Original Article

Clinical characteristics of primary hepatic angiosarcoma outcomes: a SEER database analysis

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Background: Primary hepatic angiosarcoma (PHA) is a rare malignant tumor. We explored the demographic features and prognostic factors of PHA.

Methods: We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to extract patients diagnosed with PHA from 1975 to 2016. We used the Kaplan-Meier method and Cox proportional hazards regression to evaluate the risk factors for overall survival (OS) and disease-specific survival (DSS). The nomograms were constructed and validated using the concordance index (C-index) and calibration plots.

Results: In total, 366 patients were included in this study. The disease onset was hidden, and most patients already had advanced disease when diagnosed. The prognosis of PHA was very poor, and the overall 6-month, 1-year and 2-year survival rates were 20.3%, 12.8% and 9.3%, respectively. Sex, age and surgery were all predictors of both OS and DSS in multivariate analysis. Women had better survival rates than men, and patients aged <60 years benefited from surgery in the multivariate models. The nomograms presented good accuracy, with C-index values of 0.679 and 0.665 for the OS and DSS prognostic models, respectively. The calibration plots showed good agreement between the nomogram predictions and actual observations.

Conclusions: PHA has a poor prognosis. Regular physical examinations are essential for the elderly. Patients aged <60 years could benefit from surgery. We constructed accurate nomograms to predict survival that can greatly benefit clinicians.

Keywords: Angiosarcoma; Surveillance, Epidemiology, and End Results program (SEER program); survival

Submitted Aug 23, 2020. Accepted for publication Nov 20, 2020.
doi: 10.21037/tcr-20-2780
View this article at: http://dx.doi.org/10.21037/tcr-20-2780

Introduction

Angiosarcoma is a malignant tumor that originates from vascular endothelial cells. Approximately 5.4% of cutaneous soft tissue sarcomas and 2% of soft tissue sarcomas are angiosarcomas. Angiosarcomas are widely distributed in the body, such as in the head and neck, breast, extremities, trunk, liver, heart, bone and spleen (1,2). Primary hepatic angiosarcoma (PHA) is an extremely rare malignant neoplasm and accounts for only approximately 1% of primary malignant liver tumors (3). PHA has no specific etiologic agent in most patients, while exposure to vinyl chloride and ionizing radiation may be important risk factors (4,5). Clinically, PHA shows various symptoms, such as abdominal pain, anorexia, fatigue, weight loss, fever, low back pain, jaundice, hemoperitoneum and acute

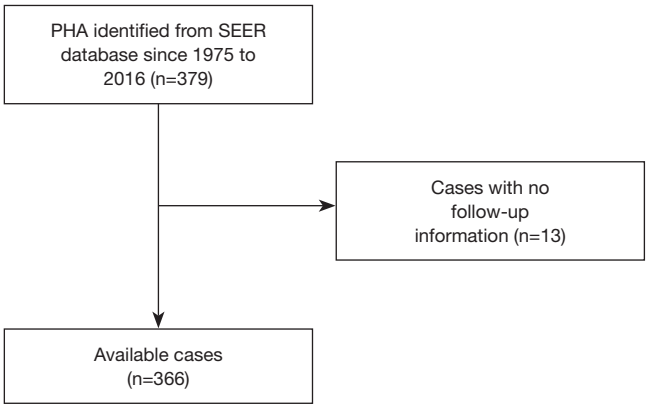

Figure 1 Schematic overview for patient identification. PHA, Primary hepatic angiosarcoma; SEER, Surveillance, Epidemiology, and End Results.

hepatic failure, although these symptoms are nonspecific (6,7). Often, no specific symptoms are observed, and the levels of tumor markers are usually not elevated in the early stages of the disease, such as alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and cancer antigen 125 (CA125), making PHA difficult to diagnose (8). Histopathological diagnosis is the gold standard for PHA. In hematoxylin and eosin staining, the neoplastic cells are represented as marked nuclear pleomorphism with a spindle shape. Endothelial markers such as CD31, CD34 and ERG are reliable immunohistochemical markers (9,10). The nonspecific symptoms of PHA and rapid progression result in a poor prognosis (11). PHA has a median survival of no more than 6 months (12). Surgery is usually the preferred method of treatment, and surgery combined with chemotherapy or chemotherapy alone are other choices in the clinical setting (13-15). However, no effective treatment guidelines have been established because of the low incidence and aggressive nature of PHA.

Currently, most studies are case reports and case series due to the rarity of PHA and are seriously limited by small patient numbers. Demographic and clinical prognostic factors were rarely considered. The Surveillance, Epidemiology, and End Results (SEER) database can overcome the problem of insufficient sample size (16). It covers approximately 28% of the United States population. In this study, we analyzed the demographics and tumor characteristics of patients with PHA and the outcomes of overall and disease-specific survival (DSS); our findings will benefit clinicians and future studies. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2780).

Methods

Data source

We retrieved data from the latest version of the SEER 18 database released in August 2019 using SEER*Stat software (version 8.3.6). All patient information was deidentified and publicly available, so institutional review board approval was not needed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient selection

The inclusion criteria were as follows: patients with tumors located in the liver (site and morphology, TNM 7/CS v0204+ Schema = liver); patients with angiosarcoma, as defined by the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) with the morphological code 9120; patients with specific prognostic data (*Figure 1*).

Covariates

First, demographic data, such as the age at diagnosis, sex, race and marital status, were collected. Next, we collected tumor characteristics, such as historic stage, CS tumor size, CS extension, CS lymph and CS metastasis. Finally, the treatment, survival months, status and cause of death were obtained. Age was categorized into <50, 50–59, 60–69, 70–79 and ≥80 years. Sex was classified as male or female. Year of diagnosis was coded as <2,000 or ≥2,000 and further categorized into 1975–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014 and 2014–2016. Marital status was categorized as married (including common law), single (never married), other (including separated, divorced and widowed) and unknown. We coded race as white, black and American Indian/AK Native, Asian/Pacific Islander. Because of the small sizes of the latter two groups, they were combined into the category of "other". The historic stage was classified as localized, regional, distant and unknown. Tumor sizes were coded as <5 cm, ≥5 cm and unknown. CS extension was categorized as T1, T2, T3, T4 and unknown. The AJCC stage was derived from the AJCC TNM 6th edition and defined as 1, 2, 3 or 4. DSS was defined as the time from diagnosis to death caused by

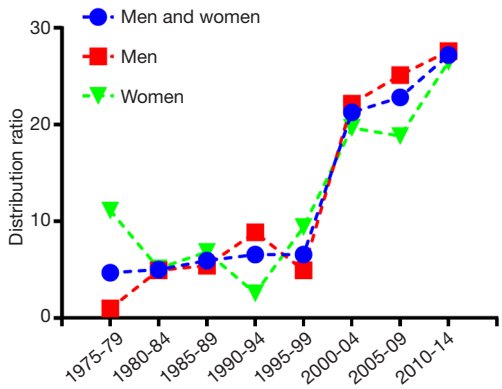

Figure 2 Analysis distribution of primary hepatic angiosarcoma patients from 1975 to 2014.

PHA. Overall survival (OS) was defined as the time from diagnosis to death from any cause.

Statistical analysis

The baseline characteristics were compared using chi-squared test. Kaplan-Meier curves were constructed to estimate the OS and DSS, and log-rank tests were used to determine the significance of any differences. Univariate and multivariate Cox proportional hazards analyses were used to determine the independent prognostic predictors for OS and DSS, and the hazard ratios and 95% confidence intervals were shown. We used SPSS ver. 20.0 (IBM Corporation) and GraphPad Prism ver. 7.02 to conduct statistical analysis. A P value <0.05 was considered statistically significant.

A nomogram for the final prognostic factors associated with the 6-month and 1-year survival rates was established. The predictive performance was evaluated using the concordance index (C-index) and calibration plots to compare the nomogram predictions with the observed outcomes. R software ver.3.6.1 was used to construct the nomograms.

Results

Demographic and clinicopathological characteristics of PHA

As shown in *Figure 2*, we computed the number of PHA patients in 5-year intervals (1975–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014) and found increasing trends in the number of both men and women.

As shown in *Table 1*, 366 patients were included in this study, 235 men and 131 women, at a ratio of 1.79:1. The patients were mainly middle-aged and elderly at the time of diagnosis, and the average age of PHA patients was 62.2 years. Additionally, 79.2% of the patients were older than 50 years and 13.7% were older than 80 years. The race distribution was white (79.0%), black (4.6%) and other (16.4%), indicating that this study mainly reflected the characteristics of white Americans. Most patients were married (58.2%), and 16.7% of the subjects were single. Most of the patients were diagnosed after the year 2000, but this finding does not indicate an increase in the incidence. Tumor sizes were categorized into <5 cm, ≥5 cm and unknown, and the proportions were 6.6%, 26.0% and 67.5%, respectively. Regarding to tumor extent, most of the patients were in stage T2, although some were missing these data. Most of the patients did not have lymph node metastasis. Among those with AJCC stages recorded, 10.1% had stage I, 19.9% had stage II, 2.5% had stage III and 16.9% had stage IV disease. Regarding the historic stage, 24.6% of the patients had local stage disease, 26.0% had regional stage disease, and 111 (30.3%) patients had distant stage disease. Regarding treatment, nearly six times as many patients (64.8%) did not receive surgery as those who received surgery (11.2%). We compared the patients' baseline characteristics between those who died because of the tumor and those who survived or died because of unrelated causes, and differences were found in year of diagnosis, tumor size, distant metastasis and surgery.

Survival

The prognosis of PHA was very poor (*Table 2*), with a median survival of only 1 month. The overall 6-month, 1-year and 2-year survival rates were 20.3% (95% CI: 16.2–24.4%), 12.8% (95% CI: 9.3–16.3%) and 9.3% (95% CI: 6.2–12.4%), respectively. The disease-specific 6-month, 1-year and 2-year survival rates were 13.6% (95% CI: 9.5–17.7%), 6.4% (95% CI: 3.5–9.6%) and 3.4% (95% CI: 1.2–5.6%), respectively.

In univariate analysis, sex, age and surgery were all predictors of both OS and DSS (*Table 3* and *Figure 3*). Male patients had a worse prognosis than female patients. In general, the younger patients had better survival than the older patients. Survival was significantly better for patients who had undergone surgery than for those who did not.

Table 1 Comparison of the baseline patient characteristics between patients who died because of the tumor and those who survived or died because of unrelated causes

Characteristic	Total	Tumor-related death	Alive or unrelated cause of death	P value
Sex				0.237
Male	235 (64.2%)	175	60	
Female	131 (35.8%)	90	41	
Age, years				0.396
<50	74 (20.2%)	56	18	
50–59	69 (18.9%)	48	21	
60–69	88 (24.0%)	69	19	
70–79	85 (23.2%)	56	29	
>80	50 (13.7%)	36	14	
Race				0.869
White	289 (79.0%)	206	83	
Black	17 (4.6%)	13	4	
Other	60 (16.4%)	46	14	
Marital status				0.577
Marred	213 (58.2%)	157	56	
Single	61 (16.7%)	41	20	
Other	79 (21.6%)	59	20	
NA	13 (3.6%)	8	5	
Year of diagnosis				0.011
<2000	92 (25.1%)	76	16	
≥2000	274 (74.9%)	189	85	
Tumor size				0.004
<5 cm	24 (6.6%)	11	13	
≥5 cm	95 (26.0%)	65	30	
NA	247 (67.5%)	189	58	
Tumor extent				0.060
T1	47 (12.8%)	29	18	
T2	107 (29.2)	74	33	
T3	1 (0.3%)	0	1	
T4	11 (3.0%)	10	1	
NA	200 (54.6%)	152	48	
LN metastasis				0.100
No	193 (52.7%)	131	62	
Yes	8 (2.2%)	7	1	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Total	Tumor-related death	Alive or unrelated cause of death	P value
NA	165 (45.1%)	127	38	
Distant metastasis				
No	165 (45.1%)	127	38	<0.001
Yes	139 (38.0%)	92	47	
NA	62 (16.9%)	46	16	
AJCC TNM stage				
I	37 (10.1%)	24	13	
II	73 (19.9%)	47	26	0.290
III	9 (2.5%)	7	2	
IV	62 (16.9%)	46	16	
NA	185 (50.5%)	141	44	
Historic stage				
Local	90 (24.6%)	59	31	
Regional	95 (26.0%)	68	27	0.077
Distance	111 (30.3%)	90	21	
NA	70 (19.1%)	48	22	
Surgery				
No	237 (64.8%)	168	69	
Yes	41 (11.2%)	25	16	0.032
NA	88 (24.0%)	72	16	

Na, not available; LN metastasis, lymph node metastasis.

Table 2 Overall survival and disease-specific survival as estimated by Kaplan-Meier analysis

Variables	6-month, % (95% CI)	1-year, % (95% CI)	2-year, % (95% CI)
Overall survival (OS)	20.3 (16.2–24.4)	12.8 (9.3–16.3)	9.3 (6.2–12.4)
Disease-specific survival (DSS)	13.6 (9.5–17.7)	6.4 (3.5–9.6)	3.4 (1.2–5.6)

Tumor size and historic stage were predictors of OS but not DSS. However, tumor extent, LN metastasis, distant metastasis and TNM stage did not significantly influence survival.

To further study the prognostic factors for PHA, we constructed multivariate models for OS and DSS. Women had better OS than men (P=0.018), and sex had a significant effect on DSS (P=0.043; *Table 4*). Multivariate analysis revealed that age was an important factor affecting survival. We divided the patients into two age groups: <60 years and ≥60 years; we then studied their baseline characteristics. The basic characteristics of the two groups were similar, and no significant difference was found in the composition (*Table 5*). Overall, older patients had a worse prognosis than younger patients. Tumor size was a predictor of OS but not DSS. Patients with a distant historic stage had worse OS than those with a local historic stage. Patients who received surgery had a much better prognosis than those who did not. However, TNM stage was not significantly correlated with prognosis.

Table 3 Univariate analyses of overall survival and disease-specific survival in PHA patients

Variables	DSS			OS		
	6-month, % (95% CI)	1-year, % (95% CI)	P value	6-month, % (95% CI)	1-year, % (95% CI)	P value
Sex			0.002			0.005
Male	16.1 (11.4–20.8)	10.1 (6.2–14.0)		10.3 (5.8–14.8)	4.6 (1.5–7.7)	
Female	27.9 (20.1–35.7)	17.8 (11.1–24.5)		20 (11.8–23.2)	10 (3.7–16.3)	
Age, years			<0.001			<0.001
<50	39.2 (28.0–50.4)	30.8 (20.2–41.4)		28.6 (16.8–40.4)	17.9 (7.9–27.9)	
50–59	30.6 (19.6–41.6)	17.8 (8.4–27.2)		18.8 (7.8–29.8)	6.3 (0–13.2)	
60–69	16.5 (8.7–24.3)	9.7 (3.1–16.1)		10.1 (3.0–17.2)	2.9 (0–6.8)	
70–79	7.5 (1.8–13.2)	2.5 (0–5.8)		5.4 (0–11.3)	3.6 (0–8.5)	
>80	6 (0–14.2)	0		2.8 (0–8.1)	0	
Race			0.896			0.659
White	21.3 (16.6–26.0)	12.9 (9.0–16.8)		13.6 (8.9–18.3)	5.8 (2.7–8.9)	
Black	17.6 (0–35.6)	0		23.1 (0.2–46.0)	7.7 (0–22.2)	
Other	21.3 (12.3–33.9)	14.2 (5.2–23.2)		10.9 (1.9–19.9)	8.7 (0.5–16.9)	
Marital status			0.062			0.170
Marred	24.3 (18.4–30.2)	13.5 (8.6–18.4)		19.7 (13.4–26.0)	8.3 (4.0–12.6)	
Single	25.9 (14.7–37.1)	22.1 (11.3–32.9)		9.8 (0.8–188)	7.3 (0–15.3)	
Other	7.6 (1.7–13.5)	3.8 (0–8.1)		1.7 (0–5.0)	0	
NA	7.7 (0–22.2)	0		0	0	
Year of diagnosis			0.336			0.082
<2000	21.7 (13.3–30.1)	13.0 (6.1–19.9)		21.1 (11.9–30.3)	13.2 (5.6–20.8)	
≥2000	19.8 (15.1–24.5)	12.7 (8.6–16.8)		10.6 (6.3–14.9)	3.7 (1.0–6.4)	
Tumor size			0.004			0.844
<5 cm	33.3 (14.5–52.1)	29.2 (11.0–47.4)		0	0	
≥5 cm	22.1 (13.7–30.5)	14.4 (7.3–21.5)		13.8 (5.4–22.2)	10.8 (3.4–18.2)	
NA	18.3 (13.4–23.2)	10.2 (6.3–14.1)		14.3 (9.4–19.2)	6.3 (2.8–9.8)	
Tumor extent			0.086			0.582
T1	29.8 (16.7–42.9)	23.4 (11.235.6)		13.8 (1.3–26.3)	10.3 (0–21.5)	
T2	20.8 (13.2–28.4)	12.9 (6.4–19.4)		10.8 (3.7–17.9)	2.7 (0–6.4)	
T3	0	0		0	0	
T4	9.1 (0–26.2)	0		0	0	
NA	18.5 (13.0–24.0)	10.4 (5.9–14.9)		15.8 (9.9–21.7)	9.2 (4.7–13.7)	
LN metastasis			0.438			0.377
No	20.4 (14.7–26.1)	13.4 (8.5–18.3)		10.7 (5.4–16.0)	3.8 (0.5–7.1)	
Yes	0	0		0	0	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	DSS			OS		
	6-month, % (95% CI)	1-year, % (95% CI)	P value	6-month, % (95% CI)	1-year, % (95% CI)	P value
NA	21.2 (14.9–27.5)	12.8 (7.5–18.1)	0.588	17.3 (10.6–24.0)	9.4 (4.3–14.5)	0.331
Distant metastasis						
No	21.2 (14.9–27.5)	12.8 (7.5–18.1)		17.3 (10.6–24.0)	9.4 (4.–14.5)	
Yes	22.5 (15.4–29.6)	16 (9.9–22.1)		9.8 (3.7–15.9)	3.3 (0–7.0)	
NA	13.0 (4.6–21.4)	5.6 (0–11.7)		10.9 (1.9–19.9)	4.3 (0–10.2)	
AJCC TNM stage			0.063			0.812
I	32.4 (17.3–47.5)	27 (12.7–41.3)		12.5 (0–28.8)	8.3 (0–19.3)	
II	23.8 (14–33.6)	15.2 (6.8–23.6)		10.6 (1.8–19.4)	2.1 (0–6.2)	
III	11.1 (0–31.7)	0		0	0	
IV	12.9 (4.521.3)	5.6 (0–11.7)		10.9 (1.9–19.9)	6.5 (0–13.6)	
NA	19.5 (13.6–25.4)	11.3 (6.6–16.1)		16.3 (10.2–22.4)	8.5 (4.0–13.0)	
Historic stage			0.003			0.785
Local	32.2 (22.6–41.8)	23.3 (14.5–32.1)		15.3 (6.1–24.5)	6.8 (0.3–13.3)	
Regional	19.3 (11.3–27.3)	11.6 (5.1–18.1)		16.2 (7.4–25.0)	7.4 (1.1–16.7)	
Distance	11.7 (5.6–17.8)	4.9 (0.8–9.0)		11.1 (4.6–17.6)	4.4 (0.1–8.7)	
NA	20.3 (10.5–30.1)	13.5 (4.5–22.5)		12.5 (3.7–21.3)	8.3 (0.5–16.1)	
Surgery			0.013			<0.001
Yes	43.5 (27.4–59.6)	31.9 (16.6–47.2)		40 (20.8–59.2)	20 (4.3–35.7)	
No	16.3 (12.0–20.6)	10.3 (6.8–13.8)		7.1 (3.2–11.0)	1.8 (0–3.8)	
NA	26.1 (13.4–38.4)	13.2 (2.8–23.6)		19.4 (10.2–28.6)	11.1 (3.9–18.4)	

NA, not available; LN metastasis, lymph node metastasis.

To identify the ages at which patients can benefit from surgery, we conducted an exploratory subgroup analysis. Patients aged < 60 years benefited more from surgery in terms of OS and DSS than those aged ≥60 years (*Table 6*).

Furthermore, nomograms were established to predict the 0.5- and 1-year OS and DSS (*Figure 4*). In the OS prognostic model, the nomograms presented good accuracy, with a C-index value of 0.679 (95% CI: 0.642–0.716), and the C-index value was 0.665 (95% CI: 0.618–0.712) in the DSS prognostic model. The calibration plots for the 0.5- and 1-year OS and 0.5- and 1-year DSS demonstrated fair agreement between the actual observations and nomogram-predicted probabilities (*Figure 5*).

Discussion

PHAs are rare malignant neoplasms, and few studies have been published on PHA. Most of the studies are case reports, and few researchers have analyzed the clinical features and long-term follow-up reports of this disease in detail. We conducted a population-based study to identify the clinical characteristics and investigate the factors related to the prognosis of PHA. To our best of knowledge, this study has the largest number of patients currently, and the findings will benefit doctors and future researchers.

Some studies have reported that PHA accounts for nearly 2% of primary liver tumors (17). However, we

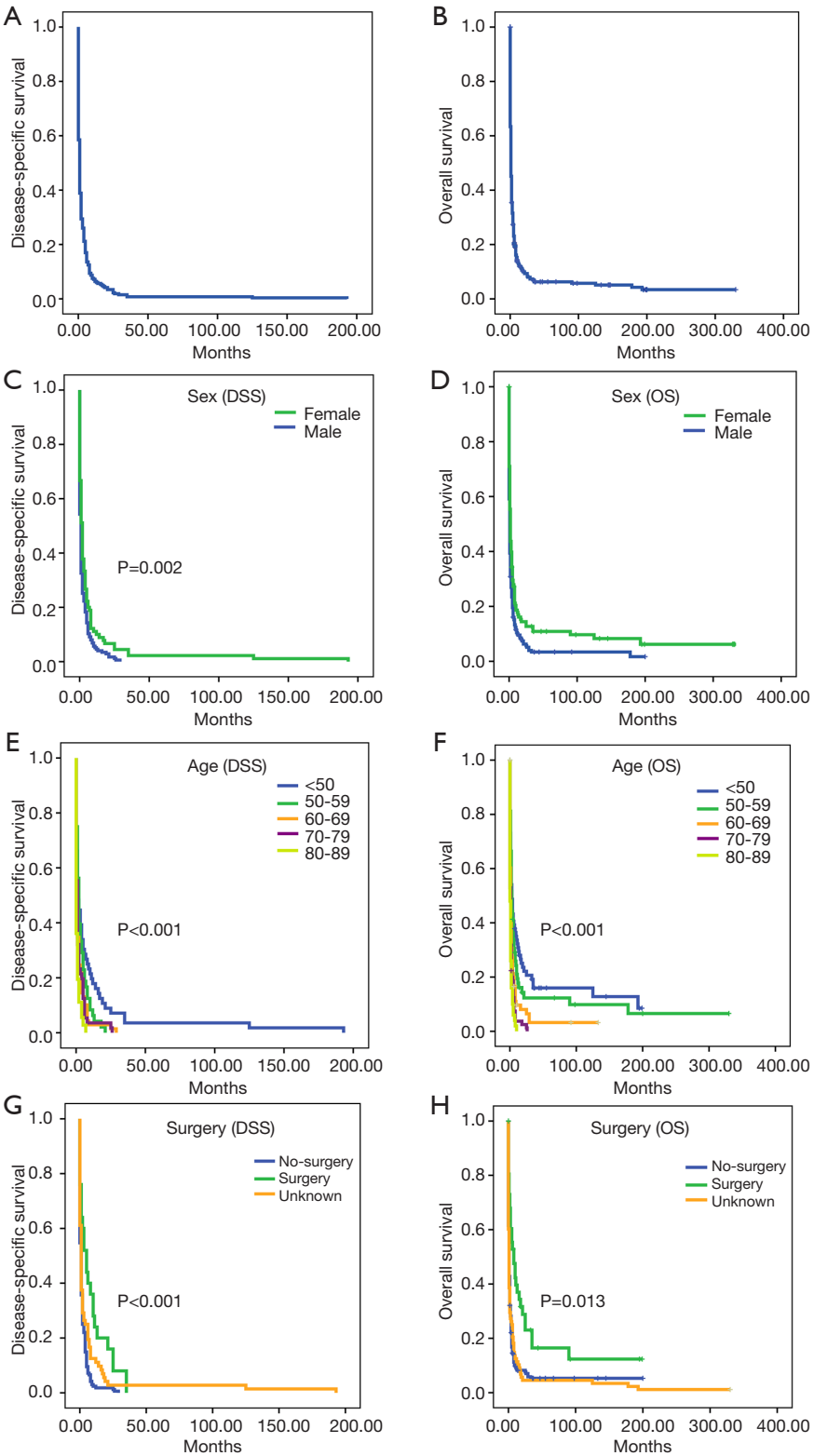

Figure 3 Kaplan-Meier survival plots for primary hepatic angiosarcoma. (A) Overall survival (OS). (B) Disease-specific survival (DSS). (C,D) Sex is a predictor of both OS and DSS. (E,F). Age is a predictor of both OS and DSS. (G,H) Surgery is a predictor of both OS and DSS.

Table 4 Multivariate analyses of overall survival and disease-specific survival in PHA

Variables	DSS		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Sex				
Male/female	0.743 (0.557–0.991)	0.043	0.735 (0.569–0.948)	0.018
Age, years				
<50		0.037		0.000
50–59	1.215 (0.804–1.836)	0.356	1.036 (0.716–1.500)	0.850
60–69	1.511 (1.011–2.257)	0.044	1.655 (1.156–2.371)	0.006
70–79	1.671 (1.087–2.567)	0.019	2.106 (1.448–3.062)	0.000
>80	2.160 (1.288–3.624)	0.004	2.581 (1.663–4.005)	0.000
Race				
White		0.715		0.235
Black	1.260 (0.672–2.363)	0.471	1.516 (0.898–2.559)	0.119
Other	1.091 (0.769–1.548)	0.627	1.140 (0.847–1.534)	0.387
Marital status				
Marred		0.451		0.272
Single	1.169 (0.8017–1.706)	0.419	0.981 (0.713–1.349)	0.904
Other	1.161 (0.8192–1.644)	0.402	1.144 (0.846–1.548)	0.382
NA	1.704 (0.802–3.618)	0.165	1.734 (0.949–3.170)	0.074
Year				
<2000/≥2000	1.557 (0.523–4.638)	0.427	1.214 (0.417–3.531)	0.722
Tumor size				
<5 cm		0.265		0.024
≥5 cm	0.686 (0.341–1.380)	0.290	0.461 (0.262–0.810)	0.007
NA	0.738 (0.500–1.089)	0.126	0.915 (0.656–1.277)	0.602
AJCC TNM stage				
I		0.697		0.748
II	0.882 (0.457–1.480)	0.514	0.823 (0.503–1.347)	0.438
III	0.931 (0.347–2.500)	0.887	1.000 (0.438–2.285)	1.000
IV	0.610 (0.289–1.284)	0.193	0.695 (0.377–1.281)	0.243
NA	0.732 (0.368–1.456)	0.374	0.788 (0.455–1.366)	0.396
Historic stage				
Local		0.524		0.106
Regional	0.905 (0.592–1.385)	0.646	1.224 (0.854–1.755)	0.271
Distance	1.260 (0.750–2.116)	0.382	1.731 (1.114–2.691)	0.015
NA	1.038 (0.619–1.741)	0.886	1.280 (0.835–1.963)	0.257

Table 4 (*continued*)

Table 4 (*continued*)

Variables	DSS		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Surgery				
No		0.047		0.016
Yes	0.571 (0.348–0.938)	0.027	0.586 (0.392–0.877)	0.009
NA	1.281 (0.422–3.888)	0.662	1.347 (0.459–3.956)	0.588

DSS, disease-specific survival; OS, overall survival; NA, not available.

identified more than 120,000 liver cancer patients in the SEER database, and fewer than 400 had PHA, accounting for less than 0.3%. This evidence supports the idea that PHA is rare. Our study showed that the number of patients increased significantly after the start of the 21st century, likely because of the direct link to improved diagnostic methods, but the reasons for this increase must be further studied. According to a previous systematic review of our team, the results showed a slight predominance of men, with a sex ratio of 1.88, a finding that was similar to this study. Additionally, 12.8% of patients had a history of vinyl chloride exposure (18). Therefore, we speculate that occupational exposure to vinyl chloride or other carcinogens may be the cause of the difference in prevalence between men and women. Unfortunately, we did not know the exact occupational exposure rates between men and women in the present study.

The average age of PHA patients was 62.2 years. Wilson GC reported that the median age was 63.7 years (19), a finding that was similar to ours. Therefore, both results indicated that PHA mainly occurs in the elderly population.

PHA lacks specific clinical symptoms and signs in the early stage, leading to delays in diagnosis and treatment. Lesions are not identified in some patients until the tumor ruptures (20-22). Among the 119 patients with clear records of tumor size, the number of patients with tumor volumes ≥5 cm was more than three times that of patients with tumor volumes <5 cm in our study. Although only a few patients had lymph node metastasis, nearly 40% of the patients had distant tumor metastasis, demonstrating the highly invasive nature of PHA. Regarding the historic stage, more than one-third of the patients were in the distant stage, also supporting the findings of the poor prognosis of PHA. Thus, the onset of the disease is insidious and the elderly should have regular physical examinations.

The delayed diagnosis and highly malignant characteristics of the tumor result in a very poor prognosis. Some studies have reported a median survival of approximately 6 months, and only 3% of patients survived for more than 2 years (23). According to our study, the median OS was only 1 month, with 12.8% of the patients surviving for more than 1 year. Moreover, the 1-year DSS rate was only 6.4%, which was an alarming result. This finding further demonstrates that the prognosis is very poor, and doctors should lower the expectations of patients or their families. Currently, only a few systematic studies have investigated the prognostic factors for this disease. Li *et al*. found that a small tumor size (<10 cm) was the only significant favorable factor for OS, while sex, age, hepatectomy, tumor rupture and adjuvant chemotherapy had no significant influence on survival (24). These results were obtained with univariate analysis. In our study, age, sex and surgery were all prognostic predictors in univariate analysis. The patients who were younger, female or received surgery had better survival than their counterparts. Tumor size and historic stage were prognostic predictors for DSS. However, tumor extent, LN metastasis, distant metastasis and TNM stage did not significantly influence survival in univariate analysis. Considering the limitations of univariate Cox analysis, we applied multivariable Cox analysis to further study the relevant factors. Consistent with univariate Cox analysis, age, sex and surgery were significant prognostic factors. Tumor size and distant historic stage were predictors of OS but not DSS. TNM stage had no significant influence on prognosis. According to a recent SEER study, age, gender, marital status, primary site, tumor size, historic stage and surgery were predictors of OS in angiosarcoma (25). The reason for the difference in results may be that the characteristics of angiosarcoma at different locations may be inconsistent.

Currently, several treatments for this disease, such as surgery, adjuvant chemotherapy, liver transplantation,

Table 5 Comparison of the baseline patient characteristics between patients aged <60 and ≥60 years

Variables	OS			DSS		
	<60 years	≥60 years	P value	<60 years	≥60 years	P value
Sex			0.058			0.354
Male	83	152		65	110	
Female	60	71		39	51	
Race			0.225			0.689
White	111	178		79	127	
Black	10	7		9	4	
Other	22	38		16	30	
Year of diagnosis			0.317			0.249
<2000	40	52		34	42	
≥2000	103	171		70	119	
Size			0.943			0.284
<5 cm	36	59		24	41	
≥5 cm	9	15		2	9	
NA	98	149		78	111	
AJCC TNM stage			0.389			0.085
I	16	21		9	15	
II	23	50		12	35	
III	2	7		1	6	
IV	28	34		23	23	
NA	74	111		59	82	
Historic stage			0.150			0.056
Local	32	58		18	41	
Regional	35	60		26	42	
Distance	53	58		45	45	
NA	23	47		15	33	
Surgery			0.107			0.287
No	84	153		60	108	
Yes	21	20		12	13	
NA	38	50		32	40	

DSS, disease-specific survival; OS, overall survival; NA, not available.

transcatheter arterial embolization, transcatheter arterial chemoembolization and symptomatic supportive treatment are available, but no consensus exists on standard treatment (26-31). To date, the mainstay of treatment comprises radical tumor resection or hepatic resection when the patient's general physical condition is adequate (32). In our study, we found that patients who received surgery had much better survival than those who did not, further

Table 6 Multivariate analyses of DSS and OS stratified by age

Variables	DSS		OS	
	P value (<60 years)	P value (≥60 years)	P value (<60 years)	P value (≥60 years)
Sex				
Male/female	0.003	0.584	0.000	0.479
Race				
White	0.839	0.831	0.675	0.611
Black	0.974	0.671	0.395	0.509
Other	0.565	0.718	0.690	0.407
Marital status				
Marred	0.459	0.470	0.218	0.525
Single	0.886	0.192	0.846	0.872
Other	0.350	0.248	0.119	0.364
NA	0.159	0.607	0.102	0.236
Year of diagnosis				
<2000/≥2000	0.214	0.680	0.483	0.567
Size				
<5 cm	0.733	0.540	0.030	0.223
≥5 cm	0.683	0.513	0.019	0.083
NA	0.453	0.282	0.702	0.461
AJCC TNM stage				
I	0.483	0.926	0.251	0.569
II	0.166	0.652	0.716	0.173
III	0.601	0.716	0.934	0.886
IV	0.215	0.438	0.047	0.293
NA	0.286	0.408	0.214	0.158
Historic stage				
Local	0.758	0.914	0.604	0.896
Regional	0.982	0.635	0.400	0.725
Distance	0.429	0.888	0.612	0.492
NA	0.928	0.893	0.782	0.519
Surgery				
No	0.003	0.619	0.049	0.199
Yes	0.004	0.334	0.045	0.073
NA	0.787	0.873	0.645	0.878

DSS, disease-specific survival; OS, overall survival; NA, not available.

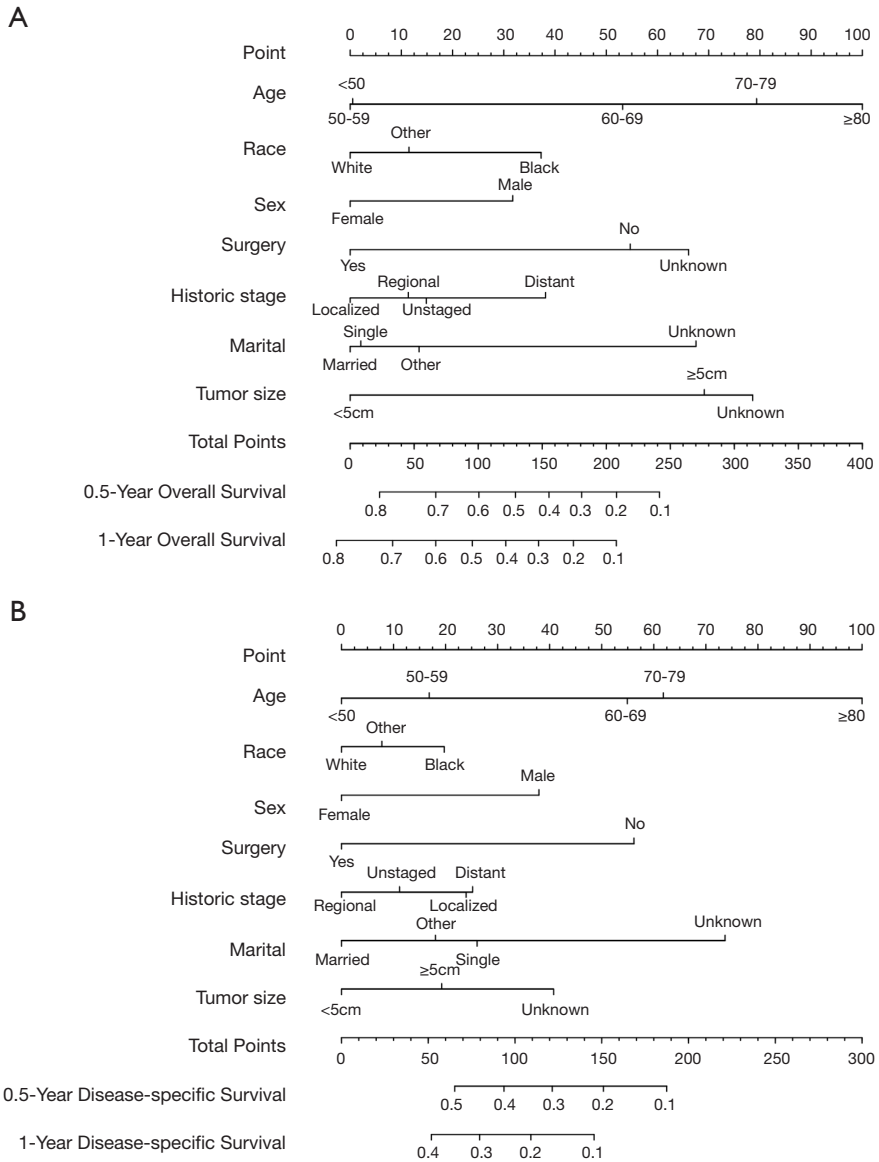

Figure 4 Nomograms for predicting patients' survival. (A) Nomograms predicting the 0.5- and 1-year overall survival. (B) Nomograms predicting the 0.5- and 1-year disease-specific survival.

supporting the choice of surgery as the primary treatment. Moreover, according to exploratory subgroup analysis, patients aged <60 years benefit from surgery, providing a more specific reference for clinicians.

Nomograms have been used to assess OS and cancer-specific survival in cancer patients and serve as a reliable tool to help clinicians evaluate patient prognosis (33,34). Patient scores are obtained based on the corresponding indicators, and the total scores can be used to assess the prognosis. To our best knowledge, no nomogram has been constructed to predict OS and DSS in PHA. In this study, we successfully constructed nomograms and evaluated them using C-index values and calibration plots. The C-index values ranged from 0.5 to 1.0. A C-index value of 0.5 indicates random chance, and 1.0 indicates perfect discriminative ability (35). The C-index values were 0.679 (95% CI: 0.642–0.716) and 0.665 (95% CI: 0.618–0.712) for the OS and DSS nomograms, respectively, indicating

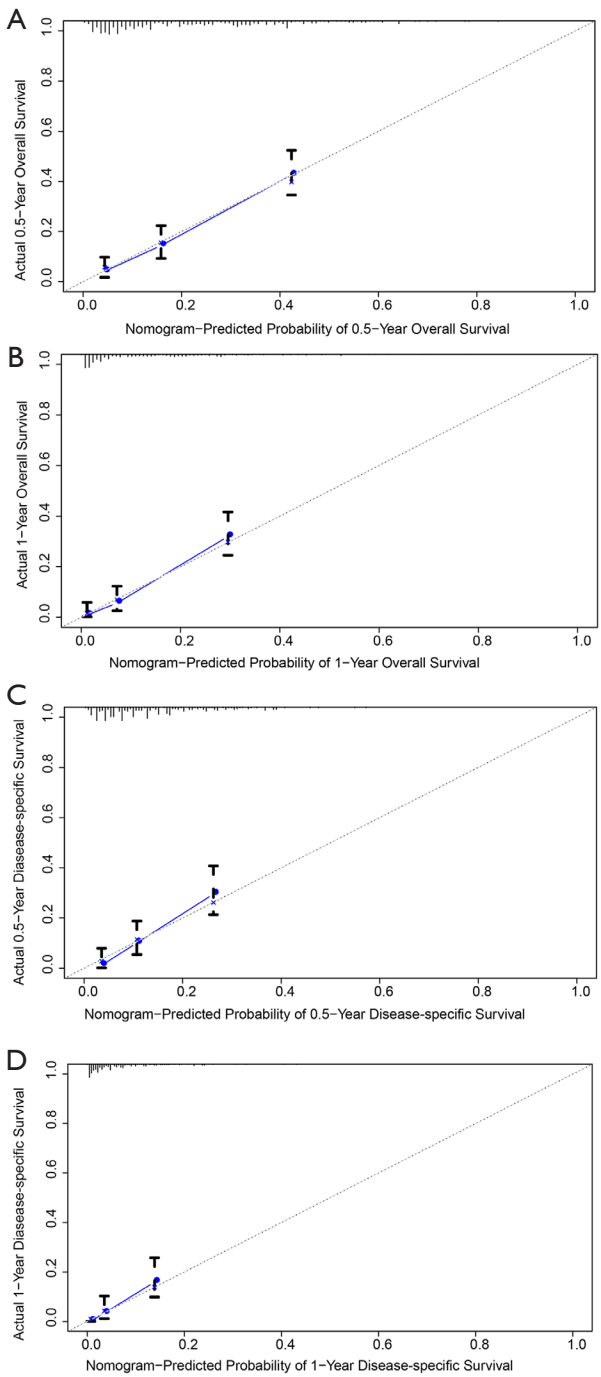

Figure 5 Calibration curves of the nomogram for predicting patients' survival. (A) Half-year overall survival (OS). (B) One-year OS. (C) Half-year disease-specific survival (DSS). (D) One-year DSS.

relatively high accuracy. Additionally, the calibration plots showed satisfactory results. Clinicians can use this model to evaluate the prognosis of patients more accurately.

This study possessed several limitations. First, data were missing in the categories of tumor size, tumor extent, lymph node metastasis and historic stage, which may have caused information bias and decreased the accuracy of the nomograms. Second, the SEER data lacked information on clinical symptoms, which may reflect the severity of the disease. Third, the SEER data mainly represented white US individuals, affecting the generalization of our results to populations of different ethnicities. Additional studies with multi-institutional cohorts are needed in the future. Additionally, the study was retrospective, and prospective cohorts will be needed to validate the accuracy of the nomograms.

Conclusions

In this study, we used the SEER database to determine the clinicopathological characteristics, treatments and outcomes of the largest cohort of PHA patients to date. The prognosis of the disease is poor, and we suggest that the elderly should have regular physical examinations. We identified age and sex as important factors affecting survival. Additionally, patients aged <60 years benefited from surgery. Finally, we constructed accurate nomograms to predict survival, and these visual representations of the prognostic factors may greatly benefit clinicians.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist Available at http://dx.doi.org/10.21037/tcr-20-2780

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2780). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patient information was deidentified and publicly available, so institutional review board approval was not needed.

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Cite this article as: Zeng D, Zeng X, Duan J, Chen D, Zhu B. Clinical characteristics of primary hepatic angiosarcoma outcomes: a SEER database analysis. Transl Cancer Res 2021;10(1):110-125. doi: 10.21037/tcr-20-2780

