Cancer Management and Research

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ORIGINAL RESEARCH

The homogeneous and heterogeneous risk factors for the morbidity and prognosis of bone metastasis in patients with prostate cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: Using the Surveillance, Epidemiology, and End Results database (SEER) to assess the incidence and risk factors of morbidity and prognosis for bone metastases in initial metastatic prostate cancer.

Patients and methods: The records of 249,331 prostate cancer patients in the SEER database, diagnosed between 2010 and 2014, were obtained were obtained to investigate the risk factors for developing bone metastasis, and the records of 9925 of them who registered before 2013 were retrieved (with at least 1 year follow up) to explore the prognostic factors for bone metastasis. Multivariate logistic and Cox regression were used to identify risk factors and prognostic factors for bone metastases, respectively.

Results: In total, 12,794 patients (5.1%) were diagnosed with bone metastases at the initial diagnosis. Older age, unmarried status, lymph node metastasis, poor tumor differentiation grade (Gleason grade), metastases at lung, brain, and liver were all positively associated with risk for the morbidity and prognosis of bone metastasis in prostate cancer. Black race and higher T stage were positively associated with bone metastasis development; however, they were not associated with a prognosis of bone metastasis.

Conclusion: The incidence of bone metastasis in prostate cancer was approximately 5% with poor survival. The prostate cancer has homogeneous and heterogeneous risk factors for incidence and prognosis of bone metastasis, which may provide potential guidelines for the screening and preventive treatment for the bone metastasis of prostate cancer.

Keywords: bone metastases, initial prostate cancer, survival, risk factor

Introduction

Globally, prostate cancer is the second most common malignancy in males and the fifth leading cancer-related cause of death.[1,2] In the US, prostate cancer is the most common malignancy in males, and takes up 19% of all newly-diagnosed male cancer cases.[1] With the development of surgical technique, radiotherapy, and chemotherapy, biotherapy regimen, and supportive treatment, the survival of prostate cancer patients has increased.[3–5] Accordingly, the higher survival rate increased the prevalence of distant metastasis. Bone metastases (BM), as one of the most common distant metastasis types, was reported to occur in at least 85% of patients who died from prostate cancer.[5] BM was accepted to lead to significant morbidity, worsening patient quality-of-life.[6]

Usually, the three most common clinical symptoms of BM can be detected, including pain, pathologic bone fractures, and spinal cord compression.[7] A large number of prostate cancer patients did not go to a doctor until they had the aforementioned symptoms. Furthermore, for asymptomatic patients, the Prostate Cancer National

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http://dx.doi.org/10.2147/CMAR.S168579

Comprehensive Cancer Network (NCCN) screening guidelines do not recommend performing routine assessment for BM.[8] Hence, to build a reliable predictive system for screening performance; a study looking into the risk factors of BM in prostate cancer patients is warranted.

Currently, prostate specific antigen (PSA) has been clinically applied as the main predictor for BM.[9] However, using PSA level as the inclusion criteria, the latest systematic review and meta-analysis suggested the lack of a robust definition for predicting high BM risk in prostate cancer patients.[10] Meanwhile, a series of clinical studies suggested the incidence of BM in prostate patients with low PSA values (<20 ng/mL) is from 12.6% to 36.1%.[11–13] A previous study reported, besides PSA, Gleason score can be another predictive factor in prostate cancer patients with BM.[14] More BM risk factors are needed to uncover the clinical metastatic characteristics of prostate cancer, and to supplement the predictive system.

The purpose of the present study was to use the Surveillance, Epidemiology, and End Results (SEER) database to assess the incidence and the risk factors of BM in initial prostate cancer. Moreover, survival estimates and prognostic factors identification were conducted for patients who had developed BM at the time of prostate cancer diagnosis.

Methods

Data source and cohort selection

Data were obtained from the National Cancer Institute's SEER program between 2010 and 2014, as the BM status and other sites of distant metastases were collected by SEER from 2010, and the latest data update was on December 31, 2014. We extracted data for all cases initially diagnosed as malignant primary prostate cancer. The flow-chart of the subjects' selection is listed in Figure 1. A total of 249,331 patients who were diagnosed as having prostate cancer with or without BM between January 1, 2010 and December 31, 2014 were utilized to identify the risk factors of BM. Among them, 9,925 patients who were diagnosed between 2010 and 2013 (with at least 1 year follow up) were retrieved for analyzing the prognosis factors for bone metastasis in prostate cancer (Figure 1).

The SEER is a freely available database, and the data released by the SEER database do not require informed patient consent, because cancer is a reportable disease in every state of the USA. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and the study was approved by the research ethics board of the Tianjin Medical University Cancer Institute and Hospital.

Statistical analysis

Multivariable logistic regression was used to determine the risk factors for developing BM at diagnosis. Variables included age (≤40, 41–60, 61-80, and ≥81 years), race [white, black, American Indian/Alaska Native (AI) and Asian or Pacific Islander (API)], marital status (married and unmarried), primary tumor (T) stage (T1, T2, T3, and T4), regional lymph node stage (N0 and N1), Gleason tumor grade (1= Gleason score ≤6; 2= Gleason score 3+4; 3= Gleason score 4+3; 4= Gleason score 8; 5= Gleason score 9–10), and the presence or absence of lung metastases, liver metastases, or brain metastases. Survival duration was obtained using the Kaplan–Meier method; the differences between the curves were tested by Log-rank test. To identify factors associated with mortality, multivariable Cox proportional hazards regression was performed using the aforementioned factors.

All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA), and all charts of survival were prepared using MedCalc 15.2.2. Two-sided *P*-values less than 0.05 were considered statistically significant. SEER*Stat Software version 8.3.4 (Information Management Sercives, Inc. Calverton, MD, USA) (The Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute) was used to extract data.

Results

Incidence of bone metastases

For the 249,331 eligible patients who were diagnosed with malignant primary prostate cancer between 2010 and 2014 in the study, the mean age was 66.08±9.22 years, and 190,863 (76.6%) were white. Of them, 12,794 (5.1%) were diagnosed with BM at the initial diagnosis (Table 1).

Risk factors for developing bone metastasis

As shown in Table 1, age over 80 years, black race, unmarried, higher T stage, lymph node involvement, poor tumor differentiated grade (Gleason grade), and the presence of lung metastases, liver metastases, and brain metastases were associated with significantly greater odds of having BM at diagnosis.

Survival and prognostic factors for BM

The mean survival of the prostate cancer patients was 28.53±17.60 months, while that of those patients with BM was only 20.44±14.57 months. Survival estimates classified by age (Figure 2A), race (Figure 2B), marital

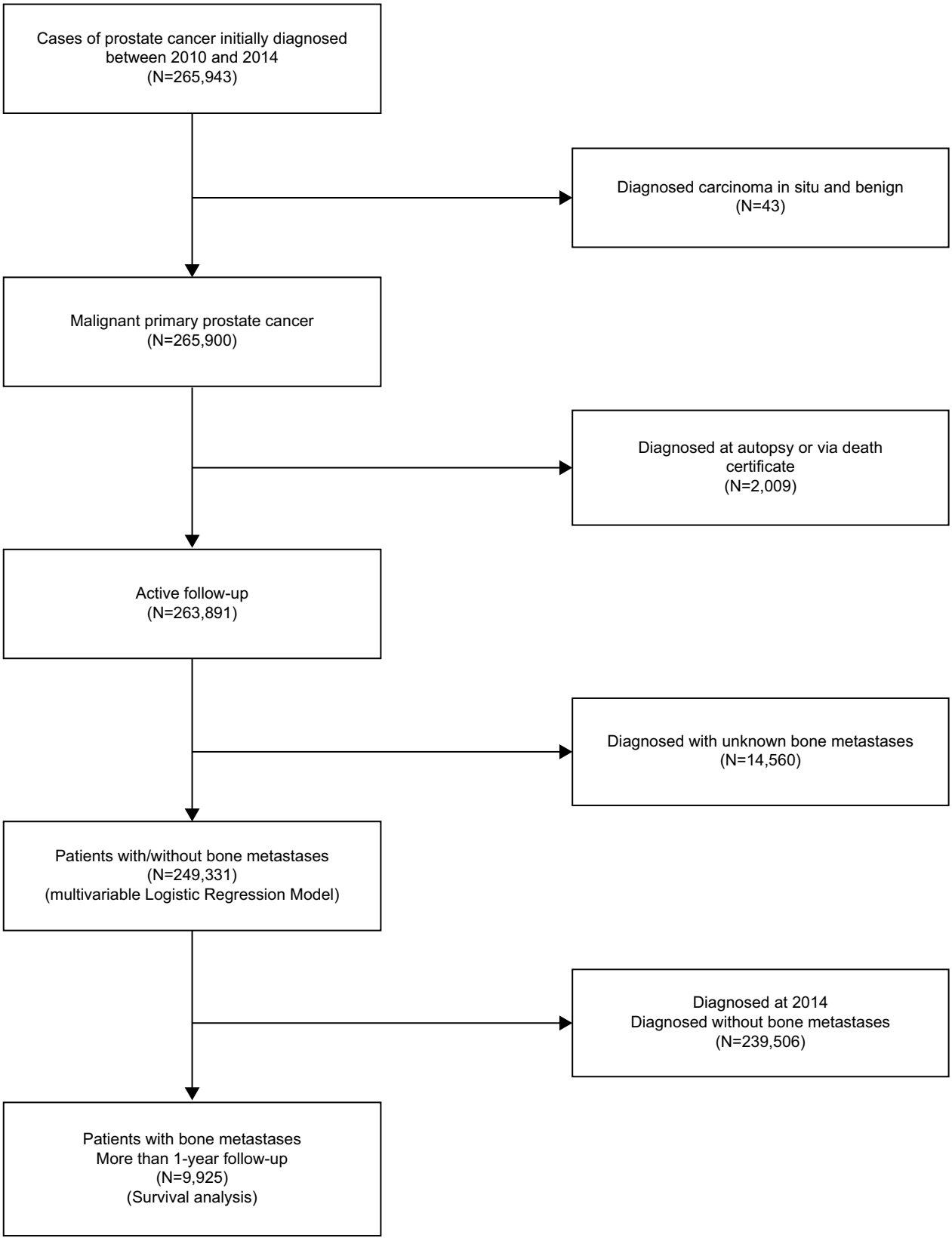

Figure 1 Flow chart of the subject's selection for analyzing the risk factors for the morbidity and prognosis of BM in prostate cancer patients.
Abbreviations: BM, bone metastases.

Table 1 Multivariable logistic regression for analyzing the demographic and related clinical characteristics for developing BM in patients diagnosed with initial primary prostate cancer (diagnosed 2010–2014)

Subject characteristics	No. of patients with PC (2010–2014)			OR (95%CI)	*P* value
	With bone metastases	Entire cohort	Incidence (%)		
Age, in years				1.45 (1.37–1.53)	<0.001
≤40	11	273	4.02	1 (Reference)	1.00
41–60	2,240	68,525	3.27	0.65 (0.21–1.99)	0.45
61–80	7,148	163,679	4.39	0.64 (0.21–1.96)	0.43
≥81	3,395	16,854	20.14	1.22 (0.40–3.75)	0.73
Race				1.06 (1.04–1.08)	<0.001
White	9,652	190,863	5.06	1 (Reference)	1.00
Black	2,270	38,370	5.92	1.19 (1.10–1.29)	<0.001
AI	91	978	9.30	0.97 (0.85–1.11)	0.63
API	688	11,471	6.00	1.00 (0.64–1.57)	0.99
Unknown	93	7,649	1.21	NA	NA
Marital status					
Unmarried	4,985	55,193	9.03	1 (Reference)	1.00
Married	6,970	157,771	4.42	0.64 (0.60–0.68)	<0.001
Unknown	839	36,367	2.31	NA	NA
T stage				0.91 (0.88–0.95)	<0.001
T1	2,753	99,988	2.75	1 (Reference)	1.00
T2	3,502	112,984	3.10	0.83 (0.77–0.89)	<0.001
T3	1,106	25,640	4.31	0.39 (0.36–0.43)	<0.001
T4	1,453	2,874	50.56	2.64 (2.31–3.01)	<0.001
Unknown	3,980	7,845	50.73	NA	NA
N stage					
N0	6,781	232,945	2.91	1 (Reference)	1.00
N1	2,932	7,922	37.01	4.80 (4.43–5.20)	<0.001
Unknown	3,081	8,464	36.40	NA	NA
Gleason grade				2.88 (2.81–2.96)	<0.001
1	232	103,197	0.22	1 (Reference)	1.00
2	456	61,745	0.74	3.06 (2.54–3.70)	<0.001
3	675	28,146	2.40	10.26 (8.60–12.25)	<0.001
4	1,905	23,513	8.10	29.40 (24.95–34.65)	<0.001
5	4,354	20,213	21.54	75.65 (64.42–88.83)	<0.001
Unknown	5,172	12,517	41.32	NA	NA
Lung Met					
None	11,222	247,403	4.54	1 (Reference)	1.00
Yes	902	1,125	80.18	22.39 (16.86–29.72)	<0.001
Unknown	670	803	83.43	NA	NA
Liver Met					
None	11,757	248,017	4.74	1 (Reference)	1.00
Yes	483	641	75.35	18.79(12.58–28.06)	<0.001
Unknown	554	673	82.32	NA	NA
Brain Met					
None	11,980	248,365	4.82	1 (Reference)	1.00
Yes	153	179	85.47	28.64 (11.92–68.77)	<0.001
Unknown	661	787	83.99	NA	NA

Note: All factors with unknown data removed from multivariable logistic regression model.
Abbreviations: BM, bone metastases; PC, prostate cancer; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastases; NA, not available.

status (Figure 2C), T stage (Figure 2D), N stage (Figure 2E), tumor grade (Figure 2F), the presence of lung metastases (Figure 2G), liver metastases (Figure 2H) or brain metastases (Figure 2I) are graphically displayed. Among patients with initial bone metastasis, the median survival of those who combined with liver metastases was the shortest (Median survival=10 months, 95% CI=8.44–11.56 months).

The prognostic factors for BM are shown in Table 2. A multivariate Cox regression model showed that patients of older age, unmarried, with lymph node involvement, poor tumor differentiated grade, and the presence of lung metas-

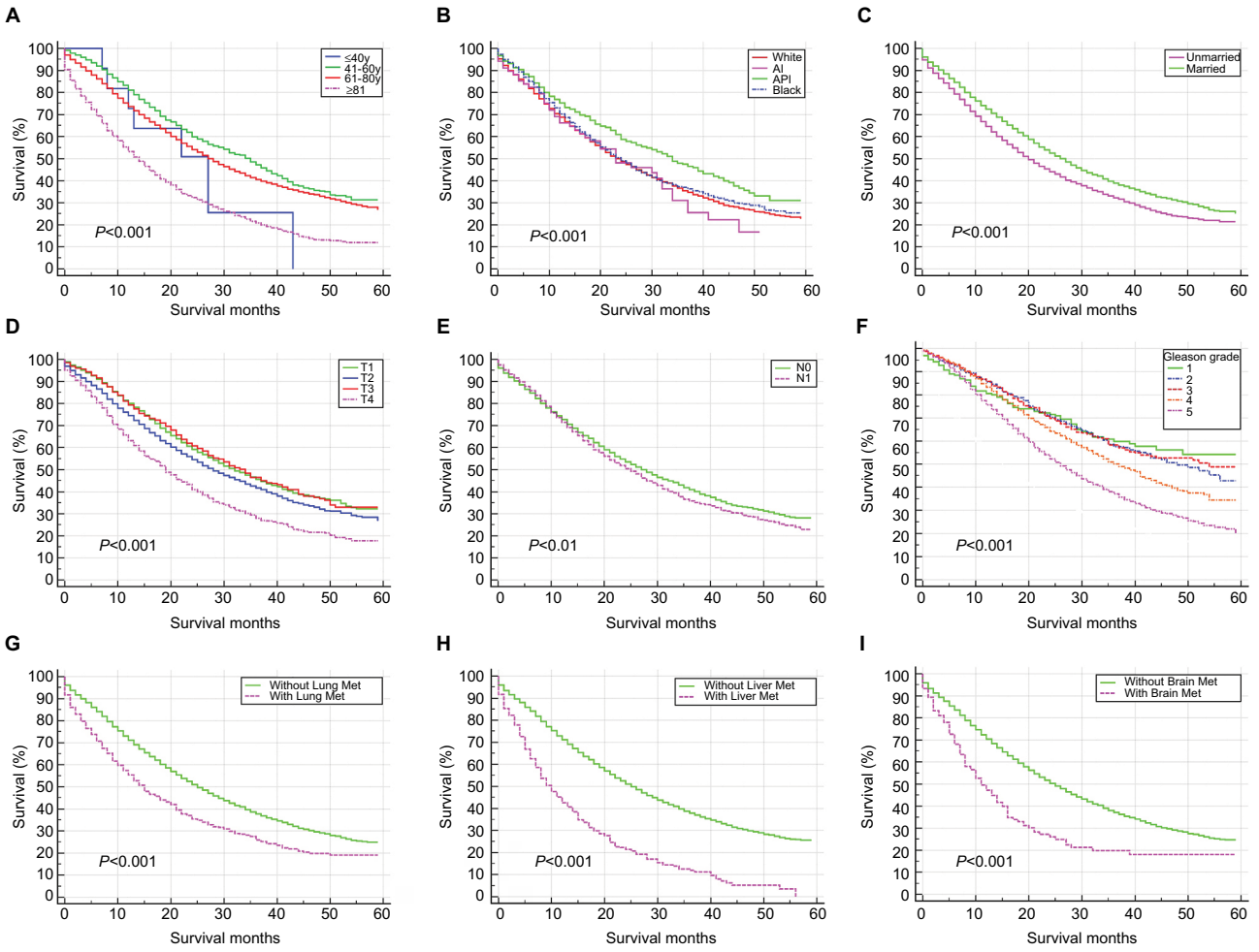

Figure 2 Kaplan–Meier analysis of overall survival among prostate cancer patients who were diagnosed with BM, when stratified by age (**A**), race (**B**), marital status (**C**), T stage (**D**), N stage (**E**), Gleason grade (**F**), and the presence of lung metastases (**G**), liver metastases (**H**), and brain metastases (**I**).
Abbreviations: BM, bone metastases; Lung Met, lung metastases; Liver Met, liver metastases; Brain Met, brain metastases; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; y, years.

tases, liver metastases, and brain metastases were correlated with higher risk of mortality. Race and T stage were not significantly associated with mortality.

In this study, the homogeneous risk factors for the morbidity and prognosis of BM in patients with prostate cancer were older, unmarried status, lymph node involvement, poor tumor differentiated, and the presence of lung, liver, or brain metastases. Patients with black race and higher T stage were prone to be associated with BM development; however, they were not associated with overall survival of BM.

Discussion

Based on a large population analysis, the present study firstly determined the incidence of BM at the initial diagnosis of prostate cancer patients. We found that 5.1% of prostate cancer patients were initially diagnosed with BM. Although the present study was conducted based on a large population, it may underestimate BM incidence in initial diagnosed prostate cancer patients for being unable to capture the asymptomatic cases. The BM cumulative incidence was differently reported from 0.8% to 53.6%.[11,15–18] The diversity of BM cumulative incidence could be due to various causes: First, most of the prostate patients chose to go to a doctor at an advanced stage in developing countries; Secondly, a high incidence of BM can also be observed in developed countries in the 1990s.[17,18] Thus, a metastatic screening for prostate cancer patients should be designed based on local economic development and local epidemiologic characteristics of prostate cancer.

A series of risk factors of initial BM in prostate cancer patients were found, including elderly patient (≥81 years), black race, unmarried, higher T stage, N stage (N1), lung metastases, brain metastases, and poor tumor differentiated grade. Thus, physicians should focus on their prostate cancer patients with these risk factors. At the same time, a skeletal scanning can be considered for the patients with high

Table 2 Multivariable Cox regression for analyzing the mortality among primary prostate cancer patients with BM (diagnosed 2010–2013)

Subject characteristics	No. of PC patients with BM		Survival, Median (IQR), mo	Cox HR (95% CI)	*P* value
	Overall	Deceased (rate, %)			
Age, in years				1.43 (1.33–1.53)	<0.001
≤40	11	7 (63.64)	27 (12.81–41.19)	1 (Reference)	1.00
41–60	1,748	839 (48.00)	35 (32.65–37.35)	0.58 (0.14–2.32)	0.44
61–80	5,521	2,958 (53.58)	27 (25.87–28.14)	0.70 (0.18–2.83)	0.62
≥81	2,645	1,936 (73.19)	14 (13.12–14.88)	1.17 (0.29–4.71)	0.82
Race				1.02 (0.99–1.05)	0.13
White	7,464	4,388 (58.79)	23 (22.14–23.86)	1 (Reference)	1.00
Black	1,790	1,037 (57.93)	24 (22.37–25.63)	1.13 (1.01–1.26)	0.03
AI	68	44 (64.70)	23 (12.42–33.58)	0.73 (0.58–0.91)	0.01
API	534	250 (46.82)	34 (28.99–39.02)	0.77 (0.40–1.48)	0.43
Unknown	69	21 (30.43)	NA	NA	NA
Marital status					
Unmarried	3,859	2,403 (62.27)	20 (18.94–21.06)	1 (Reference)	1.00
Married	5,433	3,000 (55.22)	27 (25.92–28.08)	0.81 (0.74–0.89)	<0.001
Unknown	633	337 (53.24)	NA	NA	NA
T Stage				1.04 (0.99–1.08)	0.12
T1	2,155	1,042 (48.35)	32 (29.80–34.21)	1 (Reference)	1.00
T2	2,769	1,492 (53.88)	28 (26.18–29.82)	0.94 (0.85–1.03)	0.19
T3	837	400 (47.79)	34 (30.48–37.52)	0.85 (0.74–0.98)	0.03
T4	1,105	726 (65.70)	19 (17.20–20.81)	1.23 (1.07–1.41)	0.003
Unknown	3,059	2,080 (68.00)	NA	NA	NA
N Stage					
N0	5,272	2,829 (53.66)	28 (26.67–29.33)	1 (Reference)	1.00
N1	2,156	1,227 (56.91)	25 (23.38–26.62)	1.11 (1.01–1.23)	0.036
Unknown	2,497	1,684 (67.44)	NA	NA	NA
Gleason grade				1.26 (1.20–1.32)	<0.001
1	193	72 (37.30)	NA	1 (Reference)	1.00
2	381	155 (40.68)	48 (40.20–55.80)	1.12 (0.79–1.57)	0.52
3	536	202 (37.69)	54 (NR)	1.22 (0.88–1.69)	0.23
4	1,488	672 (45.16)	37 (34.33–39.68)	1.32 (0.98–1.78)	0.07
5	3,351	1,871 (55.83)	26 (24.75–27.25)	2.03 (1.52–2.72)	<0.001
Unknown	3,976	2,798 (70.37)	NA	NA	NA
Lung Met					
None	8,694	4,912 (56.50)	25 (24.15–25.85)	1 (Reference)	1.00
Yes	687	471 (68.56)	15 (13.00–17.00)	1.43 (1.20–1.71)	<0.001
Unknown	544	357 (64.44)	NA	NA	NA
Liver Met					
None	9,084	5,118 (56.34)	25 (24.17–25.83)	1 (Reference)	1.00
Yes	388	321 (82.73)	10 (8.44–11.56)	2.51 (2.05–3.09)	<0.001
Unknown	453	301 (66.45)	NA	NA	NA
Brain Met					
None	9,257	5,280 (57.04)	25 (24.19–25.81)	1 (Reference)	1.00
Yes	133	99 (74.44)	11 (8.05–13.95)	1.80 (1.16–2.78)	0.01
Unknown	535	361 (67.48)	NA	NA	NA

Note: All factors with Unknown Data removed from Cox and Kaplan–Meier model.
Abbreviations: PC, prostate cancer; BM, bone metastases; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastases; NA, not available; NR, not reached.

metastasis risk. Meanwhile, in future research, the factors we analyzed can be involved in the predictive system for initial BM in prostate cancer patients.

A series of prognostic factors of initial BM in prostate cancer patients, which were correlated with higher mortality risk, were found, including young (≤40 years) and elderly patient (≥81 years), unmarried, N stage (N1), poor tumor grade, lung metastases, and brain metastases. The result suggested Gleason grading system's affirmative ability on prevention prognosis of advanced cancer with BM. Based on the aforementioned prognostic factors, physicians can make a preliminary estimation for the prostate patients with initial BM.

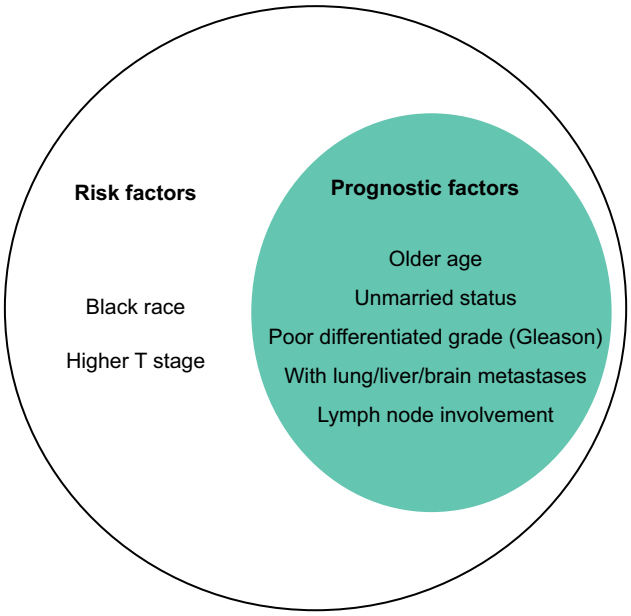

Figure 3 The homogeneous and heterogeneous risk factors and prognosis factor of BM in patients with prostate cancer. All the factors included in the larger circle represent the risk factors for developing BM, and the ones in smaller circle exhibit the factors, which were positively associated with overall death risk for prostate cancer patients with BM.
Abbreviation: BM, bone metastases.

Among the cohort of the present study, compared with black race, white patients had significantly lower risk for developing BM at diagnosis. This may suggest that prostate cancers in white patients are likely being diagnosed at an early stage. Meanwhile, black patients with BM showed worse median survival (Table 2). The latest study looking into brain metastases in newly diagnosed breast cancer also suggested a poor median survival in black patients.[19] Further studies looking into the potential explanations for black patients' poor survival in metastatic tumor is needed.

Inevitably, the present study has several limitations. First, in the present study, only the presence/absence of BM based on the initial diagnosis was analyzed. The patients who developed BM later during their disease course could not be analyzed, as they may not be recorded in the SEER database. Second, the actual rate of BM in patients with prostate cancer might be underestimated. BM cannot be captured in asymptomatic prostate cancer patients. Third, the SEER database has a lack of intact baseline information. Performance status, smoking and alcohol consumption, family history, blood type, and body mass index were not provided in the SEER database. Last, but not least, the detailed diagnosis method for BM was not available.

Conclusion

Despite the aforementioned limitations, based on the SEER database, the present study provided the incidence risk factors and prognostic factors of BM in patients with newly diagnosed initial prostate cancer. A series of risk factors for BM in prostate cancer patients were identified, which can be potentially used for clinical prediction. Survival analysis was also conducted, and a series of prognostic factors of initial BM in prostate cancer patients were found, which can be potentially used for making an individualized treatment plan.

Acknowledgments

The present study was sponsored by the Natural Science Foundation of China (81602363, 81702161), the Natural Science Foundation of Tianjin Science and Technology Committee China (17JCQNJC11000), the Natural Science Foundation of Tianjin Medical University (2016KYZQ10), the China Postdoctoral Science Foundation Grant (2017M621091), and the Doctor Start-up Grant of Tianjin Medical University Cancer Institute and Hospital (B1612, B1711).

Author contributions

XG, CZ, and XW designed the study. YX and GF collected the data. XG and XW analyzed the data. XG, CZ, and QG organized the manuscript. LL, XH, YM, FL, and GW reviewed the papers and revised the manuscript. All the authors (XG, CZ, QG, YX, GF, LL, XH, FL, YM, XW, GW) have read and approved the final manuscript. All authors contributed toward data analysis, drafting, and revising of the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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