Establishment of a Competing Risk Nomogram in Patients with Pulmonary Sarcomatoid Carcinoma

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Abstract

Background and aim: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of nonsmall cell lung cancer with a poor prognosis. This study aimed to analyze the clinicopathological characteristics and survival outcomes among patients with PSC, lung squamous cell cancer (SCC), and lung adenocarcinoma (LAC), and to construct a competing risk nomogram for patients with PSC. **Method:** Data of 3 groups of patients diagnosed with PSC, SCC, or LAC from the surveillance, epidemiology, and end results (SEER) database between 1988 and 2015 were retrospectively reviewed. A 1:1 propensity score matching (PSM) analysis was used to balance the baseline data of patients. Independent risk factors associated with survival outcomes were screened by the least absolute shrinkage and selection operator and further determined by univariate and multivariate Cox proportional risk regression analyses. The overall survival (OS) of patients was evaluated by Kaplan–Meier analysis and compared with a log-rank test. The cumulative incidence function was used to estimate the 5-year probabilities of the cancer-specific mortality of PSC. A nomogram was constructed to illustrate the competing risk model to predict the 3- and 5-year OS, and corresponding concordance indexes (C-indexes) and calibration curves were used to assess and validate the competing risk nomogram. **Results:** A total of 2285 patients with PSC were included in this study. Compared with SCC and LAC patients, the Kaplan–Meier analysis showed that patients with PSC had a worse prognosis, with a median survival of 5 months (95% confidence interval [CI]: 5-6 months) and a 5-year OS rate of 15.3 (95% CI: 13.9%-16.9%). Similar outcomes were demonstrated after 1:1 PSM. Moreover, the competing risk model showed that age, T stage, M stage, tumor size, lymph node ratio (LNR), surgery, and chemotherapy were associated with PSC-specific mortality. The 5-year C-index of the nomogram was 0.718. Calibration curves illustrated that the nomogram was well-validated and had great accuracy. **Conclusions:** Patients with PSC had a worse survival outcome compared with SCC or LAC patients. Age, T stage, M stage, tumor size, LNR, surgery, and chemotherapy were associated with PSC-specific mortality. The competing risk nomogram displayed excellent discrimination in predicting PSC-specific mortality.

Keywords

competing risk model, nomogram, prognostic factor, pulmonary sarcomatoid carcinoma, SEER

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Introduction

Lung cancer is the most common cancer and a major public health concern worldwide. About 80% to 85% of all lung cancers are nonsmall cell lung cancer (NSCLC), in which the most common 2 subtypes in clinical were squamous cell carcinomas (squamous cell cancer [SCC]) and lung adenocarcinomas (LAC), approximately 30% to 50% of NSCLC cases.[1] According to the Cancer Statistics 2021,[2] the overall incidence and mortality of NSCLC have already decreased due to the improvements in treatment and the continuous declines in smoking prevalence, especially immunotherapy and target therapy in SCC and LAC. However, there are still some rare subtypes of NSCLC that are more aggressive than SCC and LAC, have specific clinical characteristics, and are not sensitive to common chemotherapy regimens for NSCLC,[3] resulting in poor prognosis. Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of NSCLC, with the incidence ranging from 0.1% to 0.4% of all types of lung malignancies.[4] PSC is reported to be an aggressive malignant lung cancer with a worse prognosis than general NSCLC,[5] with a 5-year overall survival (OS) of 11% to 36.7%,[6–8] and a median survival of 3.5 to 19.1 months.[9–11] The 2015 World Health Organization classification system categorized PSC into 5 subgroups[4]: spindle cell carcinoma, pleomorphic carcinoma, giant cell carcinoma, pulmonary blastoma, and carcinosarcoma. Due to the rarity of PSC, almost all related studies are case reports or limited single-institution retrospective studies. The population-based studies are lacking, which led to the fact that the actual clinicopathological characteristics and prognosis of PSC remain incompletely understood. The surveillance, epidemiology, and end results (SEER) 18 database from the National Cancer Institute (NCI) used in this study, which is a population-based public database updated annually,[12] can support a large population study of PSC. Several previous published studies used the SEER database for survival analysis of PSC, and found that PSC patients were elder, male, had advanced tumor grade and stage, and had poor survival prognosis.[13,14] However, these articles ignored the clinicopathological characteristics differences between PSC and other NSCLCs and ignored the existence of comorbidities in the cause of death, which might lead to an overestimation of PSC-specific mortality.[15] To date, there are still no studies that have constructed a competing risk model based on prognostic factors for PSC-specific mortality. Therefore, a competing risk regression analysis was performed in our study to explore cancer-specific mortality factors for patients with PSC. An intuitionistic demonstration of the nomogram presented the result of the competing risk model, and a calibration curve was used for internal verification of the nomogram.

Methods

Data Source and Patient Selection

The SEER 18 database from the NCI originated in 1973 was used in the present study. It is a free public database comprising 18 states and municipal registries, covering about 28% of the United States population.[16] It includes patient demographics and tumor-specific clinicopathological characteristics, treatment information, and prognosis. We submitted an agreement to require access to the SEER current research data.

The patient data were screened using SEER*stat software version 8.3.8 (http://seer.cancer.gov/resources/), Incidence-SEER 18 Regs Custom Data (with additional treatment fields), and November 2018 Sub (1975-2016 varying). Regarding the inclusion criteria, the disease primary site and morphology restricted by the American Joint Committee on Cancer (AJCC) sixth edition was "Lung." According to the International Classification of Diseases for Oncology, third edition codes (ICD-O-3 Codes), patient with code 8022/3 (pleomorphic and carcinoma), 8032/3 (spindle cell carcinoma), 8031/3 (giant cell carcinoma), 8980/3 (carcinosarcoma), and 8972/3 (pulmonary blastoma) were extracted as a group and defined as PSC. Besides, patients with codes 8140/3 (LAC) and 8070/3 (SCC) were also included. A total of 3897 patients with PSC, 236 843 with SCC, and 359 077 with lung adenocarcinoma (LAC) were involved in the analysis. Available variables were collected from the SEER database, such as age, sex, race, year of diagnosis, marital status, laterality, histological subgroup, grade, stage, T stage, N stage, M stage, tumor size, lymph node information, surgery, radiation, chemotherapy, survival months, and vital status. T stage, N stage, and M stage were adjusted according to the AJCC eighth edition tumor–node–metastasis staging system, based on tumor size, tumor extension, collaborative staging (CS) lymph nodes, and CS Mets at dx. The study involved only patients with available clinicopathological characteristics. The exclusion criteria were as follows: (I) diagnosed from autopsy only or death certification; (II) with more than 1 primary tumor; (III) incomplete AJCC stage information; (IV) unknown survival months and incomplete follow-up information. Finally, 2285 patients with PSC, 140 749 patients with SCC, and 233 663 patients with LAC were enrolled in the analysis (Figure 1).
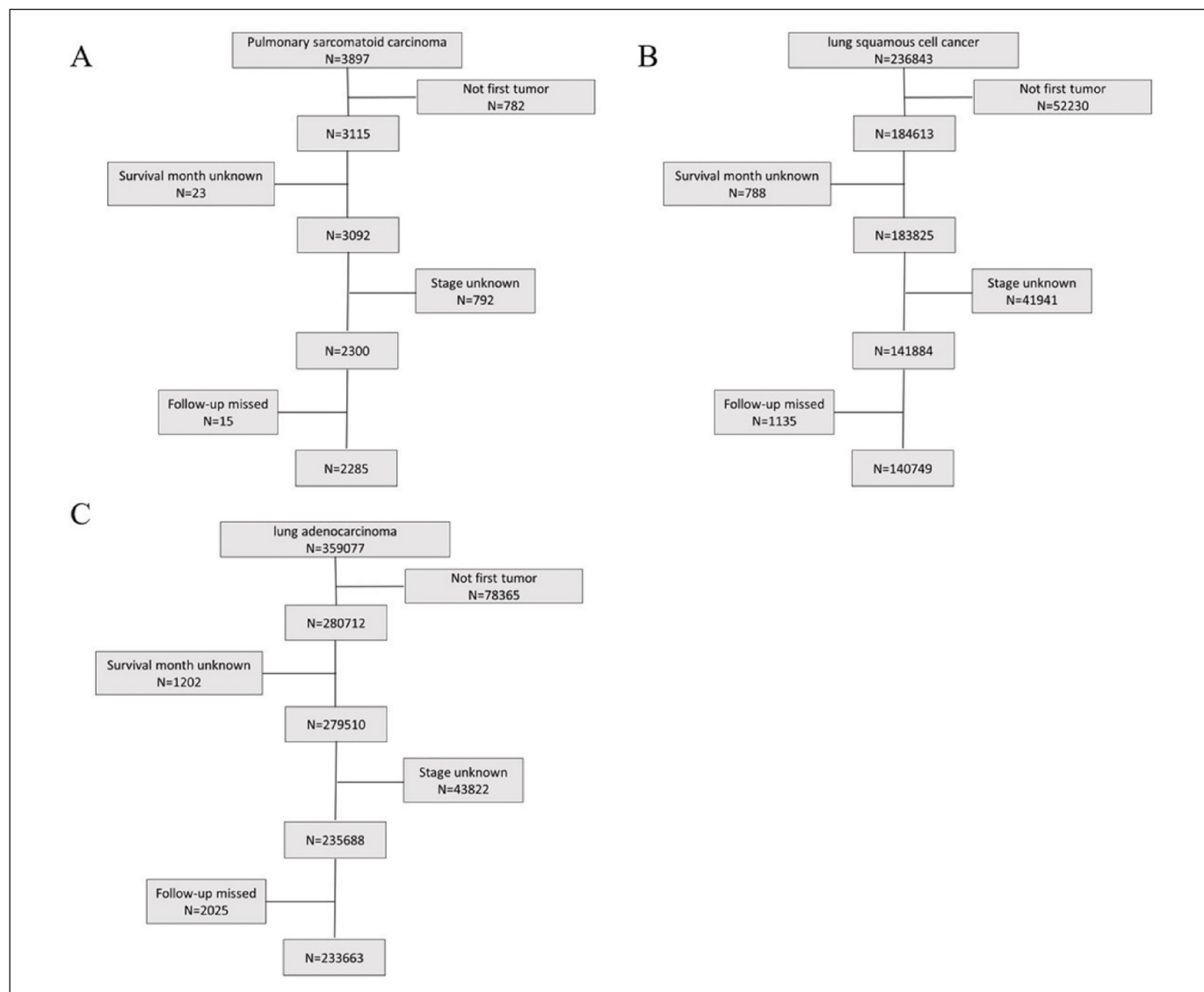
Figure 1. Flow chart for screening eligible patients in the SEER database. (A) A total of 2285 PSC patients were involved in our study, (B) a total of 140 749 SCC patients were involved in our study, and (C) a total of 233 663 LAC patients were involved in our study.
Abbreviations: SEER, surveillance, epidemiology, and end results; PSC, pulmonary sarcomatoid carcinoma; SCC, lung squamous cell cancer; LAC, lung adenocarcinoma.

Statistical Analysis

The definition of the lymph node ratio (LNR)[17] was the ratio between regional lymph nodes positive and the total number of regional nodes examined (×100%). It was reported that LNR could predict survival in NSCLC and was a more effective prognostic stratification tool than N classification.[18] Especially in patients classified as pathology N1, LNR was more valuable to identify patients with poor prognosis.[19] In this study, patients were divided into 5 groups based on previous studies[20,21]: LNR0, patients with no regional lymph nodes positive; LNR I, the ratio 0 to 0.17; LNR II, the ratio 0.18 to 0.41; LNR III, the ratio 0.42 to 0.69; and LNR IV, the ratio >0.7.

The outcomes were defined as OS and cancer-specific survival (CSS). OS was the time from the tumor diagnosis to any cause of death or the time of the last follow-up. CSS meant the status of patient death only due to lung cancer. In the competing risk model, death was defined into 2 groups: death due to lung cancer and death due to other diseases.

To compare different clinicopathological characteristics and prognoses between PSC, SCC, and LAC, continuous variables such as age, tumor size, and LNR reported as the median and interquartile range were examined using Mann–Whitney U-test. Meanwhile, these continuous variables were also categorized into categorical variables according to previous studies[22,23] (age <65 years and ≥65 years; size ≤3 cm, >3 cm but ≤5 cm, >5 cm but ≤7 cm, and >7 cm), presented as numbers (frequency percentages), and were examined with chi-square test. Multilevel analysis was performed by logistic

regression. The least absolute shrinkage and selection operator (LASSO) Cox regression was utilized with the "glmnet" R package to screen the factors associated with the prognosis of PSC. Further univariate and multivariate Cox proportional hazards regression analyses were used to report hazard ratios (HRs) and 95% confidence intervals (95% CIs). The variables significantly related to the survival in univariate analysis were enrolled in multivariate analysis. The survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. A 2-sided P-value of <.05 indicated a statistically significant difference.

The subgroup analysis was performed using a Cox regression model to minimize the bias of the confounding factors, and a forest plot was used to show the differences in characteristics.

Propensity score matching (PSM) analysis was conducted with the "MatchIt" R package to balance the baseline data of patients due to the huge difference in number between patients with PSC and those with SCC and LAC. A 1:1 matching of patients among different groups was performed, and after PSM, the differences in the variables among the groups were checked again.

In competing risk analysis, cumulative incidence function (CIF) was calculated with the "cmprsk" R package for PSC-specific mortality and other-cause-specific mortality. The significant differences between subgroups in CIF curves were estimated by Gray's test.[24,25] Cause-specific hazard was used to develop a competing risk model for PSC-specific mortality with the beforehand variables selected from LASSO cox regression. A nomogram was constructed to illustrate the competing risk model that could predict the 3- and 5-year OS. The concordance index (C-index) was used to validate the discriminative capacity of the model. Regarding the accuracy of the competing risk model, the bootstrap method was used with 1000 bootstrap samples to validate the nomogram, and the calibration curve was performed to compare the predicted survival with the actual survival. Statistical analysis of data was performed using R version 4.0.2 software.

Results

Patient and Tumor Characteristics

A total of 2285 patients with PSC, 140 749 patients with SCC, and 233 663 patients with LAC were recruited from the SEER database. The patient demographic information and tumor clinicopathological characteristics are shown in Table 1.

The majority of PSC patients were men (1366, 59.8%), with a mean age of 66.28 years and a median age of 67 years. About 59.3% of patients were over 65 years old. Additionally, 81.4% of PSC patients were White, 54.2% were married when diagnosed. The most common laterality of the tumor was right (1264, 55.3%). Most PSC patients were diagnosed with poorly differentiated or undifferentiated (grades III and IV, 1239, 54.2%), stages III and IV (1563, 68.4%), T3 and T4 (877, 38.4%), N positive (976, 42.7%), and M0

(1215, 53.2%). PSC patients had huge tumor sizes, with the highest rate of size ≥7 cm (24.9%). The LNR of PSC patients was usually 0 (18.3%). Approximately 28.6% of patients with PSC underwent surgery, especially lobectomy (20.7%). Furthermore, 40.6% of patients with PSC received radiotherapy and 35.5% received chemotherapy. The most common subtype of PSC was giant cell carcinoma (834, 36.5%), followed by spindle cell carcinoma (632, 27.7%), pleomorphic carcinoma (497, 21.8%), and carcinosarcoma (282, 12.3%). Pulmonary blastoma was the least subtype of PSC, with only 40 patients in total (1.8%).

Comparison of Patient Characteristics Between PSC, SCC, and LAC

Significant differences were found in age, sex, marriage, grade, stage, T stage, N stage, M stage, tumor size, surgery, and radiation between PSC and SCC. Differences were also observed in sex, laterality, grade, stage, T stage, N stage, M stage, tumor size, LNR, surgery, and chemotherapy between PSC and LAC. The age of patients with PSC (mean age was 66.28 years, the median age was 67 years) was lower than that of patients with SCC (mean age: 69.06 years; median age: 70 years; $P < .001$) but similar to that of patients with LAC (mean age was 66.97 years, median age was 67 years, $P = .262$). Most patients with lung cancer were men, especially patients with SCC (men 91 774, 65.2%; $P < .001$). Most patients were White, and more than half of patients were married when diagnosed with lung cancer. The most common tumor laterality of PSC was the right, which was similar to that of SCC and LAC. A majority of patients with PSC were diagnosed with grades III and IV. Only a few patients (1.6%) were diagnosed with grades I and II. The same outcome was also seen in SCC (grades I and II 28.3% vs grades III and IV 37.8%) and LAC (grades I and II 24.3% vs grades III and IV 31.2%), but the proportion was not obviously different between grades I and II and grades III and IV, compared with PSC ($P < .001$). Patients with PSC had larger tumor size (mean size was 5.88 cm, median size was 5.0 cm) than those with SCC (mean size was 4.89 cm, median size was 4.5 cm) and LAC (mean size was 3.96 cm, median size was 3.4 cm) ($P < .001$). Treatments for PSC patients also showed differences compared with 48.9% of patients with SCC ($P < .001$). Chemotherapy was performed on 35.5% of patients with PSC than 41.6% of patients with LAC ($P < .001$). Multi-level analysis was performed by logistic regression and figured out that age, sex, grade, stage, N stage, M stage, tumor size, LNR, and surgery presented significant differences between patients with PSC and SCC ($P < .05$). Similar results between patients with PSC and LAC illustrated that grade, stage, N stage, tumor size, and surgery presented significant differences ($P < .05$). Compared to patients with SCC and LAC, it seemed that patients with PSC had different demographic information and tumor clinicopathological characteristics including younger patients when diagnosed, more male patients, with high-grade, advanced-stage, and massive tumors.

Table 1. Clinical Characteristics of Patients From the SEER Database, Comparison in PSC versus SCC and LAC.

Characteristics	PSC $n = 2285$	SCC $n = 140\,749$	P-value	LAC $n = 233\,663$	P-value
Age	67(16)	70(14)	**<.001**	67(16)	.262
<65	929(40.7%)	43 637(31.0%)	**<.001**	94 137(40.3%)	.721
>65	1356(59.3%)	97 112(69.0%)		139 526(59.7%)	
Sex					
Male	1366(59.8%)	91 774(65.2%)	**<.001**	118 895(50.9%)	**<.001**
Female	919(40.2%)	48 975(34.8%)		114 768(49.1%)	
Race					
Black	289(12.6%)	17 525(12.5%)	.664	27 116(11.6%)	.294
White	1861(81.4%)	116 025(82.4%)		186 651(79.9%)	
Marriage					
Married	1238(54.2%)	73 408(52.2%)	**.037**	125 522(53.7%)	.550
Unmarried	952(41.7%)	61 799(43.9%)		99 056(42.4%)	
Laterality					
Left	934(40.9%)	59 600(42.3%)	.292	88 559(37.9%)	**.022**
Right	1264(55.3%)	77 046(54.7%)		132 325(56.6%)	
Grade					
I and II	36(1.6%)	39 878(28.3%)	**<.001**	56 721(24.3%)	**<.001**
III and IV	1239(54.2%)	53 227(37.8%)		72 946(31.2%)	
Stage					
I and II	596(26.1%)	43 586(31.0%)	**<.001**	55 932(23.9%)	**.013**
III and IV	1563(68.4%)	86 533(61.5%)		165 412(70.8%)	
T					
T1 and T2	739(32.3%)	56 582(40.2%)	**<.001**	90 735(38.8%)	**<.001**
T3 and T4	877(38.4%)	50 354(35.8%)		78 622(33.6%)	
N					
N0	873(38.2%)	51 933(36.9%)	**.005**	79 621(34.1%)	**<.001**
N positive	976(42.7%)	66 305(47.1%)		113 164(48.4%)	
M					
M0	1215(53.2%)	90 626(64.4%)	**<.001**	110 902(47.5%)	**<.001**
M1	976(42.7%)	42 127(29.9%)		113 618(48.6%)	
Size (cm)	5.0(4.3)	4.5(3.3)	**<.001**	3.4(2.8)	**<.001**
≤3	390(17.1%)	31 938(22.7%)	**<.001**	77 314(33.1%)	**<.001**
3-5	469(20.5%)	33 429(23.8%)		50 867(21.8%)	
5-7	277(12.1%)	17 775(12.6%)		19 469(8.3%)	
≥7	570(24.9%)	22 019(15.6%)		19 596(8.4%)	
LNR	0(0.2)	0(0.17)	.409	0(0.33)	**.006**
0	419(18.3%)	20 677(14.7%)	.200	31 551(13.5%)	**.011**
0-0.17	65(2.8%)	3435(2.4%)		4384(1.9%)	
0.18-0.41	57(2.5%)	3003(2.1%)		4718(2.0%)	
0.42-0.69	26(1.1%)	1462(1.0%)		3110(1.3%)	
≥0.7	87(3.8%)	3358(2.4%)		8901(3.8%)	
Surgery					
No/unknown	1631(71.4%)	112 020(79.6%)	**<.001**	186 522(79.8%)	**<.001**
Sublobar resection	97(4.2%)	4488(3.2%)		8698(3.7%)	
Lobectomy	473(20.7%)	20 274(14.4%)		36 012(15.4%)	
Pneumonectomy	76(3.3%)	3458(2.5%)		2048(0.9%)	
Radiation					
No	1358(59.4%)	71 936(51.1%)	**<.001**	138 913(59.5%)	.985
Yes	927(40.6%)	68 813(48.9%)		94 750(40.5%)	
Chemotherapy					
No	1474(64.5%)	90 704(64.4%)	.950	136 555(58.4%)	**<.001**
Yes	811(35.5%)	50 045(35.6%)		97 108(41.6%)	

Abbreviations: SEER, surveillance, epidemiology, and end results; PSC, pulmonary sarcomatoid carcinoma; SCC, squamous cell cancer; LAC, lung adenocarcinoma; LNR, lymph node ratio.
Bold values means $P < 0.05$, which indicates a statistically significant difference.
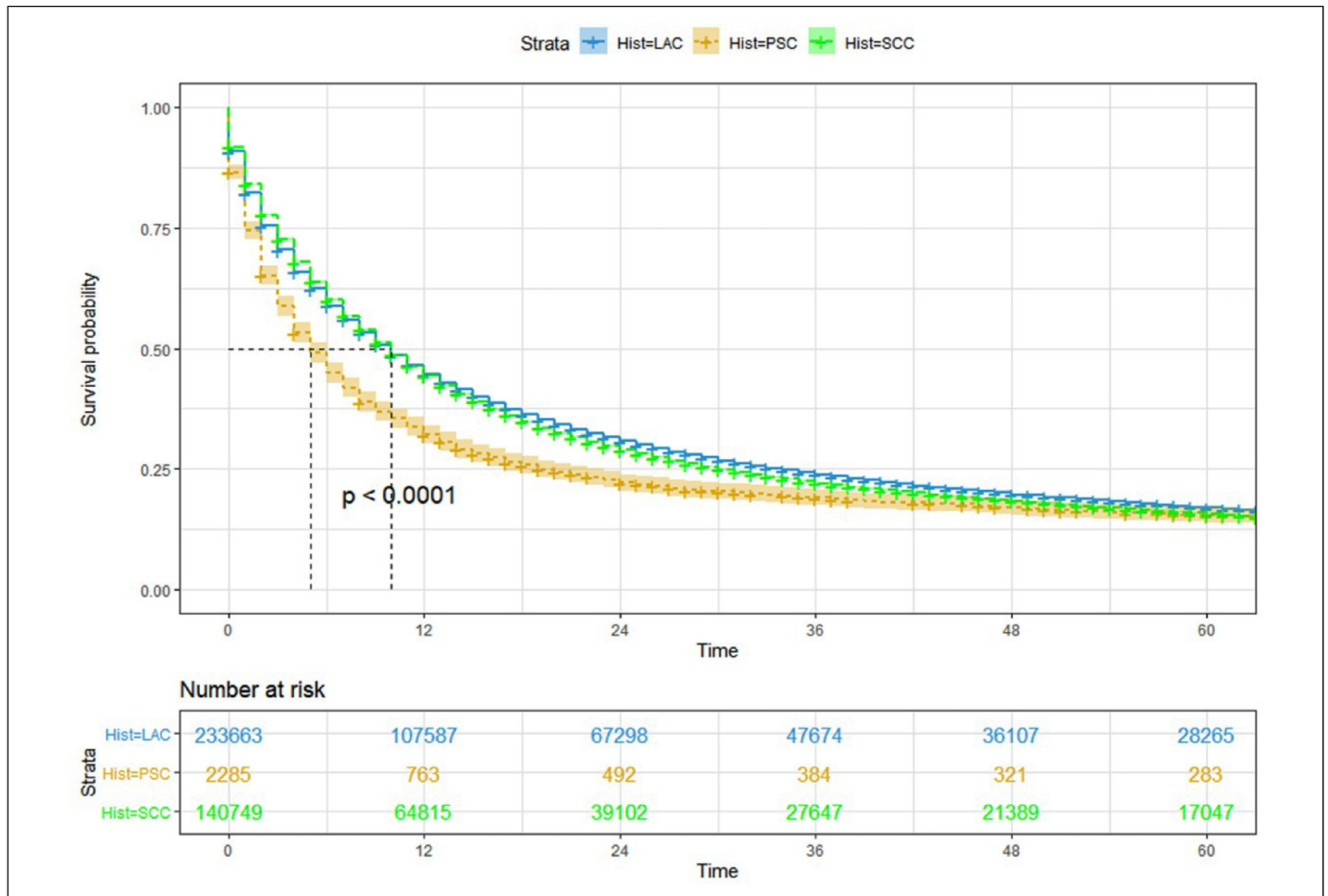
Figure 2. Kaplan–Meier curves of OS between PSC and other NSCLCs.
Abbreviations: OS, overall survival; PSC, pulmonary sarcomatoid carcinoma; NSCLC, nonsmall cell lung cancer.

The Cox proportional hazards regression was used to further analyze the prognostic factors of the baseline characteristics in PSC, SCC, and LAC (Supplemental Table 1). Patients with PSC had a poor prognosis, the 5-year OS of PSC patients was 15.3% (95% CI: 13.9%-16.9%), and the median OS was 5 months (95% CI: 5-6 months). In the Cox univariate analysis, patients with SCC (HR: 0.86; 95% CI: 0.83-0.90; $P < .001$) or with LAC (HR: 0.83; 95% CI: 0.80-0.87; $P < .001$) seemed to show better survival outcomes. The Kaplan–Meier curve was shown in Figure 2, indicating that patients with PSC had a worse outcome than those with SCC and LAC ($P < .001$). In addition, other independent factors significantly related to prognosis include age, sex, marriage, race, grade, stage, T stage, N stage, M stage, tumor size, LNR, surgery, radiation, and chemotherapy ($P < .001$) were presented in univariate analysis. All these variables were involved in the Cox multivariable analysis. The results in Supplemental Table 1 illuminated that after adjusting other prognostic factors, the histology type was still significantly associated with the OS. Patients with SCC (HR: 0.84; 95% CI: 0.75-0.94; $P = .003$) or with LAC (HR: 0.76; 95% CI: 0.68-0.85; $P < .001$) still showed better survival outcome than patients with PSC.

Survival Analysis in Subgroups

The prognosis of PSC was compared with that of SCC and LAC in different subgroups to diminish the selection bias. The patient demographic information and tumor clinicopathological characteristics between PSC and SCC showed significant differences in the subgroup analysis (Figure 3). Patients with PSC in subgroups analysis showed worse survival outcomes compared with SCC or LAC patients, especially in subgroups of patients aged ≥65 years, male patients, patients with grades III and IV, stages III and IV, T3, T4, N positive, and M1 tumors. However, compared with SCC, the PSC subtype seemed to be a protective factor for OS in a subgroup comprising patients with grades I and II and stages I and II (Figure 3A). The same results were not seen in a subgroup analysis of PSC with LAC (Figure 3B). It illustrated that no matter in what clinicopathological characteristics subgroups, patients with LAC showed a better prognosis than that of PSC patients.

Survival Comparison After PSM

A 1:1 PSM analysis, including 2285 patients for each histology type, was used to reduce the baseline data selection bias
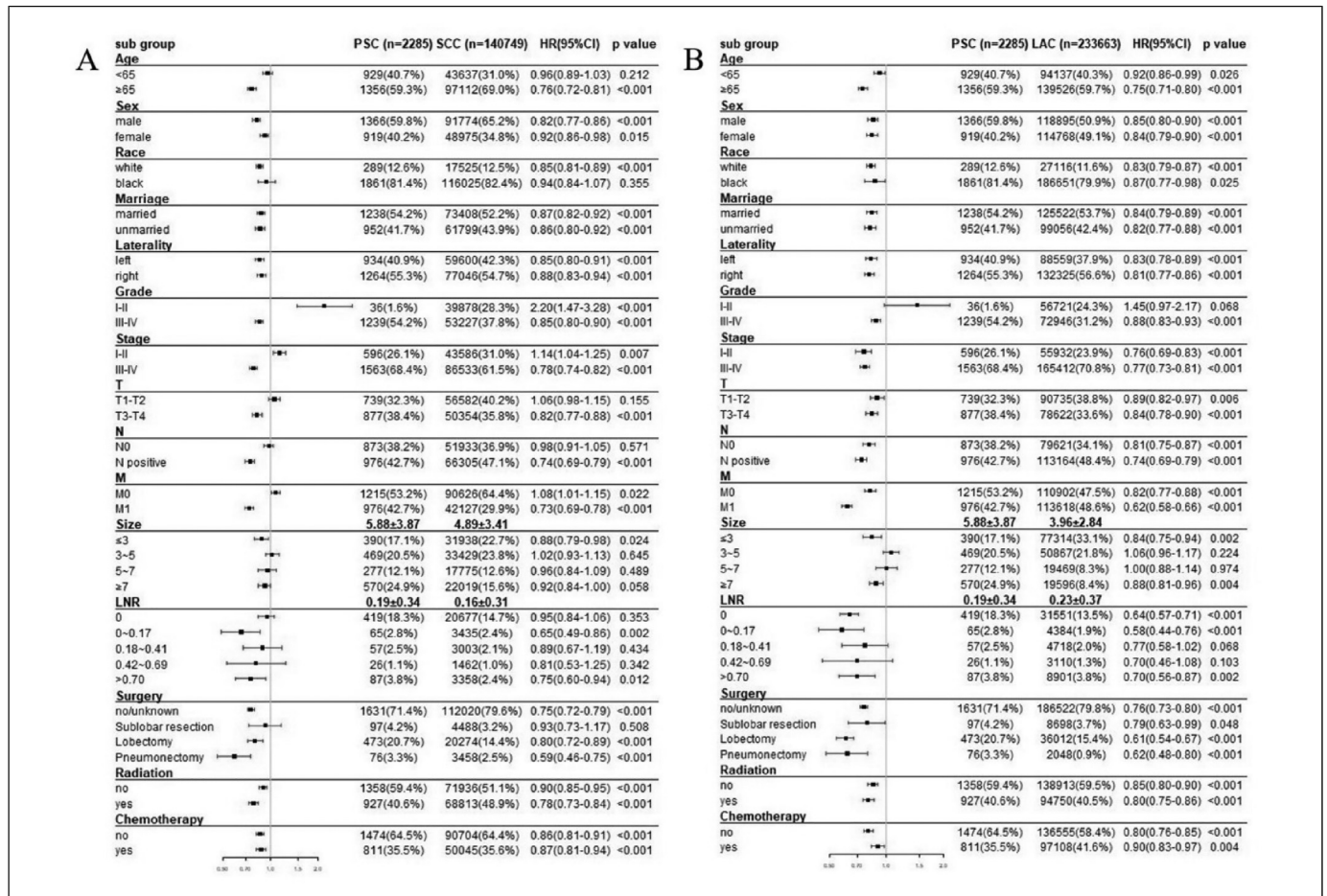
Figure 3. Subgroup survival analysis showed by Forest plot of HRs. (A) Subgroup survival analysis in PSC versus SCC and (B) subgroup analysis in PSC versus LAC. The *X*-axis shows the HR and 95% CI of each subgroup, ticks are arranged at 0.5, 1.0, and 2.0.
Abbreviations: PSC, pulmonary sarcomatoid carcinoma; SCC, lung squamous cell cancer; LAC, lung adenocarcinoma; CI, confidence interval; HR, hazard ratio.

due to the population differences. Based on 2285 patients with PSC, all baseline characteristics were 1:1 matched in the variables shown to be significantly different before PSM (Table 2). After PSM, a comparison of PSC with SCC and LAC showed that almost all the variables were balanced and no longer significantly different, even after logistic analysis. The adjuvant average age of SCC was 67.16 years, and the median age was 67 years, showing no significant difference between PSC (average age was 66.28 years, the median age was 67 years, $P = .335$), and LAC (average age was 66.10 years, the median age was 67 years, $P = .106$). Furthermore, the analysis between PSC and LAC revealed that PSC had a larger tumor size (5.88 ± 3.87 cm, median size was 5.0 cm) compared with LAC (5.56 ± 3.88 cm, median size was 5.0 cm) ($P = .027$). After PSM, the survival advantage of SCC (HR: 0.91; 95% CI: 0.85-0.96; $P = .001$) and LAC (HR: 0.87; 95% CI: 0.82-0.92; $P < .001$) was still significant. The OS survival curve in different histology subtypes is shown in Figure 4.

Analysis of the Prognostic Factors for PSC

We included 16 variables from the SEER database to estimate the relative independent prognostic factors of patients with PSC, including age, sex, year of diagnosis, marriage, histology, grade, stage, T stage, N stage, M stage, tumor size, LNR, surgery, radiation, and chemotherapy. LASSO Cox regression was used to screen variables that were associated with the prognosis, and finally identified 9 factors with significant prognostic values (Figure 5A and B). These factors were as follows: age, sex, stage, T, M stage, tumor size, LNR, surgery, and chemotherapy (Table 3). These variables were continually involved in the Cox univariate and multivariable analysis to analyze the impact of various factors on survival. Age ≥65 years (HR: 2.24; 95% CI: 1.80-2.79; $P < .001$), T3 and T4 (HR: 1.41; 95% CI: 1.05-1.90; $P = .022$), M1 (HR: 4.43; 95% CI: 2.92-6.72; $P < .001$), tumor size between 3 and 5 cm (HR: 1.41; 95% CI: 1.08-1.84; $P = .011$) or ≥7 cm (HR: 2.16; 95% CI: 1.58-2.95; $P < .001$), LNR>0 ($P < .01$), not undergo surgery (HR: 1.40; 95% CI: 1.10-1.78; $P = .006$) presented to be associated with worse survival outcomes ($P < .05$).

Table 2. Clinical Characteristics of Patients in 1:1 Matched, Comparison in PSC versus SCC and LAC.

Characteristics	PSC $n = 2285$	SCC $n = 2285$	P-value	LAC $n = 2285$	P-value
Age (years)	67(16)	67(15)	.335	67(16)	.106
<65	929(40.7%)	934(40.9%)	.880	988(43.2%)	.077
>65	1356(59.3%)	1351(59.1%)		1297(56.8%)	
Sex					
Male	1366(59.8%)	1374(60.1%)	.809	1369(59.9%)	.930
Female	919(40.2%)	911(39.9%)		916(40.1%)	
Race					
Black	289(12.6%)	330(14.4%)	.089	255(11.2%)	.236
White	1861(81.4%)	1833(80.2%)		1831(80.1%)	
Marriage					
Married	1238(54.2%)	1257(55.0%)	.789	1247(54.6%)	.919
Unmarried	952(41.7%)	951(41.6%)		953(41,7%)	
Laterality					
Left	934(40.9%)	954(41.8%)	.451	937(41.0%)	.927
Right	1264(55.3%)	1233(54.0%)		1261(55.2%)	
Grade					
I and II	36(1.6%)	34(1.5%)	.778	33(1.4%)	.595
III and IV	1239(54.2%)	1253(54.8%)		1293(56.6%)	
Stage					
I and II	596(26.1%)	579(25.3%)	.555	590(25.8%)	.780
III and IV	1563(68.4%)	1581(69.2%)		1577(69.0%)	
T					
T1 and T2	739(32.3%)	710(31.1%)	.595	733(32.1%)	.807
T3 and T4	877(38.4%)	875(38.3%)		885(38.7%)	
N					
N0	873(38.2%)	867(37.9%)	.904	878(38.4%)	.980
N positive	976(42.7%)	977(42.8%)		980(42.9%)	
M					
M0	1215(53.2%)	1184(51.8%)	.355	1223(53.5%)	.847
M1	976(42.7%)	1006(44.0%)		971(42.5%)	
Size	5.0(4.3)	5.1(4.0)	.425	5.0(4.0)	**.027**
≤3	390(17.1%)	373(16.3%)	.922	398(17.4%)	.991
3-5	469(20.5%)	478(20.9%)		475(20.8%)	
5-7	277(12.1%)	278(12.2%)		273(11.9%)	
≥7	570(24.9%)	575(25.2%)		573(25.1%)	
LNR	0(0.2)	0(0.14)	.333	0(0.19)	.903
0	419(18.3%)	400(17.5%)	.132	412(18.0%)	.983
0-0.17	65(2.8%)	74(3.2%)		65(2.8%)	
0.18-0.41	57(2.5%)	53(2.3%)		57(2.5%)	
0.42-0.69	26(1.1%)	31(1.4%)		28(1.2%)	
≥0.7	87(3.8%)	56(2.5%)		79(3.5%)	
Surgery					
No/unknown	1631(71.4%)	1676(73.3%)	.275	1650(72.2%)	.497
Sublobar resection	97(4.2%)	79(3.5%)		86(3.8%)	
Lobectomy	473(20.7%)	459(20.1%)		453(19.8%)	
Pneumonectomy	76(3.3%)	63(2.8%)		90(3.9%)	
Radiation					
No	1358(59.4%)	1371(60.0%)	.695	1372(60.0%)	.673
Yes	927(40.6%)	914(40%)		913(40.0%)	
Chemotherapy					
No	1474(64.5%)	1473(64.5%)	.975	1485(65.0%)	.733
Yes	811(35.5%)	812(35.5%)		800(35.0%)	

Abbreviations: PSC, pulmonary sarcomatoid carcinoma; SCC, squamous cell cancer; LAC, lung adenocarcinoma; LNR, lymph node ratio.
Bold values means $P < 0.05$, which indicates a statistically significant difference.

The prognosis analysis of 5 subtypes of PSC showed significant differences. Compared with carcinosarcoma, patients with giant cell carcinoma (HR: 1.23; 95% CI: 1.07-1.42; $P = .004$) or spindle cell carcinoma (HR: 1.17; 95% CI: 1.01-1.35; $P = .042$) seemed to have worse survival, while patients with pulmonary blastoma (HR: 0.35; 95% CI: 0.23-0.52; $P < .001$) had the best prognosis (Figure 6).
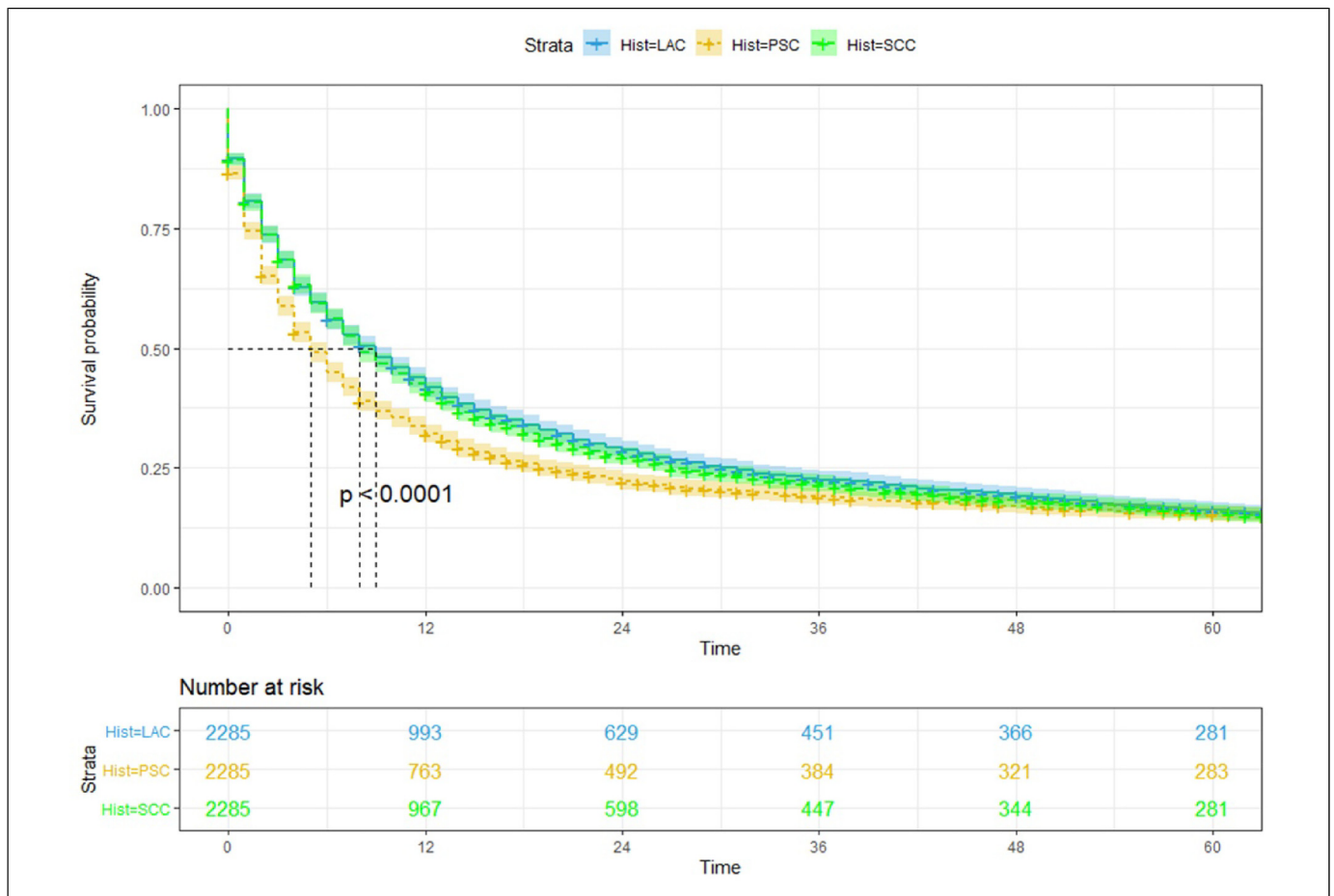
Figure 4. Kaplan–Meier curves for a 1:1 matched group, PSC (matched) versus SCC (matched) and LAC (matched).
Abbreviations: PSC, pulmonary sarcomatoid carcinoma; SCC, lung squamous cell cancer; LAC, lung adenocarcinoma.
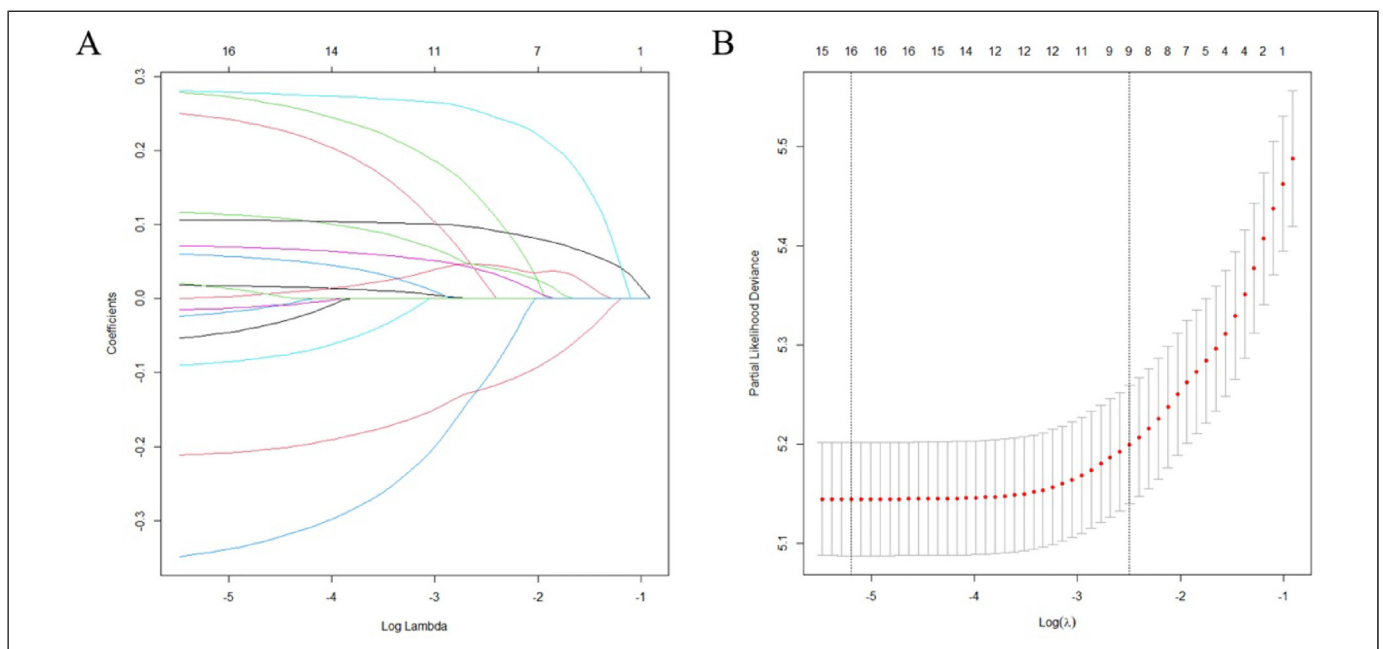

Figure 5. The identification of the 9 most prognostic factors in patients with PSC by the LASSO Cox regression.
Abbreviations: PSC, pulmonary sarcomatoid carcinoma; LASSO, least absolute shrinkage and selection operator.

Table 3. Univariate and multivariate Cox proportional hazard analyses of clinical characteristics for OS rates in patients with PSC.

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age				
<65	Reference	**<.001**	Reference	**<.001**
≥65	1.47(1.34-1.61)		2.24(1.80-2.79)	
Sex				
Female	Reference	**<.001**	Reference	.442
Male	1.21(1.11-1.32)		1.08(0.88-1.33)	
Stage				
I and II	Reference	**<.001**	Reference	.987
III and IV	2.98(2.67-3.32)		1.00(0.73-1.37)	
T				
T1 and T2	Reference	**<.001**	Reference	**.022**
T3 and T4	2.20(1.98-2.46)		1.41(1.05-1.90)	
M				
M0	Reference	**<.001**	Reference	**<.001**
M1	3.24(2.94-3.56)		4.43(2.92-6.72)	
Size				
≤3	Reference		Reference	
3-5	1.16(1.01-1.35)	**.043**	1.41(1.08-1.84)	**.011**
5-7	1.39(1.18-1.64)	**<.001**	1.20(0.85-1.69)	.297
≥7	1.78(1.54-2.05)	**<.001**	2.16(1.58-2.95)	**<.001**
LNR				
0	Reference		Reference	
0-0.17	1.48(1.10-1.99)	**.010**	1.64(1.16-2.30)	**.005**
0.18-0.41	1.48(1.10-2.01)	**.011**	1.70(1.21-2.38)	**.002**
0.42-0.69	1.83(1.18-2.86)	**.001**	1.96(1.20-3.21)	**.008**
≥0.70	3.29(2.56-4.23)	**<.001**	2.13(1.42-3.21)	**<.001**
Surgery				
Lobectomy	Reference		Reference	
No/unknown	2.93(2.60-3.30)	**<.001**	1.40(1.10-1.78)	**.006**
Sublobe	1.24(0.97-1.60)	.092	1.33(0.82-2.14)	.250
Pneu	1.53(1.18-2.00)	**.002**	1.22(0.86-1.71)	.262
Chemotherapy				
No	Reference	**<.001**	Reference	**.018**
Yes	0.79(0.72-0.86)		0.75(0.60-0.95)	

Abbreviations: OS, overall survival; PSC, pulmonary sarcomatoid carcinoma; HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio.
Bold values means *P* < 0.05, which indicates a statistically significant difference.

Competing Risk Analysis for PSC

The CIF was used to diminish the impact of the competing risk in other-cause death. The cumulative incidence of PSC mortality was estimated with cancer-specific death, and death not caused by PSC was regarded as the competing event. In the follow-up time of 5 years, the cumulative lung cancer mortality in different histology subtypes showed significant differences ($P<.001$, Figure7A): carcinosarcoma, 75.9%; giant cell carcinoma, 80.8%; pleomorphic carcinoma, 69.1%; pulmonary blastoma, 42.5%; and spindle cell carcinoma, 78.7%. Pulmonary blastoma had the best prognosis among all subtypes of PSCs. The cumulative other-cause disease mortality was not different among 5 histology subtypes ($P=.075$, Figure7B): carcinosarcoma, 11.0%; giant cell carcinoma, 7.1%; pleomorphic carcinoma, 9.4%; pulmonary blastoma, 7.5%; spindle cell carcinoma, 8.3%.

A cause-specific competing risk regression analysis was performed to illustrate the prognostic factors for patients with PSC. These independent factors related to OS selected by LASSO Cox regression were involved in the competing risk model for multivariate analysis (Table 4). Finally, the multivariate competing risk analysis showed that except receiving chemotherapy (HR: 0.77; 95% CI: 0.60-0.99; $P=.043$) seemed to be a significant protective factor of PSC-specific mortality, while patients over 65 years old (HR: 1.93; 95% CI: 1.52-2.47; $P < .001$), with late T stage (T3 and T4, HR: 1.49; 95% CI: 1.08-2.07; $P=0.016$), M1 (HR: 4.28; 95% CI: 2.76-6.64; $P < .001$), massive tumor size ($P<.05$), LNR>0 ($P <.05$), not undergo surgery (HR: 1.46; 95% CI: 1.11-1.92; $P=.007$) presented to be associated with a higher possibility of PSC-specific mortality.

A competing risk nomogram predicting the 3-year and 5-year cumulative probabilities of death for cancer-specific mortality in patients with PSC was demonstrated in Figure 8. The C-index of the competing risk nomogram
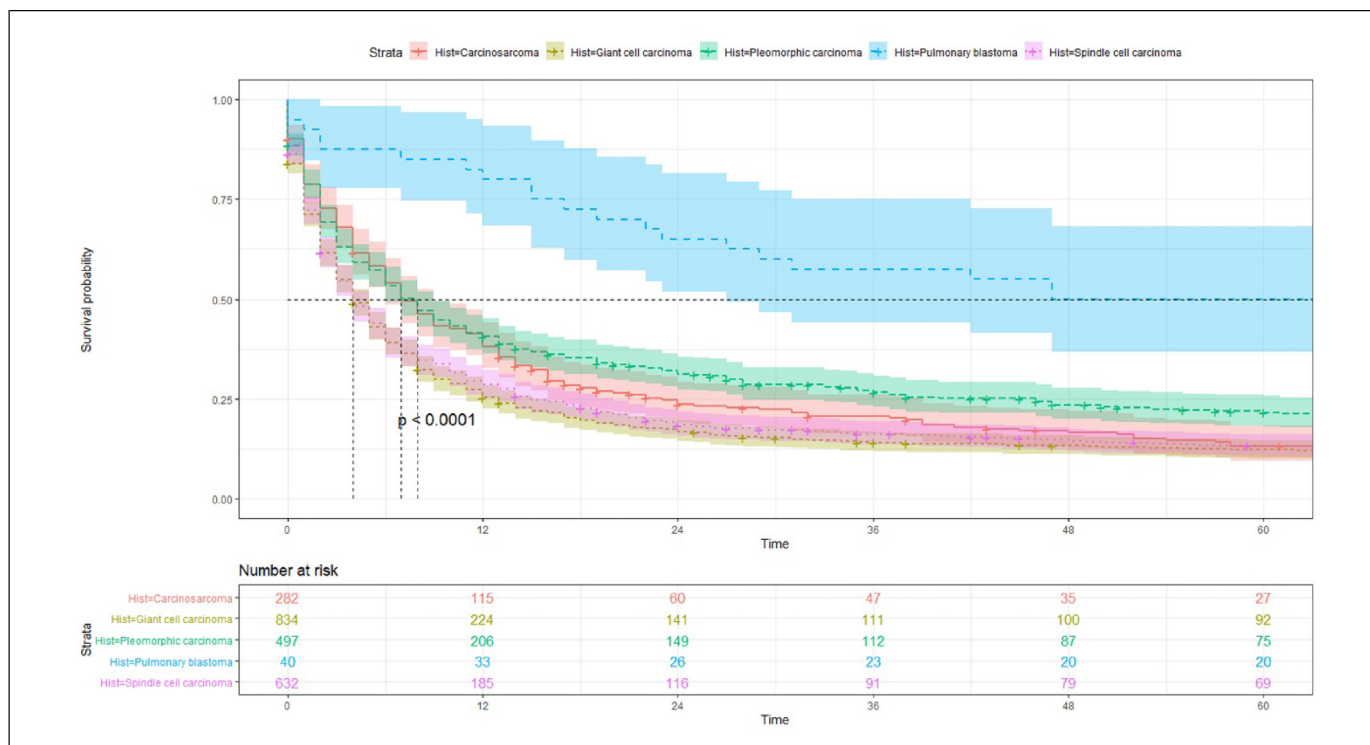
Figure 6. Kaplan–Meier curves of OS among different subtypes of PSC.
Abbreviations: OS, overall survival; PSC, pulmonary sarcomatoid carcinoma.

was 0.718. The 3-year and 5-year calibration curves of the nomogram were all close to the 45° diagonal line, illustrating the high accuracy of the competing risk model (Figure 9).

Discussion

In the present study, we analyzed the clinicopathological characteristics and survival outcomes of 2285 patients with PSC using the data from the SEER database. We found that most patients with PSC were male (59.8%), aged over 65 years (59.3%). In detail, 1366 male and 919 female patients (M/F ratio = 1.5:1) were enrolled. The average age was 66.28 years at diagnosis, which was similar to the findings by Rahouma et al[14] and Liang et al.[26] However, the M/F ratio was far lower than that in other previous reports (M/F ratio = 3.6-5.3:1).[8,27,28] The discrepancy was probably due to the small sample size in these studies. PSC patients were more
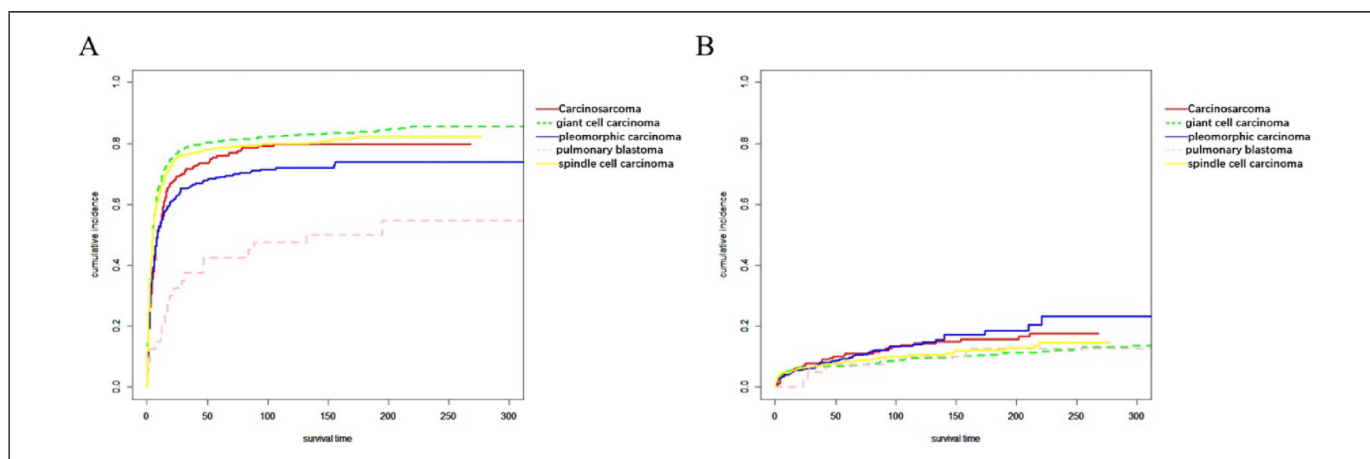

Figure 7. CIF curves of death for patients with PSC by different subtypes. (A) CIF curves of the PSC-specific mortality for patients with PSC by different subtypes and (B) CIF curves of other-cause-specific mortality for patients with PSC by different subtypes.
Abbreviations: CIF, cumulative incidence function; PSC, pulmonary sarcomatoid carcinoma.

Table 4. Multivariate Competing Risk Model for the Cancer-Specific Mortality in Patients With PSC.

	Competing risk regression	
Characteristics	HR (95% CI)	*P*-value
Age		**<.001**
<65	Reference	
≥65	1.93(1.52-2.47)	
Sex		.382
Female	Reference	
Male	1.11(0.88-1.40)	
Stage		.373
I and II	Reference	
III and IV	1.17(0.83-1.66)	
T		**.016**
T1 and T2	Reference	
T3 and T4	1.49(1.08-2.07)	
M		**<.001**
M0	Reference	
M1	4.28(2.76-6.64)	
Size		
≤3	Reference	
3-5	1.39(1.01-1.91)	**.042**
5-7	1.37(0.92-2.03)	.120
≥7	2.44(1.71-3.47)	**<.001**
LNR		
0	Reference	
0-0.17	1.81(1.26-2.61)	**.001**
0.18-0.41	1.84(1.27-2.67)	**.001**
0.42-0.69	2.09(1.23-3.54)	**.006**
≥0.70	2.44(1.71-3.47)	**.004**
Surgery		
Lobectomy	Reference	
No/unknown	1.46(1.11-1.92)	**.007**
Sublobe	1.37(0.80-2.35)	.257
Pneu	1.07(0.72-1.58)	.754
Chemotherapy		
No	Reference	**.043**
Yes	0.77(0.60-0.99)	

Abbreviations: PSC, pulmonary sarcomatoid carcinoma; HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio.
Bold values means *P* < 0.05, which indicates a statistically significant difference.

often associated with poorly differentiated or undifferentiated (grades III and IV) and advanced stage (stages III and IV) tumors. Most tumors were massive in size, which was consistent with the results of the present study.[10,14] After using a 1:1 PSM to balance the selection bias due to the population differences, the demographics and tumor-specific clinicopathological characteristics among PSC with SCC and LAC seemed to have no significant differences anymore. Nevertheless, patients with PSC had a poorer prognosis compared to SCC and LAC, the median survival of PSC was 5 months, which was inferior to those of SCC (10 months) and LAC (10 months). The 5-year OS rate was 15.3% for PSC compared with SCC (15.6%) and LAC (16.9%). Even after a 1:1 PSM analysis, PSC still had adverse survival compared with SCC and LAC. Similar outcomes were also seen in the subgroup study, probably because patients with PSC always had no typical and specific

symptoms and a high rate of distant metastasis, diagnosed at an advanced stage, often lost the opportunity of surgery treatment and did not respond well to conventional chemotherapy of NSCLC.[13,29] Even after complete resection surgery, patients with PSC are still reported to have a poor prognosis.[6,26] The median survival and 5-year OS in the present study were lower than those in other real-world studies.[30,31] This was probably because patients with PSC in the SEER database had more aggressive grades and stages at diagnosis and had less opportunity to receive surgery (28.2%), which was absolutely associated with a poor prognosis. PSC was classified into 5 subgroups with different prognoses. Compared with other subtypes, pulmonary blastoma had a survival benefit.[29] A total of 40 patients with pulmonary blastoma were enrolled from the SEER database, contributing to 1.75% of all PSC cases. Further, 57.5% were in stages I and II, and half were well-differentiated or moderately differentiated with a good prognosis. The median survival of pulmonary blastoma was 65.5 months, and the 5-year OS was close to 50%. Similar outcomes were seen in other studies.[26,30] Overall, in grades I and II subgroup analysis, the pulmonary blastoma subtype accounted for 30.6% of PSC cases, explaining why patients with grades I and II PSC showed better survival than those with SCC in the subgroup analysis.

It is integral to consider the competing risk of the other-cause-specific mortality to estimate the cancer-specific mortality of PSC accurately. Therefore, a competing risk analysis was performed to examine the factors associated with the prognosis of patients with PSC. Of the 2285 patients with PSC, 1779 (77.9%) died due to lung cancer and 266 (11.6%) died of other diseases. Age, T stage, M stage, tumor size, LNR, surgery, and chemotherapy were associated with cancer-specific mortality, which were also proved in other studies.[26] Surgery always needed to be considered at first for patients with lung cancer in the early stage. Lobectomy was the standard treatment of NSCLC, and also did well in PSC, showing better benefit to outcomes compared with no surgery, sublobar resection, and Pneumonectomy.[31–34] Although some previous studies reported that PSC patients showed poor response to the conventional chemotherapy regimens and had a high rate of progression,[3,6,35,36] we found received chemotherapy seemed to have a better performance in survival outcomes, which were also confirmed by other research studies,[37] the efficacy of chemotherapy was defined especially for patients with advanced-stage tumors and younger age.[38] Discrepancies exist among these previous studies and the present study, probably result from the limited single-institution retrospective studies with no more than 100 samples in their studies, which was unavoidable leading to selection bias. SEER database supported population-based studies with multiinstitution and reduced selection bias. However, all these studies were retrospective analyses, the selection bias could not be excluded, and the SEER database did not perform specific chemotherapy regimens. Therefore, the efficacy of chemotherapy needed further defined. Other previous articles also focused on the role of radiotherapy in PSC,[26,32] and found that patients could
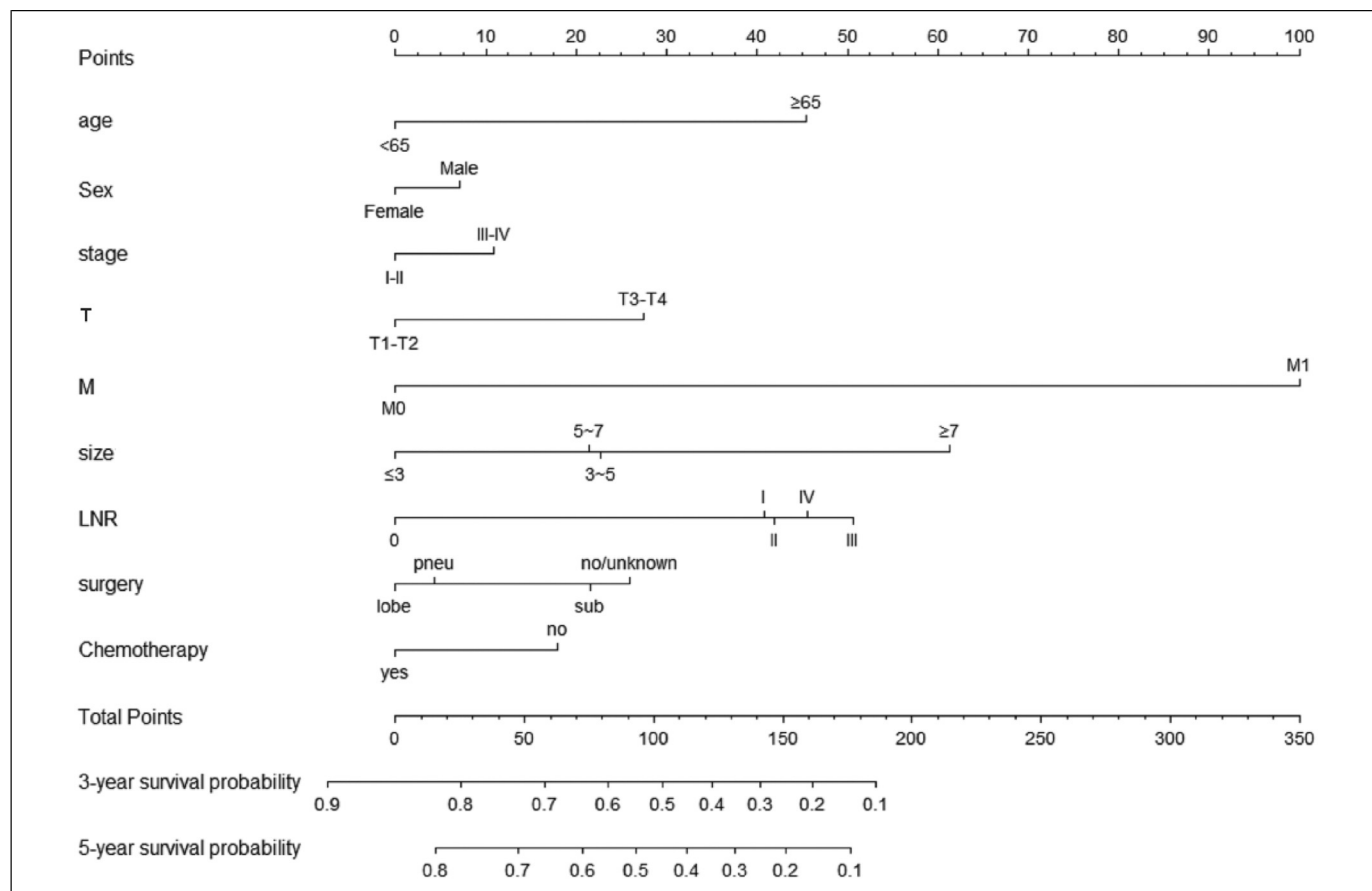
Figure 8. Competing risk nomogram predicting the 3-year and 5-year cumulative probabilities of death for the cancer-specific mortality in patients with pulmonary sarcomatoid carcinoma (PSC).
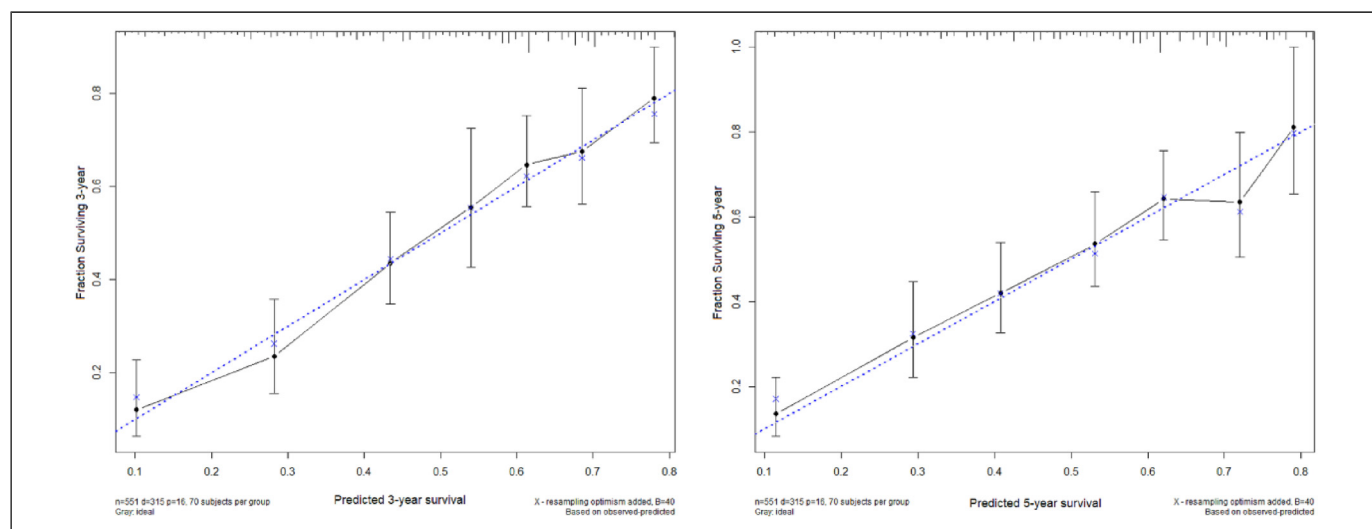

Figure 9. The calibration curves of the competing risk nomogram prediction of the 3-year and 5-year OS of PSC patients. (A) Three-year calibration curve and (B) 5-year calibration curve. The X-axes represent the predicted mortality probability according to the prediction model. The Y-axes represent the observed cumulative incidence of mortality. The blue line represents the equality of the observed and predicted probability. Abbreviations: OS, overall survival; PSC, pulmonary sarcomatoid carcinoma.

benefit from radiotherapy. The benefit of radiation in patients with PSC is controversial. In our study, we used LASSO Cox regression to screen factors that were associated with prognosis and found that radiation did not significantly affect outcomes of PSC. Some research studies even clarified that radiotherapy would reduce survival.[14,39] Hence, the role of radiation in the outcomes still needed further exploration.

A nomogram was successfully constructed and precisely presented to predict the 3-year and 5-year probabilities of cancer-specific mortality in patients with PSC. The C-index of the model was 0.718, which illustrated an excellent outcome. In addition, the 3-year and 5-year calibration curves illustrated the high accuracy of the competing risk nomogram. Therefore, with known clinicopathological information, individual survival probabilities could be successfully estimated for patients diagnosed with PSC. This study was novel in considering the competing risk events and setting up a competing risk model for patients with PSC.

The findings of this study might offer a better way to predict the cancer-specific mortality of patients with PSC and a better understanding of the clinicopathological characteristics and outcomes of PSC. However, the study still had some limitations. First, the patients were all enrolled from the SEER database established by the NCI, and all of them were from the US. Therefore, the findings and the nomogram of the competing risk model might not be propitious to other countries. Second, SEER does not involve some important variables that may play significant roles in prognoses, such as smoking history, gene mutation information, and specific chemotherapy regimens. Third, PSC has 5 different subgroups. Pulmonary blastoma was proved to have better outcomes compared with other subtypes. However, in the SEER database, only a few patients were diagnosed with pulmonary blastoma, thereby leading to a selection bias affecting the outcomes of the survival analysis. Finally, the possible selection bias might exist because of the retrospective design, leading to a confounding effect in the analysis. Therefore, a multicenter cooperation of different countries to perform randomized control trials could be better for more accurate analysis.

Conclusion

In conclusion, PSC is a rare subtype of NSCLC, without clinicopathological characteristics specific to SCC or LAC but with a worse prognosis. PSC patients were commonly male, elderly, with massive tumor size and advanced tumor grade and stage. In the competing risk analysis, age, T stage, M stage, tumor size, surgery, and chemotherapy were independent risk factors for the PSC-specific mortality of patients with PSC. The nomogram can provide an individualized prediction for the survival of patients with PSC.

Author Contributions

J.Y. and B.H. were responsible for the design. G.A. and N.W. provided administrative support. Z.L., E.Z., and L.D. were for the collection and assembly of data. Z.L. and E.Z. were responsible for manuscript writing. All the authors approved the final manuscript. Our study did not require an ethical board approval because it did not contain human or animal trials.

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Supplemental Material

Supplemental material for this article is available online.

Reference

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