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Original Article

Clinical characteristics of primary pulmonary hemangiosarcoma outcomes: a Surveillance, Epidemiology, and End Results database analysis

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Abstract: Primary pulmonary hemangiosarcoma (PPHS) is an extraordinarily rare disorder. The objective of this study was to investigate the demographic characteristics and prognostic factors of patients with PPHS. Patients diagnosed with PPHS between 2000 and 2020 based on data from the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively analyzed. Survival analysis was performed using the survival package of R (4.2.0). Univariate and multivariate Cox proportional hazards models were used to analyze independent prognostic factors. A nomogram was constructed by the R Regression Modeling Strategies (rms) package. A total of 123 patients with PPHS were included in this study; their mean survival time was 13.8 months. Further investigation revealed that the disease-specific survival rates of patients with PPHS at 1, 2, 3, and 5 years were 20.17%, 14.29%, 10.08%, and 5.88% respectively. In the regression analysis, age, tumor status, and treatment were identified as risk factors for patients with PPHS. In addition, chemotherapy was crucial for the treatment of patients with PPHS ($P < 0.05$). Finally, the nomogram we constructed to predict 0.5-, 1-, 2-, and 3-year disease-specific survival in patients with PPHS showed good accuracy (concordance index: 0.769). Age, tumor laterality, and tumor size were independent factors affecting the prognosis of patients with PPHS, and chemotherapy may significantly improve the long-term prognosis.

Keywords: Primary pulmonary hemangiosarcoma, prognostic factors, chemotherapy

Introduction

Hemangiosarcoma/angiosarcoma is a rare va scular malignant tumor originating from endothelial cells. It is widely distributed in all organs, and most commonly develops in the skin of individuals [1, 2]. The highly aggressive and metastatic biological profile of hemangiosarcoma results in short patient survival [3]. At present, there are no effective treatment guidelines due to the rarity and genetic heterogeneity of the disease [4]. Research on hemangiomas remains inadequate, and identified risk factors include genetic mutations, radio therapy, and exposure to certain chemicals [5].

Primary pulmonary hemangiosarcoma (PPHS) is an extraordinarily rare disorder with an incidence rate of 0.001%-0.030%. Due to the difficulty in diagnosis and inadequate treatment, the mortality rate of patients with PPHS is very high [6, 7]. PPHS originates from pulmonary vascular endothelial cells, and is characterized by a high degree of malignancy and strong invasive ability even from the early stage of the disease; typical clinical symptoms include thoracalgia, hemoptysis, and dyspnea [8, 9]. Moreover, the pathogenesis of this disease has not been fully elucidated. It may be associated with chronic pulmonary infections, exposure to radio therapy, and exposure to certain chemical substances (such as vinyl chloride and radon). The incidence of PPHS is higher in males than females (average age of onset: 54.7 years) [10]. In terms of clinical examination, imaging meth-

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ods such as high-resolution chest computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) are helpful for lesion detection, prompt diagnosis, and staging, while bronchoscopy and puncture biopsy can be used for histopathologic diagnosis [10, 11]. The typical PPHS cytological signature is pleomorphic; these cells can be round, polygonal or spindle-shaped, with or without an epithelioid appearance, and with an atypical or irregular nucleus [1]. In addition, vascular endothelial markers are helpful in the diagnosis of PPHS; commonly used markers include CD31, CD34, and Friend leukemia virus integration 1 (FLI-1) [12].

Although PPHS is characterized by a high degree of malignancy, the number of cases is markedly lower than that of lung cancer. At present, most studies on PPHS diseases are case reports, and there are no trait analyses of the overall population. In addition, there is no standard treatment protocol for PPHS, and the currently recommended treatment includes surgery, radiotherapy, and chemotherapy [13]. In recent years, it has been reported that immunotherapy can improve the prognosis of such patients. Nevertheless, improvement in survival remains a challenge due to the high degree of malignancy of these tumors [14].

Given the rarity and high malignancy of PPHS, as well as the limitations of current research, the aim of this study was to investigate the clinical characteristics of this disease and identify risk factors associated with prognosis, based on data from the SEER database. The ultimate objective of this effort was to fill the gaps in existing research, and provide a reference for future studies and clinical practice.

Materials and methods

Patient selection

The inclusion criteria for patients with PPHS were as follows: 1) diagnosis between 2000 and 2020; 2) age ≥ 18 years; 3) initial diagnosis of hemangiosarcoma/angiosarcoma confirmed by pathology (primary site of the tumor: lung and bronchus), with an International Classification of Diseases for Oncology-3 code of 9120/3; and 4) absence of other tumors. The exclusion criteria were: 1) insufficient demographic information (e.g., sex, age, race, and marital status); 2) insufficient follow-up data; and 3) unclear cause of death.

Data collection

The data collected for patients with PPHS included age at diagnosis, sex, marital status, race, laterality, histologic grade, tumor size, T, N, distant metastases, surgery, radiotherapy, chemotherapy, summary stage, year of diagnosis, sequence number, survival time, and survival status.

Outcome measures

Disease-specific survival (DSS) was defined as the time from diagnosis to cancer-specific death or last follow-up, and was used as the primary endpoint of this study.

Statistical analysis

Categorical data (e.g., sex, laterality, and histologic grade) were summarized using frequencies and percentages. The comparisons among these categories were performed using chi-square test or Fisher's exact test to assess the statistical significance of observed differences. In addition, the survival curve, constructed by R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), was used to analyze the DSS of patients. Univariate and multivariate Cox proportional hazards models were used to analyze independent prognostic factors. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The prognostic assessment of patients with PPHS using clinical prediction models was based on nomograms and performed with the R Regression Modeling Strategies (rms) package. The discriminative ability of the model was evaluated using the concordance index (C-index); a C-index > 0.7 indicates excellent discriminative performance. p-values < 0.05 indicated a significant difference.

Results

Demographic and clinicopathological characteristics of PPHS

The incidence of PPHS in 2000-2020 was 1.3 per 100,000 individuals. A total of 123 patients with PPHS patients, 74 males (60.2%) and 49 females (39.8%), were included in this study. The main patient characteristics are shown in **Table 1**. The age of onset for 64 patients (52%)

Table 1. Comparison of baseline characteristics between patients who survived and those who died

Characteristic	Total	Alive	Dead	χ^2	*p*-value
Sex				1.000	0.317
Female	49 (39.8%)	2 (20%)	47 (41.6%)		
Male	74 (60.2%)	8 (80%)	66 (58.4%)		
Age at diagnosis				0.000	1.000
< 65 years	64 (52%)	5 (50%)	59 (52.2%)		
≥ 65 years	59 (48%)	5 (50%)	54 (47.8%)		
Marital status					0.315
Married	67 (54.5%)	7 (70%)	60 (53.1%)		
Single	21 (17.1%)	2 (20.0%)	19 (16.8%)		
Other	26 (21.1%)	0 (0.0%)	26 (23.0%)		
Unknown	9 (7.3%)	1 (10.0%)	8 (7.1%)		
Race					0.139
White	95 (77.2%)	7 (70.0%)	88 (77.9%)		
Black	15 (12.2%)	3 (30.0%)	12 (10.6%)		
Other	13 (10.6%)	0 (0.0%)	13 (11.5%)		
Laterality					0.349
Bilateral	11 (8.9%)	0 (0.0%)	11 (9.7%)		
Left	41 (33.3%)	6 (60.0%)	35 (31.0%)		
Right	65 (52.8%)	4 (40.0%)	61 (54.0%)		
Other	6 (4.9%)	0 (0.0%)	6 (5.3%)		
Histological grade					0.728
I	1 (0.8%)	0 (0.0%)	1 (0.9%)		
II	5 (4.1%)	0 (0.0%)	5 (4.4%)		
IV	24 (19.5%)	2 (20.0%)	22 (19.5%)		
VI	17 (13.8%)	0 (0.0%)	17 (15.0%)		
Unknown	76 (61.8%)	8 (80.0%)	68 (60.2%)		
Tumor size					0.070
< 3	17 (13.8%)	1 (10.0%)	16 (14.2%)		
3-5	23 (18.7%)	4 (40.0%)	19 (16.8%)		
≥ 5	21 (17.1%)	3 (30.0%)	18 (15.9%)		
Unknown	62 (50.4%)	2 (20.0%)	60 (53.1%)		
T stage					0.016*
T1	8 (6.5%)	3 (30.0%)	5 (4.4%)		
T2	5 (4.1%)	0 (0.0%)	5 (4.4%)		
T3	4 (3.3%)	1 (10.0%)	3 (2.7%)		
T4	6 (4.9%)	1 (10.0%)	5 (4.4%)		
Unknown	100 (81.3%)	5 (50.0%)	95 (84.1%)		
N stage					0.211
N0	17 (13.8%)	3 (30.0%)	14 (12.4%)		
N1	6 (4.9%)	1 (10.0%)	5 (4.4%)		
N2	1 (0.8%)	0 (0.0%)	1 (0.9%)		
Unknown	99 (80.5%)	6 (60.0%)	93 (82.3%)		
Distant metastases					0.234
Yes	40 (32.5%)	2 (20.0%)	38 (33.6%)		
No	32 (26.0%)	5 (50.0%)	27 (23.9%)		
Unknown	51 (41.5%)	3 (30.0%)	48 (42.5%)		

Surgery				0.000	1.000
Yes	48 (39%)	4 (40%)	44 (38.9%)		
No/Unknown	75 (61.0%)	6 (60%)	69 (61.1%)		
Radiotherapy				0.375	0.540
Yes	22 (17.9%)	3 (30%)	19 (16.8%)		
No/Unknown	101 (82.1%)	7 (70%)	94 (83.2%)		
Chemotherapy				0.544	0.461
Yes	54 (43.9%)	6 (60.0%)	48 (42.5%)		
No/Unknown	69 (56.1%)	4 (40.0%)	65 (57.5%)		
Summary stage					0.291
Distant	83 (67.5%)	5 (50.0%)	78 (69.0%)		
Localized	15 (12.2%)	3 (30.0%)	12 (10.6%)		
Regional	22 (17.9%)	2 (20.0%)	20 (17.7%)		
Unstaged	3 (2.4%)	0 (0.0%)	3 (2.7%)		
Year of diagnosis					0.055
2000-2006	35 (28.5%)	1 (10.0%)	34 (30.1%)		
2007-2013	36 (29.3%)	1 (10.0%)	35 (31.0%)		
2013-2020	52 (42.3%)	8 (80.0%)	44 (38.9%)		
Sequence number				0.030	0.861
1st	83 (67.5%)	6 (60.0%)	77 (68.1%)		
2nd	40 (32.5%)	4 (40.0%)	36 (31.9%)		

*P < 0.05.

was ≤ 65 years, and more than half (54.5%) were married. In terms of racial distribution, the majority were White (77.2%), and the remaining were Black (12.2%) and other races (10.6%). Regarding tumor laterality in the lungs, the tumors were located in the right, left, and bilateral lungs in 65, 41, and 11 cases, respectively. Among the 61 patients with histologic grades, 1 (0.8%), 5 (4.1%), 24 (19.5%), and 17 (13.8%) cases had grade I, II, III, and IV disease, respectively. Data on the size of the hemangiosarcoma were available for only half of the patients (i.e., < 3 cm: n = 17; 3-5 cm: n = 23; and ≥ 5 cm: n = 21). Unfortunately, T and N staging data were missing for most patients. Notably, 40 patients developed distant metastases (32.5%), including bone, brain, and liver. 32 patients did not develop metastases (26.0%). The treatment of PPHS included surgery (n = 48; 39%), radiotherapy (n = 22; 17.9%), and chemotherapy (n = 54; 43.9%). Summary stage is the definition of tumor invasion in the SEER database, including localized, regional, and distant. After statistical analysis, 83 (67.5%), 15 (12.2%), and 22 (17.9%) cases were classified as distant, localized, and regional, respectively; the remaining three cases had no staging. Importantly, the incidence of PPHS continued to increase over time. Unfortunately, 113 patients (91.9%) died from PPHS, and only 10 patients (8.1%) were still alive or died from other causes. Of note, T staging was significantly different between these two groups (P < 0.05).

Univariate and multivariable survival analyses

Univariate and multivariable survival analyses should be based on patients with PPHS with complete follow-up data. In this study, a total of 119 patients with PPHS had valid follow-up data, and their mean survival time was 13.8 months. Further investigation revealed that the DSS rates of patients with PPHS at 1, 2, 3, and 5 years were 20.17%, 14.29%, 10.08%, and 5.88% respectively. As shown in **Table 2**, univariate survival analysis showed that age, laterality, tumor size, surgery, and chemotherapy were associated with DSS (P < 0.05). However, other factors including histologic grade, T stage, N stage, radiotherapy, and distant metastasis did not affect survival. A multivariate survival analysis was performed, yielding partially similar results to those of the univariate regression analysis. Laterality, summary stage, tumor size, and distant metastasis were significantly associated with DSS (P < 0.05) (**Table 2**). Chemotherapy was identified as crucial for

Table 2. Univariate and multivariate analyses of DSS in patients with PPHS

Factor	Category	Univariate analysis			Multivariable analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	< 65/≥ 65 years	1.477	1.005-2.170	0.047*	1.389	0.853-2.261	0.187
Sex	Female/Male	0.912	0.619-1.344	0.643	1.077	0.680-1.706	0.751
Race	White			0.569			0.372
	Black	1.123	0.611-2.064	0.708	1.107	0.534-2.295	0.785
	Other	1.365	0.757-2.462	0.301	1.675	0.816-3.436	0.159
Laterality	Right			0.050			0.192
	Bilateral	2.323	1.172-4.603	0.016*	2.285	1.071-4.761	0.032*
	Left	0.843	0.551-1.291	0.432	1.136	0.682-1.893	0.624
	Other	1.224	0.490-3.062	0.665	0.982	0.348-2.766	0.972
Histological grade	Unknown			0.717			0.343
	Grade 2	0.586	0.234-1.463	0.252	1.812	0.571-5.754	0.313
	Grade 3	0.928	0.570-1.512	0.766	1.366	0.747-2.498	0.311
	Grade 4	0.920	0.538-1.574	0.762	1.682	0.894-3.164	0.107
Summary stage	Unstaged			0.071			0.035*
	Distant	0.458	0.111-1.885	0.280	0.284	0.064-1.270	0.100
	Localized	0.250	0.054-1.150	0.075	0.109	0.019-0.620	0.012*
	Regional	0.293	0.067-1.281	0.103	0.338	0.065-1.753	0.196
T stage	Unknown			0.785			0.338
	T1	0.876	0.355-2.163	0.774	1.246	0.306-5.063	0.759
	T2	0.905	0.367-2.231	0.828	3.681	0.969-13.981	0.056
	T3	1.026	0.324-3.252	0.966	1.103	0.295-4.126	0.884
	T4	0.518	0.190-1.415	0.199	0.633	0.132-3.024	0.566
N stage	Unknown			0.413			0.127
	N0	1.045	0.582-1.877	0.882	0.775	0.281-2.134	0.622
	N1	0.476	0.174-1.299	0.147	0.595	0.120-2.953	0.525
	N2	0.418	0.058-3.021	0.387	0.048	0.004-0.591	0.018*
Surgery	Yes/No, Unknown	1.559	1.045-2.325	0.029*	1.653	0.920-2.969	0.093
Radiotherapy	Yes/No, Unknown	1.537	0.925-2.556	0.097	1.137	0.576-2.242	0.712
Chemotherapy	Yes/No, Unknown	1.679	1.137-2.479	0.009*	3.320	2.030-5.429	0.000*
Tumor size	Unknown			0.174			0.136
	≥ 5 cm	0.717	0.421-1.222	0.222	0.752	0.391-1.445	0.392
	< 3 cm	0.862	0.487-1.527	0.611	0.740	0.371-1.476	0.393
	3-5 cm	0.569	0.337-0.961	0.035*	0.467	0.247-0.882	0.019*
Distant metastases	Yes			0.122			0.035*
	No	0.650	0.391-1.082	0.098	0.523	0.273-1.001	0.050
	Unknown	0.651	0.415-1.021	0.062	0.470	0.259-0.852	0.013*

*P < 0.05. CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; PPHS, primary pulmonary hemangiosarcoma.

patients with PPHS. Both univariate and multivariate regression analyses showed that patients who received chemotherapy had a better prognosis than those who did not receive chemotherapy (P < 0.01).

This study also analyzed risk factors within age and summary stage subgroups (**Table 3**). For patients aged < 65 years, summary stage, N stage, and distant metastasis were significantly associated with DSS. For those aged ≥ 65 years, sex, summary stage, and tumor size were significantly associated with DSS (P < 0.05). In addition, chemotherapy was the most important factor in both subgroups (P < 0.01). For patients aged ≥ 65 years, radiotherapy also

Table 3. Multivariate analyses of DSS in patients stratified by age

Factor	Category	Multivariable analysis					
		Patients aged < 65 years			Patients aged ≥ 65 years		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Sex	Female/Male	0.660	0.321-1.356	0.258	3.102	1.232-7.811	0.016*
Race	White			0.072			0.529
	Black	1.972	0.520-7.477	0.318	1.264	0.319-5.014	0.739
	Other	4.216	1.225-14.507	0.022*	2.558	0.499-13.103	0.260
Laterality	Right			0.827			0.172
	Bilateral	1.490	0.362-6.130	0.581	3.252	0.872-12.126	0.079
	Left	1.453	0.623-3.389	0.388	0.806	0.291-2.229	0.677
	Other	1.344	0.141-12.810	0.797	0.716	0.136-3.762	0.693
Histologic grade	Unknown			0.997			0.999
	Grade 2	0.976	0.247-3.851	0.972			
	Grade 3	1.106	0.324-3.771	0.872	1.018	0.372-2.787	0.972
	Grade 4	1.084	0.433-2.714	0.863	0.985	0.343-2.826	0.977
Summary stage	Unstaged			0.069			0.102
	Distant	0.066	0.006-0.704	0.024*	0.201	0.016-2.509	0.213
	Localized	0.022	0.001-0.366	0.008*	0.040	0.002-0.831	0.038*
	Regional	0.086	0.007-1.109	0.060	0.166	0.012-2.280	0.179
T stage	Unknown			0.417			0.878
	T1	0.676	0.058-7.822	0.754	0.363	0.017-7.861	0.519
	T2	10.654	0.820-138.428	0.071	1.165	0.088-15.518	0.908
	T3	0.368	0.026-5.120	0.456	1.648	0.270-10.062	0.589
	T4	1.311	0.097-17.791	0.839	0.299	0.014-6.433	0.441
N stage	Unknown			0.074			0.570
	N0	0.411	0.099-1.714	0.222	3.037	0.360-25.651	0.308
	N1	0.349	0.029-4.231	0.409	1.532	0.025-93.490	0.839
	N2	0.016	0.001-0.513	0.019*			
Surgery	Yes/No, Unknown	1.362	0.483-3.835	0.559	1.456	0.548-3.867	0.451
Radiotherapy	Yes/No, Unknown	1.673	0.652-4.293	0.284	0.146	0.032-0.674	0.014*
Chemotherapy	Yes/No, Unknown	3.727	1.654-8.397	0.002*	9.476	2.866-31.328	0.000*
Tumor size	Unknown			0.251			0.116
	< 3 cm	1.415	0.468-4.282	0.539	0.758	0.257-2.239	0.617
	≥ 5 cm	0.801	0.302-2.127	0.656	0.330	0.100-1.090	0.069
	3-5 cm	0.428	0.161-1.134	0.088	0.257	0.071-0.931	0.039*
Distant metastases	Yes			0.001*			0.691
	No	0.181	0.041-0.813	0.026*	0.787	0.248-2.499	0.685
	Unknown	0.171	0.068-0.426	0.000*	1.170	0.344-3.980	0.802

*P < 0.05. CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio.

improved outcomes (P < 0.05). For patients with local and regional PPHS, low pathologic grade and surgery similarly improved prognosis (P < 0.05) (**Table 4**). Of note, chemotherapy significantly improved patient prognosis regardless of the tumor status (i.e., *in situ* or metastatic) (P < 0.01).

Furthermore, we constructed a Kaplan-Meier survival curve based on the aforementioned prognostic factors. **Figure 1** shows that the prognosis of patients aged < 65 years and of those with distant metastasis was poor (P < 0.05 for both). However, treatment with chemotherapy (P < 0.01) and surgery (P < 0.05) improved patient prognosis.

Finally, to enhance the applicability of the clinical prediction model, we developed a nomogram to predict 0.5-, 1-, 2-, and 3-year DSS in

Table 4. Multivariate analyses of DSS in patients stratified by summary stage

Factor	Category	Multivariable analysis					
		Localized/Regional stage			Distant stage		
		HR	95% CI	*p*-value		HR	95% CI	*p*-value
Age	< 65/≥ 65 years	0.345	0.080-1.489	0.154		0.844	0.464-1.537	0.580
Sex	Female/Male	0.877	0.133-5.805	0.892		1.197	0.683-2.099	0.530
Race	White			0.379				0.379
	Black	0.000	0.000	0.974		1.456	0.625-3.392	0.384
	Other	9.771	0.395-241.946	0.164		1.666	0.764-3.635	0.199
Laterality	Right/Left	0.461	0.062-3.423	0.449	Right			0.402
					Bilateral	1.935	0.888-4.217	0.097
					Left	1.046	0.550-1.989	0.891
					Other	0.978	0.330-2.892	0.967
Histologic grade	Unknown			0.069				0.301
	Grade 2	0.004	0.000-0.595	0.030*		1.326	0.273-6.437	0.726
	Grade 3	2.855	0.665-12.268	0.158		1.229	0.555-2.722	0.611
	Grade 4	0.652	0.089-4.793	0.674		2.120	0.980-4.584	0.056
T stage	Unknown			0.193				0.898
	T1	1.582	0.010-243.747	0.858		0.785	0.134-4.604	0.789
	T2	16.128	0.447-581.381	0.128				
	T3	0.505	0.054-4.697	0.548		1.594	0.145-17.509	0.703
	T4	584.618	1.152-296777.331	0.045*		0.585	0.114-3.006	0.521
N stage	Unknown			0.038*				0.418
	N0	0.014	0.000-2.301	0.101		1.004	0.346-2.911	0.994
	N1	7.509	0.071-789.072	0.396		0.258	0.034-1.931	0.187
	N2	0.003	0.000-0.824	0.043*				
Surgery	Yes/No, Unknown	18.535	2.534-135.602	0.004*		0.960	0.466-1.977	0.912
Radiotherapy	Yes/No, Unknown	4.969	0.889-27.777	0.068		0.717	0.325-1.585	0.411
Chemotherapy	Yes/No, Unknown	14.727	2.652-81.793	0.002*		3.074	1.620-5.834	0.001*
Tumor size	Unknown			0.405				0.172
	< 3 cm	2.135	0.149-30.495	0.576		0.788	0.326-1.908	0.598
	≥ 5 cm	0.292	0.30-2.858	0.290		0.633	0.271-1.479	0.291
	3-5 cm	1.253	0.127-12.345	0.847		0.416	0.188-0.919	0.030
Distant metastases	No/Unknown	0.484	0.130-1.802	0.279	Yes			0.195
					No	0.609	0.285-1.302	0.201
					Unknown	0.581	0.300-1.125	0.107

*$P < 0.05$. CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio.

patients with PPHS (**Figure 2A**). The C-index of the nomogram was 0.769 (> 0.7 indicates a better prediction model). Furthermore, **Figure 2B** shows that the calibration and reference lines almost overlapped, confirming the good performance of the predictive model.

Discussion

PPHS, a type of malignant tumor of the lungs, has a low incidence rate and a high degree of malignancy. The investigation of PPHS is currently limited. Few basic research studies have focused on PPHS, and the existing relevant literature mostly consists of case reports. Case reports do not include clinicopathological feature analysis and follow-up. Hence, their usefulness for an in-depth study of PPHS is limited. Therefore, to fully investigate PPHS, we retrospectively analyzed the clinical features, treatment, and prognostic factors of patients with PPHS based on data from the SEER database.

In this study, 123 patients with PPHS were analyzed. The majority of those patients were diagnosed with PPHS based on autopsy. The relative inadequacy of diagnosis and screening results in a low detection rate. The incidence of

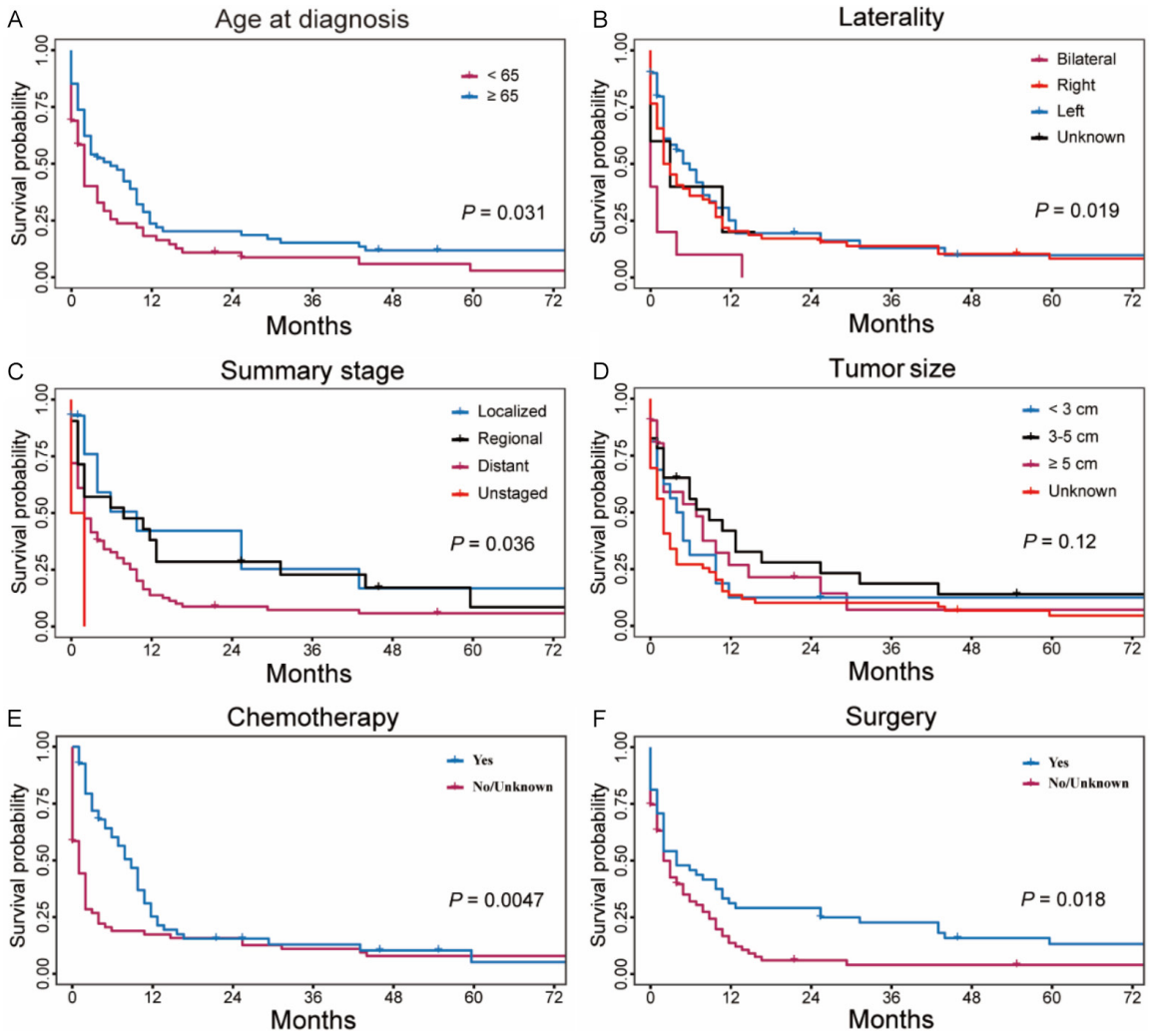

Figure 1. Kaplan-Meier estimated DSS in patients with PPHS stratified by age (A), tumor laterality (B), summary stage (C), tumor size (D), chemotherapy (E), and surgery (F). DSS disease-specific survival; PPHS, primary pulmonary hemangiosarcoma.

PPHS is very low, and its etiology remains unknown. Moreover, the early clinical manifestations are not specific, thereby complicating the diagnosis. Screening by imaging and biomarker analysis facilitates the detection and diagnosis of PPHS. At present, CT and PET-CT have made great contributions to the screening, staging, and follow-up of PPHS [15]. CT, particularly high-resolution CT, plays an important role in the early screening of PPHS; the advantage of PET-CT lies in the early detection of lesions and the evaluation of curative effect [16, 17]. In recent years, magnetic resonance imaging and transesophageal echocardiography have also been used in PPHS. Nonetheless, they have not been widely used due to simple medical record reports or the small numbers of samples included in clinical analyses. Since the imaging findings of patients with PPHS are not specific, it is often difficult to distinguish them from diseases such as tuberculosis and other types of metastatic tumors. Therefore, imaging data can only provide a certain reference for the diagnosis of this disease.

As vascular endothelial cells, PPHS can express endothelial markers, such as CD31, CD34, FLI-1, and cytokeratin (CK). Among them, CD31 is relatively specific but extremely sensitive [18]. Histopathologic analysis remains the gold standard for the diagnosis of malignancy. Use of hematoxylin and eosin staining alone for the diagnosis of primary pulmonary angiosarcoma is very difficult. Hence, the combination

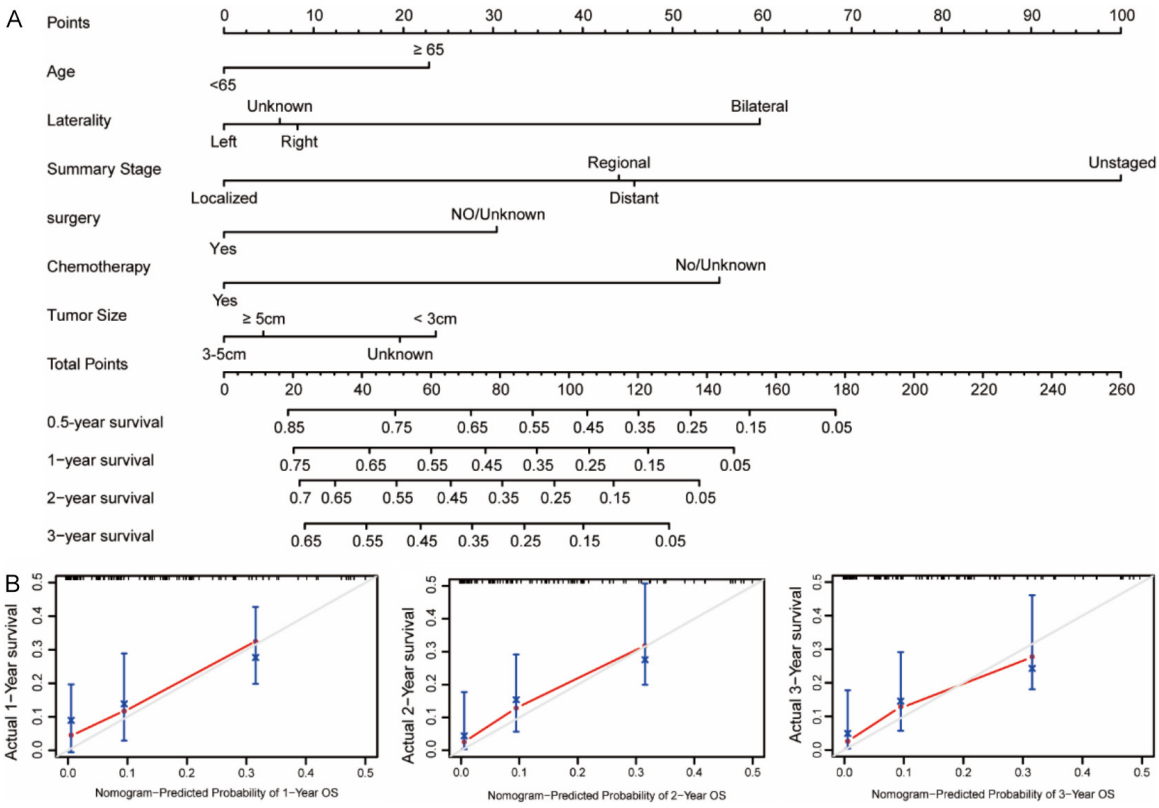

Figure 2. A. Nomogram predicting 0.5-, 1-, 2-, and 3-year DSS in patients with primary pulmonary hemangiosarcoma. B. Calibration plots of the nomogram for DSS prediction. DSS disease-specific survival; OS, overall survival.

of these approaches with immunohistochemistry (CD34, CD31, factor VIII-related antigen [VIII -Ag], S-100, HMB - 45, epithelial membrane antigen [EMA], CK, thyroid termination factor [TTF]) is important for certainty. The prognosis of patients with hemangiosarcoma is extremely poor, with an average survival time of < 1 year for those with PPHS [19]. In this study, the average survival time of patients with PPHS was only 13.8 months. This longer survival may be related to the availability of more treatment options. In the regression analysis, age, tumor status, and treatment were identified as risk factors for patients with PPHS. Clinically, PPHS needs to be differentiated from lung cancer (both small cell and non-small cell types), pulmonary sarcoma, and pulmonary lymphoma [6, 21, 22].

In terms of pathology, PPHS originates from pulmonary vascular endothelial cells, pulmonary sarcoma arises from interstitial tissues of the lung (e.g., smooth muscle and fibrous tissue), and pulmonary lymphoma originates from lymphoid tissue. Regarding clinical manifestations, all three conditions can present with cough, dyspnea, and chest pain, while hemoptysis is more commonly associated with PPHS. In terms of imaging, PPHS is characterized by multiple pulmonary nodules or consolidation, pulmonary sarcoma typically manifests as single or multiple pulmonary nodules, and pulmonary lymphoma is characterized by hilar or mediastinal lymphadenopathy and pulmonary parenchymal infiltration. In terms of prognosis, the average survival time of PPHS is less than 1 year. Pulmonary sarcoma has a 5-year survival rate mostly ranging between 10% and 30%. Pulmonary lymphoma has a more diverse prognosis, with 5-year survival rates for Hodgkin's lymphoma and non-Hodgkin's lymphoma of 60%-80% and 30%-50%, respectively.

Both survival and regression analyses showed that patients aged < 65 years had a worse prognosis than those aged ≥ 65 years. A possible reason for this observation is that older patients tend to have insufficient functional reserves. The poor prognosis linked to bilateral-lung tumors may be associated with the large

tumor burden [20]. However, there were no statistically significant differences observed in common tumor status indicators, such as stage and grade, which may have ben caused by missing follow-up data. Similar to other tumors, treatment options for PPHS include surgery, radiotherapy, and chemotherapy [21]. The results suggested that chemotherapy could significantly improve the prognosis of patients with PPHS. At present, the chemotherapy regimen for hemangiosarcoma includes doxorubicin, ifosfamide, and paclitaxel [22]. Findings from retrospective studies suggested that paclitaxel improves survival in patients with cutaneous hemangiosarcoma [23-25].

Although PPHS is a vascular endothelial disease, antivascular endothelial growth factor (antiVEGF) therapy has not shown efficacy [2, 26]. In recent years, the advent of immunotherapy has achieved great progress in antitumor therapy, and studies showed that immune checkpoint inhibitors can improve the prognosis of patients with hemangiosarcoma [27]. Nonetheless, surgery remains the first treatment choice for hemangiosarcoma [26]. In terms of subgroups, patients aged ≥ 65 years may benefit from radio therapy (P = 0.014), while those with local and regional PPHS may benefit from surgery (P = 0.004). Importantly, the survival analysis suggested that patients with bilateral-lung tumors (P = 0.019) and distant metastases (P = 0.036) have a very poor prognosis, which may be associated with the larger tumor burden in the body. Moreover, both surgery (P = 0.018) and chemotherapy (P = 0.0047) can improve the prognosis of patients with PPHS. Based on the above analysis, patients with PPHS in specific subgroups may benefit from more tailored treatment plans.

For patients aged < 65 years with bilateral- lung tumors or distant metastases, the prognosis is generally poor. Hence, more aggressive treatment strategies, such as combination therapies, may be warranted. In contrast, for patients aged ≥ 65 years, treatment tolerance and priorities may differ, necessitating adjusted treatment plans. Additionally, for patients who are ineligible for surgery, the combination of radiotherapy and chemotherapy may offer additional therapeutic benefits [28-30]. The limitation of this analysis is that the database does not include information on the exact chemotherapy regimen administered to the patients. Notably, there has been an increasing number of reports on the treatment and prognosis of PPHS. Lin et al. reported a male patient with recurrent and metastatic PPHS after surgery who achieved a sustained remission of 6 months with liposomal doxorubicin treatment [6]. Basiri et al. reported that pazopanib and paclitaxel were used to treat a female patient with PPHS; however, due to the critical condition of the patient, she survived for approximately 1 month [31]. Luan et al. retrospectively analyzed 11 patients with PPHS. The longest survival (i.e., 44 months) was observed in a patient who received surgery followed by chemotherapy with cyclophosphamide, doxorubicin, and vincristine; the remaining patients received chemotherapy with or without vascular-targeted drugs [32]. Wei et al. demonstrated that the combination of paclitaxel and gemcitabine could reduce tumor size and improve clinical symptoms [33].

The nomogram developed in this study is capable of predicting 0.5-, 1-, 2-, and 3-year DSS based on individual patient characteristics, thus providing clinicians with a practical tool for prognostic assessment. The model exhibited good predictive accuracy, with a C-index of 0.769. The calibration curves further demonstrated that the nomogram performed well in estimating survival probabilities. This tool may assist clinicians in making more informed treatment decisions and help patients gain a better understanding of their prognosis.

This study had several limitations. First, the follow-up data for some patients in the SEER database are missing; hence, the regression analysis may have failed to fully reflect the influence of certain prognostic factors. The absence of T and N stage data were particularly common, and this may have affected the accuracy of the prognostic analysis. Since T and N stages are important indicators for tumor staging, lack of these data may lead to inaccurate assessment of patient conditions, thereby influencing the identification of prognostic factors and risk assessment. Second, although this study demonstrated the importance of chemotherapy in the treatment of patients with PPHS, the specific chemotherapy regimens received by the patients were not provided in the database. This limits further analysis and comparison of the efficacy of different chemotherapy regimens. In addition, despite the large amount of data analyzed in this study from the SEER

database, the database itself has certain limitations, such as the lack of some clinical characteristics (e.g., functional status of patients, comorbidities) and treatment details (e.g., extent of surgery, radiation dose). The lack of this information may not allow a more comprehensive assessment of patient prognosis. Finally, due to the retrospective nature of this study, it is subject to inherent selection and information biases. Future prospective studies are required to further validate the findings of this study and to explore the optimal treatment strategies for PPHS.

Conclusions

Through an analysis of the clinicopathologic characteristics of patients of PPHS using data from the SEER database, this study showed that age, tumor laterality, and tumor size were independent factors affecting the prognosis of patients with PPHS, and chemotherapy may significantly improve the long-term prognosis of such patients.

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Disclosure of conflict of interest

None.

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