The effect of marital status on the survival of patients with bladder urothelial carcinoma
A SEER database analysis

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Abstract
To identify whether marital status is associated with survival in patients with bladder urothelial carcinoma (UC). Using Surveillance, Epidemiology, and End Results population-based data, 133,846 patients diagnosed with bladder UC between 1988 and 2009 were identified. Kaplan–Meier methods and multivariable Cox regression models were used for survival analyses and evaluation of the association between marital status and survival, after controlling for gender, age, race, primary site, tumor (topography), lymph node, metastasis stage, pathological grading, and surgery. Patients in the married group had a higher proportion of men within group comparisons, more often white, older, earlier clinical stage at diagnosis, surgical treatment, all of which were statistically significant (P < .001). Widowed patients had the worst bladder UC cause-specific survival (CSS) compared with married, never married, and so on groups classified by stage and grade. The 5-year CSS of widowed patients compared with that of married patients was, respectively, all (P < .001), 89.8% versus 95.8% at noninvasive papillary carcinoma stage, 84.1% versus 91.6% at occur in situ stage, 74.3% versus 86.1% at I stage, 41.2% versus 61.6% at II stage, 39.2 versus 52.5% at III stage, and 8.8% versus 17.0% at IV stage. Widowed patients tend to have a significantly higher risk of bladder-cancer-specific mortality. Marital status was relevant to improved CSS in patients with bladder UC.

Abbreviations: CI = confidence interval, CSS = cause-specific survival, HR = hazard ratio, MPBC = micropapillary urothelial bladder carcinoma, OA = noninvasive papillary carcinoma, OIS = occur in situ, SEER = Surveillance, Epidemiology, and End Results, TNM = tumor (topography), lymph node, metastasis, UC = urothelial carcinoma, VEGF = vascular endothelial growth factor.

Keywords: bladder urothelial carcinoma, grade, marital status, Surveillance, Epidemiology, and End Results (SEER), TNM stage

1. Introduction
Bladder cancer is the fourth most common cancer in the United States and the ninth most common malignancy worldwide, urothelial carcinoma (UC) that originates from the bladder is the most common subtype.1,2 Marital status has been confirmed to affect the survival rates in many tumors. Cancer patients being married have better survival, with colorectal, gallbladder, prostate, and breast carcinoma.3–6 Similarly, Klaassen et al7 and Gore et al8 reported that patients with bladder cancer who were unmarried had higher mortality than those who had been married. There are many different mechanisms to explain the association between cancer survival and marital status. Marital status is commonly used as a marker of social support. Those patients who are married may enjoy increased financial resources, can experience social support,9 may have high quality of life, tend to have a healthier lifestyle,10 will receive better treatment11 than those who are unmarried.

In addition, Li et al12 have demonstrated that despite favorable clinic-pathological characteristics, widowed patients in colorectal cancer were at highest risk of death compared with other groups in a larger population-based study on data from the Surveillance, Epidemiology, and End Results (SEER) database. However, there are few studies explored the effect of marital status on the survival of bladder UC according to stage and grade at diagnosis. Therefore, we used the data from the SEER cancer registries diagnosed between 1988 and 2009 to explore the relationship between marital status and the survival of bladder UC.

2. Methods
2.1. Patient selection in the SEER database
The SEER Cancer Statistics Review is an authoritative source of information on cancer incidence and survival in the United States. The current SEER database consists of
17 population-based cancer registries that represent approximately 28% of the population in the United States. The SEER data contains cancer-based demographics, the tumor primary site and stage at diagnosis, surgical treatment, the follow-up of survival, and so on.

Using the National Cancer Institute’s SEER*Stat software (Version 8.3.4; www.seer.cancer.gov/seerstat), we identified bladder UC patients diagnosed between 1988 and 2009 with a known marital status. Primary site codes C67.0 to C67.9 and histological type codes were UC (8120/3, 8122/3, 8130/3, 8131/3, 8082/3, 8020/3, 8031/3). Patients with nonprimary bladder UC were excluded. The cause of death and survival of all patients were clearly known, as well as, ethnic information and tumor (topography), lymph node, metastasis (TNM) stage.

2.2. Ethical approval

The current research does not contain any studies with human participants or animals performed by any of the authors.

2.3. Description of covariates

Gender, age, race, primary site, pathology grade, survival, cause-specific survival (CSS), and reason no cancer-directed surgery were recruited from the SEER database. The TNM stage group derived by the American Joint Committee on Cancer, Cancer Staging Manual (7th edition, 2010). We divided patients into 4 groups “married,” “widowed,” “single (never married),” and “divorced/separated.” Patients with unknown marital status and TNM stage were excluded. Pathology grade was divided into 3 groups, low grade (well differentiated; grade I), high grade (poorly differentiated; grade III/undifferentiated; anaplastic, grade IV), and unknown group. Primary sites include wall of bladder (C67.2, C67.3, C67.4), trigone of bladder (C67.0, 67.5, C67.6), dome of bladder (C67.1, C67.7), bladder (C67.8, C67.9). Other covariates involved, race recode (white, black, other), age group (<60 or ≥60), and surgery performed (yes or no).

2.4. Statistical analysis

Descriptive statistics for the patient baseline characteristics were analyzed using the chi-square test. Using the Kaplan–Meier method compared the death rate of bladder UC between groups and generated the survival curves. Multivariate Cox regression models were built to analyze the risk factors on survival outcomes. The primary observation point of present study was the CSS of bladder UC, which referred to the time between the date of diagnosis and cancer-specific death. Deaths attributed to bladder UC were treated as events and deaths from other causes were treated as censored observations. All statistical analyses were performed using the statistical software package SPSS (SPSS Inc, Chicago, IL) 22.0. All tests were 2-sided, and statistical significance was defined as P < .05.

3. Results

3.1. Patient baseline characteristics

A total of 133,846 eligible patients were identified from SEER database during the 21-year study period (between 1988 and 2009), including 101,411 male and 32,435 female patients. Bladder UC is 3 times more common in men than in women in the United States. Among these patients, 89,187 (66.6%) married, 20,893 (15.6%) widowed, 13,274 (9.9%) single (never married), and 10,492 (7.8%) divorced/separated. Within group comparisons, the widowed group had the higher proportion of women (53.9%), white race (90.8%), older (≥60 years) patients (97.4%), bladder (primary site) (49.9%), low grade (46.7%), noninvasive papillary carcinoma (Oa) stage (47.9%), and surgery performed (95.5%), all of which were statistically significant (P < .001). In our view, it is interesting about gender (man vs women) in different marital status, married group (83.8% vs 16.2%), widowed group (46.1% vs 53.9%), single group (73.4% vs 26.6%), and divorced/separated group (69.6% vs 30.4%). It seemed that only widowhood had higher effect on women than man. Patient demographics and clinical characteristics are summarized in Table 1.

3.2. Effect of marital status on CSS in the SEER database

The 5-year CSS of married group (85.7%) was highest than other groups. The widowed group had the lowest 5-year CSS (72.7%) of bladder UC. All the differences were significant according to the univariate log-rank test (P < .001) (Table 2). Female sex (P < .001), black race (P < .001), older patients (P < .001), dome of bladder (P < .001), high grade (P < .001), IV stage (P < .001), no surgery performed (P < .001), and the widowed group (P < .001) had been confirmed as significant risk predictors for poor survival on univariate analysis (Table 2). Multivariate modeling analysis with Cox regression revealed that all the aforementioned variables were validated as independent risk predictors associated with poor survival (Table 2). These consisted of sex (female, hazard ratio [HR] 0.962, 95% confidence interval [CI] [0.935–0.990]), age (≥60 years, HR 2.105, 95% CI [2.031–2.181]), race (black, HR 1.299, 95% CI [1.239–1.361]; other, HR 0.849, 95% CI [0.799–0.903]), primary site (trigone, HR 1.157, 95% CI [1.112–1.205]; dome, HR 1.032, 95% CI [0.969–1.099]; bladder, HR 1.279, 95% CI [1.244–1.315]), high grade (poor/anaplastic, HR 1.712, 95% CI [1.653–1.771]; unknown, HR 1.472, 95% CI [1.395–1.553]), TNM stage II, HR 2.477, 95% CI [2.384–2.572]; III stage, HR 2.942, 95% CI [2.816–3.073]; IV stage, HR 9.463, 95% CI [9.079–9.833]; Oa stage, HR 0.480, 95% CI [0.462–0.498]; occur in situ (Ois) stage, HR 0.663, 95% CI [0.621–0.708]), marital status (widowed, HR 1.674, 95% CI [1.621–1.729]; single, HR 1.282, 95% CI [1.232–1.335]; divorced/separated, HR 1.253, 95% CI [1.200–1.307]), surgery performed (no, HR 1.892, 95% CI [1.796–1.993]).

3.3. Subgroup analysis for evaluating the effect of marital status according to TNM stage

We analyzed the effects of marital status on survival in bladder UC of different clinical stage. First, marital status was an independent factor for CSS in each TNM stage, both in univariate and multivariate analysis (P < .001). Second, the widowed group patients always had the lowest 5-year survival rate compared with other groups. The married group patients almost had the highest 5-year survival rate compared with other groups, except Ois stage. Married patients 5-year CSS compared with widowed patients at Oa stage 95.8% versus 89.8% (P < .001), Ois stage 91.6% versus 84.1% (P < .001), I stage 86.1% versus 74.3% (P < .001), II stage 61.6% versus 41.2% (P < .001), III stage 52.5% versus 39.2% (P < .001), IV stage 17.0% versus 8.8% (P < .001) (Table 3). Interestingly, the 5-year CSS of
divorced/separated group compared with married group at Ois stage was 92.5% versus 91.6% ($P$=.001) (Table 3). This phenomenon may be related to the good prognosis of bladder carcinoma in situ. Third, the single (never married) group and the divorced/separated group had no significant difference. They have an approximate 5-year CSS and a similar survival curve (Fig. 1).

3.4. Subgroup analysis for evaluating the effect of marital status according to pathology grade

We further analyzed the effects of marital status on survival in bladder UC of different pathology grades. We observed some interesting findings in the subgroup of pathological grading among the different marital status groups (Table 4). First, pathology grade was an independent factor for CSS, both in the univariate and multivariate analysis ($P$<.001). Second, widowed patients had the lowest survival rate in comparisons at all grades: For low-grade (well differentiated/moderately differentiated) carcinoma, 5-year CSS of widowed patients had 6.6%, 5.6%, and 5.3% reductions compared with that of married patients, single (never married) patients, and divorced/separated patients, respectively (all $P$<.001). For high-grade (poorly differentiated/undifferentiated; anaplastic) carcinoma, 5-year CSS of widowed patients had 16%, 8.2%, and 6.6% reductions compared with that of married patients, single (never married) patients, and divorced/separated patients, respectively (all $P$<.001). Even for unknown pathological grading carcinoma, widowed patients had a 13.9% reduction in 5-year CSS compared with married patients ($P$<.001), a 9.7% reduction in 5-year CSS compared with single patients ($P$=.001), and a 5.9% reduction in 5-year CSS compared with divorced/separated patients ($P$<.001) (Table 4 and Fig. 2).

4. Discussion

In present study, female gender, black race, older (≥60), dome of bladder, high grade, IV stage, no surgery performed, and widowed patients had worst CSS (Table 2). Approximately 70% of all suicides in patients aged >60 years are attributed to physical illness, with higher rates noted in patients with cancer. Schiffmann et al[13,14] pointed that presence of lymph node invasion at radical cystectomy regardless of T2 or T3/4a stage was the most important variable that increased the use of adjuvant chemotherapy. However, older individuals were less likely to receive adjuvant chemotherapy. Because age influenced the choice of treatment[16] and age was related to the decline of immunity in the elderly.[17] These factors may explain why older patients had lower survival.

Although men are diagnosed with bladder cancer with a rate 3 times higher than women, women experience poorer survival[18] Meanwhile, there are many studies reported that women diagnosed with bladder cancer commonly had lower survival.[19–22] On the other hand, Soave et al[23] made a study on 398
In the present study, we found that approximately 66.6% of patients with bladder UC were married. The effect of marital status on cancer-specific survival of many cancers had been correlated with lower vascular endothelial growth factor expression.

White patients with urinary tumors consistently have a survival advantage over black patients despite similar patient and treatment characteristics. Previous reports also indicated that blacks presented with higher stage disease and had worse disease-specific survival compared to whites. In our study, black patients tend to have significantly lower 5-year CSS compared to whites (72.0% vs 83.4%), which may be associated with black race having worse social status, economic income, medical insurance, and other unknown factors. Marital status also had been implicated as a prognostic factor in each pathological grading and each TNM stage in patients with bladder UC. Meanwhile, we found the widowed group had lowest 5-year CSS in each classification compared with other groups (Figs. 1 and 2).

Univariate and multivariate survival analysis for evaluating the influence of marital status on bladder urothelial carcinoma cause-specific survival in SEER database.

| Variable                  | 5-year CSS | Univariate analysis |          |          |
|---------------------------|------------|---------------------|----------|----------|
|                           |            | Log rank χ² test    | P        | HR (95% CI) |
| Sex                       |            |                     |          |          |
| Male                      | 83.9%      | 178.085             | <.001    | Reference |
| Female                    | 79.6%      | 0.962 (0.935–0.990) | <.001    |          |
| Age                       |            | 2267.374            | <.001    | Reference |
| <60                       | 90.2%      | 2.105 (2.031–2.181) | <.001    |          |
| ≥60                       | 80.7%      | 1.299 (1.239–1.361) | <.001    |          |
| Race                      |            |                     |          |          |
| White                     | 83.4%      | 1.253 (1.200–1.307) | <.001    |          |
| Black                     | 72.0%      | 1.282 (1.232–1.335) | <.001    |          |
| Other                     | 82.8%      | 1.307 (1.256–1.361) | <.001    |          |
| Primary site              |            | 1351.581            | <.001    |          |
| Wall                      | 87.2%      | 1.712 (1.655–1.771) | <.001    |          |
| Trigone                   | 85.4%      | 1.472 (1.395–1.553) | <.001    |          |
| Dome                      | 77.8%      | 1.344 (1.283–1.408) | <.001    |          |
| Bladder                   | 79.3%      | 1.321 (1.263–1.381) | <.001    |          |
| Pathological grading      |            | 14,594.256          | <.001    | Reference |
| Well/moderate             | 94.1%      | 1.712 (1.655–1.771) | <.001    |          |
| Poor/anaplastic           | 67.5%      | 1.282 (1.232–1.335) | <.001    |          |
| Unknown                   | 85.4%      | 1.472 (1.395–1.553) | <.001    |          |
| TNM stage                 |            | 63,707.418          | <.001    | Reference |
| I stage                   | 83.9%      | 1.472 (1.395–1.553) | <.001    |          |
| II stage                  | 56.2%      | 2.477 (2.384–2.572) | <.001    |          |
| III stage                 | 49.4%      | 2.942 (2.816–3.073) | <.001    |          |
| IV stage                  | 14.7%      | 4.963 (9.107–9.833) | <.001    |          |
| Oa stage                  | 95.0%      | 0.480 (0.462–0.498) | <.001    |          |
| Ois stage                 | 90.6%      | 0.663 (0.621–0.708) | <.001    |          |
| Surgery performed         |            | 786.481             | <.001    | Reference |
| Yes                       | 83.4%      | 1.892 (1.796–1.993) | <.001    |          |
| No                        | 69.0%      | 1.253 (1.200–1.307) | <.001    |          |
| Marital status            |            | 2296.031            | <.001    | Reference |
| Married                   | 85.7%      | 1.674 (1.621–1.729) | <.001    |          |
| Widowed                   | 72.7%      | 1.282 (1.232–1.335) | <.001    |          |
| Single                    | 81.4%      | 1.253 (1.200–1.307) | <.001    |          |
| Divorced/separated        | 79.7%      | 1.553 (1.493–1.616) | <.001    |          |

CI = confidence interval, CSS = cause-specific survival, HR = hazard ratio, Oa = noninvasive papillary carcinoma, Ois = occur in situ, TNM = tumor (topography), lymph node, metastasis.

Includes American Indian/Alaska native, Asian/Pacific Islander, and so on.

Marital status also had been implicated as a prognostic factor in bladder cancer survival. We identified marital status was an independent prognostic factor in each pathological grading and each TNM stage in patients with bladder UC. Meanwhile, we found the widowed group had lowest 5-year CSS in each classification compared with other groups (Figs. 1 and 2).

Psychosocial factors and social support may play an important role in the relationship between marital status and survival. Epidemiological studies indicate that stress, chronic depression, and lack of social support might serve as risk factors for cancer development and progression.

Married people have better health, because they have more material resources, less stress, indulge in less risky health behavior, and have more social support.

Unmarried and especially widowed patients may suffer from a lack of emotional support and social attention.

One meta-analysis presented reasonable evidence that depression predicts mortality in cancer patients and depression may play a causal role. Meanwhile, another meta-analysis presented that depression diagnosis and higher levels of depressive symptoms predicted elevated mortality.

Higher levels of social wellbeing were correlated with lower vascular endothelial growth factor expressions.
Among parents of cancer patients, chronic stress results in a wide range of physiological and psychological effects. This can include an increased level of stress hormones, such as cortisol, which can suppress the immune system and affect the body's inflammatory response. In vitro studies have shown that stress can diminish the anti-inflammatory cytokine interleukin-6 in cancer cells, thereby promoting tumor growth and progression. In addition, chronic stress can lead to prolonged infection and delayed wound healing, which can contribute to disease progression.

In the present study, we divide the patients into low-grade, high-grade, and unknown groups according to the tumor differentiation. In high-grade group, widowed patients had worst 5-year CSS (88.5%) compared with married (94.1%), and divorced/separated (94.0%) patients (all P < .001). Similarly, the patients with low grade, the widowed group had worst 5-year CSS (84.5%) compared with married (95.1.0%), never married (94.1%), and divorced/separated (94.0%) patients (all P < .01). However, 1 study reported that after controlling for stage and grade, no survival difference could be detected between micropapillary urothelial bladder carcinoma (MPBC) and UC. Low-grade nonmuscle invasive MPBC behaved similarly to both high-grade MPBC and UC stage.

Table 3

| Variable | 5-year CSS | Univariate analysis | Multivariate analysis |
|----------|------------|---------------------|----------------------|
|          |            | Log rank χ² test P  | HR (95% CI) P         |
| TNM stage |            |                     |                      |
| I stage  |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 86.1%      | 438.374 < .001      |                      |
| Widowed   | 74.3%      |                     |                      |
| Single    | 84.2%      |                     |                      |
| Divorced/separated | 82.8%      |                     |                      |
| II stage  |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 61.6%      | 382.361 < .001      |                      |
| Widowed   | 41.2%      |                     |                      |
| Single    | 57.0%      |                     |                      |
| Divorced/separated | 53.8%      |                     |                      |
| III stage |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 52.5%      | 108.371 < .001      |                      |
| Widowed   | 39.2%      |                     |                      |
| Single    | 47.5%      |                     |                      |
| Divorced/separated | 50.8%      |                     |                      |
| IV stage  |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 17.0%      | 195.691 < .001      |                      |
| Widowed   | 8.8%       |                     |                      |
| Single    | 12.2%      |                     |                      |
| Divorced/separated | 15.1%      |                     |                      |
| Oa stage  |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 95.8%      | 725.881 < .001      |                      |
| Widowed   | 89.8%      |                     |                      |
| Single    | 95.6%      |                     |                      |
| Divorced/separated | 95.0%      |                     |                      |
| Ois stage |            |                     |                      |
| Marital status |            |                     |                      |
| Married   | 91.6%      | 65.924 < .001       |                      |
| Widowed   | 84.1%      |                     |                      |
| Single    | 90.0%      |                     |                      |
| Divorced/separated | 92.5%      |                     |                      |

P values refer to comparisons between 2 groups and were adjusted for sex, age, race, pathological grading, primary site, and surgery performed as covariates. CI = confidence interval, CSS = cause-specific survival, HR = hazard ratio, Oa = noninvasive papillary carcinoma, Ois = occur in situ, TNM = tumor (topography), lymph node, metastasis.
Figure 1. Survival curves in tumor (topography), lymph node, metastasis stage of bladder urothelial carcinoma patients according to marital status. (A) Noninvasive papillary carcinoma stage: $\chi^2 = 725.881, P < .001$; (B) occur in situ stage: $\chi^2 = 65.924, P < .001$; (C) I stage: $\chi^2 = 438.374, P < .001$; (D) II stage: $\chi^2 = 382.361, P < .001$; (E) III stage: $\chi^2 = 108.371, P < .001$; (F) IV stage: $\chi^2 = 195.691, P < .001$.

Table 4

Univariate and multivariate analysis of marital status on bladder urothelial carcinoma cause-specific survival based on different pathological grading.

| Variable | 5-year CSS | Univariate analysis | Multivariate analysis |
|----------|------------|---------------------|----------------------|
|          |            | Log rank $\chi^2$ test | $P$ | HR (95% CI) | $P$ |
| Pathological grading | | | | | |
| Well/moderate | | | | | |
| Marital status | | | | | |
| Married | 95.1% | 732.324 | <.001 | Reference | |
| Widowed | 88.5% | 1.914 (1.795–2.041) | <.001 | |
| Single | 94.1% | 1.284 (1.182–1.386) | <.001 | |
| Divorced/separated | 94.0% | 1.280 (1.170–1.401) | <.001 | |
| Poor/anaplastic | | | | | |
| Marital status | | | | | |
| Married | 71.7% | 105.805 | <.001 | Reference | |
| Widowed | 55.7% | 1.559 (1.500–1.622) | <.001 | |
| Single | 63.9% | 1.270 (1.210–1.333) | <.001 | |
| Divorced/separated | 62.3% | 1.214 (1.154–1.278) | <.001 | |
| Unknown | | | | | |
| Marital status | | | | | |
| Married | 88.5% | 228.342 | <.001 | Reference | |
| Widowed | 74.6% | 1.919 (1.704–2.163) | <.001 | |
| Single | 84.3% | 1.315 (1.124–1.538) | .001 | |
| Divorced/separated | 80.5% | 1.447 (1.238–1.692) | <.001 | |

$P$ values refer to comparisons between 2 groups and were adjusted for sex, age, race, TNM stage, primary site and surgery performed as covariates. CI = confidence interval, CSS = cause-specific survival, HR = hazard ratio.
are some potential limitations in our study. First, some data of patient were not complete. Health behaviors including past/present smoking and alcohol use were factors linked to survival among patients with cancer.\(^{15,16}\) Smoking is a risk factor for bladder cancer diagnosis and recurrence.\(^{17}\) But the SEER database lacks the information about smoking. Second, the SEER database only provides marital status at the time of tumor diagnosis. We could not determine whether the marital status whether had a change or not after the diagnosis of bladder cancer. Moreover, the quality of marriage is not clear. It is reported that marital distress had a variety of negative effect on health and immunity.\(^{18}\) Furthermore, the SEER database lacks enough information on therapy options, subsequent therapy, comorbidities, and recurrence. Finally, our study is a retrospective research, which may weaken our conclusion.

Despite there are some potential limitations, the results in present study confirmed that unmarried patients had greater risk of cancer-specific mortality. Furthermore, our study showed the widowed patients were at the highest risk of bladder-cancer-specific mortality than those in other groups. Social and psychosocial factors may be some of main reasons for poor survival outcomes in unmarried patients. Therefore, to improve postoperative survival, close social and family care may improve the survival outcomes for unmarried patients, especially for those who were widowed.

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