Clinical features and outcome of small cell lung cancer in female patients: a large-cohort retrospective study

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Research article

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Abstract

Background: Currently, female small cell lung cancer (SCLC) incidence has been increasing. However, there have been few large database-based studies on female patients with SCLC. In this study, we used Surveillance, Epidemiology, and End Results (SEER) database to describe the clinical characteristics and prognosis of female SCLC patients.

Methods: SCLC patients from the SEER database between 1973 and 2015 were included. Gender, age, race, stage, tumor size, and metastasis status were included in our study. Clinical characteristics were analyzed among females and males with SCLC. Survival analyses were conducted with log-rank tests and Cox proportional hazard models.

Results: A total of 18234 patients were extracted from SEER database. 50.2% of the whole SCLC patients were females. Compared with males, females were less likely to be Asians, carry bigger size of tumor, have later TNM stage, and have distant metastases ($P < 0.05$). Gender proved to be an independent prognostic factor for SCLC patients (CSS:HR:1.105;95% CI: 1.068 1.143; $P < 0.001$; OS: HR, 1.120;95% CI: 1.084 1.158; $P < 0.001$). Female patients presented more favorable survival than male patients (Median OS/CSS:11 vs. 9 months, $P < 0.001$). Our results confirmed that age≥65, white race, later stage, tumor size ≥ 50mm and distant metastases were all associated with poor prognosis in female patients.

Conclusions: Female gender is associated with more favorable outcome of SCLC. For females, patients who are senile, white people, and have poorer pathological features were associated with a shorter OS, which need to be more circumspectly treated in clinical practice.

Background

Small cell lung cancer (SCLC) has been an extremely aggressive cancer for researchers and clinicians to cope with, which is typified by rapid recurrence, extensive metastasis and poor prognosis. It is one of the most lethal cancers and difficult to be cured [1, 2]. Despite the urgent requirement of SCLC exploration, the pace of its investigation has been tardy over the past two decades. Gender has been shown to be an independent prognostic factor for NSCLC in multiple studies [3-5], whereas the clinical prognostic value of gender in SCLC is still unclear, gender-related differences in SCLC needs to be explored. In the past 30 years, although the incidence of SCLC has been declining, the incidence of SCLC in females has been increasing [6, 7], and the higher incidence of lung cancer in young males than females has been reversed [8].

With the increasing incidence of SCLC, female patients are in urgent need of attention from researchers. However, there was no large database-based studies have been focused on the epidemiologic features and therapeutic efficacy of females with SCLC. Hence, we performed a retrospective study of a large series of SCLC patients from Surveillance, Epidemiology, and End Results (SEER) registered database, aimed at exploring the clinical characteristics and survival prognosis of female patients with SCLC.

Methods

Patient selection

A total of 18234 SCLC patients from 1973 to 2015 were screened from SEER*Stat8.3.5 (https://seer.cancer.gov/seerstat/). The variable "site recode icd-o-3" was defined as "lung and bronchus", and the variable "histological type icd-o-3" was defined as "8041,8042,8043,8044,8045". Patients with incomplete survival information were excluded, and variables "race", "stage", "tumor size", "age", "metastasis at bone", "metastasis at brain", "metastasis at liver" and "metastasis at lung" were included. Staging included AJCC seventh edition I-IV, T and N staging.

Statistical analysis

The baseline data of the patients were categorical variables, and the chi-square test was used to compare the clinical characteristics of male and female patients. Overall survival (OS) and cancer-specific survival (CSS) were the primary study endpoints. OS was defined as the date of pathological diagnosis to the date of death, loss to follow-up, or final follow-up. CSS was defined as the time from pathological diagnosis until death from the tumor. Survival curves were generated by Kaplan-Meier method, and statistical differences were compared by log-rank test. The effects of gender on OS and CSS are presented in Cox univariate and multivariate regression analysis, and the factors associated with outcomes of female and male patients separately were analysed by Cox multivariate regression analysis. The variables included in Cox multivariate regression model contained age, race, tumor size, stage, and metastasis statuses.

All statistical analyses were performed by statistical software Statistical Package for Social Sciences (SPSS) for Windows, version 24, and statistical significance was defined as bilateral $P < 0.05$.

Results

Clinical characteristic differences between females and males

As presented in Table 1, we finally included 18,234 SCLC patients from SEER database, among which the number of female patients (50.2%) were slightly higher than male patients (49.8%); and the majority of these cases were white people (87.5%). SCLC patients of other races, mostly Asians, had higher male-female ratio (1.77: 1). Notably, female patients tended to carry smaller size of tumor than male patients. In addition, we found an earlier TNM stage at diagnosis in female patients, and similar patterns also showed in N stage individually. It was noteworthy that there were fewer lung, liver, bone and brain metastases in female rather than male patients.

Survival differences for female patients in SEER

We used Cox multivariate regression model in an effort to test whether gender was an independent predictor of OS and CSS. At the same time, age, race, stage, tumor size, lung metastasis, liver metastasis, brain metastasis and bone metastasis were included in the model. The results showed that elder age,

white race, later stage, larger size of tumor and distant metastases were all independent prognostic factors of SCLC (Table S1, S2). Most importantly, gender was an independent predictor of OS and CSS, and the prognosis of male patients was worse than that of female patients (CSS:HR:1.102;95% CI: 1.065-1.141; $P < 0.001$; OS: HR: 1.117;95% CI: 1.080-1.155; $P < 0.001$) (Table 2). Fig. 1 illustrates that female patients had better OS and CSS than male patients (Median CSS: 11 vs. 9 months; Median OS: 11 vs. 9months, $P < 0.001$).

Next, we stratified these SCLC patients by different age, stage and race. Univariate log-rank tests showed that female gender was associated with better OS in each of these subgroups, except that median OS of female patients had not been proven to have significant advantage in other race subgroup ($P = 0.0592$). More remarkable, the influence of gender on survival showed difference in different subgroups. The gender-related survival difference is more obvious in younger, white race and limited stage SCLC patients (HR: white vs. black: 1.210 vs. 1.163, $P < 0.05$; 65 vs. ≥65: 1.284 vs. 1.151, $P < 0.001$; LD vs. ED: 1.169 vs. 1.135, $P < 0.001$) (Fig. 2).

Prognostic factors among female patients

To explore factors associated with outcomes of female patients, we conducted a Cox multivariate regression model. Our results confirmed that age ≥ 65, white race, later stage, tumor size ≥ 50mm and distant metastases were all associated with poor CSS in female patients ($P < 0.05$) (Fig. 3A), which pattern was similar in male patients (Fig. S1). In addition, bone metastasis was not related to poor OS in female patients (Fig. 3B).

Discussion

A sharp increase over recent decades in the number of female patients diagnosed with SCLC has been reported in several countries [6, 7]. Over the past two decades, the female-to-male incidence rate ratios among 40 to 54 years of age non-hispanic whites of SCLC had generally increased [8]. A research from China showed the proportion of women with SCLC increased from 17.95% to 24.75%, compared to all patients diagnosed with SCLC from West China Hospital between 1995 and 2015 [9]. Our study identified 18234 patients from SEER database, more than half of whom were females (50.2%), which indicated an urgent need for the clinical characteristics in female population to be further investigated with an eye to diagnoses and treatment.

The prognosis of SCLC in female patients is controversial. Several previous works reported that gender had no prognostic significance in SCLC [10, 11], nevertheless, a French study included 967 patients diagnosed with SCLC showed that median survival was better among males in patients older than 70 years old [12]. However, various other studies reported that females had significantly better survival than males with SCLC [13-17]. Singh et al. demonstrated that females were more susceptible to chemotherapy and its associated toxicity, which probably due to pharmacokinetic difference and higher baseline BMI of females, and this result was confirmed by Wheatley et al. in 2018 [18, 19]. In our study, gender was an

independent prognostic factor in patients with SCLC, females had preferable OS and CSS compared with males.

Gender-related differences in SCLC patients have not been reported previously. Our study found that females were more likely to carry with smaller tumors. Tumor size is also closely related to prognosis of SCLC patients. A prospective study reported that gross tumor volume significantly influenced survival of stage I to III SCLC patients treated with concurrent chemoradiation therapy [20]. In our study, females tended to have more favorable TNM stage compared with males with SCLC. We have already known that stage groupings using the TNM category clearly identified SCLC patient subgroups with different prognoses [21], and the survival of stage IV was significantly worse than that of earlier stages for SCLC patients from IASLC database [22]. A previous study reported that N-stage (OR = 4.94; $P < 0.01$) was associated with survival of SCLC patients according to AJCC TNM category, seventh edition [23]. Our results showed that females had earlier N stage than males with SCLC. These results may serve as evidence that females have a better survival than males with SCLC. In Herndon et al' s study, liver metastasis and bone metastasis were significantly associated with poor prognosis of SCLC [16]. These patterns were also seen in our results. Our study demonstrated that all of lung metastasis, liver metastasis, brain metastasis and bone metastasis were less common in females than in males with SCLC. After drawing a conclusion that females had favorable OS and CSS compared with males with SCLC, we stratified these patients for further analysis. Our results showed that females significantly associated with better survival both in elderly cohort and younger cohort. Similar results were obtained when stratifying these patients by stage and race.

To further investigating Chinese female SCLC patterns, we enrolled 342 SCLC patients from First Affiliated Hospital of Xi'an Jiaotong University from 2014 to 2017, approximately one-quarter of which were female patients (21.3%), which was distinctive compared with SEER database (50.2%) (Fig. S2). This pattern was probably on account of the different smoking status in Chinese females. Generally, smoking is closely related to the mortality and morbidity of SCLC [24], and smoking is often associated with worse prognosis [10, 25]. Malvezzi et al. demonstrated mortality rates of lung cancer in males were declining, which were rising in females, and this fact was strongly linked to smoking status in Europe [26]. Moreover, a meta-analysis of 27 studies, and concluded that smoking cessation could reduce the incidence of SCLC, especially in female patients [27]. Paradoxically, Lorraine et al.'s study indicated an increased incidence of SCLC in non-smokers [28]. In a 2016 study of SCLC, María et al. published a result that the prognosis of non-smokers was as poor as that of smokers [29]. A previous work reported that the tobacco-attributed proportion was increasing in men, but low, and decreasing in women in Chinese population [30]. Similar to preceding results, few female patients were smokers in our cohort (2.7%). Females had better OS than males in the entire cohort (Median OS: 16 vs. 12months, $P < 0.05$), whereas no significant difference of prognosis was found between males and females in the non-smoker cohort ($P = 0.957$) (Fig. S2). Whether the inconformity of prognosis between female and male SCLC patients is related to living habits such as exposure to tobacco or real gender difference like hormones and genetics is remain unclear. Further studies are required to address these questions.

This population-based study has many virtues. First, SEER database is an authoritative source for cancer statistics in the United States, which ensures the reliability of cases in our research. Second, the sources of case data from SEER database have a wide range of regions and a long span of time, which guarantees the representativeness of the outcomes in this study. Third, we contained 18234 patients with SCLC in our study, including the largest number of cases of any homogeneous studies. This research adds to current knowledge by answering more in-depth research questions about gender and prognosis through analysis of population-based data from the large SEER database. Nonetheless, this study has some potential limitations. First, like all retrospective studies, this study was not capable of avoiding selective bias. Second, smoking status was not able to be considered as a confounding factor in the analysis of the relationship between gender and survival due to the limitations of SEER database itself. Third, previous studies reported that females were more responsive to chemotherapy compared with males with SCLC [18, 19]. However, the SEER database does not contain detail information of chemotherapy regimen and toxicity, which limits our ability to calculate its effect on prognosis of SCLC.

Conclusions

In conclusion, our results showed that female SCLC patients had smaller size of tumor, fewer metastasis, and they were at earlier stages than male patients. We confirmed that females had significantly better OS and CSS than males with SCLC. Clinicians should consider gender in their assessments and treatment decisions for patients with SCLC.

Abbreviations

SCLC: Small cell lung cancer

SEER: Surveillance, Epidemiology, and End Results

icd-o-3: International Classification of Diseases for Oncology, Third Edition

AJCC: American Joint Committee on Cancer

OS: Overall survival

CSS: Cancer-specific survival

CI: Confidence intervals

HR: Hazard ratio

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used in this study are available from the corresponding author on reasonable request.

Competing interests

No actual or potential conflict of interest exists connected to any of authors of this manuscript and its content.

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Authors' contributions

HG and WJW designed the study and selected the study methodology. WYL, XW and JCH collected the data. LLJ and MJ analyzed and interpreted the data. JH and YW performed the statistical analysis and wrote the manuscript.TT, XL, YY, HS and TJQ edited the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Variables	Female (%)	Male (%)	*P*
Total	9156(50.2)	9087(48.2)	
Age			0.196
<65	3681(40.2)	3735(41.1)	
≥65	5475(59.8)	5343(58.9)	
Race			<0.001
White	8015(87.5)	7680(84.6)	
Black	861(9.4)	903(9.9)	
Others	280(3.1)	495(5.5)	
Stage			<0.001
I	465(5.1)	393(4.3)	
II	411(4.5)	332(3.7)	
III	2657(29.0)	2176(24.0)	
IV	5623(61.4)	6177(68.0)	
T Stage			0.141
T0	125（1.4）	148（1.6）	
T1-4	9031（98.6）	8930（98.4）	
N Stage			0.009
N0	1533（16.7）	1451（16.0）	
N1	727（7.9）	677（7.5）	
N2	5083（55.5）	4978（54.8）	
N3	1813（19.8）	1972（21.7）	
Tumor Size			<0.001
<50mm	5005(54.7)	4466(49.1)	
≥50mm	4151(45.3)	4612(50.9)	
Lung metastasis			<0.001
Yes	1118(12.2)	1324(14.6)	
No	8038(87.8)	7754(85.4)	
Liver metastasis			<0.001

Yes	2414(26.4)	2815(31.0)	
No	6742(73.6)	6263(69.0)	
Brain metastasis			<0.001
Yes	1374(15.0)	1655(18.2)	
No	7782(85.0)	7423(81.8)	
Bone metastasis			<0.001
Yes	1785(19.5)	2300(25.3)	
No	7371(80.5)	6778(74.7)	

Table 2

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	***P***	**HR (95%CI)**	***P***
Gender on CSS				
Female	Reference		Reference	
Male	1.176(1.137-1.217)	<0.001	1.102(1.065-1.141)	<0.001
Gender on OS				
Female	Reference		Reference	
Male	1.189(1.150-1.229)	<0.001	1.117(1.080-1.155)	<0.001

Figures

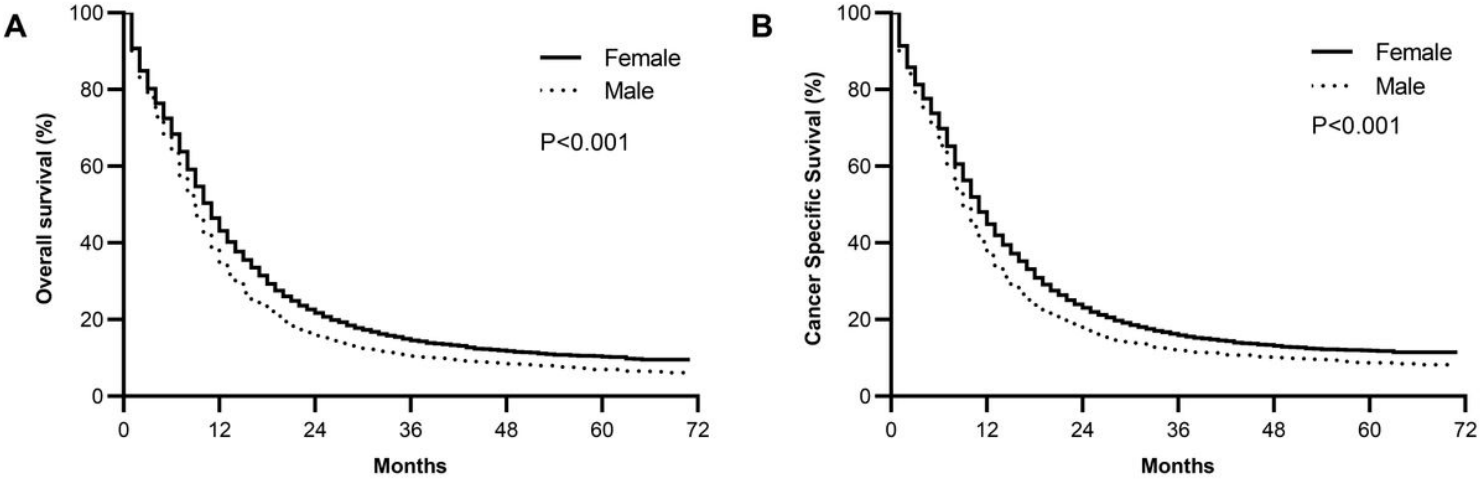

Figure 1

The survival difference between female and male patients. (A) The OS difference between female and male patients; (B) the CSS difference between female and male patients. CSS, cancer specific survival; OS, overall survival.

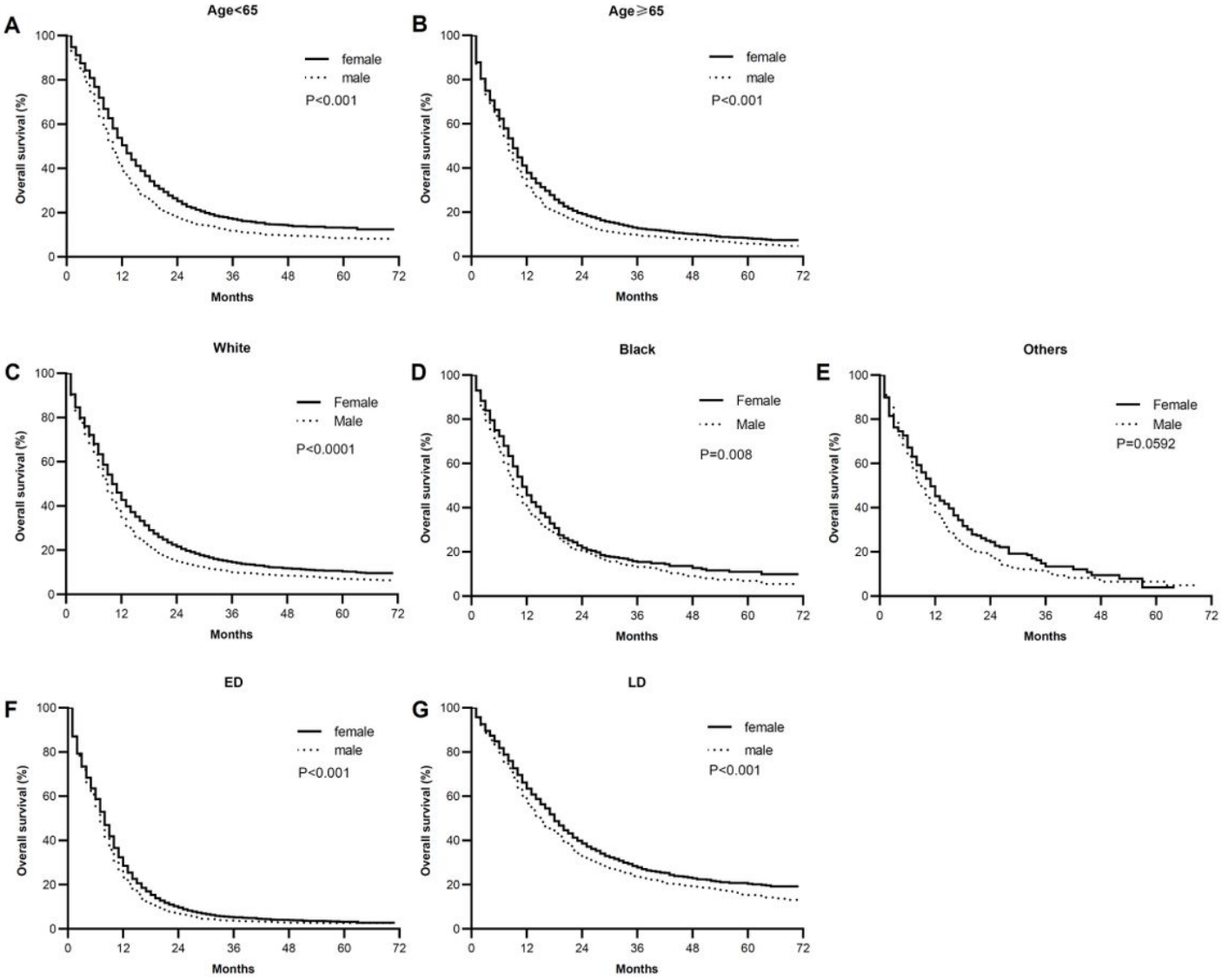

Figure 2

The survival difference for subgroups of interest. (A-B) The OS difference between females and males for patients at younger (<65 years) and elder (≥65 years) group; (C-E) the OS difference between females and males for patients of white, black and other race group; (F-G) the OS difference between females and males for patients at limited-stage (LD) and extensive-stage (ED) group.

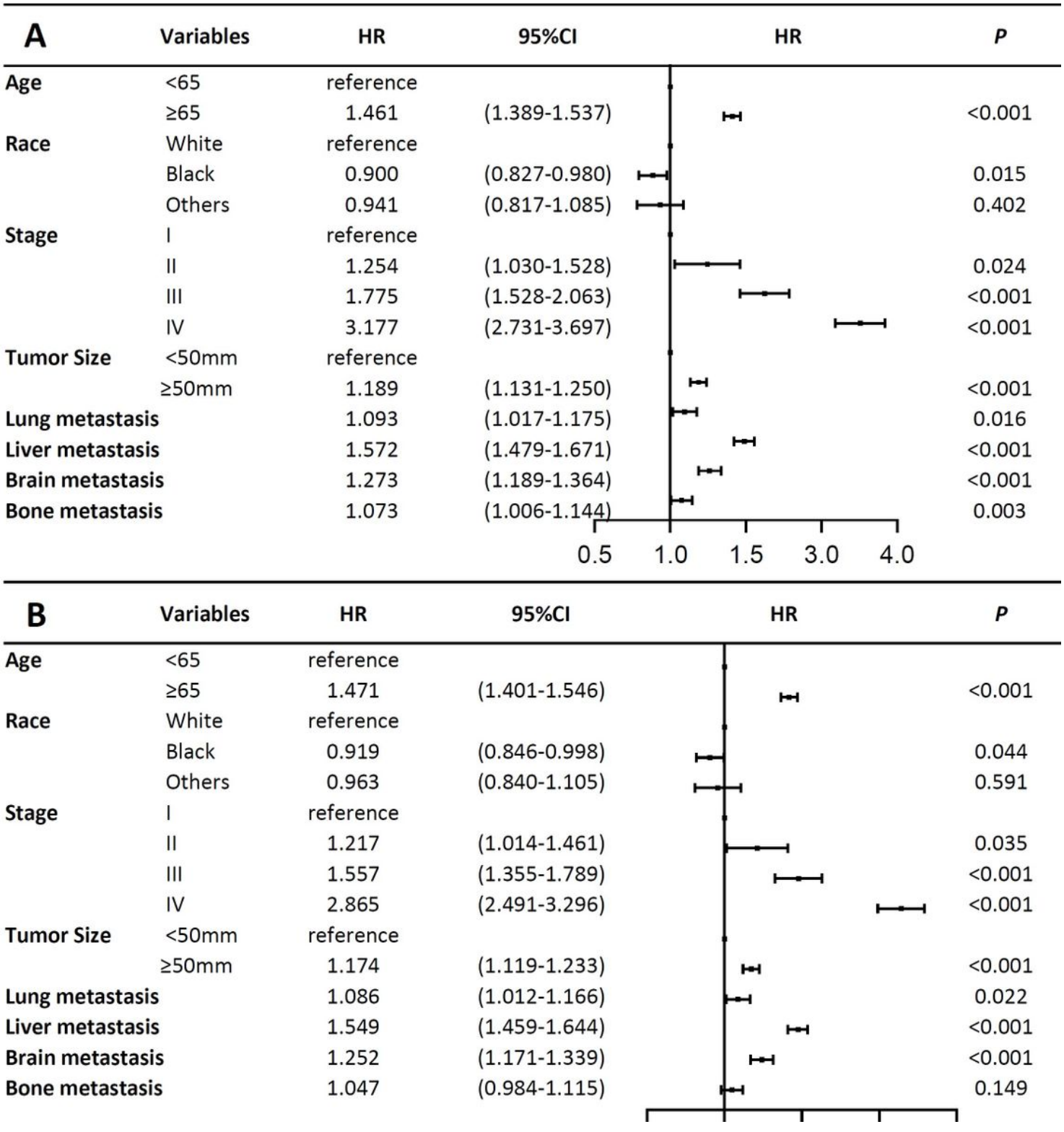

Figure 3

Factors associated with prognosis in female patients. (A) Factors associated with CSS in female patients; (B) Factors associated with OS in female patients. HR, hazard ratio; CI, Confidence interval.

Supplementary Files

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