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Marital status and gender affect stage, tumor grade, treatment type and cancer specific mortality in $T_{1-2} N_0 M_0$ renal cell carcinoma

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Abstract

Purpose   To examine the effect of marital status and gender on stage at diagnosis, tumor grade, treatment type and cancer specific mortality (CSM) in patients with localized renal cell carcinoma (RCC).

Methods   Within Surveillance, Epidemiology, and End Results registry (2001–2013), we identified 57,700 patients with $T_{1-2} N_0 M_0$ RCC. Logistic regression and competing-risks regression models tested the effect of marital status and gender on stage, tumor grade, treatment type and cancer specific mortality (CSM).

Results   Of all patients, 8.8, 10.6 and 14.8% were, respectively, widowed, separated/divorced and never married. The three categories accounted for 3.9, 9.0 and 14.9% of males (35,641) and for 16.7, 13.1 and 14.7% of females (22,059). Widowed (OR 1.13, $p = 0.04$), separated/divorced (OR 1.16, $p = 0.02$) and never married status (OR 1.38, $p < 0.001$) predisposed to higher rate of no surgical treatment. Widowed (HR 1.32, $p < 0.001$) and separated/divorced (HR 1.32, $p < 0.001$) status predisposed to higher CSM. Male gender predisposed to higher T-stage (OR 1.12, $p < 0.001$), higher tumor grade (OR 1.35, $p < 0.001$), no surgical treatment (OR 1.23, $p < 0.001$) and higher CSM (1.13, $p = 0.01$). Interaction tests between gender and marital status failed to reach independent predictor status in all analyses.

Conclusions   Male patients are at higher risk of less favorable baseline characteristics. Additionally, male, widowed and separated/divorced patients exhibit worse cancer control outcomes after treatment for $T_{1-2} N_0 M_0$ RCC. These observations indicate the need of more focused attention to those patients prior to, as well as after treatment for localized RCC.

Keywords   Marital status · Renal cell carcinoma · Oncological outcomes · Gender

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Introduction

Unmarried status, such as widowed, separated/divorced and never married, represent an adverse predictor of stage and/ or cancer control outcomes in various urological malignancies, such as prostate and bladder cancer [1, 2], as well as in non-urological cancers [3].

However, to date no study examined the effect of marital status and gender on stage, tumor grade, treatment type and cancer specific mortality (CSM) in patients with localized non-metastatic RCC. To address this void, we examined these risk factors in a comprehensive analysis within a contemporary, population-based cohort. We also hypothesized that an interaction may exist between gender and marital status.

Methods

Data source and study population

The study cohort consisted of individuals diagnosed with $T_{1-2} N_0 M_0$ RCC (International Classification of Disease for Oncology C64.9) from Surveillance, Epidemiology, and End Results (SEER) database (2001–2013).

We focused on patients with renal parenchymal tumors aged ≥18-years-old with histologically confirmed RCC. Death certificate only, autopsy cases and bilateral tumors were removed from the analysis. Included histological subtypes were: clear cell RCC (ccRCC), papillary, chromophobe, sarcomatoid, cyst-associated RCC, collecting duct carcinoma and any RCC. Papillary and chromophobe tumors were grouped as non-ccRCC; while sarcomatoid, cyst-associated RCC, collecting duct carcinoma and any RCC were grouped as "other". Finally, patients with missing data on tumor stage, tumor size, tumor grade, treatment type and marital status were excluded.

Variables definition

Marital status was coded as married, widowed, separated/ divorced and never married according to SEER database categories [4]. Other variables consisted of gender, age categories (18–49, 50–64, 65–74, 75–84, ≥85), race (white, black, other), T-stage (T_1, T_2), histologic subtype (ccRCC, non-ccRCC, other RCC), tumor grade (G_1/G_2, G_3/G_4), treatment type (no-surgery, surgery), year of diagnosis (2001–2008, 2009–2013) and socio-economic (SES) status [1, 5]. CSM was defined according to SEER mortality code. All other deaths were considered as other-cause mortality (OCM).

Statistical analysis

Descriptive statistics relied on tests of means and proportions and used the Chi-square for categorical and the t test for continuous variables. Five sets of analyses were performed. First, we evaluated the temporal trends of marital status, defined as widowed, separated/divorced and never married. To quantify temporal trends, we relied on annual percentage change (APC) with the least squares linear regression. Since differences may exist between males and females, the analyses were stratified according to gender.

Second, we examined the effect of marital status and gender on distribution of T-stage (T_2 vs. T_1), tumor grade (G_3/G_4 vs. G_1/G_2) and treatment type (no-surgery vs. surgery) using multivariable logistic regression models (LRMs). Covariates in multivariable LRMs consisted of marital status, gender, age, year of diagnosis, race, socio-economic status, histologic subtypes, as well as T-stage, tumor grade and treatment type when appropriate.

Third, we examined the effect of marital status and gender on CSM using competing-risks regression (CRR) models [6]. Multivariable CRR models accounted for the effect of OCM to provide the most unbiased estimate of CSM, after controlling for all covariates.

Fourth, interaction tests focused on the potential combined effect of marital status and gender in all LRMs and CRR models. Fifth, since ccRCC may behave differently from other histologic subtype, we relied on subgroup analyses that focused on ccRCC. Here, we repeated LRMs and CRR models, as previously described. Finally, we repeated all five steps of the analyses using a simplified coding of marital status. Specifically, married patients were compared to the combined category of separated/divorces, widowed and never married (unmarried).

All statistical tests were two-sided. The level of significance was set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.2; http://www.r-project.org/).

Results

Descriptive analyses and trends over time

We identified 57,700 patients with $T_{1-2} N_0 M_0$ RCC. Median age at diagnosis was 61 years (IQR 52–73). Majority were married (65.8%), male (61.8%), Caucasian (81.9%) and of high SES (52.4%). Most harbored T_1 stage (84.9%), tumor grade G_1/G_2 (73.7%) and ccRCC (62.6%). Virtually, all underwent surgery (94.9%). Of all, 8.8, 10.6 and 14.8% were widowed, separated/divorced and never married. These three categories respectively accounted for, 3.9, 9.0 and 14.9% of males (35,641); and respectively

for, 16.7, 13.1 and 14.7% of females (22,059) (Table 1). Temporal trends (2001–2013) revealed that in males, the proportion of separated/divorced increased from 5.4 to 9.7% (APC +2.5%, CI 1.1–3.9, $p = 0.005$), as well as the proportion of never married increased from 12.8 to 16.1% (APC +2.5%, CI 2.0–2.9, $p < 0.001$). Conversely, the proportion of widowed was stable: 3.9–2.6% (APC −1.3%, CI −2.9 to 0.4, $p = 0.2$). In females, no significant changes in proportions of individuals within examined marital status categories were recorded over time. Specifically, between 2001 and 2013 separated/divorced ranged from 11.0 to 13.7% (APC 0.6%, CI −0.6 to 1.8, $p = 0.4$), never married ranged from 12.9 to 17.8% (APC 2.3%, CI −0.1 to 4.7, $p = 0.08$) and widowed ranged from 17.8 to 13.8% (APC −1.4%, CI −2.8 to 0.1, $p = 0.1$).

The effect of marital status and gender on stage, grade and treatment type

In multivariable LRMs predicting pathological stage T_2 vs. T_1, marital status only showed an increased risk in never married patients with ccRCC histology (OR 1.11, CI 1.02–1.21; $p = 0.02$). Male gender predicted higher risk of T_2 stage in the entire cohort (OR 1.12, CI 1.07–1.18; $p < 0.001$), as well as in the ccRCC subgroup (OR 1.14, CI 1.07–1.21; $p < 0.001$).

In multivariable LRMs predicting tumor grade G_3/G_4 vs. G_1/G_2, marital status failed to show an increased risk of tumor grade G_3/G_4. Male gender predicted higher risk of tumor grade G_3/G_4 in the entire cohort (OR 1.35, CI 1.30–1.41; $p < 0.001$), as well as in the ccRCC subgroup (OR 1.48, CI 1.40–1.55; $p < 0.001$).

Table 1 Clinical and pathological characteristics of patients with $T_{1-2} N_0 M_0$ renal cell carcinoma, stratified according to marital status

Variables name	Overall	Married	Widowed	Separated/divorced	Never married
No of patients (%)	57,700 (100)	37,965 (65.8)	5067 (8.8)	6094 (10.6)	8574 (14.89)
Age group					
18–49	11,210 (19.4)	6913 (18.2)	96 (1.9)	1133 (18.6)	3068 (35.8)
50–64	23,410 (40.6)	15,992 (42.1)	877 (17.3)	2958 (48.5)	3583 (41.8)
65–74	14,700 (25.5)	10,093 (26.6)	1727 (34.1)	1508 (24.87)	1372 (16.0)
75–84	7426 (12.9)	4527 (11.9)	1949 (38.5)	457 (7.5)	493 (5.7)
≥85	954 (1.67)	440 (1.2)	418 (8.2)	38 (0.6)	58 (0.7)
Year of diagnosis					
2001–2008	27,184 (47.1)	18,163 (47.8)	2616 (51.6)	2754 (45.2)	3651 (42.6)
2009–2013	30,516 (52.9)	19,802 (52.2)	2451 (48.4)	3340 (54.8)	4923 (57.4)
Gender					
Female	22,059 (38.2)	12,247 (32.3)	3681 (72.6)	2879 (47.2)	3252 (37.9)
Male	35,641 (61.8)	25,718 (67.7)	1386 (27.4)	3215 (52.8)	5322 (62.1)
Race					
White	47,257 (81.9)	32,029 (84.4)	4160 (82.1)	4832 (79.3)	6236 (72.7)
Black	6842 (11.9)	3370 (8.9)	653 (12.9)	995 (16.3)	1824 (21.3)
Other	3601 (6.2)	2566 (6.87)	254 (5.0)	267 (4.4)	514 (6.0)
SES					
High	30,212 (52.4)	19,335 (50.9)	2759 (54.5)	3220 (52.8)	4898 (57.1)
Low	27,485 (47.6)	18,628 (49.1)	2307 (45.5)	2874 (47.2)	3676 (42.9)
T-stage					
T1	48,969 (84.9)	32,239 (84.9)	4326 (85.4)	5191 (85.2)	7213 (84.1)
T2	8731 (15.1)	5726 (15.1)	741 (14.6)	903 (14.8)	1361 (15.9)
Tumor grade					
G1–G2	42,540 (73.7)	27,903 (73.5)	3827 (75.5)	4497 (73.8)	6313 (73.6)
G3–G4	15,160 (26.3)	10,062 (26.5)	1240 (24.5)	1597 (26.2)	2261 (26.4)
Histologic subtype					
ccRCC	36,141 (62.6)	23,927 (63.0)	3209 (63.3)	3770 (61.9)	5235 (61.1)
Non-ccRCC	10,996 (19.1)	7156 (18.98)	824 (16.3)	1188 (19.5)	1828 (21.3)
Other	10,563 (18.3)	6882 (18.1)	1034 (20.4)	1136 (18.6)	1511 (17.6)
Therapy					
Surgery	54,745 (94.9)	36,181 (95.3)	4639 (91.6)	5795 (95.1)	8130 (94.8)
No-surgery	2955 (5.1)	1784 (4.7)	428 (8.4)	299 (4.9)	444 (5.2)

In multivariable LRMs predicting treatment type, no-surgery vs. surgery, marital status showed an increased risk in widowed (OR 1.13, CI 1.00–1.28; $p = 0.04$), separated/divorced (OR 1.16, CI 1.02–1.32; $p = 0.02$) and never married (OR 1.38, CI 1.23–1.54; $p < 0.001$) patients. However, in the ccRCC subgroup, only never married status showed higher risk of no-surgery treatment type (OR 1.24, CI 1.08–1.44; $p < 0.001$). Male gender also predicted higher risk for no-surgery treatment type in the entire cohort (1.23, CI 1.13–1.33; $p < 0.001$), as well as in the ccRCC subgroup (1.17, CI 1.06–1.29; $p = 0.002$) (Table 2).

Virtually the same results were recorded for the combined category of unmarried predicting the rates of T_2 stage (OR 1.05, $p = 0.07$), G_3/G_4 (OR 1.00, $p = 0.8$) and no-surgery treatment type (OR 1.23, $p < 0.001$) in the entire cohort, as well for the same three endpoints in ccRCC subgroup: (OR 1.07, $p = 0.04$), (OR 0.99, $p = 0.9$), (OR 1.16, $p = 0.004$).

The effect of marital status and gender on CSM

During the study period, a total of 6062 deaths were recorded in the entire cohort. Of those, 62.8% were OCM. Similarly, in the ccRCC subgroup a total of 3572 deaths were recorded. Of those 63.1% were OCM.

In multivariable CRR models, after accounting for OCM, widowed (HR 1.32, CI 1.15–1.52; $p < 0.001$), separated/divorced (HR 1.32, CI 1.15–1.51; $p < 0.001$) status and male gender (HR 1.13, CI 1.03–1.23; $p = 0.01$) were associated with higher CSM, but not never married status (HR 1.12, CI 0.98–1.28; $p = 0.09$) (Table 3).

Additionally, established predictors such as T_2-stage (HR 3.46, CI 3.17–3.77; $p < 0.001$), tumor grade G_3/G_4 (HR 2.02, CI 1.85–2.20; $p < 0.001$) and no surgical treatment (HR 1.48, CI 1.22–1.81; $p < 0.001$) were also associated with higher CSM. All analyses were repeated in the ccRCC subgroup and yielded virtually the same results. Virtually the same results were recorded for the combined category of unmarried predicting the rates of CSM (HR 1.24, $p < 0.001$) in the entire cohort, as well as in the ccRCC subgroup (HR 1.25, $p < 0.001$).

Interaction tests between marital status and gender

Interaction tests that focused on the potential combined effect of gender and marital status failed to reach independent predictor status in LRMs and in CRR models, in the entire cohort and in the ccRCC subgroup.

Table 2 Multivariable logistic regression analyses predicting T-stage (T_2 vs. T_1), grade (G_3/G_4 vs. G_1/G_2) and treatment type (no-surgery vs. surgery) in $T_{1-2} N_0$ patients with all histologic subtype ($n = 57,700$) and in $T_{1-2} N_0$ patients with clear cell renal cell carcinoma only ($n = 36,141$)

	T-stage (T_2 vs. T_1)		Tumor grade (G_3/G_4 vs. G_1/G_2)		Treatment type (no-surgery vs. surgery)	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Entire cohort ($N = 57,700$)						
Marital status						
Married	Ref.		Ref.		Ref.	
Widowed	1.07 (0.97–1.17)	0.2	0.95 (0.88–1.02)	0.1	1.13 (1.00–1.28)	**0.04**
Separated/divorced	1.01 (0.93–1.09)	0.9	1.03 (0.96–1.09)	0.4	1.16 (1.02–1.32)	**0.02**
Never married	1.07 (0.99–1.14)	0.06	1.03 (0.97–1.08)	0.4	1.38 (1.23–1.54)	**<0.001**
Gender						
Female	Ref.		Ref.		Ref.	
Male	1.12 (1.07–1.18)	**<0.001**	1.35 (1.30–1.41)	**<0.001**	1.23 (1.13–1.33)	**<0.001**
Clear cell renal cell carcinoma ($N = 36,141$)						
Marital status						
Married	Ref.		Ref.		Ref.	
Widowed	1.12 (0.99–1.27)	0.05	0.89 (0.81–0.98)	**0.02**	1.09 (0.94–1.28)	0.2
Separated/divorced	0.97 (0.87–1.08)	0.6	1.02 (0.94–1.10)	0.7	1.13 (0.96–1.33)	0.1
Never married	1.11 (1.02–1.21)	**0.02**	1.04 (0.97–1.12)	0.3	1.24 (1.08–1.44)	**0.002**
Gender						
Female	Ref.		Ref.		Ref.	
Male	1.14 (1.07–1.21)	**<0.001**	1.48 (1.40–1.55)	**<0.001**	1.17 (1.06–1.29)	**0.002**

Bold values are indicating significant p values

Analyses adjusted for age, year of diagnosis, race, socio-economic status as well as histologic subtype, T-stage, tumor grade, treatment type when appropriated

Ref reference, *OR* odds ratio, *CI* confidence interval

Table 3 Multivariable competing-risk regression analyses predicting cancer specific mortality in $T_{1-2} N_0 M_0$ patients

	Entire cohort (N = 57,700)		Clear cell renal cell carcinoma (N = 36,141)	
	CSM HR (95% CI)	p value	CSM HR (95% CI)	p value
Marital status				
Married	Ref.		Ref.	
Widowed	1.32 (1.15–1.52)	**<0.001**	1.42 (1.19–1.70)	**<0.001**
Separated/divorced	1.32 (1.15–1.51)	**<0.001**	1.24 (1.04–1.49)	**0.02**
Never married	1.12 (0.98–1.28)	0.09	1.13 (0.95–1.34)	0.2
Gender				
Female	Ref.		Ref.	
Male	1.13 (1.03–1.23)	**0.01**	1.15 (1.03–1.30)	**0.02**

Bold values are indicating significant *p* values

All histologic subtype (*n* = 57,700) and clear cell renal cell carcinoma only (*n* = 36,141). Analyses adjusted for: age, year of diagnosis, race, socio-economic status, tumor grade, T-stage, treatment type as well as histological subtype when appropriate. Interaction test between marital status and gender was not significant in all the analyses ($p > 0.05$)

Ref reference, *HR* hazard ratio, *CI* confidence interval

Discussion

Widowed, separated/divorced and never married patients are known for more unfavorable outcomes in several cancers, other than RCC [1–3]. To the best of our knowledge despite rich literature focusing on biological outcomes determinants such as stage, grade and even molecular tumor make-up [7, 8], no study examined marital status and gender effect on $T_{1-2} N_0 M_0$ RCC in a comprehensive analysis. We hypothesized that marital status and gender may affect stage, tumor grade, treatment modality and CSM. Moreover, we hypothesized that an interaction may exist between gender and marital status.

Our results showed several important observations. First, marital status defined as widowed, separated/divorced and never married affected treatment type. Specifically, it conferred higher risk of no surgical treatment. Second, marital status showed no increased risk for higher T-stage and tumor grade at presentation. The exception consisted of never married status that increased the risk of T_2 vs. T_1 stage in the ccRCC subgroup. Third, marital status defined as widowed or separated/divorced conferred higher CSM risk, even after accounting for OCM. Fourth, when marital status was dichotomized between married and unmarried patients (separated/divorced, widowed and never married), unmarried status maintained the same effect on all examined endpoints. Fifth, similar to marital status, male gender invariably conferred higher risk of no surgical treatment, but also indicated higher risk of higher T-stage, higher tumor grade and higher CSM. Sixth, despite the existence of increased risk related to specific marital status categories and according to male gender, formal testing of the interaction between these two risk variables failed to demonstrate that their combined effect accounts for more than just the sum of their individual effects. In consequence, the effects of maleness and marital status do not require being multiplied by another in risk assessment.

These observations indicate that widowed, separated/divorced or simply all unmarried patients, as well as male patients deserve more focused attention prior to, as well as after treatment for localized RCC. This suggestion is based on the predisposing effects of marital status and gender towards less favorable stage, tumor grade and cancer control outcomes.

It is noteworthy that only a small proportion of male patients were widowed (3.9%) and a larger proportion were separated/divorced (9.0%). In consequence, the combination of these two categories resulted of 12.9% of male patients treated for localized RCC that deserve such particular attention.

It is also noteworthy, that the proportion of widowed as well as, separated/divorced patients differs between males and females. In females, the rates of widowed (16.7%) and separated/divorced (13.1%) were substantially higher than in males: 3.9 and 9.0%, respectively. In consequence, in females, marital status predisposes a larger proportion of patients to less favorable post-treatment cancer control outcomes.

The rationale for worse disease characteristics at presentation, higher rates of no surgical treatment and worse cancer control outcomes according marital status and gender have been also examined in malignances other than RCC. Differences were shown between married and unmarried patients regarding treatment type [1, 3], access to care [3], and social support [2]. Moreover, married patients might be better capable of managing distresses secondary to cancer diagnosis [3]. Additionally, differences in sexual hormone levels and their effect on immune function, as well as differences

in inflammatory response between male and females might also contribute [9, 10].

To the best of our knowledge, no other investigators addressed the effect of marital status in localized RCC, in an equally comprehensive fashion. Partial analyses were performed in smaller and more historical cohorts by Hallenthal et al. [11]. They found that married patients are more likely to undergo nephrectomy [11]. Similarly, Trudeau et al. showed that male gender and unmarried status were associated with lower access to local tumor ablation [12]. Others specifically addressed the effect of marital status in prostate [1], bladder [2], liver [4] and colorectal [13] cancers.

In a recent SEER database analysis, investigators focused on ten leading causes of cancer-related deaths in the United States. Those did not include RCC. The results showed significantly higher risk of metastases, under-treatment and CSM in unmarried patients [3].

Similarly, smaller scale and more historical analyses examined gender in RCC. Rampersaud et al. described lower risk of advanced RCC and CSM in women [14]. Kates et al. showed higher risk of non-localized disease, in males with small renal masses (≤ 3 cm) [15]. Finally, the Collaborative Research on Renal Neoplasms Association (CORONA) database reported improved survival in females [16].

To the best of our knowledge, our analysis represents the first report on marital status in which CRR models were applied. This step allows to control for the confounding effect of OCM, that represent a particularly important competing-risk in patients with $T_{1-2} N_0 M_0$ RCC. Indeed, in our analysis 62.8% of mortalities represented OCM events. Such elevated proportion of OCM validates the need for CRR methodology. Moreover, the use of CRR obviates the need for adjustment for comorbidities that may culminate in OCM.

Several limitations apply to this study. First, outside of the SEER database, a different distribution of marital status may exist and our findings may not apply to patients that differ from the SEER database population. Second, marital status was recorded at diagnosis and may change during the disease course. Third, other social characteristics, such as relationships that modify marital status cannot be investigated in SEER database, since the database relies on predetermined marital status definitions. Fourth, all the limitations related to the retrospective nature of the SEER database apply to this, as well as all other SEER database or population-based analyses. Fifth, we exclusively focused on patients with $T_{1-2} N_0 M_0$ stages to avoid the effects associated with locally advanced or metastatic disease on CSM that leave little if any role for marital status or gender or other sociodemographic aspects.

Conclusion

Male patients are at higher risk of less favorable baseline characteristics. Additionally, male, widowed and separated/divorced patients exhibit worse cancer control outcomes after treatment for $T_{1-2} N_0 M_0$ RCC. These observations indicate the need of more focused attention to those patients prior to, as well as after treatment for localized RCC.

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