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Unmarried status is a barrier for access to treatment in patients with metastatic renal cell carcinoma

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Abstract

Purpose We tested the effect of marital status on cytoreductive nephrectomy, metastasectomy, and systemic therapy rates, as well as on cancer-specific mortality (CSM) in patients with metastatic clear cell renal carcinoma (mccRCC).

Methods Within the Surveillance, Epidemiology and End Results database (2004–2015), we identified 6975 patients (4806 men and 2169 women) with metastatic clear cell renal carcinoma. Temporal trend analyses, logistic regression models, cumulative incidence plots, and competing-risk regression models were used.

Results Overall, 1450 men and 1018 women were unmarried (30.2% and 47.0%, respectively). In men, unmarried status was an independent predictor of lower cytoreductive nephrectomy rate (OR: 0.54), lower metastasectomy rate (OR: 0.70), and lower systemic therapy rate (OR: 0.70). Conversely, in women, unmarried status was an independent predictor of lower cytoreductive nephrectomy rate (OR: 0.63) and of lower systemic therapy rate (OR: 0.80), but not of lower metastasectomy rate (OR: 0.83; $p = 0.12$). In multivariable competing-risk regression analyses, unmarried status was an independent predictor of higher CSM in men (HR: 1.15), but not in women (HR 0.97, $p = 0.6$).

Conclusions Unmarried men are at higher risk of not benefiting of cytoreductive nephrectomy, metastasectomy, or systemic therapy than their married counterparts. Unmarried women are at higher risk of not benefiting of cytoreductive nephrectomy or systemic therapy. These gender-related differences cumulate in higher CSM in unmarried men, but not in unmarried women.

Keywords Clear cell · Kidney cancer · Marital status · Metastatic · SEER database · Survival

Introduction

Several studies described the effect of unmarried status, defined as separated/divorced, widowed, or single, as an adverse risk factor for cancer control outcomes and survival, including urological malignancies, such as prostate and bladder cancers [1–9]. To the best of our knowledge, only few studies tested the effect of marital status in kidney cancer according to gender and none of these focused on metastatic disease [7, 9–11]. Based on lack of data regarding the

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effect of marital status, and even more to according to gender, on survival in metastatic clear cell renal carcinoma, we examined this relationship. Specifically, based on data from primaries other than RCC, we hypothesized that unmarried status may represent a risk factor for lower rates of cytoreductive nephrectomy, metastasectomy or systemic therapy, and in consequence that unmarried status may adversely affect cancer-specific mortality (CSM). Moreover, we postulated that the relationship between unmarried statuses may be different between men and women.

Materials and methods

Study population

Within the Surveillance, Epidemiology and End Results (SEER) database, we identified 155,597 patients with renal cell carcinoma (International Classification of Disease for Oncology C64), between 2004 and 2015. Of those, 74,231 harbored the clear cell variant and 7333 had metastatic disease. We focused on patients with histologically confirmed metastatic clear cell renal carcinoma older than 18 years. Death certificate only, autopsy cases, and patients with missing marital status information, cytoreductive nephrectomy, and metastasectomy status were excluded (Fig. 1).

Variable definition

Marital status was defined as married or unmarried. Unmarried included never married, separated/divorced, and widowed patients, according to SEER marital status categories. Other variables included continuously coded age, year of diagnosis, ethnicity (Caucasian, Afro-American, other), socio-economic status (high, low), tumor grade (G1/G2, G3/G4, GX), T stage (T1–T2 and T3–T4), N stage (N0 and N1), cytoreductive nephrectomy status (performed vs. no performed), metastasectomy status (performed vs. no performed), and systemic therapy status (treated vs. unexposed). Cancer-specific mortality (CSM) was defined as a death related to kidney cancer, according to SEER mortality code. All other deaths were considered as other-cause mortality (OCM).

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The Chi-square tested the statistical significance in proportions' differences. The *t* test and Kruskal–Wallis test examined the statistical significance of means' and medians' differences. Three sets of analyses were performed. First, temporal trend analyses were performed to estimate the annual percentage changes

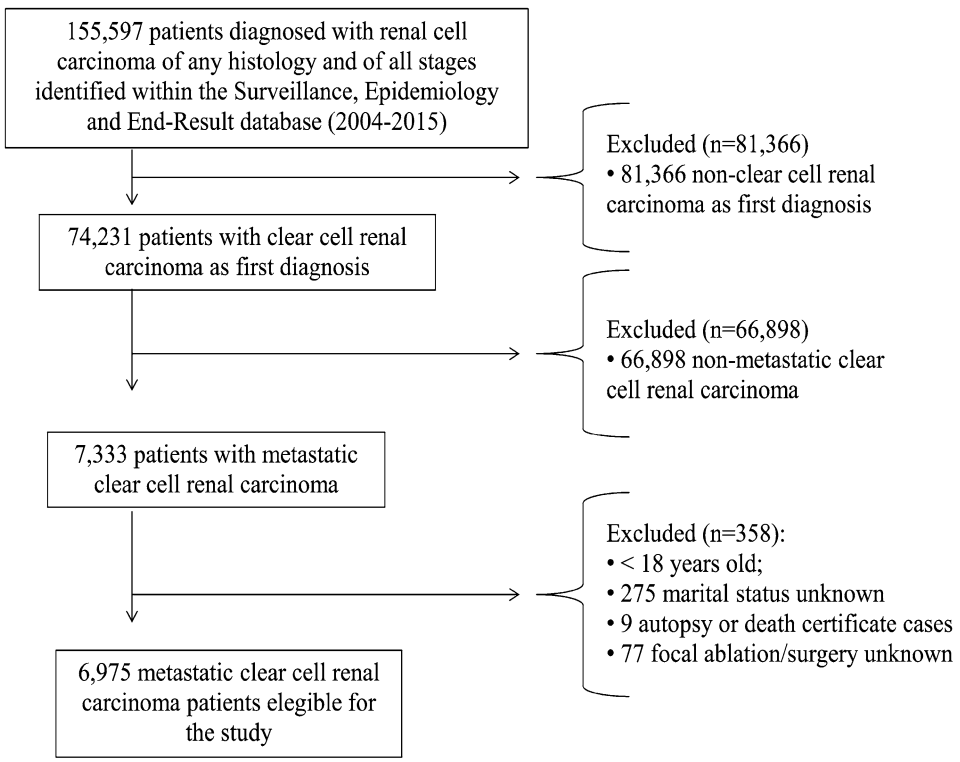

Fig. 1 CONSORT diagram of 6975 patients with metastatic clear cell renal carcinoma eligible for the study

(EAPC) in marital status. Separate analyses were fitted for males and females. Second, we examined the effect of marital status according to gender on cytoreductive nephrectomy rates, metastasectomy rates, and systemic therapy rates using multivariable logistic regression (LRMs) models. Covariates in multivariable LRMs consisted of marital status, age at diagnosis, year at diagnosis, ethnicity, socio-economic status (SES) Fuhrman grade, T stage, N stage, and treatment modalities. Third, survival analyses relied on cumulative incidence plots to illustrate CSM and OCM rates. Competing-risk regression models that accounted for the effect of OCM, provided the most unbiased estimates of CSM. For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two sided with a level of significance set at $p < 0.05$.

Results

Descriptive analyses and time trend tests

Of 4806 men, 30.2% were unmarried. Unmarried males were younger (mean 60.6 vs. 63.1, $p < 0.001$; median 60 vs. 63, $p < 0.001$) and less frequently treated with cytoreductive nephrectomy (51.3 vs. 63.0%; $p < 0.001$), metastasectomy (15.2 vs. 19.5; $p < 0.001$), or systemic therapy (45.2 vs. 51.8; $p < 0.001$).

Of 2169 women, 47.0% were unmarried. Unmarried females were older (mean 67.0 vs. 62.7, $p < 0.001$; median 67 vs. 63, $p < 0.001$) and less frequently treated with cytoreductive nephrectomy (50.9 vs. 63.9%; $p < 0.001$), metastasectomy (14.9 vs. 18.7%; $p = 0.02$), or systemic therapy (42.3 vs. 49.6%; $p < 0.001$) (Table 1).

In men, temporal trends demonstrated no statistically significant change over time in unmarried status (2004: 18.0% vs. 2015: 20.9%; EAPC: +1.0%, CI −0.1–2.1%; $p = 0.1$). In women, a decrease was recorded (2004:17.5% vs. 2015: 13.3%; EAPC: −1.6%, CI −2.8 to −0.3%; $p = 0.03$) (Fig. 2).

The effect of marital status on rates of cytoreductive nephrectomy, metastasectomy, and systemic therapy

In men, multivariable logistic regression models identified unmarried status as an independent predictor of lower cytoreductive nephrectomy (OR: 0.54, CI 0.45–0.65), metastasectomy (OR: 0.70, CI 0.59–0.83), and systemic therapy (OR: 0.70, CI 0.62–0.80) rates.

In women, multivariable logistic regression models identified unmarried status as an independent predictor of lower cytoreductive nephrectomy (OR: 0.63, CI 0.48–0.81) and systemic therapy (OR: 0.80, CI 0.67–0.96; $p = 0.02$) rates, but not of metastasectomy rates (OR: 0.83, CI 0.65–1.05; $p = 0.12$) (Table 2).

The effect of marital status on cancer-specific mortality

In men, in cumulative incidence plots, 5-year CSM was 77.4 vs. 70.5% in unmarried vs. married patients ($p < 0.001$), and 5-year OCM was, respectively, 6.0 vs. 4.6% ($p = 0.1$) (Fig. 3a). In multivariable competing-risk regression models predicting CSM, unmarried status was an independent predictor of higher CSM (HR: 1.15, CI 1.06–1.25; $p < 0.001$). In addition, cytoreductive nephrectomy (HR: 0.38, CI 0.34–0.43; $p < 0.001$) and systemic therapy (HR: 0.91, CI 0.84–0.98; $p = 0.01$) were also independent predictors of lower CSM (Table 3).

In women, in cumulative incidence plots, 5-year CSM was 76.6 vs. 74.5% in unmarried vs. married patients ($p = 0.1$) and 5-year OCM was, respectively, 6.3 vs. 4.3% ($p = 0.01$) (Fig. 3b). In multivariable competing-risk regression models, unmarried status was not an independent predictor of CSM (HR: 0.97, CI 0.86–1.09; $p = 0.60$). However, cytoreductive nephrectomy (HR: 0.40, CI 0.34–0.47; $p < 0.001$), metastasectomy (HR: 0.77, CI 0.66–0.90; $p < 0.001$), and systemic therapy (HR: 0.81, CI 0.72–0.91; $p < 0.001$) were independent predictors of lower CSM.

All multivariable analyses were adjusted for age at diagnosis, ethnicity, Fuhrman grade, T stage, N stage, and treatment type (cytoreductive nephrectomy, metastasectomy and systemic therapy) (Table 3).

Further stratification according to marital status revealed a statistically significant difference in access to cytoreductive nephrectomy, that was lower in unmarried men (OR: 0.74, $p = 0.01$), relative to unmarried women. Conversely, all other analyses that tested for gender-related differences failed to reveal statistically significant results (all $p > 0.05$).

Discussion

Unmarried status represents a risk factor for unfavorable cancer control outcomes in several non-urological and in some urological malignancies [1–9]. However, the effect of unmarried status on access to different treatment modalities was not tested in the context of metastatic clear cell renal carcinoma, in contemporary patients. In the current study, we examined the effect of unmarried status on rates of cytoreductive nephrectomy, metastasectomy, and systemic therapy, as well as on cancer-specific mortality. We hypothesized that unmarried status may show a different relationship between the examined endpoints in men compared to women. This hypothesis was based on previous observations that demonstrated a different effect of marital

Table 1 Descriptive characteristics of 6975 patients (4806 men and 2169 women) with metastatic clear cell renal carcinoma within Surveillance, Epidemiology and End Results database (2004–2015), stratified according to marital status: married vs. unmarried

	Male ($n=4806$; 68.9%)			Female ($n=2169$; 31.1%)		
	Unmarried ($n=1450$; 30.2%)	Married ($n=3356$; 69.8%)	p value	Unmarried ($n=1018$; 47.0%)	Married ($n=1151$; 53.0%)	p value
Age at diagnosis, *n*						
Mean	60.6	63.1	**< 0.001**	67.0	62.7	**< 0.001**
Median	60	63	**< 0.001**	67	63	**< 0.001**
Interquartile range	52–68	56–70		59–76	55–71	
Age group, *n* (%)						
18–49	254 (17.5)	315 (9.4)	**< 0.001**	62 (6.1)	138 (12.0)	**< 0.001**
50–64	676 (46.6)	1585 (47.2)		371 (36.4)	500 (43.4)	
65–74	315 (21.7)	957 (28.5)		297 (29.2)	343 (29.8)	
75–84	162 (11.2)	441 (13.1)		231 (22.7)	156 (13.6)	
≥ 85	43 (3.0)	58 (1.7)		57 (5.6)	14 (1.2)	
Year at diagnosis, *n* (%)						
2004–2010	715 (49.3)	1701 (50.7)	0.39	540 (53.0)	591 (51.3)	0.45
2011–2015	735 (50.7)	1655 (49.3)		478 (47.0)	560 (48.7)	
Ethnicity, *n* (%)						
Caucasian	1209 (83.4)	2943 (87.7)	**< 0.001**	855 (84.0)	1010 (87.7)	**< 0.001**
African–American	146 (10.1)	156 (4.6)		98 (9.6)	50 (4.3)	
Other	95 (6.6)	257 (7.7)		65 (6.4)	91 (7.9)	
Fuhrman grade, *n* (%)						
G1/G2	273 (18.8)	637 (19.0)	**< 0.001**	228 (22.4)	228 (19.8)	**< 0.01**
G3/G4	613 (42.3)	1652 (49.2)		415 (40.8)	553 (48.0)	
GX	564 (38.9)	1067 (31.8)		375 (36.8)	370 (32.1)	
T stage, *n* (%)						
T1–T2	484 (33.4)	1078 (32.1)	**< 0.001**	361 (35.5)	388 (33.7)	**< 0.001**
T3–T4	725 (50.0)	1854 (55.2)		469 (46.1)	623 (54.1)	
T0–TX	241 (16.6)	424 (12.6)		188 (18.5)	140 (12.2)	
Nodal status, *n* (%)						
N1	322 (22.2)	766 (22.8)	**0.04**	231 (22.7)	275 (23.9)	0.5
NX	200 (13.8)	377 (11.2)		144 (14.1)	146 (12.7)	
Cytoreductive nephrectomy, *n* (%)						
Performed	744 (51.3)	2113 (63.0)	**< 0.001**	518 (50.9)	735 (63.9)	**< 0.001**
Metastasectomy, *n* (%)						
Performed	220 (15.2)	655 (19.5)	**< 0.001**	152 (14.9)	215 (18.7)	**0.02**
Systemic therapy, *n* (%)						
Treated	656 (45.2)	1740 (51.8)	**< 0.001**	431 (42.3)	571 (49.6)	**< 0.001**

Bold values are statistically significant ($p < 0.05$)

status, according to gender, on cancer control outcomes and survival in several malignancies [2, 6, 7, 9, 10, 12, 13]. Our study showed several important observations.

First, we identified important differences in rates of cytoreductive nephrectomy, metastasectomy, and systemic therapy according to marital status. Specifically, unmarried status was invariably associated with lower rates of cytoreductive nephrectomy, metastasectomy, and systemic therapy in men. However, in women, unmarried status was only associated with lower rates of cytoreductive nephrectomy and systemic therapy, but was unrelated to metastasectomy rates. Further testing of the relationship between unmarried status and cytoreductive nephrectomy, metastasectomy and systemic therapy rates confirmed its independent predictor status in men. However, in women, unmarried status was only an independent predictor of lower cytoreductive nephrectomy and systemic therapy rates, but not of metastasectomy rates. Taken together, these observations validate

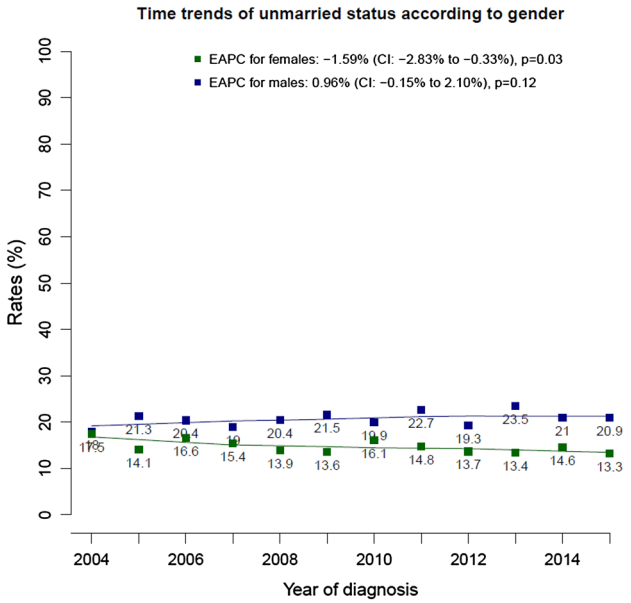

Fig. 2 Time trend of unmarried status according to gender (*EAPC* estimate annual percentage changes)

our hypothesis that unmarried status may undermine the rates of access to treatment in patients with metastatic clear cell renal carcinoma. Our results also validate our hypothesis that unmarried status may have a different effect on access to these therapies according to gender. Specifically, unmarried status is invariably associated with lower access to all three examined treatment modalities for metastatic clear cell renal carcinoma in men. Conversely, unmarried status in females is only related to lower cytoreductive nephrectomy and systemic therapy. In consequence, preventative measures aimed at providing equal access to care should be prioritized in male patients. Nonetheless, similar efforts should also be directed at ensuring equal access to cytoreductive nephrectomy and systemic therapy in females. In both genders, unmarried status should be regarded as a risk factor for lower access to treatment.

Second, we also examined the effect of unmarried status on cancer-specific mortality, after adjusting for other-cause mortality. Competing-risk analyses allowed us to maximally reduce the effect of other-cause mortality that is associated with comorbidities. Our analyses revealed that unmarried status is an independent predictor of higher cancer-specific mortality in men, but not in women. These observations are consistent with our results regarding of cytoreductive nephrectomy, metastasectomy, and systemic therapy rates, where unmarried men had lower access to those treatment modalities to a greater extent than unmarried women, as exemplified by universally lower ORs in men and by three statistically significant treatment categories in men vs. two in women. Nonetheless, equal access to cytoreductive nephrectomy and systemic therapy should still be ensured in unmarried women, as much as in unmarried men. Unfortunately, the current database does not allow a more detailed testing of the reason why such discrepancy exists between genders. Hypotheses may include other variables that compensate for lack of access to cytoreductive nephrectomy and systemic therapy in women, so that access barriers do not culminate in higher cancer-specific mortality. Those variables may consist of better coping mechanisms, better social support, and other socio-economic variables that may favor better survival in females, but not in males. Such variables, except for socio-economic status, are unavailable in the SEER database.

Third, it is of interest to note that an important difference exists in the rates of unmarried men and unmarried women. Specifically, a smaller proportion of females were unmarried. It is also of interest that an increase in the rates of unmarried males was recorded (+ 1.0%) over the span of the study, albeit in a non significant fashion. The opposite effect was recorded in females where a statistical significant decrease was recorded (− 1.6%). It may be postulated that the decreasing already lower proportion of unmarried females relative to males accounts for that lack of effect of unmarried status on cancer-specific mortality in females. The opposite trend may explain the situation in males, where a higher proportion of unmarried status that increases over time results in worse cancer-specific mortality.

To the best of our knowledge, our study represents the first analysis of the association between unmarried status and rates of use of cytoreductive nephrectomy, metastasectomy, and systemic therapy in metastatic clear cell

Table 2 Multivariable logistic regression analyses predicting rates of cytoreductive nephrectomy, metastasectomy, and systemic therapy according to gender, in 6975 patients with metastatic clear cell renal carcinoma

		Male			Female		
		Odds ratio	Confidence interval	*p* value	Odds ratio	Confidence interval	*p* value
Cytoreductive nephrectomy	Unmarried vs. married	0.54	0.45–0.65	**< 0.001**	0.63	0.48–0.81	**< 0.001**
Metastasectomy	Unmarried vs. married	0.70	0.59–0.83	**< 0.001**	0.83	0.65–1.05	0.1
Systemic therapy	Unmarried vs. married	0.70	0.62–0.80	**< 0.001**	0.80	0.67–0.96	**0.02**

Bold values are statistically significant ($p < 0.05$)

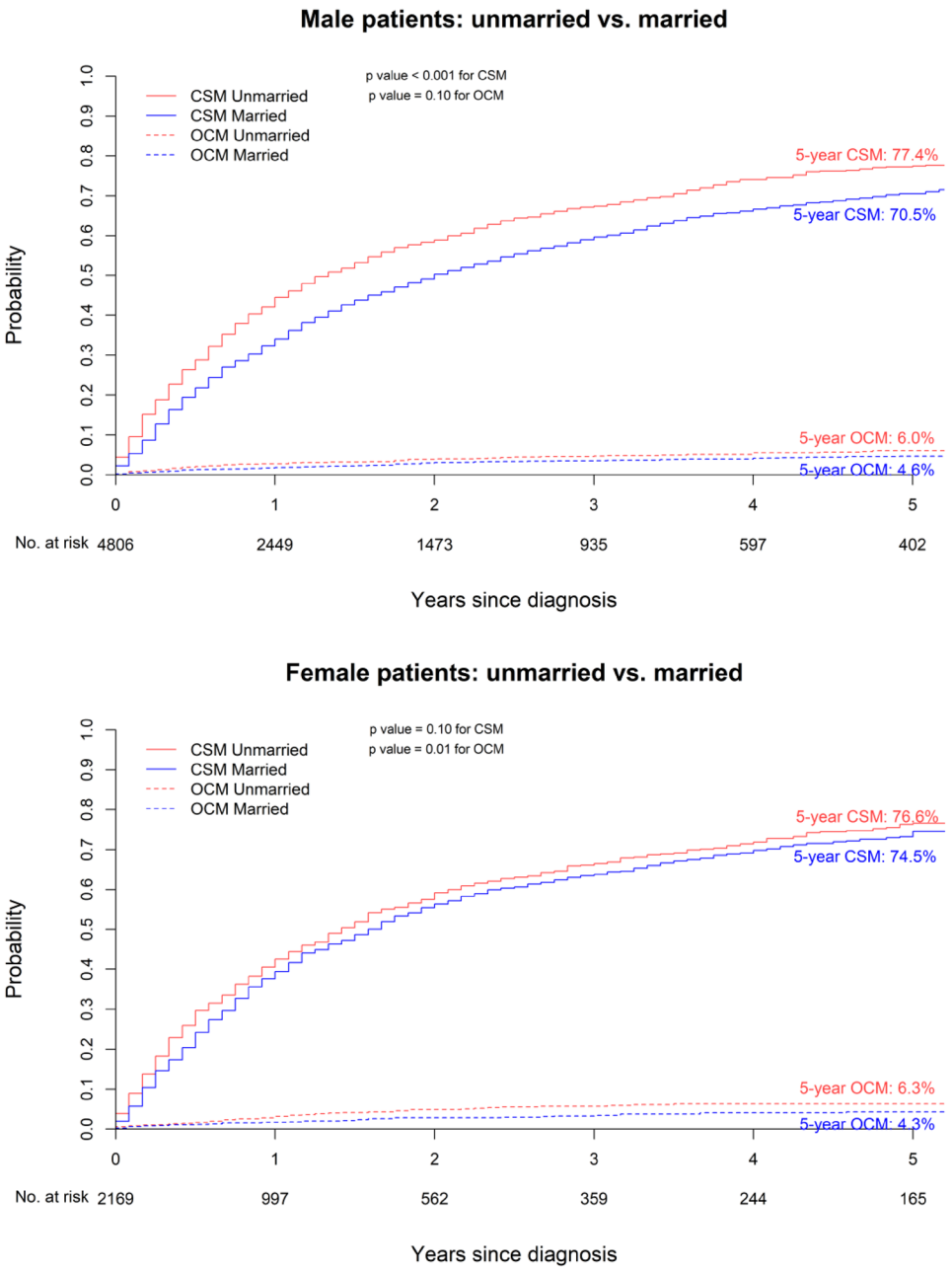

Fig. 3 Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates according to marital status (unmarried vs. married) in men ($n=4806$; **a**) and women ($n=2169$; **b**)

renal carcinoma, as well as its effect on cancer-specific mortality, according to gender. In consequence, we cannot compare the results of this study with similar analyses in metastatic clear cell renal carcinoma. Nonetheless, our study is in agreement with the other studies that examined these relationships in other primaries [1–12]. For example, our observations are consistent with Aizer et al. [8], who examined survival and oncologic outcomes in patients with different malignancies. They found a higher risk of no definitive treatment in unmarried patients, compared to their married counterparts. Likewise, Marchioni et al. [9] reported that unmarried status is associated with a higher rate of no surgical treatment in $T_{1–2}$ renal cell carcinoma patients. Moreover, they also described a higher risk of no surgical treatment in men compared to women. Hellenthal et al. [11] demonstrated a lower rate of cytoreductive nephrectomy in unmarried patients with metastatic renal carcinoma in pre-targeted therapy era. Krongrad et al. [13] also analyzed the association between marital status and prostate cancer in the SEER database and showed better survival in married individuals. Finally, Miao et al. [7] showed similar results in metastatic kidney cancer, but the effect of marital status was not tested according to gender. Moreover, in their study, no consideration was given to

Table 3 Multivariable competing-risk analyses predicting cancer-specific mortality and other-cause mortality, according to gender, in 6975 patients (4806 men and 2169 women) with metastatic clear cell renal carcinoma

	Cancer-specific mortality in males			Cancer-specific mortality in females		
	HR	CI	*p* value	HR	CI	*p* value
Marital status						
Unmarried vs. married	1.15	1.06–1.25	**< 0.001**	0.97	0.86–1.09	0.6
	Other-cause mortality in males			Other-cause mortality in females		
	HR	CI	*p* value	HR	CI	*p* value
Marital status						
Unmarried vs. married	1.28	0.94–1.73	0.1	1.31	0.85–2.02	0.2

Bold value is statistically significant ($p < 0.05$)

Adjustment variables were: age at diagnosis, ethnicity, tumor stage, nodal stage, and treatment modalities

the effect of marital status on cytoreductive nephrectomy, metastasectomy, or systemic therapy rates.

Several studies demonstrated a beneficial effect of cytoreductive nephrectomy, metastasectomy, and systemic therapy on cancer-specific mortality in metastatic renal carcinoma [14–20]. Our findings may not be directly comparable to those of clinical trials, including CARMENA trial [21, 22]. In addition, marital status did not represent one of the pre-planned risk factors in the CARMENA trial. As such, it cannot be stated with certainty that marital status either could or could not represent an independent predictor of overall mortality in a prospective setting, such as examined in CARMENA. Certainly, the current data would militate in favor of considering marital status among pre-planned predictors of survival in future prospective trials, providing that the strict sample size consideration in this rare entity allows the use of an additional risk variable. Finally, our results demonstrate lower access to those modalities in unmarried patients, which may be interpreted as a poor quality of care indicator. Thus, our findings should sensitize the medical community about added vulnerability of unmarried patients and possibly grater vulnerability of unmarried males.

Despite its novelty, our study has limitations. First, the SEER database does not include more specific information about marital status than the categories that were examined. However, more granular information about marital status could provide deeper and better understanding of underlying causes behind the definition of unmarried. Second, the SEER database does not contain information about comorbidities. Nonetheless, in our analyses, we accounted for other-cause mortality using competing-risk regression models to provide the most unbiased estimate of cancer-specific mortality. Moreover, the SEER database not allows us to stratify according to IMDC classification. Indeed, variables required by the Heng criteria, such as performance status, time to metastasis, serum levels of hemoglobin, neutrophils, platelets, and calcium, are unavailable in the SEER database [23, 24]. Third, within the SEER database, information on specific systemic therapy type administrated (such as tyrosine-kinase inhibitor vs. immunotherapy) and its dose and duration are not available. Fourth, we relied on the SEER database, which includes North American patients. For this reason, our findings can be applied to this population, but may be not generalizable to other parts of the world, such as Europe or even Canada. Fourth, no information regarding laboratory variables and performance status was available. However, these limitations as well as all the limitations related to the retrospective nature of the SEER database apply to all other population-based analyses that were derived from the SEER, NCDB (National Cancer DataBase), or other similar large-scale data repositories.

Conclusion

Unmarried men are at higher risk of not benefiting of cytoreductive nephrectomy, metastasectomy, or systemic therapy than their married counterparts. Unmarried women are at higher risk of not benefiting of cytoreductive nephrectomy or systemic therapy. These gender-related differences cumulate in higher cancer-specific mortality in unmarried men, but not in unmarried women.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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