

## Association between Marital Status and Prognosis in Patients with Prostate Cancer: A Meta-Analysis of Observational Studies

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**Purpose:** The impact of marital status on the prognosis amongst patients diagnosed with prostate cancer remains controversial. Thus, a meta-analysis was performed to determine whether marital status can influence the prognosis in patients with prostate cancer.

**Materials and Methods:** Literature search of the MEDLINE, PsycINFO, Embase and Cochrane Library databases was conducted to identify eligible studies published before April 2020. Multivariate adjusted risk estimates and corresponding 95% confidence intervals (CIs) were extracted and calculated using the random effects model. Results: A total of 11 observational studies comprising 1,457,799 patients diagnosed with prostate cancer were identified. Results indicated that unmarried status (separated, divorced, widowed or never married) was associated with an increased risk of all-cause mortality (hazard ratio, HR = 1.39, 95% CI: 1.30–1.50;  $P < .001$ ;  $I^2 = 92.2\%$ ) compared with married status, especially for divorced and never-married patients. Similarly, being unmarried had an elevated risk of cancer-specific mortality (HR = 1.29, 95% CI: 1.17–1.41;  $P < .001$ ;  $I^2 = 82.5\%$ ) in patients with prostate cancer. A significant difference was also observed between unmarried status and shorter overall survival (HR = 1.37, 95% CI: 1.20–1.56;  $P < .001$ ;  $I^2 = 94.5\%$ ).

**Conclusion:** Results demonstrated that unmarried status is associated with a worse prognosis regarding mortality and survival in patients diagnosed with prostate cancer, particularly in divorced and never-married patients. Hence, further research should explore the potential mechanisms which can benefit the development of novel, more personalized management methods for unmarried patients with prostate cancer.

**Keywords:** marital status; prostate cancer; prognosis; meta-analysis

### INTRODUCTION

Prostate cancer has become a major health problem and a leading cause of morbidity and mortality in men worldwide.<sup>(1,2)</sup> In the United States in 2018, patients newly diagnosed with prostate cancer reached 164,690, while 26,730 patients with prostate cancer died despite the high overall survival (OS) for the disease.<sup>(3)</sup> However, only a few risk factors for prostate cancer have been identified, including age, family history, race, and certain genetic polymorphisms, thereby limiting the prevention of prostate cancer.<sup>(4,5)</sup> Interestingly, some research demonstrated that being unmarried (never married, separated, widowed or divorced) is associated with shorter survival and higher mortality for several malignancies compared with married status.<sup>(6–10)</sup> Nonetheless, the impact of marital status on the prognosis amongst patients diagnosed with prostate cancer is still inconclusive.

Several studies revealed that unmarried men have consistently been found to be associated with worse prognosis in patients with prostate cancer,<sup>(11,12)</sup> whereas other studies reported conflicting results.<sup>(13,14)</sup> Spe-

cifically, Nepple et al.<sup>(13)</sup> reported that never-married men diagnosed with prostate cancer have an elevated risk of all-cause mortality (ACM) compared with those who were married, but this significant association was not observed amongst divorced or widowed men with prostate cancer. In light of these different findings reported in previous literature, we performed a systematic review and meta-analysis to explore how married status influences the prognosis (survival, mortality, etc.) in patients with any form of diagnosed prostate cancer.

### MATERIAL AND METHODS

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration criterion.<sup>(15)</sup> Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines<sup>(16)</sup> and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.<sup>(17)</sup>

#### Search strategy

Literature search of the MEDLINE (via PubMed), Psy-

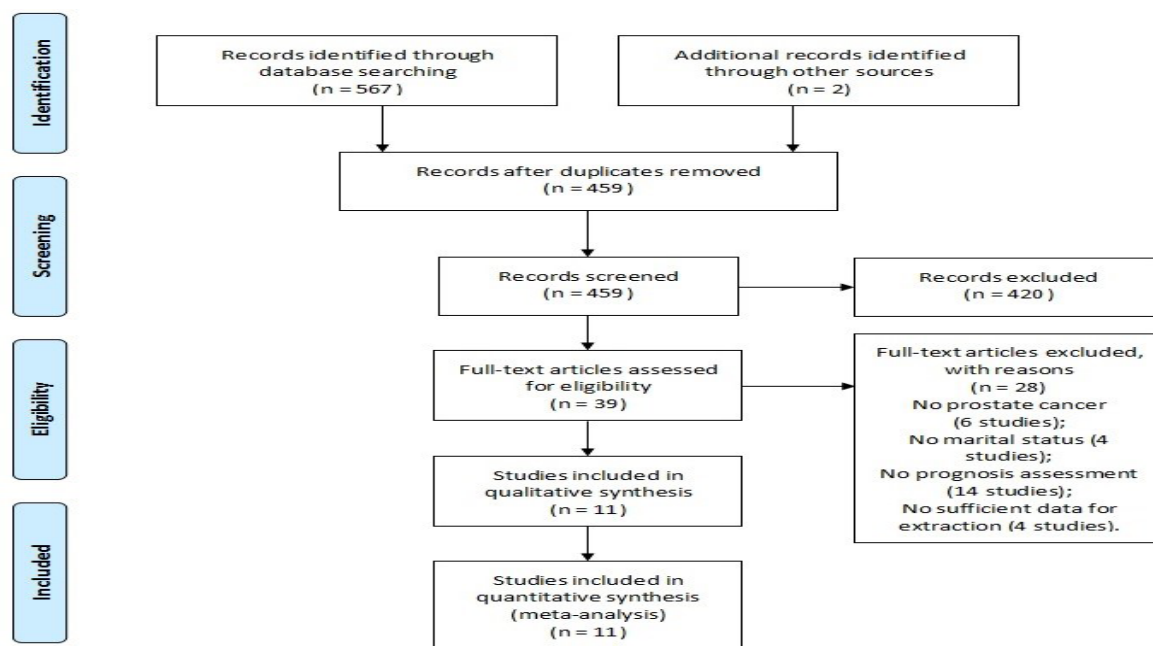
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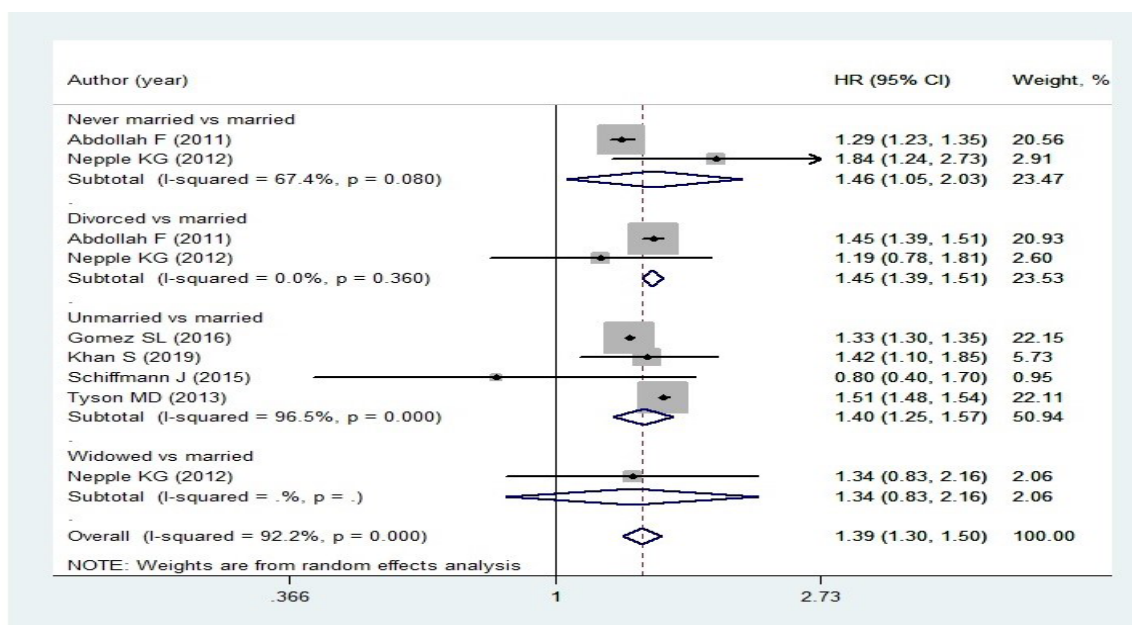
**Figure 1.** Flow diagram of literature searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

cINFO, Embase and Cochrane Library databases was conducted to identify eligible studies from database inception up to April 2020 using a combination of Medical Subject Headings (MeSH) and non-MeSH terms, including ‘marital status’, ‘marriage’, ‘married’, ‘unmarried’, ‘divorced’ or ‘widowed’ and ‘prostate cancer’, ‘prostate carcinoma’, ‘prostate tumor’ or ‘prostate neoplasms’ and ‘prognosis’, ‘survival’ or ‘mortality’, with no language, region or publication status restriction. Furthermore, important citation database such as Scopus was searched, and manual searches of reference

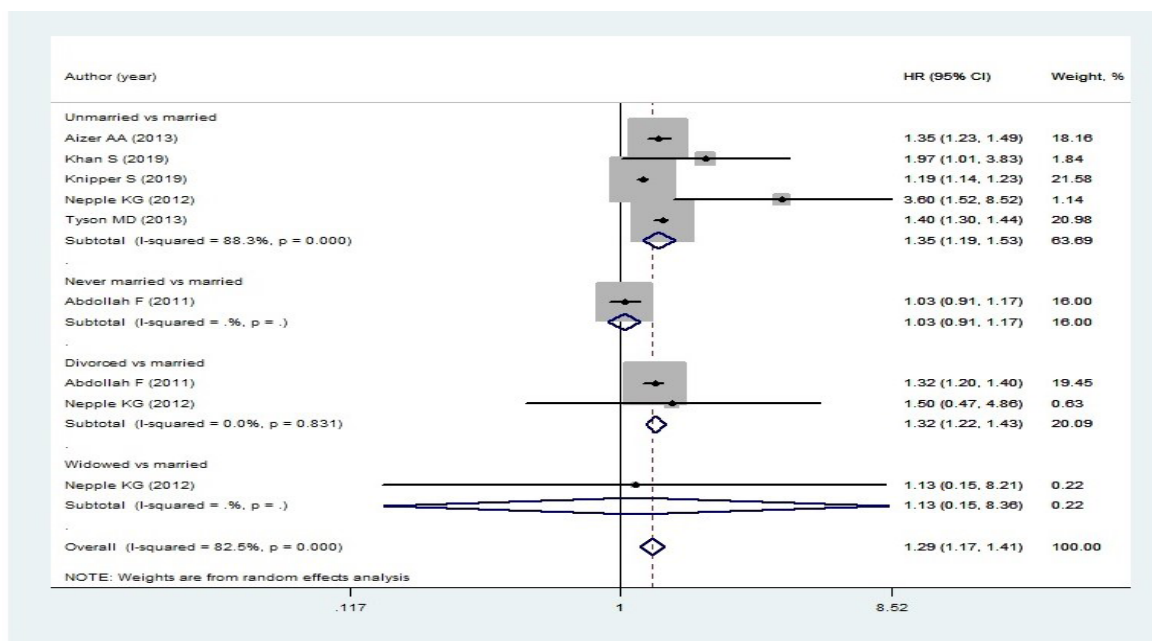
lists were also performed in relevant original and review articles for additional eligible studies. The main search was carried out independently by the senior investigator (ZL. Guo). Disagreement was resolved by consulting another investigator (SS. Wang) who was not involved in the initial search procedure.

**Eligibility criteria**

All published eligible studies were included if they met the following inclusion criteria; (1) men diagnosed with any stage of prostate cancer only; (2) married sta-



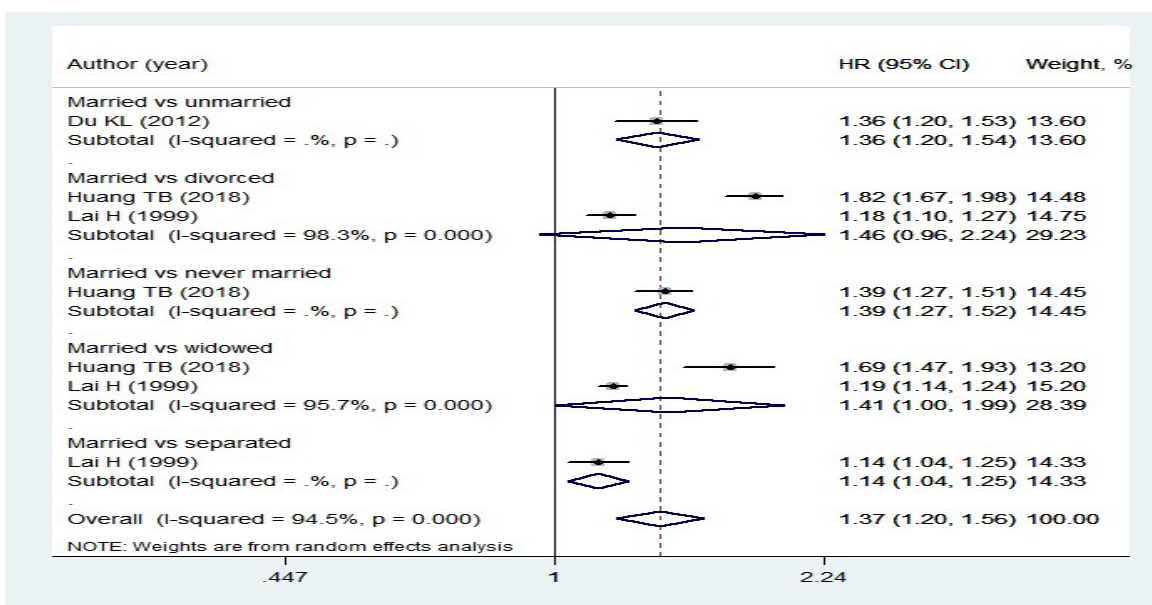
**Figure 2.** Marital status and all-cause mortality in patients with prostate cancer. **Abbreviations:** CI, confidence interval; HR, Hazard Ratio



**Figure 3.** Marital status and cancer-specific mortality in patients with prostate cancer.  
**Abbreviations:** CI, confidence interval; HR, Hazard Ratio

tus is defined as married and/or living with a partner or family, while unmarried status is defined as widowed, divorced or living alone; (3) original trials regarding the impact of marital status on prognosis (survival or mortality) in patients with any form of diagnosed prostate cancer; (4) studies using an observational study design (i.e. prospective or retrospective cohort, cross-sectional or case-control study); and (5) studies reporting sufficient data on risk estimates (hazard ratio, HR; odds ratio, OR; relative risk, RR) with associated 95% confidence intervals (CIs) or sufficient raw data

for calculation. For studies from the same population, only the largest studies with the longest follow-up period were retained. In addition, certain articles, such as case series, case reports, and review articles were excluded. Disagreement was resolved through discussion amongst the investigators. Data extraction and methodological quality assessment Two investigators (ZL. Guo and CM. Gu) independently extracted data from the eligible studies by using an predefined data extraction form. The following data were extracted: first author, study design, country, ba-



**Figure 4.** Marital status and overall survival in patients with prostate cancer.  
**Abbreviations:** CI, confidence interval; HR, Hazard Ratio

**Table 1.** Characteristics of the included studies.

First author year	Study design	Country	Total participants (married, %)	Age, y, Mean (Range)	Follow-up, y, Mean (Range)	Treatments	Marital status	Outcomes	Adjustments	
Abdollah F 2011. (21)	Retro-spective population-based cohort	USA	163,697 (83.1%)	63 (35-90)	NA	RP	Married SDW Never married	CSM ACM	Age, race, socioeconomic status, tumor grade, and year of surgery	
Aizer AA 2013. (22)	Retro-spective population-based cohort	USA	190,648 (76.7%)	63 ± (SD: 12)	3.1 ± (0.1-5.9)	Mitox-antrone	Married Unmarried	CSM	Demographic factors (age, race, income, education, and urban or rural residence), tumor stage, nodal stage, and whether definitive treatment administered	
Du KL 2012. (23)	Prospective cohort	USA	3,570 (76%)	69.2 (41-48)	NA	Radiation therapy	Married SDW	OS	Age, clinical stage, Karnofsky Performance Score (KPS), Gleason Score, Prostate Specific Antigen (PSA), Biologic Effective Dose (BED), and type of treatment received	
Gomez SL 2016. (11)	Retro-spective population-based cohort	USA	178,586 (75.4%)	NA	NA	NA	Married Unmarried	ACM	Cancer site, race/ethnicity, and treatment	
Huang TB 2018. (24)	Retro-spective population-based cohort	USA	95,846 (81.6%)	NA	6.5 ± (SD: 1.9)	RP	Married SDW	OS CSS	Age, ethnicity, grade, stage, Gleason scores, and sequence number	
Khan S 2019. (12)	Retro-spective cohort	USA	3,579 (86.8%)	60.4	NA	RP	Married Unmarried CSM	ACM	Age, race, comorbidity status, PSA, and biopsy Gleason grade	
Knipper S 2019. (25)	Retro-spective population-based cohort	USA	433,197 (75.4%)	65.4 (59-71)	NA	RP	External beam Brachytherapy	Married Unmarried	CSM	Prostatic-specific antigen value, age at diagnosis, year of diagnosis, treatment, clinical tumor stage, and race in all groups
Lai H 1999. (26)	Retro-spective population-based cohort	USA	261,070 (70%)	65.4 ± (SD: 13.6)	NA	NA	Married	SDW OS	Age, race, and treatment	
Nepple KG 2012. (13)	Retro-spective cohort	USA	3,596 (86.9%)	NA	NA	RP	Married Divorced Widowed Never married	CSM ACM	PSA, clinical stage, and biopsy Gleason grade, comorbidity, ethnicity, age, and marital status at time of treatment	
Schiffmann J 2015. (14)	Retro-spective cohort	Germany	8,088 (91.1%)	63.5 (35.8–79.8)	4 ± (3.1)	RP	Married Unmarried	ACM	PSA, biopsy Gleason score, number of biopsy cores taken, number of positive biopsy cores, clinical tumor stage	
Tyson MD 2013. (27)	Retro-spective population-based cohort	USA	115,922 (78%)	NA	NA	NA	Married Single Divorced Widowed Separated	CSM ACM	Age, AJCC stage, tumor grade, and race	

**Abbreviations:** ACM, all-cause mortality; AJCC, American Joint Committee on Cancer; CSM, cancer-specific mortality; CSS, cancer-specific survival; NA, not applicable; OS, overall survival; SD, standard deviation; SDW, separated/divorced/widowed; RP, Radical prostatectomy; y, year.

sic characteristics (i.e. sample size, age, and follow-up), definitive therapy (i.e. radical prostatectomy, androgen deprivation therapy, and radiation therapy), marital status, adjusted confounders, and risk estimates (HR, OR

or RR) with associated 95% CIs or sufficient raw data. If the information reported in the eligible studies were insufficient, we contacted the primary authors to obtain and verify the data.

**Table 2.** Results of subgroup analyses.

Overall ACM risk	Studies, N	Participants, N	HR (95% CI)	p value	p of heterogeneity	I <sup>2</sup> (%)
Different definite therapies	6	910,639	1.39 (1.30–1.50)	< 0.001	< 0.001	92.2
RP	4	178,960	1.37 (1.25–1.51)	< 0.001	0.006	67.2
Other therapies	2	178,586	1.42 (1.25–1.60)	< 0.001	< 0.001	98.8
Overall CSM risk	Studies, N	Participants, N	HR (95% CI)	p value	p of heterogeneity	I <sup>2</sup> (%)
Different definite therapies	6	473,468	1.29 (1.17–1.41)	< 0.001	< 0.001	82.5
RP	3	170,872	1.34 (1.05–1.71)	0.017	0.002	73.3
Mitoxantrone RP	1	190,648	1.35 (1.23–1.49)	< 0.001	NA	NA
External beam Brachy therapy	1	433,197	1.19 (1.15–1.24)	< 0.001	NA	NA
Other therapies	1	115,922	1.40 (1.33–1.47)	< 0.001	NA	NA

**Abbreviations:** ACM, all-cause mortality; CI, confidence interval; CSM, cancer-specific mortality; HR, Hazard Ratio; NA, not applicable; RP, Radical prostatectomy.

The methodological quality and risk of bias assessment were performed by two investigators according to the Newcastle–Ottawa scale (NOS),<sup>(18)</sup> which consists of nine items that evaluate the representativeness of included studies. Each item was assessed as either ‘unclear’, ‘yes’ or ‘no’, which corresponded to ‘0’, ‘1’ or ‘0’ in accordance with the information reported by the studies. The total score ranged from 0 to 9, and a study was categorised as follows: a score of 8–9 was considered high quality, a score of 6–7 was considered moderate quality, and a score of  $\leq 5$  was considered low quality. Any disagreements were settled through a discussion amongst the authors.

### Statistical analyses

In general, the total risk estimates (HR and RR with associated 95% CIs) extracted from the included studies were calculated via Stata version 15.0 (serial number: 10699393; StataCorp Wyb). HR and RR with associated 95% CIs were calculated through inverse variance using random or fixed effects models. For consistent definitions, HR with associated 95% CIs was used as a common measure because marital status and prostate cancer-related survival or mortality were considered as rare events. The differences amongst the various measures of risk estimates could be generally ignored. Hence, the RRs extracted from the included studies could be considered approximations of HRs.<sup>(19)</sup> I<sup>2</sup> was used to assess heterogeneity across studies, with I<sup>2</sup> values of 0%, 25%, 50% and 75% representing no, low, moderate and high heterogeneity, respectively.<sup>(15)</sup> Specifically, a severe heterogeneity of I<sup>2</sup>  $\geq 50\%$  warrants the use of random effects models. Otherwise, a fixed effects model should be used.<sup>(15)</sup> Statistical significance was set at  $P < .05$ . Moreover, weight estimation was conducted in the meta-analysis according to the validity or risk of bias for included studies. Note that if all the weights are the same then the weighted average is equal to the mean intervention effect. The bigger the weight given to the study, the more it will contribute to the weighted average. The weights are therefore chosen to reflect the amount of information that each study contains. In the presence of heterogeneity, a random-effects meta-analysis weights the studies relatively more equally than a fixed-effect analysis. Subgroup analysis based on different treatments was performed to explore the possible origins of heterogeneity. Sensi-

tivity analysis could assess the quality and consistency of the results through omitting each study individually. In addition, meta-regression analysis was conducted to explore the possible sources of heterogeneity in several variables, and restricted maximum likelihood was used in the analysis. However, the application of Egger<sup>(20)</sup> and Begg–Mazumdar<sup>(21)</sup> tests was limited because of the low number of studies evaluated.

## RESULTS

### Study identification and selection

The search process and study selection are described in **Figure 1**. In general, 569 articles were identified through the initial assessment, and 459 articles were retrieved after duplicates were removed. Next, 420 articles were removed after title/abstract evaluation from the remaining articles. Finally, 39 articles were evaluated on the basis of the full text, and 28 were excluded for the following reasons: no prostate cancer (6 articles), no marital status (4 articles), no prognostic assessment (14 articles), and not sufficient data for extraction (4 articles). Therefore, 11 articles<sup>(11–14, 22–28)</sup> comprising 1,457,799 patients diagnosed with prostate cancer were identified for systematic review and meta-analysis according to the eligibility criteria.

### Study characteristics and methodological quality

The basic characteristics of studies included in this systematic review and meta-analysis are described in Table 1. These studies (1 prospective cohort<sup>(24)</sup> and 10 retrospective cohort studies<sup>(11–14, 22, 23, 25–28)</sup>) were published between 1999 and 2019. There were 10 studies<sup>(11–13, 22–28)</sup> from the United States and 1 from Germany<sup>(14)</sup>. The sample sizes also varied between 3,570 and 433,197 patients with prostate cancer who were treated with various definitive therapies, including radical prostatectomy (RP), radiation therapy, external beam, brachytherapy, and mitoxantrone. The follow-up duration ranged from 3.1 years to 6.5 years. All the included studies reported risk estimates adjusted for confounding factors. Overall, the methodological quality and risk bias assessment of the included studies<sup>(11–14, 22–28)</sup> was performed according to the NOS. Five articles<sup>(14, 22–24, 26)</sup> acquired 8 or 9 points and were considered as high quality, eight articles<sup>(11–13, 25, 28)</sup> acquired 6 or 7 points and were con-

**Table 3.** Results of meta-regression.

Covariates	Exp(b)	Standard error	t	P >  t	95% CI	R-squared
ACM						
Treatment	1.40693	1.242582	0.39	0.711	0.174297	11.35678 -8.97%
CSM						
Treatment	0.7745458	0.7430051	-0.27	0.798	0.0801535	7.484653 -11.64%

**Abbreviations:** ACM, all-cause mortality; CI, confidence interval; CSM, cancer-specific mortality.

sidered as moderate quality and one study<sup>(27)</sup> scored 5 points and was considered as low quality.

### Marital status and mortality in patients with prostate cancer

Six studies<sup>(12,13,22,23,26,28)</sup> comprising 910,639 patients diagnosed with prostate cancer used the random effects model (Figure 2) and demonstrated that unmarried status (separated, divorced, widowed or never married) was associated with an increased risk of ACM (HR = 1.39, 95% CI: 1.30–1.50;  $P < .001$ ;  $I^2 = 92.2\%$ ) compared with married status. Specifically, both divorced and never-married men had an excess risk of ACM (divorced men, HR = 1.45, 95% CI: 1.39–1.51;  $P < .001$ ; never-married men, HR = 1.46, 95% CI: 1.05–2.03;  $P < .001$ ), whereas this significant association was not observed amongst widowed patients (HR = 1.34, 95% CI: 0.83–2.16;  $P = .23$ ) owing to the limited number of studies included. In the subgroup analyses stratified according to different definitive therapies, unmarried men who were treated with RP was associated with a higher risk of ACM (HR = 1.37, 95% CI: 1.25–1.51;  $P < .001$ ) compared with other treatments (Table 2).

In six studies<sup>(11–14,22,28)</sup> comprising 473,468 patients diagnosed with prostate cancer, unmarried men had an elevated risk of cancer-specific mortality (CSM) (HR = 1.29, 95% CI: 1.17–1.41;  $P < .001$ ;  $I^2 = 82.5\%$ ) than those married men using a random effects model (Figure 3). However, this significant association was not observed in never-married (HR = 1.03, 95% CI: 0.91–

1.17;  $P = .645$ ) or widowed men (HR = 1.13, 95% CI: 0.15–8.36;  $P = .905$ ), except for divorced patients (HR = 1.32, 95% CI: 1.22–1.43;  $P < .001$ ) with prostate cancer. When stratified by different treatments, the results were significant and consistent (Table 2).

The results of meta-regression analyses regarding the heterogeneity amongst studies for ACM and CSM revealed that definitive therapy (ACM,  $P = .711$ ; CSM,  $P = .798$ ) could not result in heterogeneity amongst the included studies. Therefore, the other important confounding factors such as age should be fully explored in future relevant studies. Moreover, the adjusted R-squared values from -11.64% to -8.97% because the regression line is worse than using a horizontal line, which indicated that the regressors slightly contributed to the explanation of the response variables (Table 3). When any study was omitted in turn, the stability of the results by sensitivity analysis did not show any significant change for ACM and CSM (Table 4).

### Marital status and survival in patients with prostate cancer

Three studies<sup>(24,25,27)</sup> comprising 360,486 patients diagnosed with prostate cancer reported risk estimates of overall survival (OS) and marital status. A significant difference was observed between unmarried status and shorter OS (HR = 1.37, 95% CI: 1.20–1.56;  $P < .001$ ;  $I^2 = 94.5\%$ ) through a random effects model (Figure 4). However, meta-regression and subgroup analyses were limited because of the small number of studies included. Notably, the results of sensitivity analysis revealed that the stability of meta-analysis had no significant change after each study was omitted in turn. For cancer-specific survival (CSS), only one retrospective population-based cohort reporting the risk of CSS and the impact of marital status was included. Huang et al.<sup>(25)</sup> found that divorced and never-married men were significantly associated with shorter CSS (HR = 1.61, 95% CI: 1.34–1.93;  $P < .001$  and HR = 1.20, 95% CI: 1.00–1.40;  $P < .001$ , respectively). By contrast, this association was not observed amongst widowed men (HR = 1.13, 95% CI: 0.81–1.58;  $P > .05$ ).

## DISCUSSION

### Main findings

The systematic review and meta-analysis identified 11 studies comprising 1,457,799 patients diagnosed with prostate cancer regarding the association between marital status and prognosis in prostate cancer. We found that higher mortality and shorter survival in patients diagnosed with prostate cancer are associated with unmarried status, particularly in divorced and never-married patients, than in married men. However, this significant association does not seem to be validated in widowed populations because of the limited number of relevant studies evaluated. Note that the risk estimates

**Table 4.** Results of sensitivity analyses.

Study omitted	HR	95% CI
<b>ACM</b>		
Abdollah F 2011. [21]	1.42	1.31 1.54
Abdollah F 2011. [21]	1.38	1.26 1.50
Gomez SL 2016. [11]	1.41	1.30 1.53
Khan S 2019. [12]	1.39	1.29 1.50
Nepple KG 2012. [13]	1.38	1.28 1.48
Nepple KG 2012. [13]	1.40	1.30 1.50
Nepple KG 2012. [13]	1.39	1.29 1.50
Schiffmann J 2015. [14]	1.40	1.30 1.50
Tyson MD 2013. [27]	1.36	1.28 1.43
Combined	1.39	1.30 1.50
<b>CSM</b>		
Aizer AA 2013. [22]	1.27	1.14 1.42
Abdollah F 2011. [21]	1.34	1.22 1.47
Abdollah F 2011. [21]	1.28	1.14 1.44
Khan S 2019. [12]	1.28	1.16 1.40
Knipper S 2019. [25]	1.31	1.18 1.46
Nepple KG 2012. [13]	1.28	1.17 1.41
Nepple KG 2012. [13]	1.29	1.17 1.42
Nepple KG 2012. [13]	1.27	1.16 1.39
Tyson MD 2013. [27]	1.25	1.13 1.38
Combined	1.29	1.17 1.41

**Abbreviations:** ACM, all-cause mortality; CI, confidence interval; CSM, cancer-specific mortality; HR, Hazard Ratio.

extracted from all included articles were based on the adjustment of confounding factors. Finally, sensitivity analysis revealed that the stability of the results had no significant change after each study was omitted in turn, and the meta-regression could not identify the potential confounding factors that might affect the level of heterogeneity between studies.

Most of the included studies revealed that unmarried men have consistently been found to be associated with worse prognosis in patients with prostate cancer, whereas few studies reported conflicting results.<sup>(14, 22)</sup> A retrospective cohort comprising 8,088 patients with prostate cancer conducted by Schiffmann et al.<sup>(14)</sup> in Germany failed to reveal a significant association between unmarried men and ACM (HR = 0.80, 95% CI: 0.40–1.70;  $P = .6$ ). Apart from that, Abdollah et al.<sup>(22)</sup> demonstrated that divorced patients were statistically associated with an increased risk of CSM (HR = 1.32, 95% CI: 1.20–1.40;  $P < .001$ ) compared with married men. By contrast, this significant association was not observed in never-married patients (HR = 1.03, 95% CI: 0.91–1.17;  $P > .05$ ). In the subgroup analyses stratified by different definitive therapies, unmarried men who have been treated with RP were associated with higher risks of ACM and CSM compared with those who underwent other treatments. However, of all included studies, three did not report definitive treatments for patients with prostate cancer.<sup>(11,27,28)</sup>

#### **Comparison with another previous study**

One systematic review that assessed a similar topic was published by Buja et al.<sup>(29)</sup> Several differences between Buja et al. and the current work should be noted. Firstly, the previous review included only 3 articles that involved 372,412 patients with prostate cancer and marital status. By comparison, our meta-analysis involved 11 studies comprising 1,457,799 patients diagnosed with prostate cancer. With the added statistical power of 8 studies and at least 1,085,387 cases, our meta-analysis, which was inconsistent with the results of Buja et al., was the latest and the most comprehensive review to date. Secondly, the association between marital status and prognosis (i.e. survival and mortality) was evaluated amongst patients with prostate cancer treated by any therapy in line with the predefined inclusion criteria. Sensitivity analysis and meta-regression failed to identify confounding factors that might affect the level of heterogeneity between studies, thereby reinforcing the main findings.

#### **Implications for clinical practice**

Some researchers recently suggested that the choice of treatment therapy for prostate cancer in married men may be different from that of unmarried men. For married men, their spouse can encourage them to choose a treatment, such as RP or radiation therapy.<sup>(30,31)</sup> The association between marriage and treatment for prostate cancer has been confirmed and positively correlated. However, researchers did not evaluate survival or mortality as an endpoint.<sup>(30)</sup> Overall, unmarried status represents an important determinant of a worse prognosis. Note that the detrimental influence of unmarried status remains consistent when stratified by different therapies. Hence, the negative impact of unmarried status on mortality or survival may still be explained through the later diagnosis or treatments in these unmarried patients. Lifestyle choice is also an important risk factor for the prognosis between unmarried and married men. For in-

stance, unmarried men are more likely to abuse tobacco or alcohol than do married men.<sup>(33)</sup> Similarly, married men are more likely to avoid unhealthy habits post-diagnosis because of their responsibility to their spouse and family.<sup>(33)</sup> Therefore, the possible mechanisms by which marriage may potentially influence the prognosis in men with prostate cancer can be shown as follows.<sup>(1)</sup> Patients with prostate cancer may receive more psychological support from their spouse or the society after diagnosis, which can improve their likelihood of survival.<sup>(2)</sup> The spouse may affect the postoperative compliance (such as follow-up) and reception of adjuvant or secondary treatment, such as androgen deprivation therapy and adjuvant or salvage radiation therapy.<sup>(3)</sup> The lack of physical activity is more common in men with insufficient emotional support, which may be associated with higher mortality.<sup>(34–39)</sup> Nevertheless, our understanding on the association between marital status and different stages of prostate cancer remains unclear because of the lack of studies that examine such a relationship. Thus, further research is warranted to investigate the personalised intervention and management methods for unmarried patients with prostate cancer.

This systematic review and meta-analysis demonstrated several crucial strengths in multiple ways. Firstly, our study comprehensively investigated the association between marital status and prognosis amongst patients with prostate cancer, and subgroup analyses stratified according to definitive therapy were conducted to determine whether this variable moderated such an association and the level of heterogeneity between the studies. Secondly, multivariate-adjusted risk estimates were applied to minimise other relevant risk factors that might affect the overall results. Finally, sensitivity analysis and meta-regression validated the rationality and reliability of the results for our study.

Several limitations of this study should be noted. Firstly, most of the studies used retrospective cohort design, which has the disadvantages of missing data and risk of bias. Secondly, the number of articles included in this study was limited, especially in the subgroup, which may lead to unreliable results and might not reflect the comprehensiveness of the overall results. Lastly, significant heterogeneity was observed and the random effects model was applied in the pooled analysis. However, subgroup analysis and meta-regression analyses failed to explore the potential factors leading to significant heterogeneity. Therefore, other important factors should be adequately studied in further high-quality researches regarding this topic.

#### **CONCLUSIONS**

Existing evidence indicates that unmarried status is associated with a worse prognosis regarding mortality and survival in patients diagnosed with prostate cancer, particularly in divorced and never-married patients. Hence, further research should explore the potential mechanisms which can benefit the development of novel, more personalised management methods for unmarried patients with prostate cancer, who was considered as representatives of high-risk groups.

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