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Research Paper

The homogeneous and heterogeneous risk factors for occurrence and prognosis in lung cancer patients with bone metastasis

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ABSTRACT

Purpose: To analyse the homogeneous and heterogeneous risk factors for occurrence and prognosis in lung cancer patients diagnosed with bone metastasis (BM) by using the Surveillance, Epidemiology, and End Results (SEER) database.

Patients and methods: The medical records of lung cancer patients with or without bone metastasis were identified in the SEER database between 2010 and 2015. A multivariate logistic regression analysis was performed to identify risk factors, and a multivariate Cox regression was used to determine the prognostic effects of every variable on survival.

Results: In total, 34,585 eligible patients from the SEER database were included in the analysis. Male gender and metastasis to the liver were factors that were both positively associated with a risk for the development and prognosis of bone metastasis in patients with lung cancer. Younger age, poor tumour differentiation grade, higher N stage (N3), adenocarcinoma and metastasis to the brain were all positively correlated with a risk of occurrence of BM, but these factors were not correlated with an unfavourable prognosis. Age, race, marital status, tumour size and pathologic type were independent risk factors for the prognosis of bone metastasis.

Conclusion: The morbidity of bone metastasis in lung cancer patients is dismal, with a rate of 25.9%. The findings of this study estimate the homogeneous and heterogeneous risk factors for the occurrence and prognosis of bone metastasis in lung cancer patients, which may provide clinical guidelines for physicians.

1. Introduction

Lung cancer is the most common cancer in men and the leading cancer-related death in women in most developed countries, which lead to an enormous burden on family and social [1]. Even if the technology of lung cancer screening have been growing for several years, the reduction in lung cancer mortality was not extremely lower than before [2]. Although the number of smokers has decreased significantly in recent years, lung cancer still remained high mortality accounting for nearly 27.4% of all cancer deaths and 5-year survival rates of lung cancer ranged from 4 to 17% for regional differences [3,4]. Lung cancer incidence trends was significantly different by gender, race, sex and histology in different countries [5–10].

Bone metastasis (BM) was one of the most common distant metastases in patients with lung cancer, which brought about poor prognosis as an incurable disease. Nearly 20% of lung cancer patients aged ≥65 years were diagnosed with BM [11]. BM in non-small cell lung cancer was predominant in different metastatic patterns, with a rate of 37.1% [12]. Although survival time for lung cancer patients has been increased through improving medical care, the risk of BM which resulted in poor prognosis remained increasing [13–15]. It was a great pity that there was not a standard and palliative management strategy to reduce the odds of BM and an assessment method for prognosis.

The purpose of this study is to use the Surveillance, Epidemiology, and End Results (SEER) to analyze the risk factors of BM and estimate prognosis for BM in patients diagnosed with lung cancer, as well as

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further analyze homogeneous and heterogeneous factors. Factors include age, race, histological type, marital status, T stage, N stage, grade classification, the tumor size, brain metastasis, and liver metastasis.

2. Methods

2.1. Study population

Lung and bronchus cancer cases were obtained from the National Cancer Institute's SEER program (https://seer.cancer.gov), which consisted of 18 population-based cancer registries. The SEER database collected and published cancer data covering nearly 28% of the total population in the United States. We send the data agreement to the SEER administration and accepted the agreement from the administrator. We had the right to obtain the information of patients with personal account. In the SEER database, all available data were retrospective, so Institutional Review Board approval was not required in our study.

Because this database began collecting the information on bone metastases at the time of diagnosis in 2010 and related information was updated until 2015, we extracted data on lung cancer patients with the presence or absence of BM at the time of diagnosis from 2010 to 2015. The data was selected and listed in flow-chart (Fig. 1). In total, 9212 patients who were diagnosed as lung cancer with BM and 26,374 patients who were diagnosed as lung cancer without BM from 2010 to 2015 were selected. Subsequently, we removed patients with invalid information, leaving 8954 patients eligible for survival analysis and 25,631 patients eligible for multivariable logistic regression model.

2.2. Statistical analysis

Demographic data, including sex(male and female), age ($\leq$40, 41–60, 61–80, and $\geq$81years), race [white, black, American Indian/Alaska Native (AI) and Asian or Pacific Islander (API)], marital status (married and unmarried), tumor sites ($<2; \geq 2, <4; \geq 4, <6; >6, \leq 8; \geq 8, <10; \geq 10, <12; \geq 12, <14; \geq 14$), grade(I,II,III,IV), T stage(T0,T1, T2, T3, and T4), N stage(N0,N1, N2 and N3), metastasis at brain(yes and no) and metastasis at liver(yes and no). In addition, the histology codes were grouped into five categories based largely on the International Agency for Research on Cancer (IARC) classifications [16]: adenocarcinoma (histologic codes 8140,8230,8244,8255,8260,8310,8323,8480,8481,8490,8507,8550,8570,-8574,8576),squamous cell carcinoma (histologic code 8050,8070-8074,8123), large cell carcinoma(histologic codes 8012-8014,8020–8022,8030,8031), small cell carcinoma (8041-8045,8246) and others(8000-8004,8010,8032-8034,8046,8082,8200,8240,8241,8247,8249-8254,8342,8430,8560,8575,8980).

Multivariable logistic regression was used to show the odds ratios (ORs) with 95% confidence intervals (CIs) and distinguish the risk factors for developing BM at diagnosis. Kaplan-Meier method was used to analyze survival duration; Log-rank test were tested to distinguish the differences between the curves. Multivariable Cox proportional hazards regression was performed to show the hazard ratios (HRs) with 95% CIs and determine prognostic effects of every variable on survival.

All statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA). Two-sided P-values < 0.05 were considered significant statistically.

3. Results

3.1. Morbidity analysis

For the 34,585 eligible lung cancer patients who were diagnosed with BM or without BM between 2010 and 2015 in the study, Table 1 shows the number of the two cohorts according to different variables in the SEER. Of them, 8954 (25.9%) were diagnosed with BM at the initial diagnosis and we had their complete information. Thus, they were included in the survival analysis, and their demographic and clinical characteristics were shown in Table 2. Within this cohort, the median survival time was only 2 ± 0.12 months and the mean was just 6.61 ± 0.26 months, while the time was 4 ± 0.16 months and 13.18 ± 0.27 month for the patients without BM respectively.

3.2. Risk factors for developing bone metastasis

As shown in Table 1, the possibility of BM at diagnosis were significantly associated with male, younger age, adenocarcinoma, poor tumor differentiation grade, higher N stage(N3), brain metastasis and liver metastasis, while the tumor size was demonstrated not to be an independent risk factor. In addition, there was no difference between T0 and higher T stage, but patients with T1 showed less chance of BM.

3.3. Survival and prognostic factors for BM

Vital prognostic factors selected by sex (Fig. 2A), age (Fig. 2B), race (Fig. 2C), marital status (Fig. 2D), pathologic type (Fig. 2E) and liver metastasis (Fig. 2F) were graphically displayed.

AS shown in Table 2, the prognostic factors for BM in lung cancer patients were observed clearly. In the multivariate Cox regression model, patients of male, older age, unmarried status, large cell carcinoma, squamouscell carcinoma, metastasis at liver were correlated with higher risk of poor prognosis. Grade, T stage, N stage and brain metastasis were not significantly correlated with survival. Although the tumor size was also an independent prognostic factor, the larger tumor size resulting in the worse the outcome was not observed. Patients with BM in Asian or Pacific Islander (PAI) displayed the better outcome, while there was no difference among other races on survival.

In our study, the homogeneous risk factors for the odds and prognosis of BM in lung cancer patients were male and metastasis at liver (Fig. 3). However, younger age, married status, poor tumor differentiation grade, higher T stage, higher N stage, metastasis at brain were all positively correlated with the development of BM but they were not the prognostic factors of BM. Older age and unmarried status both cause the worse survival of patients with BM but not influenced the occurrence of BM. Meanwhile, adenocarcinoma was prone to be the most risk factors for the occurrence of BM in different pathologic types, but did not cause the worst prognosis.

4. Discussion

Based on the SEER database, we found that the amount of BM in lung cancer patients was staggering, accounting for 25.89%. In addition, BM morbidity still might be underestimated for ineligible cases. Therefore, it is vital to estimate the risk factors for patients in lung cancer and the prognosis for patients diagnosed with BM. Previously, only some small sample size has been used to estimate the prognosis of BM [17,18]. Li Zhang et al. and Sugiura et al. only retrospectively observed 168 and 118 patients with BM and discussed the prognostic factors, respectively. In the large population-based cohort study, larger cases were carried out to analyze and predict the prognosis. In the study, we observed a number of lung cancer patients whose survival time is less than two months, and the dismal median survival of lung cancer with BM observed was lower than previous reports [17,19]. This was not difficult to understand that lots of patients with lung cancer were not willing to accept treatment in hospital and chose natural death because of the poor physical state, so the part of cases might be missed and not be included in the previous literatures. However, based on the reliable and large data from SEER program, the survival time obtained from this study could reflect the real length of life of cancer patients.

A number of risk factors of BM development in lung cancer patients were found, including male, younger age, adenocarcinoma, poor tumor differentiation grade, higher N stage, metastasis at brain and metastasis

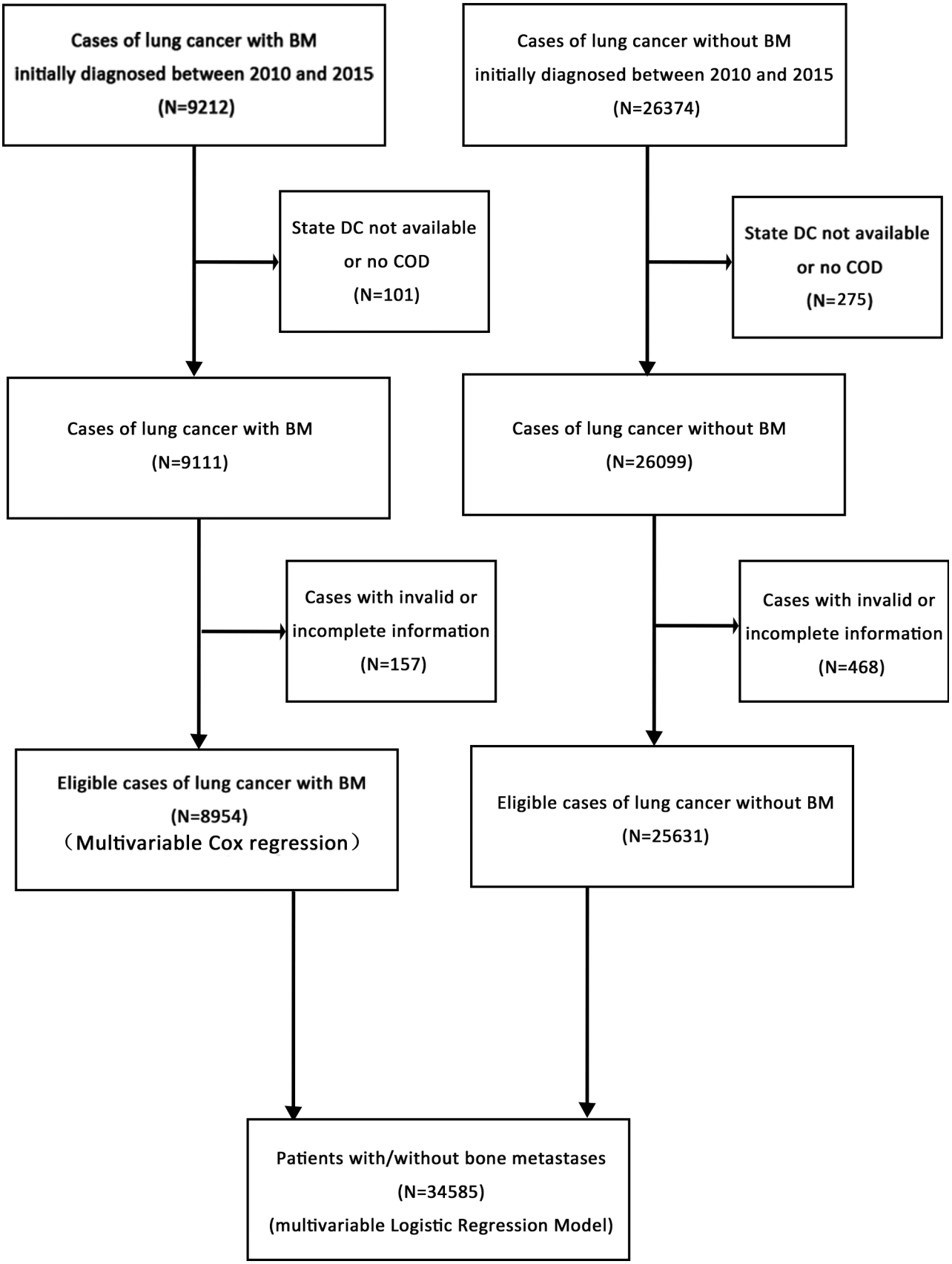

Fig. 1. The flow-chart of the data selection for analyzing the risk factors of the morbidity and prognosis of bone metastasis from lung cancer patients
Abbreviations: BM, bone metastasis.

Table 1
Multivariable logistic regression for analyzing the demographic information and risk factors for occurrence of bone metastasis in patients diagnosed lung cancer (diagnosed 2010–2015).

Subject characteristics	No. of patients with LC		OR (95%CI)	*P* value
	With bone metastasis	Without bone metastasis		
Sex				<0.001
Male	5163	13,253	1 (reference)	1.000
Female	3791	12,378	0.804 (0.763–0.847)	<0.001
Age, in years				<0.001
≤40	94	188	1 (reference)	1.000
41–60	2254	5000	0.876 (0.670–1.145)	0.331
61–80	5221	14,766	0.739 (0.567–0.963)	0.025
≥81	1385	5677	0.536 (0.409–0.702)	<0.001
Race				0.004
Black	1002	3002	1 (reference)	1.000
White	7265	20,851	1.080 (0.995–1.171)	0.066
AI	46	145	0.915 (0.637–1.314)	0.631
API	631	1556	1.153 (1.016–1.307)	0.027
Unknown	10	77	NA	NA
Marital status				0.012
Married	4343	11,573	1 (reference)	1.000
Unmarried	4168	12,554	0.953 (0.903–1.007)	0.084
Unknown	443	1504	NA	NA
Hist				
AD	4144	10,235	1 (reference)	1.000
SQCC	833	3319	0.629 (0.574–0.688)	<0.001
LCLC	166	424	0.786 (0.646–0.956)	0.016
SCLC	1768	5220	0.544 (0.504–0.586)	<0.001
Other	2043	6433	NA	NA
Gleason grade				<0.001
I	90	656	1 (reference)	1.000
II	348	1528	1.456 (1.124–1.887)	0.004
III	1209	3760	1.778 (1.400–2.258)	<0.001
IV	230	708	2.044 (1.542–2.710)	<0.001
Unknown	7077	18,979	NA	NA
tumor size(cm)				0.313
≤2	795	2805	1 (reference)	1.000
>2, ≤4	874	2959	1.140 (0.989–1.315)	0.071
>4, ≤6	723	2142	1.177 (1.010–1.373)	0.037
>6, ≤8	449	1364	1.099 (0.929–1.300)	0.270
>8, ≤10	245	746	1.080 (0.887–1.314)	0.444
>10, ≤12	122	339	1.168 (0.909–1.501)	0.225
>12, ≤14	31	144	0.772 (0.506–1.177)	0.229
>14	38	130	0.935 (0.628–1.393)	0.743
Unknown	5677	15,002	NA	NA
T Stage				<0.001
T0	400	1238	1 (reference)	1.000
T1	200	1129	0.685 (0.553–0.848)	0.001
T2	867	3204	0.836 (0.692–1.010)	0.064
T3	1736	4128	1.195 (0.999–1.429)	0.051
T4	2468	7158	1.021 (0.858–1.215)	0.811
TX	3283	8774	NA	NA
N Stage				<0.001
N0	1695	7452	1 (reference)	1.000
N1	610	1504	1.544 (1.377–1.731)	<0.001
N2	3338	9010	1.372 (1.279–1.472)	<0.001
N3	1718	3843	1.605 (1.476–1.744)	<0.001
NX	1593	3822	NA	NA
Brain Met				<0.001
Yes	1733	3352	1 (reference)	1.000
None	6678	22,101	0.708 (0.661–0.758)	<0.001
Unknown	543	178	NA	NA
Liver Met				<0.001
Yes	2985	3617	1 (reference)	1.000
None	5473	21,807	0.304 (0.286–0.323)	<0.001
Unknown	496	207	NA	NA

Abbreviations: LC, lung cancer; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastasis; AD, adenocarcinoma; SQCC, squamouscell carcinoma; LCLC, large cell carcinoma; SCLC, small cell carcinoma; NA, not avail.

at liver. Thus, doctors should pay more attention to these risk factors for their lung cancer patients. Furthermore, a skeletal scanning should be advised timely for their patients with these risk factors. In the future, the risk factors might be considered to be predictive factors of BM for lung cancer patients.

A number of prognostic factors of BM in lung cancer patients were correlated with male, older age, large cell carcinoma, squamouscell carcinoma, unmarried status, metastasis at liver and the tumor size. It was surprising that grade, T and N stage were able to confirm the prognosis of BM. Based on the above prognostic factors in the study,

Table 2
Multivariable Cox regression for analyzing prognostic factors among lung cancer patients diagnosed bone metastasis (diagnosed 2010–2015).

Subject characteristics	No. of patients with LC with bone metastasis	Survival, Median (IQR), mo	Cox HR (95% CI)	*P* value
Sex				<0.001
Male	5163	2 (1.848–2.152)	1 (reference)	1
Female	3791	3 (2.823–3.177)	0.883 (0.843–0.924)	<0.001
Age, in years				<0.001
≤40	94	9 (5.101–12.899)	1 (reference)	1
41–60	2254	4 (3.667–4.333)	1.651 (1.297–2.100)	<0.001
61–80	5221	2 (1.852–2.148)	2.091 (1.647–2.655)	<0.001
≥81	1385	1 (0.846–1.154)	2.701 (2.116–3.448)	<0.001
Race				<0.001
Black	1002	2 (1.672–2.328)	1 (reference)	1
White	7265	2 (1.871–2.129)	0.978 (0.912–1.050)	0.544
AI	46	2 (0.792–3.208)	0.785 (0.567–1.087)	0.145
API	631	3 (2.164–3.836)	0.733 (0.656–0.819)	<0.001
Unknown	10	NA	NA	NA
Marital status				<0.001
Married	4343	3 (2.807–3.193)	1 (reference)	1
Unmarried	4168	2 (1.839–2.161)	1.196 (1.142–1.254)	<0.001
Unknown	443	NA	NA	NA
Hist				<0.001
AD	4144	3 (2.814–3.186)	1 (reference)	<0.001
SQCC	833	2 (1.678–2.322	1.170 (1.081–1.266)	0.011
LCLC	166	2 (1.394–2.606)	1.232 (1.050–1.466)	0.024
SCLC	1768	4 (3.560–4.440)	0.929 (0.871–0.990)	0.001
Other	2043	NA	NA	NA
Gleason grade				0.106
I	90	4 (2.495–5.505)	1 (reference)	1
II	348	3 (2.236–3.764)	1.257 (0.978–1.616)	0.074
III	1209	3 (2.713–3.287)	1.342 (1.064–1.693)	0.013
IV	230	3 (2.286–3.714)	1.402 (1.076–1.827)	0.012
Unknown	7077	NA	NA	NA
Tumor size (cm)				0.015
≤2	795	4 (3.449–4.551)	1 (reference)	1
>2, ≤4	874	3 (2.628–3.372)	1.144 (1.007–1.301)	0.039
>4, ≤6	723	3 (2.622–3.378)	1.187 (1.036–1.360)	0.013
>6, ≤8	449	2 (1.478–2.522)	1.237 (1.066–1.436)	0.005
>8, ≤10	245	3 (2.071–3.929)	1.111 (0.932–1.324)	0.239
>10, ≤12	122	1 (0.414–1.586)	1.382 (1.114–1.716)	0.003
>12, ≤14	31	2 (0.971–3.029)	1.564 (1.053–2.322)	0.027
>14	38	3 (0.448–5.552)	1.318 (0.928–1.873)	0.123
Unknown	5677	NA	NA	NA
T Stage				0.465
T0	400	3 (2.247–3.753)	1 (reference)	1
T1	200	4 (3.079–4.921)	0.829 (0.678–1.013)	0.067
T2	867	3 (2.602–3.398)	0.989 (0.835–1.171)	0.899
T3	1736	2 (1.738–2.262)	0.965 (0.823–1.131)	0.657
T4	2468	3 (2.791–3.209)	0.975 (0.833–1.141)	0.749
TX	3283	NA	NA	NA
N Stage				0.113
N0	1695	3 (2.734–3.266)	1 (reference)	1
N1	610	2 (1.608–2.392)	1.077 (0.976–1.188)	0.142
N2	3338	2 (1.799–2.201)	1.084 (1.018–1.155)	0.012
N3	1718	3 (2.706–3.294)	1.029 (0.957–1.107)	0.443
NX	1593	NA	NA	NA
Brain Met				0.071
Yes	1733	2 (1.770–2.230)	1 (reference)	1
None	6678	3 (2.863–3.137)	0.936 (0.884–0.992)	0.025
Unknown	543	NA	NA	NA
Liver Met				<0.001
Yes	2985	2 (1.835–2.165)	1 (reference)	1
None	5473	3 (2.836–3.164)	0.760 (0.723–0.798)	<0.001
Unknown	496	NA	NA	NA

Abbreviations: LC, lung cancer; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastasis; AD, adenocarcinoma; SQCC, squamouscell carcinoma; LCLC, large cell carcinoma; SCLC, small cell carcinoma; NA, not available.

doctors might be capable of making a prognostic estimation and clinical guidelines for the lung cancer patients with BM effectively.

In our study, male carried a higher risk for the development of BM and poorer prognosis in lung cancer patients with BM. A previous study have shown that the median survival time did make the difference between two genders in lung cancer with bone metastasis; for male patients was 7.9 months, versus 13 months in female [17]. Male has been shown to portend poor survival in that study, and the difference was demonstrated to be statistically significant in our larger cohort study. We suspect that this phenomenon may be related to smoking and social stress in men, but we can't capture some basic information in the database.

Adenocarcinoma was considered to be the highest risk factors of BM development as a kind of pathologic type. To our knowledge, this is the first report to identify the risk factor at the time of diagnosis of BM. However, the prognosis of BM with large cell carcinoma or

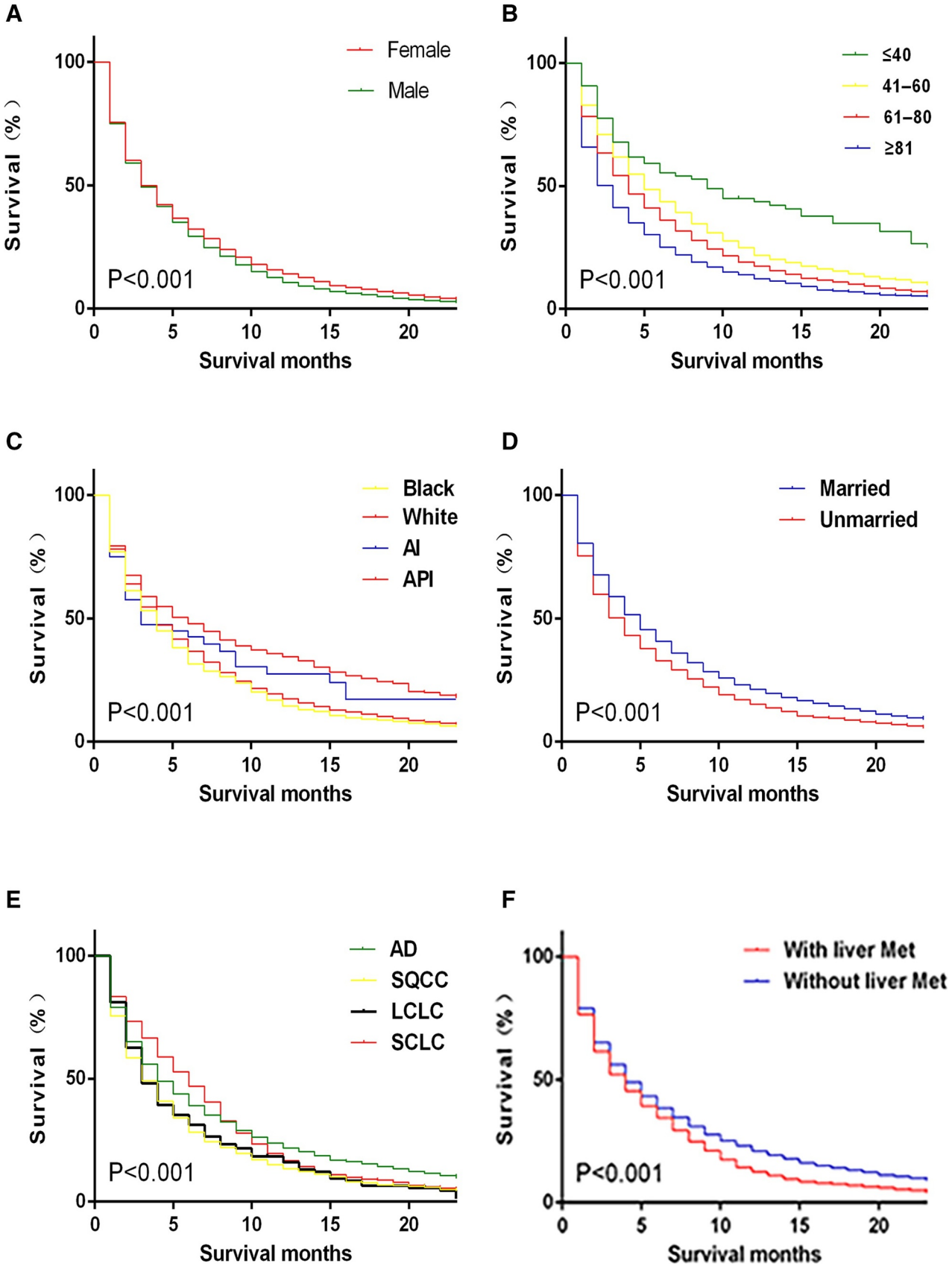

Fig. 2. Kaplan–Meier analysis of overall survival among lung cancer patients with bone metastasis were displayed by sex (A), age (B), race (C), marital status (D), pathologic type (E) and liver metastasis (F).

Abbreviations: AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastasis; AD, adenocarcinoma; SQCC, squamouscell carcinoma; LCLC, large cell carcinoma; SCLC, small cell carcinoma.

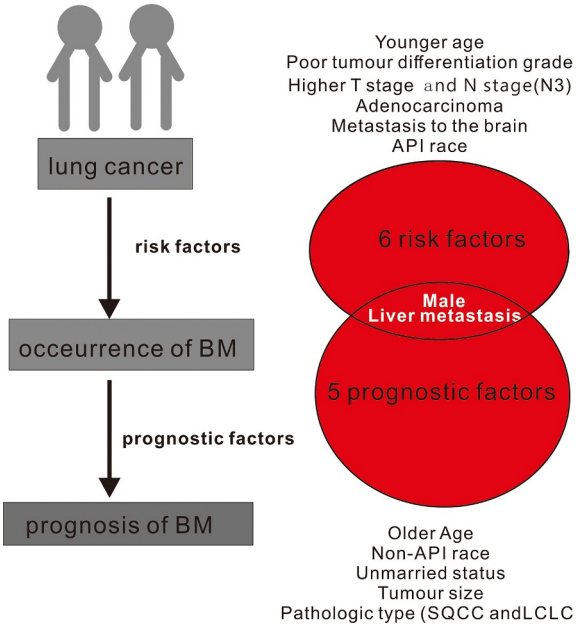

Fig. 3. The homogeneous and heterogeneous risk factors and prognosis factor of BM in patients with lung cancer.
Abbreviation: BM, bone metastases; API, Asian or Pacific Islander; SQCC, squamous cell carcinoma; LCLC, large cell carcinoma.

squamouscell carcinoma becomes worse than adenocarcinoma. The previous study by Sugiura et al. has reported that the patients of BM with nonadenocarcinoma had a worse prognosis, while those with adenocarcinoma alone had the favorable prognosis, which was consistent with our finding [17].

In addition, black race compared with whites were not found to have a higher risk of development and prognosis of BM, while PAI had the best outcome. As we all known, race diversity in cancer patients have been still existing and black men have higher cancer rates than other races. Probably, blacks were diagnosed with more advanced cancers than other races in the US [20]. In a latest report, the five-year survival of blacks was lower than whites for most cancers, but the disparity has been narrowed in men which can explain our founding to some extent [21]. Anyway, in our study, race diversity is not only a risk factor for the occurrence of BM, but also a risk factor for the prognosis of patients with BM. Therefore, racial disparities must be focused efforts on reducing.

Lung cancer with liver metastasis or brain metastasis continues to have a poor prognosis despite recent advances in medical level [22–27]. Interestingly, BM patients with liver metastasis had a worse prognosis, but the presence or absence of brain metastasis did not affect survival. Because brain metastasis was not, like liver metastasis, significantly associated with the survival of lung cancer with BM, oncologists could try to conversely evaluate the risks of BM and/or liver metastasis on lung cancer with brain metastasis. Alternatively, they could evaluate the risks of brain metastasis and/or BM on lung cancer with liver metastasis. By doing these, they may hopefully identify factors which prolong patients' survival significantly longer than those identified by us in our manuscript. Similarly, younger people with lung cancer is more likely to have BM, but older patients with BM have a worse prognosis. The poorer prognosis related to age in non-small cell lung cancer with bone metastasis have been observed by Bae et al. [28]. Since unmarried status has a serious impact on the prognosis of patients with BM, we advocated maintaining a good marriage which could extend the life span of patients.

These astonishing discoveries deserved further analysis and exploration by medical researchers for the unclear causes. As mentioned above, it would be important that physicians must pay more attention to the heterogeneous risk factors for occurrence and prognostic of BM in patients with lung cancer. Based on our research, further studies looking into the potential explanations on the heterogeneous and heterogeneous risk factors were needed.

Except for the intention of estimating the risk factors, the other significance of this research related to the factors was the finding of cancer care and management. Even if, most of the factors, except age, associated with improved prognosis of lung cancer patients with BM only averagely prolong patients' survival for one month. But significant, it seemed that one month survival clinically also impacted and benefited patients too much on account of the poor prognosis. Furthermore, based on several meaningful risk factors observed in our study, patients' survival might be more different in the process of clinical evaluation or intervention. At the same time, we acknowledged that the difference of the possibility of BM or the survival time would be more significant through interfering with these factors, if we collected the cancer patient whose survival time was more than one year. However, oncologists were not able to recognize the accurate life span, so we considered that all lung cancer patients with adequate information initially diagnosed should be included.

Of course, several limitations existed in the present study. Firstly, a certain number of patients with incomplete and invalid information were excluded. Secondly, we can't research some basic information in the SEER database which could had an impact on patients, such as smoking, Body Mass Index, family history. Thirdly, several selection bias might exist in the retrospective trial.

5. Conclusion

In this study, we estimated the risk factors for occurrence and prognosis of lung cancer patients with BM in an effort to provide some information for making a potential treatment plan and clinical evaluation. In addition, there were two homogeneous risk factors and a number of heterogeneous factors, which deserved our attention.

CRediT authorship contribution statement

Wang Ben: . **Chen Lijie:** Writing - review & editing. **Huang Chongan:** Writing - review & editing. **Lin Jialiang:** Writing - review & editing. **Pan Xiangxiang:** Writing - review & editing. **Shao Zhenxuan:** Software. **Hu Sunli:** Software. **Zhang Xiaolei:** . **Wang Xiangyang:** .

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Disclosure

The author reports no conflict of interest in this work.

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