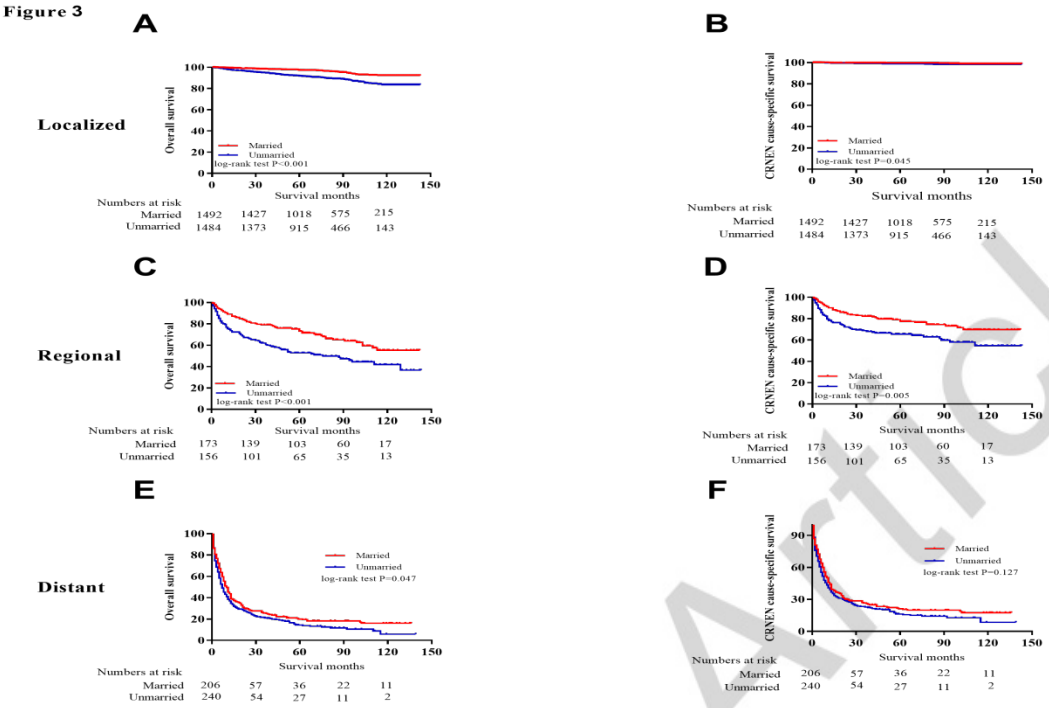

Fig. 3. Survival curves in different stage subgroups according to marital status of CRNEN patients. A. Localized, OS: $Chi^2 = 42.986$, $p < 0.001$. B. Localized, CSS: $Chi^2 = 4.020$, $p = 0.045$. C. Regional, OS: $Chi^2 = 12.690$, $p < 0.001$. D. Regional, CSS: $Chi^2 = 7.865$, $p = 0.005$. E. Distant, overall survival (OS): $Chi^2 = 3.950$, $p = 0.047$. F. Distant, CSS: $Chi^2 = 2.325$, $p = 0.127$.