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Original Article

Establishment and validation of prognostic nomograms to predict the overall and cancer-specific survival in patients with hepatic malignant vascular tumors

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Abstract: Objective: To characterize the clinicopathologic features and to investigate the prognostic nomograms for overall survival (OS) and cancer-specific survival (CSS) in patients with Hepatic malignant vascular tumors (HMVT). Method: Patients diagnosed with HMVT between 1973 and 2015 were screened from the Surveillance, Epidemiology, and End Results (SEER) database. The Kaplan-Meier (KM) was used for survival analysis. The univariate and multivariate Cox analyses were performed to identify independent predictors. Furthermore, the prognostic nomograms were established and evaluated. Results: A total of 510 HMVT patients were collected, and randomly divided into HMVT-training (N=308) and validation cohort (N=202) groups. The 3- and 5-year OS for overall HMVT were 21.3% and 19.8%, and the corresponding CSS was 29.8% and 27.7% respectively. Age at diagnosis, grade, tumor size, and histological type were identified as prognostic factors for OS and CSS in patients with HMVT. However, sex was just for predicting CSS, and T stage was only an indicator of OS. These factors were further utilized to construct the nomograms for OS and CSS in the HMVT-training cohort showing credible performance with the C-index of 0.763 and 0.762, respectively. Moreover, the AUC value for 1-, 3-, 5-year OS was 0.873, 0.905 and 0.898, and the corresponding value for CSS was 0.808, 0.794 and 0.788 respectively. Additionally, the calibration curves demonstrated a favorable agreement between the predicted and actual 1-, 3- and 5-year survival rates both in the training and validated cohorts. Conclusion: This was the largest population-based study to describe the clinicopathologic characteristics in patients with HMVT. Moreover, we established and validated prognostic nomograms that indicated an accurate prediction for 1-, 3- and 5-year of OS and CSS.

Keywords: Hepatic malignant vascular tumors, prognostic factor, nomogram, overall survival, cancer-specific survival, SEER database

Introduction

Malignant vascular tumors (MVT) are rare types of tumors and can occur in various organs, including the liver, lung, bone, pleura, spleen, and lymph nodes et al. To date, the number of reported cases of hepatic malignant vascular tumors (HMVT) is limited. Angiosarcoma (AS), hemangioendothelioma (HE), epithelioid hemangioendothelioma (EHE), and hemangiopericytoma (HP) are the most common histological types of HMVT [1-3]. With regard to primary liver tumors such as hepatocellular carcinoma and cholangiocarcinoma, standard criteria have been established to determine the curative or palliative outcomes of surgical treatment or systematic therapies. However, because of the extremely rare incidence of these types, little is known about the pathogenesis and progression of HMVT both in clinical trials and laboratory research, which hindered the researchers from elaborating the pathological

mechanisms and determining the prognostic factors that are closely correlated with patients' survival [1, 4, 5].

AS is a subtype of soft tissue sarcoma and has aggressive and malignant features derived from the endothelial cell tumors in the vessels or lymph nodes [2]. Although the development of several vascular-targeted treatments has attracted much interest in identifying the molecular pathogenesis and clinical investigations, currently, the feasible treatments for AS are still limited and the prognosis is poor. The most common primary sites of AS included the neck (37%), head (52%), extremities (15.3%), trunk (9.5%), and liver (6.0%). Meanwhile, AS accounts for one-third of all cases of HMVT and is more generally diagnosed in patients aged 50-70 years [6]. Histologically, it is composed of vascular channels that are lined by variably atypical endothelial cells with large nucleoli, nuclei, and incremental mitosis [7, 8]. In 1949, Stout first described HE as neoplasms arising from pericytes with neoplastic cellular infiltration in the sinusoids and intrahepatic veins [9]. HE less commonly occurs in the liver compared to AS, preferably develops in patients aged 40-50 years, and accounts for 2% of soft tissue tumors. However, the overall malignancy of HE is weaker than that of AS. Patients with HE have a better prognosis with a 5-year overall survival (OS) of 60% [2, 10]. In such cases, epithelioid-type tumors would develop in the infiltrating cells, leading to a subtype classified as EHE. To date, only a few studies have reported the risk factors associated with OS in patients with HE and EHE, such as tumor size, invasiveness, and foci of hemorrhage or necrosis [5, 11, 12]. The HP is an extremely rare type of tumor, accounting for less than 1% of all vascular neoplasms, and develops more often in women than in men. It is usually detected in several body sites, including the lower limbs, abdominal and retroperitoneal cavity, and liver, with features of single or multiple cases [1, 13, 14]. Pericytes are myofibroblast-like cells that wrap around the capillaries and venules, and their malignant transformation finally results in HP [15, 16]. Hitherto, aside from a few sporadic cases, knowledge about the natural pathogenesis, etiologic causes, and prognostic factors of HP is extremely scarce.

To date, local disease control and improvement of survival probability in patients with HMVT remain a challenge. Only a few studies systematically described the clinical features or reported the significant morbidity and complications associated with surgical treatment and other therapeutic approaches. Therefore, further investigations are warranted to determine whether a uniform therapeutic strategy should be applied to all patients regardless of histopathology or whether an individualized treatment should be adopted. Moreover, the potential prognostic factors associated with survival are deserved to clarify.

This retrospective analysis was performed on patients with HMVT based on the data from the Surveillance, Epidemiology, and End Results (SEER) database, which is supported by the United States (US) National Cancer Institute's surveillance program. It is a real-world cancer clinical document database that has been widely utilized for cancer clinical studies, especially for evaluating the incidence of rare tumor types. A total of 510 HMVT cases were retrieved from the SEER database between 1973 and 2015. In the current, this is the largest retrospective study to perform an in-depth analysis of the clinicopathological traits and establish the prognostic nomograms models for predicting 1-, 3- and 5-year OS and cancer-specific survival (CSS) in patients with HMVT, respectively.

Materials and method

Data source and acquisition

The patient data between 1973 and 2015 were extracted from the SEER database, the world's largest publicly accessible cancer registry, supported by the US National Cancer Institute. Approval from the institutional review board is not required when using SEER data due to the absence of patient identifiers. SEER* Stat (version 8.3.6) was used to screen patients diagnosed with HMVT according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3rd). All selected patients met the inclusion criteria based on the corresponding morphological codes, including 9120 (angiosarcoma), 9130 (hemangioendothelioma), 9133 (epithelioid hemangioendothelioma), and 9150 (hemangiopericytoma), all of which were combined with site code C22.0 (liver) and the sequence number of one primary only.

The demographic and clinicopathological characteristics of each patient were carefully collected and classified by age, sex, race, year of diagnosis, alpha-fetoprotein protein (AFP) level, degree of fibrosis, tumor number, tumor size, tumor-node-metastasis (TNM) stage, histologic types, radiation, chemotherapy, and surgery. Simultaneously, the 4-grade system in the SEER database was used to define the level of tumor differentiation: well-differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), and undifferentiated (grade IV). Additionally, the SEER database also provided straightforward reports of OS, defined as the period from diagnosis to death from any cause or last follow-up, and CSS, defined as the overall time from diagnosis to death specifically due to cancers.

Establishment and validation of the nomogram

The univariate and multivariate Cox regression analyses were conducted to determine the independent prognostic factors correlated with survival probability. Then the predictive nomograms for OS and CSS in patients with HMVT were established based on the screened risk factors. To further evaluate the predictive performance of the nomogram models in both the training and validation cohorts, the concordance index (C-index) and the area under the curve (AUC) of time-dependent receiver operating characteristic (ROC) were conducted. Generally, the value of C-index is 0.7 or higher indicating a credible prediction. The range of AUC value is from 0 to 1, and a model was thought of as a poor, reliable, or excellent performance with the AUC value interval of 0.5 to 0.6, 0.6 to 0.7, or more than 0.7, respectively. Besides, the calibration curve analysis was performed to evaluate the consistency between the predicted and practical survival times. The whole assessment process of the nomogram was operated in R software (4.0.3 version) (https://www.r-project.org/) by R packages of rms, survival, and survminer.

Risk score calculation and risk group classification

The risk score formula was constructed to quantitatively calculate the risk of inferior survival probability for each patient according to the coefficients of the independent clinicopathological risk factors determined by multivariate Cox regression analysis. The "survival" R package was used for the process. We eventually divided the patients into low-risk and high-risk groups based on the median risk scores. The OS and CSS for patients in different risk stratification classified by clinical-pathological factors were further evaluated.

Statistical analysis

Statistical analyses were carried out using the universal statistical SPSS software (version 22.0) from BM Corp, Armonk, NY, USA, and a *P*-value of <0.05 was considered statistically significant. Categorical and continuous variables were analyzed using the Pearson chi-square test and 2-sample t-test, respectively. The Kaplan-Meier (KM) method was used to calculate the survival rates and median survival time, while the log-rank test was applied to thoroughly evaluate the deviations. All variables with a *P*-value of <0.05 in univariate analysis were selected for the multivariate proportional hazard model to identify independent predictors for OS and CSS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated.

Results

Demographic and clinicopathological characteristics of patients

Between 1973 and 2015, a total of 510 patients with HMVT were identified from the SEER database, of whom 350 had AS, 37 had HE, 114 had EHE, and 9 had HP. These patients were randomly divided into the training cohort (N=308) and the validation cohort (N=202). The demographic and clinicopathological characteristics of all included patients are summarized in **Table 1**. The detailed distribution of the age at diagnosis of patients with different types of HMVT ranged from 0 to ≥84 years and was presented in Figure S1. Meanwhile, we used X-title software to determine the cutoff value of age at diagnosis to divide all patients into three groups, namely age <40, 40-59, and ≥60 years (Figure S2). Among patients with HMVT, 69 (13.5%) were aged <40 years, 179 (35.1%) were aged 40-59 years, and 262 (51.4%) were aged 60 years and older. Moreover, the incidence rates of HMVT in men and women showed no obvious difference (45.7% and

Table 1. Demographics and clinicopathological characteristics of patients with hepatic malignant vascular tumor (HMVT)

Categories	Number (%)							*P* value
	AS (N=350)	HE (N=37)	EHE (N=114)	HP (N=9)	HMVT (N=510)	HMVT (Training) (N=308)	HMVT (Validation) (N=202)	
Age, years								<0.001
<40	29 (8.3)	9 (24.3)	30 (26.3)	1 (11.1)	69 (13.5)	48 (15.6)	21 (10.4)	
40-59	111 (31.7)	14 (37.8)	48 (42.1)	6 (66.7)	179 (35.1)	104 (33.8)	75 (37.1)	
≥60	210 (60)	14 (37.8)	36 (31.6)	2 (22.2)	262 (51.4)	156 (50.6)	106 (52.5)	
Race								0.442
white	275 (78.6)	32 (86.5)	92 (80.7)	6 (66.7)	405 (79.4)	237 (76.9)	178 (83.2)	
black	17 (4.9)	2 (5.4)	11 (9.6)	1 (11.1)	31 (6.1)	19 (6.2)	12 (5.9)	
other	58 (16.6)	3 (8.1)	11 (9.6)	2 (22.2)	74 (14.5)	52 (16.9)	22 (10.9)	
Sex								<0.001
female	126 (36)	24 (64.9)	77 (67.5)	6 (66.7)	233 (45.7)	149 (48.4)	84 (41.6)	
male	224 (64)	13 (35.1)	37 (32.5)	3 (33.3)	277 (54.3)	159 (51.6)	118 (58.4)	
Year of diagnosis								0.017
1973-1999	95 (27.1)	20 (54.1)	15 (13.2)	3 (33.3)	133 (26.1)	76 (24.7)	57 (28.2)	
2000-2005	84 (24)	6 (16.2)	35 (30.7)	2 (22.2)	127 (24.9)	83 (26.9)	44 (21.8)	
2006-2010	66 (18.9)	4 (10.8)	33 (28.9)	3 (33.3)	106 (20.8)	65 (21.1)	41 (20.3)	
2010-2015	105 (30)	7 (18.9)	31 (27.2)	1 (11.1)	144 (28.2)	84 (27.3)	60 (29.7)	
Grade								0.066
I	8 (2.3)	0 (0.0)	4 (3.5)	0 (0.0)	12 (2.4)	7 (2.3)	5 (2.5)	
II	10 (2.9)	0 (0.0)	10 (8.8)	1 (11.1)	21 (4.1)	13 (4.2)	8 (4.0)	
III	33 (9.4)	0 (0.0)	4 (3.5)	1 (11.1)	38 (7.5)	23 (7.5)	15 (7.4)	
IV	35 (10)	0 (0.0)	1 (0.9)	1 (11.1)	37 (7.3)	24 (7.8)	13 (6.4)	
unknown	264 (75.4)	37 (100.0)	95 (83.3)	6 (66.7)	402 (78.8)	241 (78.2)	161 (79.7)	
AFP								0.94
normal	86 (24.9)	5 (13.5)	29 (25.4)	2 (22.2)	122 (23.9)	75 (24.4)	47 (23.3)	
elevated	9 (2.6)	0 (0.0)	5 (4.4)	0 (0.0)	14 (2.7)	8 (2.6)	6 (3.0)	
unknown	255 (72.9)	32 (86.5)	80 (70.2)	7 (77.8)	374 (73.3)	225 (73.1)	149 (73.8)	
Fibrosis								0.402
none to moderate	7 (2.0)	0 (0.0)	6 (5.3)	1 (11.1)	14 (2.7)	11 (3.6)	3 (1.5)	
Severe	16 (14.6)	0 (0.0)	2 (1.8)	0 (0.0)	18 (3.5)	11 (3.6)	7 (3.5)	
unknown	327 (93.4)	37 (100.0)	106 (93.0)	8 (88.9)	478 (93.7)	286 (92.9)	192 (95.0)	
Tumor number								0.64
1	309 (88.3)	36 (97.3)	103 (90.4)	7 (77.8)	455 (89.2)	270 (87.7)	185 (91.6)	
2	34 (9.7)	1 (2.7)	11 (9.6)	2 (22.2)	47 (9.2)	31 (10.1)	16 (7.9)	
≥3	7 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.4)	6 (1.9)	1 (0.5)	
Tumor size								0.001
≤5 cm	29 (8.3)	5 (13.5)	30 (26.3)	0 (0.0)	64 (12.5)	44 (14.3)	20 (9.9)	
>5 cm	88 (25.1)	4 (10.8)	17 (14.9)	3 (33.3)	112 (22.0)	66 (21.4)	46 (22.8)	
unknown	233 (66.6)	28 (75.5)	67 (58.8)	6 (66.7)	334 (65.5)	198 (64.3)	136 (67.3)	
Surgery								0.048
Yes	14 (4)	4 (10.8)	0 (0.0)	1 (11.1)	19 (3.7)	8 (2.6)	11 (5.4)	
No	37 (10.6)	3 (8.1)	9 (7.9)	2 (22.2)	51 (10.0)	24 (7.8)	27 (13.4)	
unknown	299 (85.4)	30 (81.1)	105 (92.1)	6 (66.7)	440 (86.3)	276 (89.6)	164 (81.2)	
Radiation								0.567
Yes	12 (3.4)	0 (0.0)	2 (1.8)	0 (0.0)	14 (2.7)	8 (2.6)	6 (3.0)	
No	338 (96.6)	37 (100.0)	112 (98.2)	9 (100.0)	496 (97.3)	300 (97.4)	196 (97.0)	
Chemotherapy								0.369
yes	48 (13.7)	9 (24.3)	18 (15.8)	1 (11.1)	76 (14.9)	51 (16.6)	25 (12.4)	

No	302 (86.3)	28 (75.7)	96 (84.2)	8 (88.9)	434 (85.1)	257 (83.4)	177 (87.6)	
T stage								0.521
T1	48 (13.7)	4 (10.8)	21 (18.4)	2 (22.2)	75 (14.7)	48 (15.6)	27 (13.4)	
T2	24 (6.9)	4 (10.8)	21 (18.4)	0 (0.0)	49 (9.6)	29 (9.4)	20 (9.9)	
T3	43 (12.3)	2 (5.4)	10 (8.8)	1 (11.1)	56 (11.0)	35 (11.4)	21 (10.4)	
T4	11 (3.1)	1 (2.7)	5 (4.4)	1 (11.1)	18 (3.5)	11 (3.6)	7 (3.5)	
unknown	224 (64.0)	26 (70.3)	57 (50.0)	5 (55.6)	312 (61.2)	185 (60.1)	127 (62.9)	
N stage								0.051
N0	154 (44.0)	10 (27.0)	59 (51.8)	3 (33.3)	226 (44.3)	136 (44.2)	90 (44.6)	
N1	8 (2.3)	0 (0.0)	9 (7.9)	1 (11.1)	18 (3.5)	11 (3.6)	7 (3.5)	
unknown	188 (53.7)	27 (73.0)	46 (40.4)	5 (55.6)	266 (52.2)	161 (52.3)	105 (52)	
M stage								0.159
M0	117 (33.4)	7 (18.9)	39 (34.2)	3 (33.3)	166 (32.5)	100 (32.5)	66 (32.7)	
M1	62 (17.7)	6 (16.2)	35 (30.7)	1 (11.1)	104 (20.4)	65 (21.1)	39 (19.3)	
unknown	171 (48.9)	24 (64.9)	40 (35.1)	5 (55.6)	240 (47.1)	143 (46.4)	97 (48.0)	
OS								
1 year-OS	51 (12.6)	17 (45.3)	83 (71.9)	4 (44.4)	155 (28.9)	94(29.3)	61 (28.4)	
3 year-OS	31 (5.9)	16 (42.5)	72 (60.5)	3 (33.3)	122 (21.3)	76 (22.6)	46 (19.4)	
5 year-OS	31 (5.9)	15 (39.2)	67 (54.8)	3 (33.3)	116 (19.8)	71 (20.6)	45 (18.7)	
CSS								
1 year-CSS	113 (20.0)	20 (51.0)	92 (78.9)	5 (53.3)	230 (37.9)	144 (39.8)	86 (35.1)	
3 year-CSS	98 (11.2)	20 (51.0)	81 (66.4)	5 (53.3)	204 (29.8)	130 (32.5)	74 (25.8)	
5 year-CSS	98 (11.2)	19 (47.1)	76 (60.1	5 (53.3)	198 (27.7)	125 (29.6)	73 (24.9)	

AS: angiosarcoma. HE: hemangioendothelioma. EHE: epithelioid hemangioendothelioma. HP: hemangiopericytoma. HMVT: hepatic malignant vascular tumor. TNM: tumor-node-metastasis. OS: overall survival. CSS: cancer-specific survival. Chi-square was used for statistical analysis, $P<0.05$ was considered statistically significant.

54.3%, respectively). The majority of patients with AS (78.6%), HE (86.5%), EHE (80.7%), HP (66.7%), and overall HMVT (79.4%) were white people. With regard to the year of diagnosis for HMVT, 133 patients (26.1%) were diagnosed between 1973 and 1999, 127 patients (24.9%) between 2000 and 2005, 106 patients (20.8%) between 2006 and 2010, and 144 patients (28.2%) between 2011 and 2015. Only 136 (26.6%) and 32 (6.3%) patients with HMVT had data to define AFP level and degree of fibrosis. Approximately 2.6% of AS patients and 4.4% of EHE patients showed elevated AFP levels. Correspondingly, 16 patients (14.6%) with AS and 2 patients (1.8%) with EHE showed severe fibrosis. Among HMVT patients, 89.2% had a single lesion and 12.5% had tumor sizes of ≤5 cm.

Histologically, there were no HE patients with the information of grade levels. Among the HMVT patients, 402 (78.8%) had an unknown tumor grade, 33 (6.5%) had low-grade tumors (grade I+II), and 75 (14.8%) had high-grade tumors (grade III+IV). Concerning the T stage, 124 (24.3%) patients with HMVT had early T stage (T1+T2), while 74 (14.5%) had advanced T stage (T3+T4). In the early T stage group, 72 (20.6%) patients had AS, while 42 (36.8%) had EHE; in the advanced T stage group, 54 (15.4%) patients had AS, while 15 (13.2%) had EHE. A total of 226 (44.3%) patients with HMVT had N0 stage, while only 3.5% had N1 stages. Likewise, 166 (32.5%) patients had M0 stage, while 104 (20.4%) had M1 stage.

As to the treatments, only 19 (3.7%), 14 (2.7%), 76 (14.9%) patients with HMVT received surgery, radiation, and chemotherapy treatment, separately. While the major population had an unknown treatment record. Furthermore, the OS and CSS were calculated for HMVT and the corresponding histologic types (**Figure 1**). It was indicated that the 1- and 3-year OS and CSS rates for AS were 12.6% and 5.9%, and 20.0% and 11.2%, respectively. The 5-year OS and CSS rates were 39.2% and 47.1% for HE, 54.8% and 60.1% for EHE, 33.3% and 53.3% for HP, and 19.8% and 27.7% for HMVT, respectively. Additionally, the description of clinicopathologic features of patients in the HMVT-training and -validation group was also analyzed in **Table 1**.

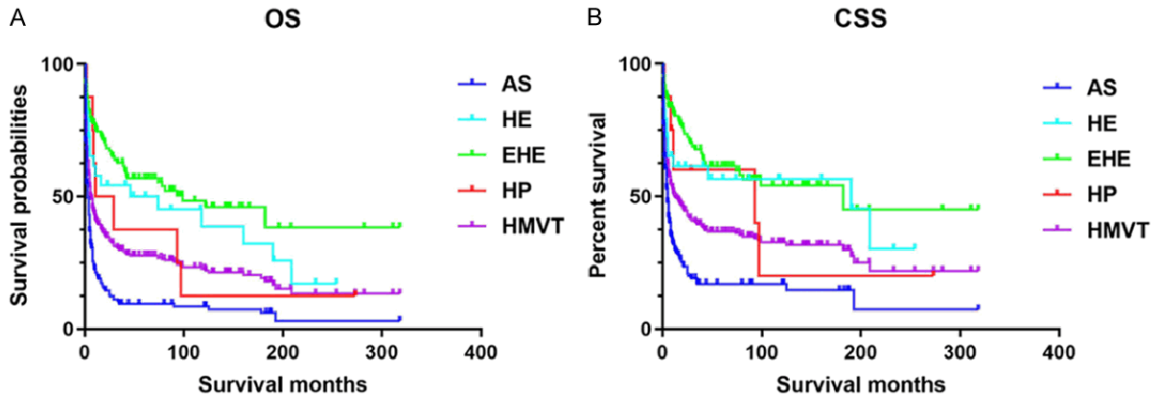


Figure 1. The tendency of overall survival (OS) and cancer-specific survival (CSS) for patients with angiosarcoma (OS), hemangioendothelioma (HE), epithelioid hemangioendothelioma (EHE), hemangiopericytoma (HP), and all hepatic malignant vascular tumors (HMVT) respectively using the data from Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2015. A, B: Indicated the OS and CSS for AS, HE, EHE, HP, and HMVT respectively.

Univariate analysis of variables correlated with OS and CSS

At first, the univariate analysis using the log-rank test was performed to identify the potential prognostic factors correlated with OS and CSS in the AS, EHE, and HMVT-all, and HMVT-training cohorts (**Table 2**). Our tests indicated that age ≥60 years was significantly associated with poorer OS and CSS in the AS (P<0.001 and P=0.003), EHE (P<0.001 and P=0.01), HMVT-all (both P<0.001), and HMVT-training (both P<0.001). Similarly, sex was also a poorer predictor of OS and CSS in the AS, HMVT-all, and HMVT-training cohorts (P=0.010 and P=0.015 for AS, both P<0.001 for HMVT-all, and both P<0.001 for HMVT-training, respectively). Neither race nor AFP level was significantly associated with OS or CSS in any type of HMVT cohorts. Moreover, tumor grade was a significant predictor for predicting OS and CSS in the HMVT-all and -training cohort but just associated with CSS (P=0.0307) in the EHE cohort. Patients with severe fibrosis exhibited lower survival probability in both OS and CSS than those with no to moderate level of fibrosis in the EHE (P=0.022 and P=0.014, respectively) and HMVT-all cohorts (P=0.017 and P=0.006, respectively). The significant difference in CSS brought by tumor numbers was observed in the AS (P<0.001), HMVT-all (P<0.001), and HMVT-training (P=0.004) cohorts. Notably, a smaller tumor size (≤5 cm) was a beneficial predictor for both OS and CSS in the AS, EHE, HMVT-all, and -training cohorts. In the current study, AS patients who underwent surgery showed better OS (P=0.016) and CSS (P=0.062). Similarly, the patients with AS treated by chemotherapy lived a longer time than those who didn't receive this treatment (P=0.033 for OS). As well, statistical differences were observed in the OS and CSS between patients with early T stage and those with advanced T stage in the EHE (P=0.025 and P=0.016), HMVT-all (P=0.001 and P=0.003), and HMVT-training (P=0.008 and P=0.024) cohorts. Meanwhile, the difference for CSS in patients stratified by N stage was only identified in the EHE cohort with a *P*-value of 0.036. However, regarding M stages, we did not identify any significant differences in the OS and CSS for HMVT patients with various histological types. Additionally, we found that the histological type of HMVT is a predictive factor associated with survival probability both for OS and CSS.

Next, the KM method was performed to calculate the survival probability of OS (**Figure 2**) and CSS (**Figure 3**) for patients in the AS, EHE, and HMVT-all cohorts classified by the variables showing a significant correlation with prognosis. Correspondingly, we analyzed the median OS and CSS associated with these variables in the three cohorts, as shown in Table S1.

Multivariate analysis of the independent prognostic factors for OS and CSS

To adjust for the interaction between various covariates, the multivariate Cox proportional hazard model of AS, EHE, HMVT-all, and -train-

Table 2. Univariate analysis of OS and CSS for patients with hepatic malignant vascular tumor (HMVT)

Categories	AS (N=350)		EHE (N=114)		HMVT-all (N=510)		HMVT-training	
	P-value, HR (95% CI)							
	OS	CSS	OS	CSS	OS	CSS	OS	CSS
Age								
<40	reference		reference		reference		reference	
40-59	0.185, 1.37 (0.86-2.19)	0.277, 1.32 (0.80-2.18)	0.378, 1.41 (0.66-3.05)	0.637, 1.21 (0.55-2.68)	0.005, 1.69 (1.18-2.43)	0.026, 1.56 (1.06-2.29)	0.005, 1.95 (1.22-3.12)	0.03, 1.73 (1.06-2.83)
≥60	<0.001, 2.55 (1.63-4.01)	0.003, 2.07 (1.27-3.38)	<0.001, 4.08 (1.92-8.66)	0.01, 2.87 (1.28-6.40)	<0.001, 3.94 (2.76-5.61)	<0.001, 3.09 (2.12-4.52)	<0.001, 4.39 (2.79-6.89)	<0.001, 3.08 (1.90-5.00)
Race								
white	reference		reference		reference		reference	
black	0.712, 1.10 (0.67-1.80)	0.702, 0.94 (0.68-1.30)	0.840, 1.10 (0.44-2.78)	0.491, 1.39 (0.54-3.56)	0.427, 0.84 (0.55-1.29)	0.646, 0.90 (0.56-1.43)	0.289, 0.74 (0.42-1.30)	0.396, 0.76 (0.40-1.44)
other	0.95, 0.99 (0.74-1.33)	0.974, 1.01 (0.55-1.87)	0.800, 1.13 (0.45-2.85)	0.796, 0.84 (0.36-2.73)	0.106, 1.25 (0.95-1.63)	0.081, 1.30 (0.97-1.75)	0.16, 1.27 (0.91-1.76)	0.100, 1.36 (0.94-1.97)
Sex								
female	reference		reference		reference		reference	
male	0.01, 1.36 (1.08-1.71)	0.015, 1.39 (1.07-1.80)	0.347, 1.31 (0.75-2.29)	0.243, 1.45 (0.78-2.69)	<0.001, 1.73 (1.41-2.11)	<0.001, 1.80 (1.44-2.26)	<0.001, 1.75 (1.35-2.26)	<0.001, 1.71 (1.28-2.30)
Grade								
low-grade	reference		reference		reference		reference	
high-grade	0.145, 1.52 (0.87-2.67)	0.499, 1.22 (0.69-2.16)	0.058, 3.88 (0.96-15.77)	0.0307, 7.13 (1.12-45.23)	0.001, 2.16 (1.34-3.46)	0.005, 2.11 (1.25-3.55)	0.008, 2.32 (1.25-4.32)	0.026, 2.24 (1.10-4.54)
AFP								
normal	reference		reference		reference		reference	
elevated	0.801, 1.11 (0.51-2.40)	0.878, 0.93 (0.38-2.31)	0.119, 2.76 (0.77-9.90)	0.257, 2.43 (0.52-11.23)	0.686, 1.14 (0.60-2.20)	0.878, 0.94 (0.44-2.04)	0.462, 1.37 (0.59-3.19)	0.792, 1.14 (0.41-3.20)
Fibrosis								
none to moderate	reference		reference		reference		reference	
Severe	0.067, 1.53 (0.62-3.78)	0.058, 2.829 (0.80-1.06)	0.022, 10.07 (1.39-73.07)	0.014, 12.35 (1.68-90.82)	0.017, 2.60 (1.19-5.70)	0.006, 4.36 (1.53-11.87)	0.123, 2.09 (0.82-5.31)	0.096, 2.85 (0.83-9.78)
Tumor number								
1	reference		reference		reference		reference	
≥2	0.684, 0.93 (0.66-1.32)	<0.001, 0.041 (0.01-0.22)	0.09, 2.06 (0.97-4.38)	0.215, 0.044 (0.00-6.18)	0.545, 1.11 (0.80-1.53)	<0.001, 0.04 (0.01-0.22)	0.399, 1.19 (0.80-1.78)	0.004, 0.04 (0.01-0.36)
Tumor size								
≤5 cm	reference		reference		reference		reference	
>5 cm	0.03, 1.70 (1.05-2.75)	0.075, 1.67 (0.95-2.96)	0.003, 4.79 (1.73-13.25)	0.004, 6.01 (1.80-20.07)	<0.001, 2.86 (1.90-4.32)	<0.001, 2.81 (1.74-4.54)	<0.001, 2.90 (1.77-4.74)	0.003, 2.39 (1.35-4.25)
Surgery								
Yes	reference		reference		reference		reference	
No	0.016, 2.20 (1.16-4.18)	0.062, 1.96 (0.97-3.97)	0.814, 1.11 (0.47-2.63)	0.803, 0.89 (0.37-2.16)	0.521, 1.20 (0.69-2.07)	0.488, 1.24 (0.67-2.30)	0.854, 1.09 (0.47-2.47)	0.893, 1.07 (0.41-2.78)
Radiation								
Yes	reference		reference		reference		reference	
No	0.411, 1.28 (0.71-2.35)	0.35, 1.40 (0.69-2.83)	0.164, 0.37 (0.09-1.51)	0.588, 0.58 (0.08-4.22)	0.625, 0.87 (0.50-1.51)	0.998, 0.99 (0.52-1.94)	0.762, 1.12 (0.53-2.38)	0.412, 1.51 (0.56-4.08)
Chemotherapy								
Yes	reference		reference		reference		reference	
	0.033, 1.41 (1.03-1.93)	0.117, 1.32 (0.93-1.87)	0.996, 1.00 (0.49-2.05)	0.476, 0.77 (0.37-1.60)	0.208, 1.19 (0.91-1.55)	0.417, 1.13 (0.84-1.52)	0.267, 1.20 (0.87-1.66)	0.533, 1.12 (0.78-1.62)
Histological type								
AS					reference		reference	
HE					0.019, 2.33 (1.15-4.72)	0.034, 2.41 (1.07-5.45)	0.037, 2.90 (1.06-7.90)	0.074, 2.88 (0.90-9.18)
EHE					0.896, 0.95 (0.43-2.09)	0.890, 0.94 (0.38-2.34)	0.783, 1.17 (0.39-3.50)	0.921, 1.07 (0.29-3.83)

HP					0.077, 0.51 (0.24-1.08)	0.160, 0.54 (0.23-1.27)	0.258, 0.55 (0.19-1.56)	0.361, 0.57 (0.17-1.92)
T stage								
early stage	reference		reference		reference		reference	
advanced stage	0.053, 1.45 (1.00-2.11)	0.113, 1.43 (0.92-2.22)	0.025, 2.60 (1.13-5.98)	0.016, 3.03 (1.23-7.46)	0.001, 1.74 (1.25-2.42)	0.003, 1.80 (1.23-2.63)	0.008, 1.75 (1.16-2.63)	0.024, 1.76 (1.08-2.88)
N stage								
N0	reference		reference		reference		reference	
N1	0.206, 1.59 (0.78-3.24)	0.135, 1.80 (0.83-3.87)	0.142, 1.96 (0.80-4.84)	0.036, 2.72 (1.07-6.92)	0.711, 1.11 (0.65-1.88)	0.454, 1.24 (0.70-2.20)	0.662, 0.85 (0.41-1.75)	0.683, 0.841 (0.37-1.93)
M stage								
M0	reference		reference		reference		reference	
M1	0.089, 1.33 (0.96-1.83)	0.124, 1.34 (0.92-1.93)	0.080, 1.90 (0.93-3.87)	0.073, 2.08 (0.93-4.64)	0.198, 1.16 (0.88-1.54)	0.277, 1.19 (0.87-1.64)	0.513, 1.13 (0.79-1.62)	0.419, 1.19 (0.79-1.79)

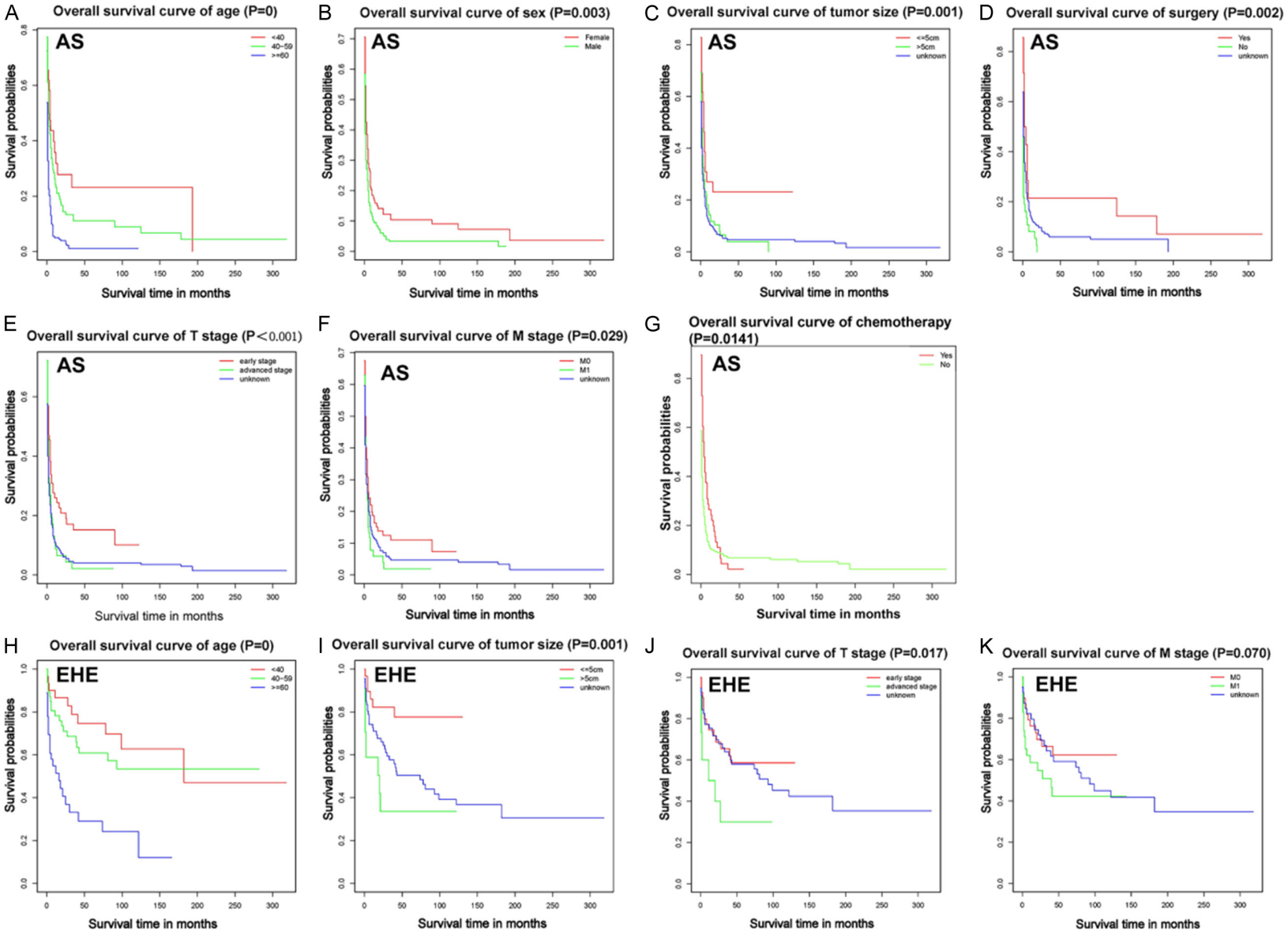
HR: Hazard Ratio. CI: Confidence Interval. Low-grade included grades I and II. Grade III and IV were classified into high-grade. T1 and T2 were included in the early stage. T3 and T4 were included in the advanced stage. AS: angiosarcoma. HE: hemangioendothelioma. EHE: epithelioid hemangioendothelioma. HP: hemangiopericytoma.

ing cohort was conducted to determine the independent risk factors associated with OS and CSS (**Table 3**). The factors with a *P*-value of <0.05 and several significant clinicopathological indicators, such as surgery, chemotherapy, fibrosis, and TNM stages, were all included in the Cox multivariate analysis. For AS patients, results indicated that age ≥60 years (HR=2.46, 95% CI: 1.54-3.92, P<0.001), sex (HR=1.24, 95% CI: 0.97-1.57, P=0.043), surgery (HR=2.16, 95% CI: 1.12-4.17, P=0.022), and chemotherapy (HR=1.48, 95% CI: 1.06-2.06, P=0.021) were independent predictors of OS. Simultaneously, they are also the prognostic factors for predicting inferior CSS in patients within AS cohort. Moreover, the advanced T stage also exhibited an inferior influence on OS (HR=0.54, 95% CI: 0.28-1.02, P=0.059).

Among patients with EHE, age ≥60 years (HR=5.41 and P<0.001; HR=3.91 and P=0.003), severe fibrosis (HR=17.92 and P=0.009; HR=30.33 and P=0.009), tumor size >5 cm (HR=0.24, P=0.016; HR=6.47, P=0.009), and M1 stage (HR=2.34 and P=0.028; HR=2.81 and P=0.039) were associated with poor OS and CSS. Furthermore, the advanced T stage (HR=2.77, 95% CI: 1.03-7.44, P=0.044) was a significant risk factor of OS in patients with EHE. In the HMVT-all cohort, age ≥60 years (HR=3.09 and P<0.001; HR=2.49 and P<0.001), high tumor grade (HR=1.78 and P=0.023; HR=1.77 and P=0.042), and larger tumor size (HR=1.55, P=0.039; HR=2.38, P=0.003) were negatively correlated with both OS and CSS. Similarly, the histological type is another significant independent predictor of survival time for patients with HMVT. In addition, the prognostic difference was found in the OS between the patients diagnosed at advanced T stage and those at early T stage in the HMVT-all cohort, with a *P*-value of 0.041. Concurrently, the risk factors including age, tumor size, and histological type were also the independent predictors for OS and CSS in patients within HMVT-training group.

Establishment and evaluation of the prognostic nomograms

To evaluate survival probability for individual patients, the predictive nomogram models for OS and CSS in the HMVT-training cohort were established. The significantly prognostic factors screened from the multivariate analysis including age, sex, T stage, tumor size, and histological type were integrally operated. However, the risk factor of the grade was excluded since the number of patients with a clear grade ranking was not enough for model construction (**Figure 4A** and **4B**). The detailed points of each factor were presented in the nomogram, the 1-, 3- and 5-year OS and CSS could be predicted by calculating these scores to the total on the bottom axis. In the training cohort, the C-index for OS and CSS was 0.763 (95% CI: 0.708-0.819) and 0.722 (95% CI: 0.653-0.791) respectively. Meanwhile, the calibration curves estimating the 1-, 3- and 5-year OS and CSS rates showed an optimal agreement between the nomogram-predicted and the actual observation (**Figure 4C** and **4D**). Moreover, the ROC was performed to assess the accuracy of the prognostic models. The AUC value for 1-, 3- and 5-year OS in the training cohort was 0.873, 0.905, and 0.898. The corresponding AUC value for CSS was 0.808, 0.794, and 0.788 (**Figure 4E** and **4F**). These


A
Overall survival curve of age (P=0)
AS
<40
40~59
>=60
Survival probabilities
Survival time in months
B
Overall survival curve of sex (P=0.003)
AS
Female
Male
Survival probabilities
Survival time in months
C
Overall survival curve of tumor size (P=0.001)
AS
<=5cm
>5cm
unknown
Survival probabilities
Survival time in months
D
Overall survival curve of surgery (P=0.002)
AS
Yes
No
unknown
Survival probabilities
Survival time in months
E
Overall survival curve of T stage (P<0.001)
AS
early stage
advanced stage
unknown
Survival probabilities
Survival time in months
F
Overall survival curve of M stage (P=0.029)
AS
M0
M1
unknown
Survival probabilities
Survival time in months
G
Overall survival curve of chemotherapy (P=0.0141)
AS
Yes
No
Survival probabilities
Survival time in months
H
Overall survival curve of age (P=0)
EHE
<40
40~59
>=60
Survival probabilities
Survival time in months
I
Overall survival curve of tumor size (P=0.001)
EHE
<=5cm
>5cm
unknown
Survival probabilities
Survival time in months
J
Overall survival curve of T stage (P=0.017)
EHE
early stage
advanced stage
unknown
Survival probabilities
Survival time in months
K
Overall survival curve of M stage (P=0.070)
EHE
M0
M1
unknown
Survival probabilities
Survival time in months

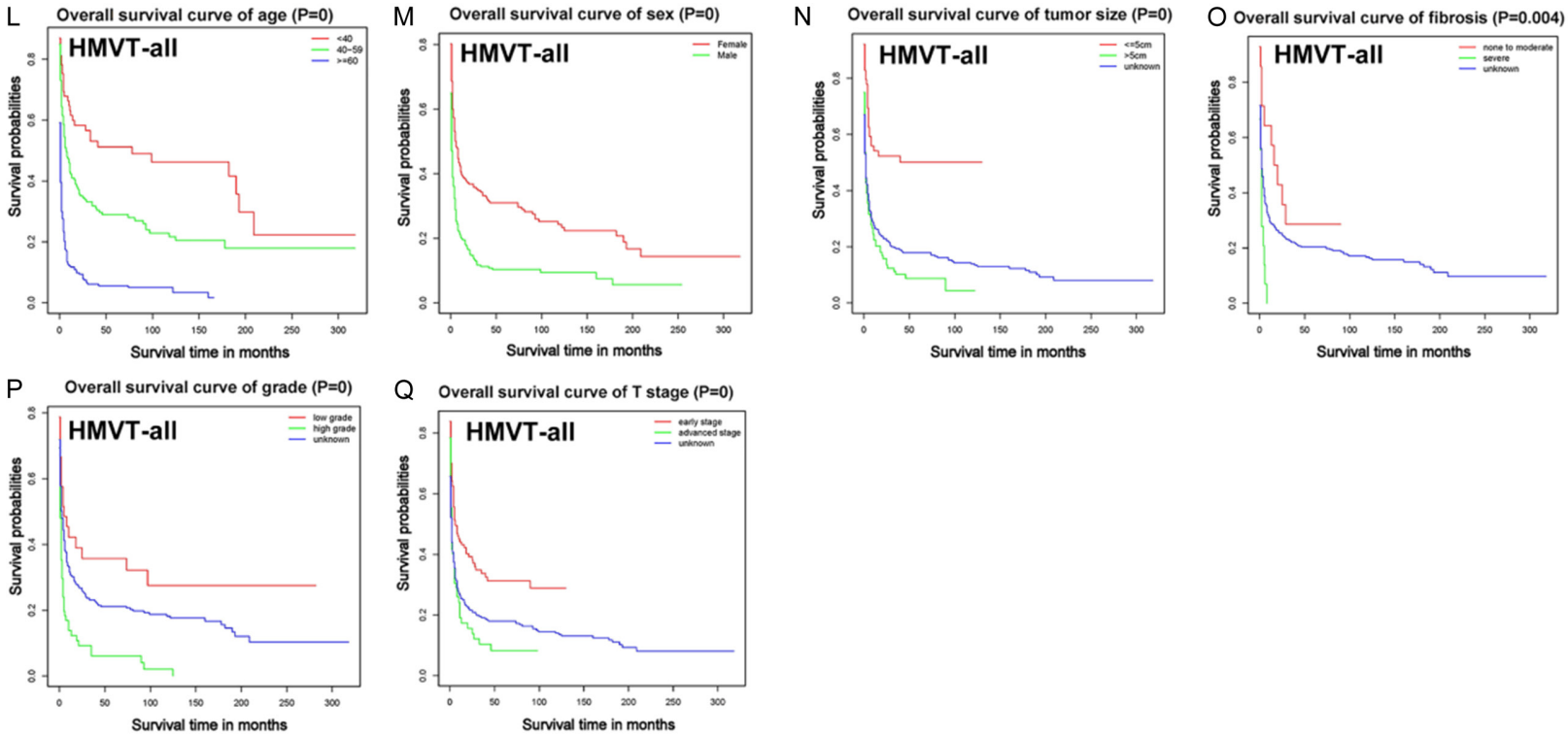
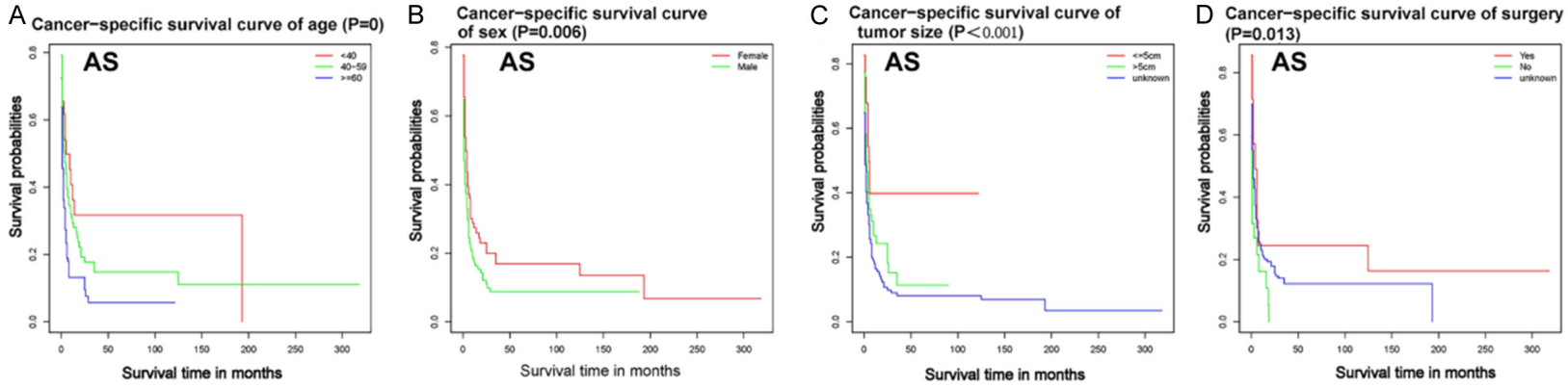


Figure 2. The Kaplan-Meier (KM) method was performed to calculate the OS classified by clinical pathologic factors for patients from diverse HMVT cohorts including AS (A-G), EHE (H-K), and HMVT-all (L-Q).



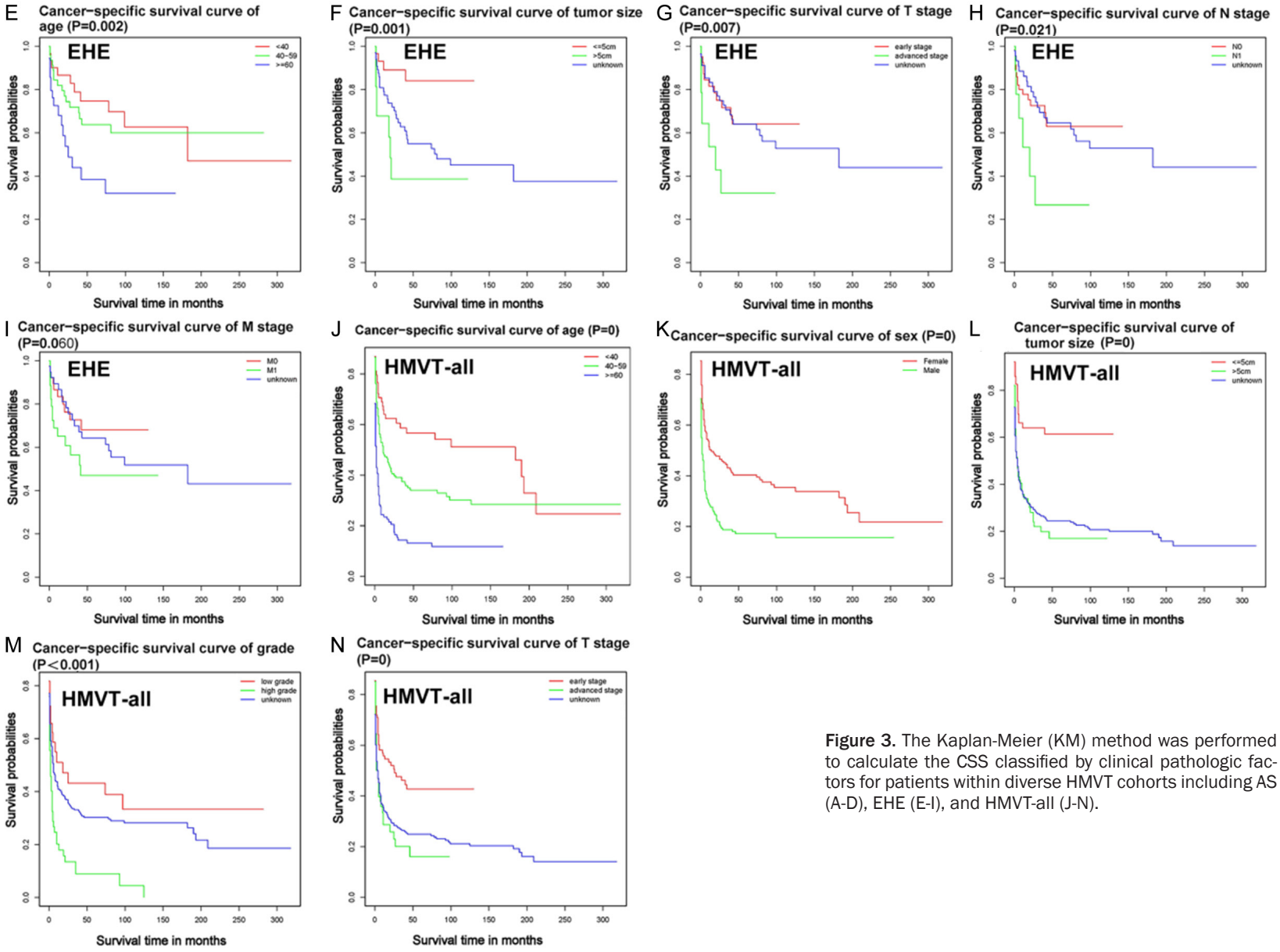


Figure 3. The Kaplan-Meier (KM) method was performed to calculate the CSS classified by clinical pathologic factors for patients within diverse HMVT cohorts including AS (A-D), EHE (E-I), and HMVT-all (J-N).

Table 3. Multivariate analysis of OS and CSS for patients with hepatic vascular tumor (HMVT)

Categories	AS (N=350)		EHE (N=114)		HMVT-all (N=510)		HMVT-training (N=308)	
	P-value, HR (95% CI)							
	OS	CSS	OS	CSS	OS	CSS	OS	CSS
Age								
<40	reference		reference		reference		reference	
40-59	0.240, 1.33 (0.83-2.16)	0.554, 1.17 (0.70-1.96)	0.548, 1.28 (0.57-2.91)	0.965, 0.98 (0.40-2.38)	0.119. 1.34 (0.93-1.94)	0.287, 1.24 (0.84-1.84)	0.063, 1.57 (0.98-2.59)	0.224, 1.37 (0.82-2.28)
≥60	<0.001, 2.46 (1.54-3.92)	0.014, 1.87 (1.13-3.08)	<0.001, 5.41 (2.41-12.16)	0.003, 3.91 (1.59-9.63)	<0.001, 3.09 (2.14-4.46)	<0.001, 2.49 (1.68-3.71)	<0.001, 3.27 (2.03-5.19)	0.002, 2.27 (1.36-3.78)
Sex								
female	reference		reference		reference		reference	
male	0.043, 1.24 (0.97-1.57)	0.042, 1.33 (1.01-1.74)			0.116, 1.18 (0.96-1.46)	0.030, 1.30 (1.03-1.65)	0.155, 1.22 (0.93-1.60)	0.119, 1.28 (0.94-1.75)
Grade								
low-grade	reference		reference		reference		reference	
high-grade				0.072, 6.62 (0.85-51.86)	0.023, 1.78 (1.08-2.91)	0.042, 1.77 (1.02-3.08)	0.089, 1.75 (0.92-3.32)	0.137, 1.75 (0.84-3.68)
Fibrosis								
none to moderate	reference		reference		reference		reference	
severe	0.311, 1.64 (0.63-4.24)	0.973, 0.98 (0.27-3.55)	0.009, 17.92 (2.04-157.43)	0.009, 30.33 (2.38-386.40)	0.334, 1.49 (0.66-3.34)	0.567, 1.37 (0.47-3.97)		0.363, 0.55 (0.15-2.01)
Tumor number								
1	reference		reference		reference		reference	
≥2		0.921, 0.00 (0.00-infinite)				0.917, 0.00 (0.00-0.005)		0.935, 0.00 (0.00-infinite)
Tumor size								
≤5 cm	reference		reference		reference		reference	
>5 cm	0.595, 1.18 (0.64-2.16)	0.964, 0.98 (0.45-2.15)	0.016, 0.24 (1.30-12.91)	0.009, 6.47 (1.61-26.06)	0.039, 1.55 (0.97-2.50)	0.003, 2.38 (133-4.26)	0.009, 2.21 (1.22-4.000)	0.043, 2.21 (1.02-4.44)
Surgery								
Yes	reference		reference		reference		reference	
No	0.022, 2.16 (1.12-4.17)	0.047, 2.08 (1.01-4.27)						
Chemotherapy								
Yes	reference		reference		reference		reference	
No	0.021, 1.48 (1.06-2.06)	0.023, 1.54 (1.06-2.22)						
Histological type								
AS					reference		reference	
HE					<0.001, 0.47 (0.31-0.71)	0.001, 0.46 (0.28-0.74)	0.004, 0.45 (0.26-0.77)	0.001, 0.34 (0.18-0.66)
EHE					<0.001, 0.30 (0.22-0.41)	<0.001, 0.30 (0.21-0.43)	<0.001, 0.27 (0.18-0.41)	<0.001, 0.23 (0.14-0.38)
HP					0.131, 0.58 (0.28-1.18)	0.314, 0.65 (0.28-1.50)	0.086, 0.41 (0.15-1.14)	0.185, 0.45 (0.14-1.47)
T stage								
early stage	reference		reference		reference		reference	
advanced stage	0.059, 0.54 (0.28-1.02)		0.044, 2.77 (1.03-7.44)	0.201, 2.19 (0.66-7.32)	0.041, 1.50 (1.02-2.20)	0.128, 1.42 (0.90-2.22)	0.464, 1.21 (0.73-1.99)	0.891, 1.05 (0.55-1.97)
N stage								
N0	reference		reference		reference		reference	
N1				0.232, 2.48 (0.56-11.02)				
M stage								
M0	reference		reference		reference		reference	
M1	0.110, 1.31 (0.94-1.84)	0.072, 1.43 (0.97-2.10)	0.028, 2.34 (1.10-4.98)	0.039, 2.81 (1.06-7.47)				

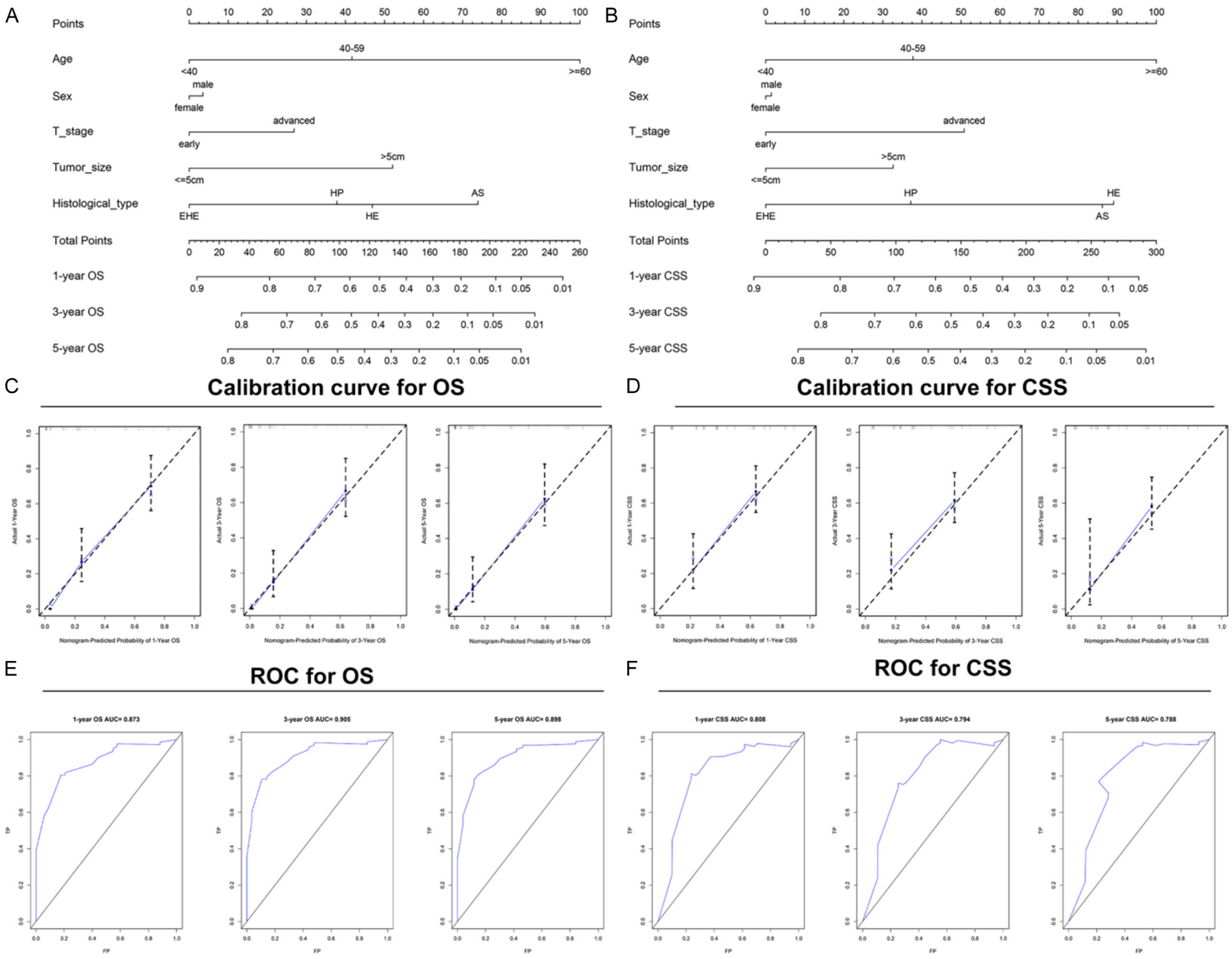

A
Points
Age
Sex
T_stage
Tumor_size
Histological_type
Total Points
1-year OS
3-year OS
5-year OS
B
Points
Age
Sex
T_stage
Tumor_size
Histological_type
Total Points
1-year CSS
3-year CSS
5-year CSS
C
Calibration curve for OS
D
Calibration curve for CSS
E
ROC for OS
1-year OS AUC= 0.873
3-year OS AUC= 0.905
5-year OS AUC= 0.898
F
ROC for CSS
1-year CSS AUC= 0.808
3-year CSS AUC= 0.794
5-year CSS AUC= 0.788

Figure 4. The establishment and evaluation of clinical prognostic nomogram models to predict 1-year, 3-year, and 5-year of OS and CSS for patients via HMVT-training cohort. (A and B) The nomogram for OS and CSS respectively. The calibration and area under the receiver operating characteristic curve (AUC) of 1-year, 3-year, and 5-year to assess the performance of predictive models for OS (C and E) and CSS (D and F). The function of this nomogram, the value of each variable for an individual patient is recorded on the corresponding axis, and the number of points obtained for each variable value is determined by drawing a line upward to the point axis. The overall scores for each patient could be found in the corresponding location in the axis of "Total Points axis". Then a line is drawn downward to the survival axes to determine the possibility of a 1-, 3- or 5-year survival rate. ROC: receiver operating characteristic curve. TP: true positive. FP: false positive.

Table 4. The detailed information of C-index and AUC for patients with HMVT within the HMVT-training, validation, and all cohort

Survival types	cohort	C-index	AUC		
		(value, 95% CI)	1-year	3-year	5-year
OS	HMVT-training	0.763 (0.708-0.819)	0.873	0.905	0.898
	HMVT-validation	0.741 (0.661-0.745)	0.788	0.843	0.843
	HMVT-all	0.751 (0.704-0.798)	0.826	0.89	0.886
CSS	HMVT-training	0.722 (0.653-0.791)	0.808	0.794	0.788
	HMVT-validation	0.743 (0.653-0.833)	0.762	0.909	0.909
	HMVT-all	0.731 (0.677-0.786)	0.781	0.895	0.885

C-index: concordance index. AUC: area under the receiver operating character curve. CI: confidence interval. OS: overall survival. CSS: cancer-specific survival.

data indicated that the nomograms based on HMVT-training cohort exhibited an authentically predictive ability.

Subsequently, the validation for the nomograms was executed in various test cohorts to further verify the reliability. The C-index values for predicting OS and CSS were 0.741 (95% CI: 0.661-0.745) and 0.743 (95% CI: 0.653-0.833) in HMVT-validation, 0.751 (95% CI: 0.704-0.798) and 0.731 (95% CI: 0.677-0.786) in HMVT-all (**Table 4**). The analysis of AUC and the calibration curves in these validated cohorts showed the consistent results that have been observed in the training cohort (**Table 4**; **Figure 5**). Collectively, these results confirmed that the established nomograms were strongly convinced and valuable in clinical practice to predict prognosis for HMVT patients. Furthermore, the nomograms for OS in the histologic type of AS and EHE were developed and the accuracy was assessed as well, exhibiting credible discrimination (Figure S3).

Next, we quantitatively calculated the risk score based on survival-related clinicopathologic factors (age, sex, grade, tumor size, and T stage) in HMVT pa-tients. To further ex-plore whether risk score could be regarded as an independent prognostic trait, we determined the median risk scores as the cutoff value to divide the patients in the HMVT-training cohorts into low-risk and high-risk groups. The OS and CSS for patients at different risk groups were analyzed using KM curves classified by clinicopathologic factors and histological types. For the analysis of OS, the patients included in the high-risk group had a shorter survival time than those who are in the low-risk group in most variables except for in the stratification of HE histologic type (**Figure 6**). Similarly, when the CSS was evaluated stratified by age at 40-59 years, sex, grade, T stage, and AS type, a longer survival time was observed in the patients within the low-risk group instead of those in the high-risk group (**Figure 7**).

Discussion

Due to the rarity of HMVT, only a few studies investigated the profile of demographic traits, clinical manifestation, and survival probability of these patients [17-19]. SEER database, maintained by the US National Cancer Institute, is the largest institution that collects and reports cancer survival and incidence data. Since this database has the feature of high quality and collecting clinical cases in a uniformly standard criterion, it would give rise to a low rate of errors and make these recorded documents more accurate and reliable. To better understand the clinicopathological traits and risk factors of this disease, we investigated the largest sample of patients with HMVT retrieved from the SEER database.

In this study, a total of 510 patients diagnosed with HMVT between 1973 and 2015 were extracted from the SEER database, which

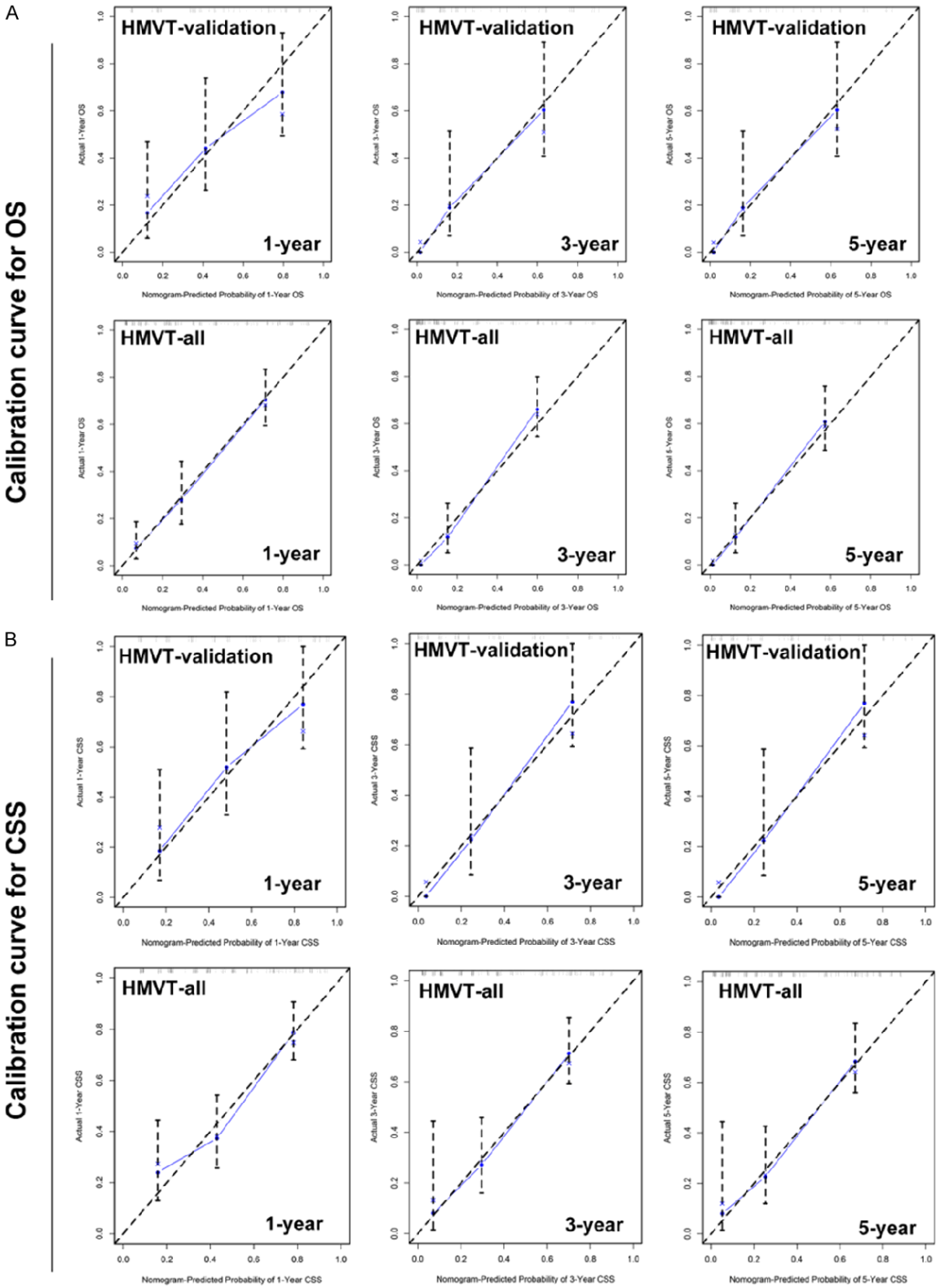


Figure 5. The calibration plots for 1-year, 3-year, and 5-year of OS (A) and CSS (B) respectively in patients from HMVT-validation and HMVT-all cohort.

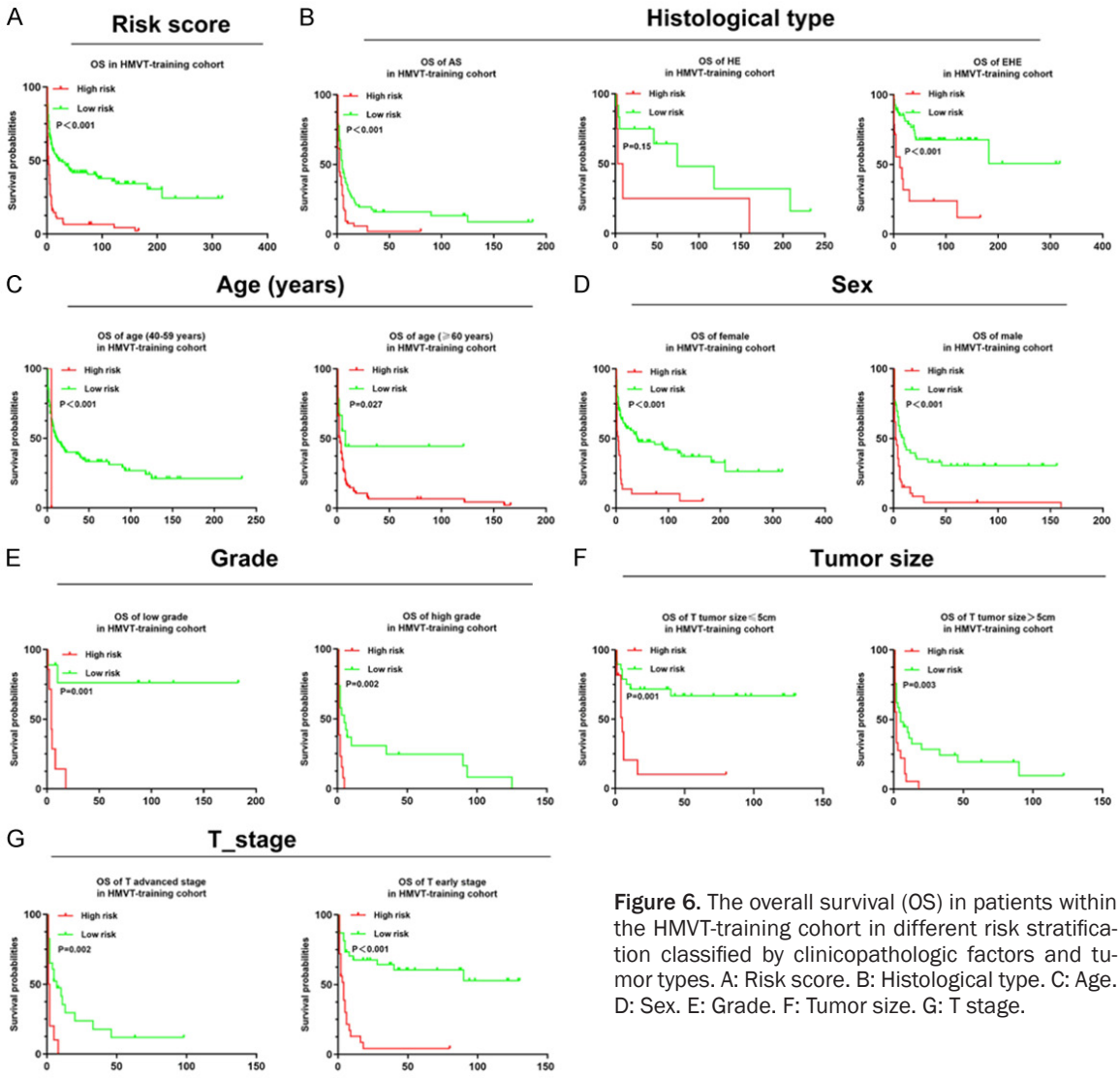


Figure 6. The overall survival (OS) in patients within the HMVT-training cohort in different risk stratification classified by clinicopathologic factors and tumor types. A: Risk score. B: Histological type. C: Age. D: Sex. E: Grade. F: Tumor size. G: T stage.

included those with AS (N=350), HE (N=37), EHE (N=114), and HP (N=9). Results revealed that the 1-, 3- and 5-year OS and CSS in the overall HMVT cohort were 28.9% and 37.9%, 21.3% and 29.8%, and 19.8% and 27.7% respectively. Concerning the specific types of HMVT, AS had the lowest 3- and 5-year OS and CSS compared with HP, EHE, and HE. HP cases were sporadic and only 9 patients were reported, of whom 5 survived 5 years after diagnosis. Recently, a retrospective study, including 42 patients with pathologically confirmed HMVT, was conducted. It was indicated that 13 patients with HE and 15 with EHE had the longest survival time, with a follow-up time of 96 and 88 months respectively, followed by 3 patients with HP (23 months). By contrast, 11 patients with AS experienced the shortest survival time (15 months) [19].

In our study, we found that the clinicopathologic traits of age ≥60 years, high tumor grade, larger tumor size (>5 cm), advanced T stage, and histological type are independent prognostic predictors associated with poorer OS in the HMVT-all cohort. However, the M stage is not a predictor of prognosis for patients in the HMVT-all cohort. In separate analyses, we further noticed that the M stage is an independent indicator of predicting survival probability for individual patients with EHE, although it was not significantly associated with prognosis in the AS cohort. Then, we reviewed the currently published researches relevant to AS and found that patients are easily diagnosed at a late stage with larger lesions of >5 cm since many patients didn't have any notably obvious anomalies in the early stage. Meanwhile, secondary symptoms including tumor bleeding, tumor rup-

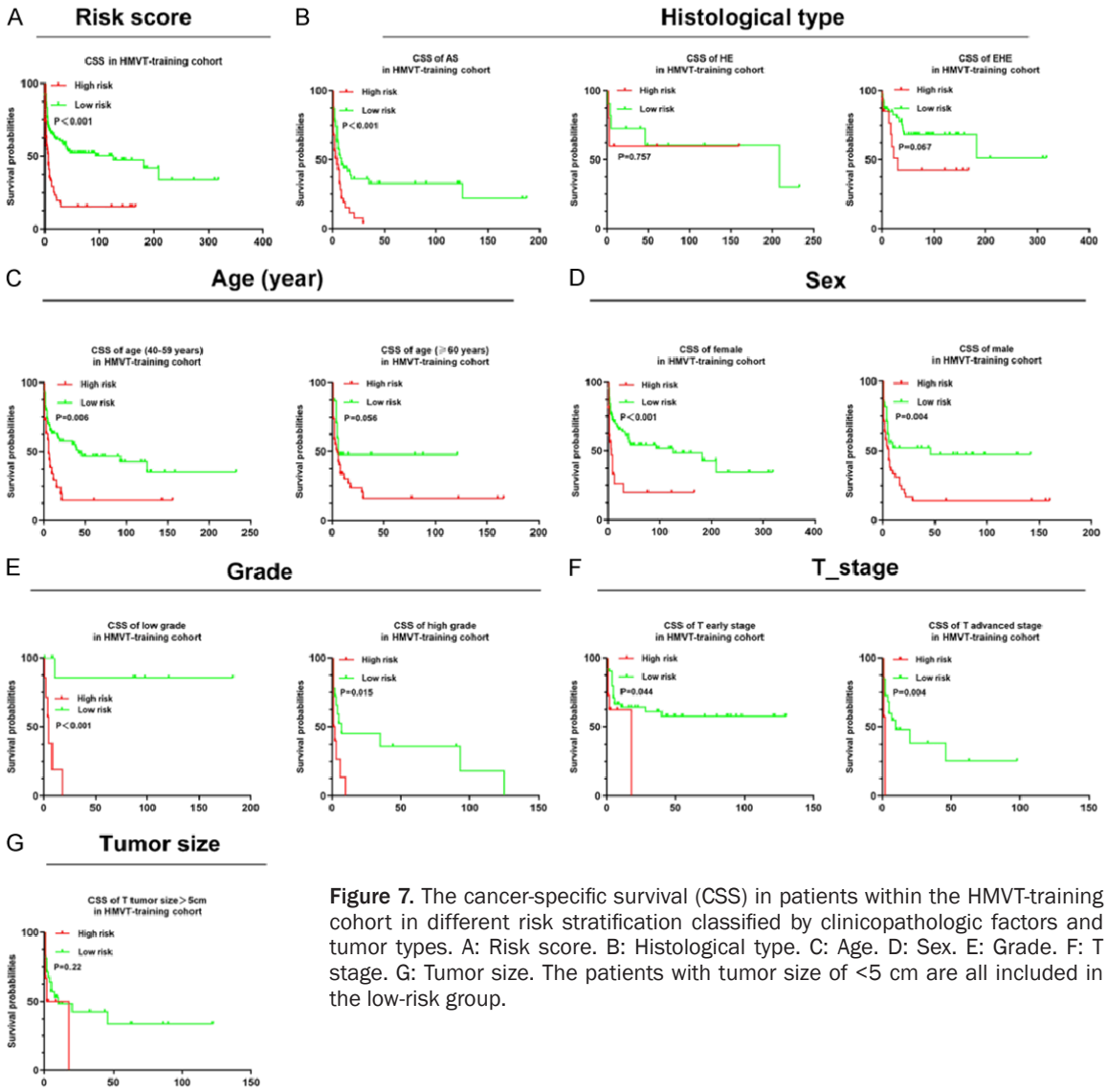


Figure 7. The cancer-specific survival (CSS) in patients within the HMVT-training cohort in different risk stratification classified by clinicopathologic factors and tumor types. A: Risk score. B: Histological type. C: Age. D: Sex. E: Grade. F: T stage. G: Tumor size. The patients with tumor size of <5 cm are all included in the low-risk group.

ture, and other complications (such as severe pneumonia, multisystem organ failure, and recurrence after surgery) are preferable to occur in AS patients at late stages. These factors could result in patients' death no matter whether or not distant metastasis is presented [20-23]. Zeng et al. performed a systematic review of the published studies worldwide from 1990 to 2019 to comprehensively analyze the main clinical traits, demographics, therapeutic strategy, and prognosis of 219 patients with AS. They also indicated that although patients with metastasis at the time of diagnosis had a significantly shorter survival time, the metastasis didn't show independent prognostic value in multivariate Cox regression. The patients who have tumor rupture would have an obviously worse prognosis [24].

Subsequently, the prognostic nomograms were established for estimating OS and CSS exhibiting a credible performance with the C-index of 0.763 and 0.722, respectively. The predictive models could be used to calculate the 1-, 3- and 5-year OS for individual patients with HMVT, with great importance in clinical practice. According to the findings in our study, we could know that the survival probability in patients with HMVT is different from hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) that ranked the first and second most common liver cancer, respectively. For the patients diagnosed with HCC or CCA at an early stage, the curative treatments including surgical resection, liver transplantation, and ablation were widely considered to be the first-line strategies. It was reported that the 5-year OS

for HCC patients referred to 70%, and the median survival time underlying intention-to-treat analysis of CCA is 36 months. However, the recurrence rate after surgery at 5-years in HCC patients was up to 70%, correspondingly, 65% for CAA. Furthermore, more than 70% of patients with HCC and CAA were at advanced stages when diagnosed, with only being left chance of palliative treatments such as transcatheter arterial chemoembolization (TACE), chemotherapy, and molecular targeted therapeutic strategies [25, 26].

Among various histological types of HMVT, AS showed the highest incidence, accounting for one-third of primary sarcomas. Histologically, AS is composed of endothelial cells with variable differentiation ability [27, 28]. Several chemical factors such as vinyl chloride, arsenic, thorotrast, and thorium dioxide were intimately associated with the development of AS, but most cases are still idiopathic and are reported worldwide [28, 29]. Molina E et al. described the survival probability of AS in five case reports, of which two patients underwent surgical treatment, and another two patients were found to have unresectable bilateral disease intraoperatively. The median survival time of the five patients was 6 months (range: 3 days to 18 months) [27]. Another retrospective study, including 60 patients with AS, indicated that the OS rate at 5 years was 20%, and surgical therapy was a significant predictor for better prognosis [30]. Although these studies provided us with some meaningful information on the survival probability of AS, due to the small sample size, knowledge on its clinicopathological traits was still limited and the prognostic predictors associated with the clinical outcomes were not explored yet. Therefore, a large sample of AS patients was used in the current study by acquiring reliable demographic and clinicopathological data from the SEER database. In this population-based study, we found that most cases with AS were diagnosed in patients aged 55-74 years, and AS infrequently occurred in those aged ≤34 years, which was consistent with the previous reports [27, 30, 31]. Meanwhile, the 1-, 3-, and 5-year OS rates were 12.6%, 5.9%, and 5.9%, respectively. The potential predictors associated with OS for AS cases were including age ≥60 years, male sex, surgery, and chemotherapy. Whereas, neither the treatment of surgery and chemotherapy nor radiation indicated the independent prognostic value in the HMVT-all cohort. The low ratio of the patients with the clear medical document of therapeutic strategies may be the potential limitation leading to the reduced analysis performance of multivariate Cox regression. In the further, the large population of patients with HMVT including treatment information is still requested to precisely elaborate the role of treatments in predicting survival probability.

HE is an extremely rare type of tumor, and its incidence rate is lower than that of AS among HMVT, the majority of previous studies on HE indicated the epithelioid type (EHE). It originates from the soft tissues and rarely occurs in the liver, suggesting its intermediate and malignant potential, although the World Health Association classification still considers EHE as a malignant sarcoma [32, 33]. The morphological features of EHE were first described by Weiss and Enzinger in 1982. The main components of EHE included rounded or slightly spindled eosinophilic endothelial cells and obvious cytoplasmic vacuolization. The absence of pleomorphism and mitotic activity in most cases and the focal features of vascular channels could distinguish this neoplasm from a carcinoma, although its growth pattern is similar to that of solid tumors and exhibits an epithelioid appearance in the endothelium [34]. The first series of hepatic EHE cases (32 cases) were reported by Ishak et al. in 1984, which described the clinical, morphologic, and follow-up data [35]. Based on this retrospective study, women (62.5%) were more affected than men (37.5%), and the average age was 49.65 years (range: 19-86 years). Meanwhile, nine patients were followed-up for 5 years or longer after the initial diagnosis. Another single institution from Pittsburgh also studied a small cohort of hepatic EHE patients, including 25 cases who either underwent surgery or embolization. The recorded median OS for all patients was 13.9 years. Two patients who underwent partial resection survived after a follow-up of 19 and 71 months respectively. Among 17 patients who had a liver transplant, lymphatic metastasis and vascular invasion were found in 6 patients (35.3%) and 11 patients (64.7%), respectively [36].

Although EHE is a rare malignant sarcoma, the number of EHE cases that occurred in various organs including the liver, are gradually increasing with the robust improvement of diagnostic techniques. To some extent, these sporadic reports contribute to our understanding of this neoplasm, such as symptoms, preferable age

at diagnosis, survival probability, effective treatments, and predictors of OS and CSS. However, these studies usually were conducted in small sample series or were case reports, and some information was contradictory since the methods of diagnosis or treatment varied in various hospitals. To further systematically describe the clinicopathological characteristics of hepatic EHE, a large sample cohort was required in future retrospective analyses. Therefore, we collected the clinical documents of patients diagnosed with hepatic EHE who were included in the SEER database between 1973 and 2015, all cases were registered according to a uniform standard. The 3- and 5-year OS rates of hepatic EHE were 60.5% and 54.8%, respectively, showing better survival trends than AS. This finding was also consistent with those of previous studies [32, 37, 38]. Moreover, we found that age ≥60 years, fibrosis level, tumor size, T stage, and M stage were risk factors associated with patients' prognosis. The prognostic nomogram model also demonstrated its reliable predictive performance that could help clinicians assess the progression of the disease and evaluate the survival probability at 3-, and 5-year for individual patients.

HP is the rarest type of HMVT derived from pericytes, which are wrapped by blood vessels and capillaries. HP commonly develops in the lower extremities, pelvis, meninges, and lung, but occurs less likely in the breast, bones, liver, and stomach [5, 39, 40]. Previous studies revealed that this tumor type is more common in middle-aged patients than in infants and children. Generally, a biopsy or tumor resection is required to verify the histopathological type, however, it is usually misdiagnosed as another type of soft tissue sarcoma due to the lack of classical traits. Therefore, the diagnosis of HP in clinical practice often relies on exclusion criteria [5, 41]. In the current study, we finally extracted the clinical data of 9 patients diagnosed with hepatic HP, the 3-and 5-year OS rates were 33.3% (3 patients) and 33.3% (3 patients). Among nine patients, only one was diagnosed at the age of <40 years, and six were diagnosed at the age of 40-59 years. The findings were similar to those reported in previous studies, indicating that HP commonly affected older adults [40, 41]. To date, surgery remains the recommended treatment for HP patients. As expected, the OS and CSS in patients with HP could be improved by surgery. However, disease recurrence after surgery remains a challenge, with an incidence of more than 30%. In this cohort, only one patient with HP underwent surgical resection and survived for 8 months.

In this study, all clinical data were carefully extracted from the same database. Uniform standards and approaches were used to evaluate practical conditions for individual patients from various aspects, which supplied strong statistical power for this retrospective study and allowed us to comprehensively analyze the clinicopathological traits of rare tumors such as HMVT. However, there are still some limitations. First, the ratio of the number of patients in the HMVT cohort with specific treatment information is low, which restricted the further precise analyses. Second, since the SEER database contained qualitative or semiquantitative data, the statistical reliability was compromised to some extent. Finally, biases were inevitably introduced due to the nature of the retrospective research.

In all, this is the largest population-based retrospective study to describe the demographic and clinicopathological characteristics of HMVT, especially concerning AS, HE, EHE, and HP. Univariate and multivariate analyses were performed to identify independent predictors associated with OS and CSS including age ≥60 years, high tumor grade, tumor size (>5 cm), and the histological type. Besides, the advanced T stage was the prognostic factor for prediction of OS in the HMVT cohort. The prognostic nomograms for estimating 1-, 3- and 5-year OS and CSS indicated a credible performance. Although our findings and novel model need to be improved by conducting further in-depth research, our results may provide new insight regarding the features and outcomes of patients with HMVT.

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Disclosure of conflict of interest

None.

Abbreviations

HMVT, Hepatic malignant vascular tumors; OS, overall survival; CSS, cancer-specific survival; AS, angiosarcoma; HE, hemangioendothelioma; EHE, epithelioid hemangioendothelioma; HP, hemangiopericytoma; MVT, Malignant vascular tumors; SEER database, Surveillance, Epidemiology, and End Results database; AFP, alpha-fetoprotein protein; TNM, tumor-node-metastasis; AUC, area under the curve; ROC, receiver operating characteristic; HRs, Hazard ratios; CIs, confidence intervals.

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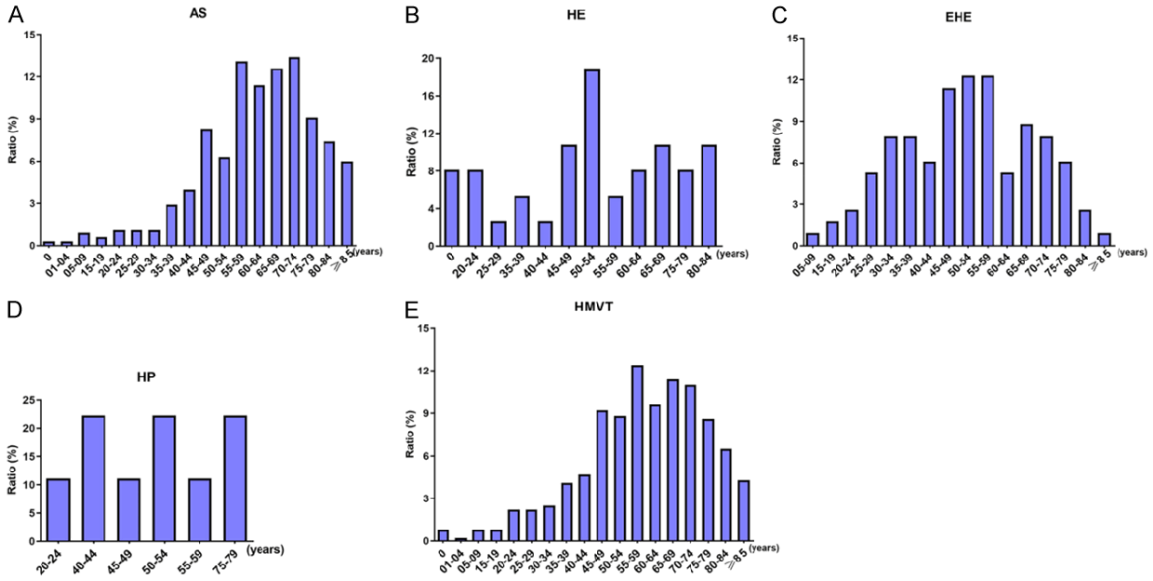

Figure S1. The age distribution for the patients with AS (A), HE (B), EHE (C), HP (D), and HMVT (E).

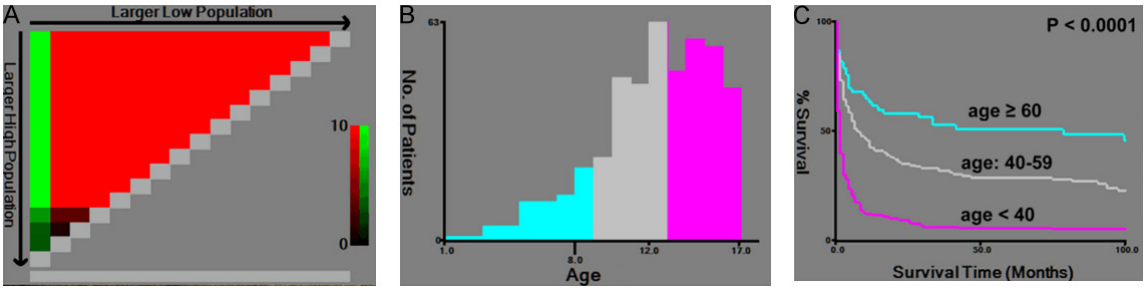

Figure S2. The X-tile software was executed to determine the cutoff value of patients' age when diagnosed with HMVT to optimize the group classification stratified by age. A and B: Showed the age distribution in all the patients with HMVT. The number of 1-17 represented the age period of 0, 1-4, 5-9, 10-19, 20-24, 35-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, and ≥80 years old respectively retrieved from SEER database. C: Indicated the overall survival (OS) among three age groups showing statistically significant with a *P*-value of <0.0001.

Table S1. Median survival time (months) for OS and CSS in patients with HMVT

Categories	AS (N=350)				EHE (N=114)				HMVT-all (N=510)			
	median time (months), 95% CI (low, high)											
	OS		CSS		OS		CSS		OS		CSS	
Age, years												
<40	4	(1.47-6.53)	5	(0.00-11.30)	182	NA	182	NA	78	(0.00-206.94)	182	(49.22-314.78)
40-59	2	(0.51-3.50)	4	(2.11-5.89)	NA		NA		7	(3.68-10.32)	11	(3.23-18.77)
≥60	1	NA	1	(0.49-1.51)	16	(1.05-30.95)	25	(8.59-41.41)	1	(0.70-1.30)	2	(1.493-2.507)
Sex												
female	2	(1.38-2.62)	3	(1.72-4.28)	93	(22.50-163.40)	182	NA	6	(3.46-8.54)	14	(0.00-28.34)
male	1	(0.68-1.32)	1	(0.45-1.55)	27	(0.00-108.82)	42	(0.00-136.59)	1	(0.55-1.45)	2	(1.15-2.85)
Grade												
low-grade									5	(0.00-13.88)	18	(0.00-44.31)
high-grade									1	(0.34-1.67)	2	(0.44-3.56)
Fibrosis												
none to moderate	2	(0.72-3.28)	25	NA	NA		NA		16	(3.17-28.83)	NA	
severe	2	(1.32-2.68)	2	(1.13-2.87)	0	NA	0	NA	2	(1.26-2.75)	2	(1.06-2.94)
Tumor number												
1	1	(0.70-1.30)	1	(0.56-1.44)	99	(0.00-201.13)	NA		2	(1.04-2.96)	4	(2.88-5.12)
≥2	2	(1.10-2.90)	NA		8	(0.00-73.46)	NA		2	(0.47-3.534	NA	
Tumor size												
≤5 cm	4	(2.06-5.94)	5	(2.17-7.83)	NA		NA		NA		NA	
>5 cm	1	(0.35-1.65)	2	(0.19-3.81)	20	(0.00-47.66)	20	(15.63-24.37)	2	(1.4322.57)	4	(2.05-5.95)
Surgery												
Yes	2	(0.00-4.75)	4	(0.00-8.36)	81	(72.24-89.77)	81	(72.24-89.77)	6	(0.38-11.62)	6	(2.01-9.99)
No	0	NA	1	(0.41-1.59)	122	(53.70-190.30)	182	(0.00-410.07)	1	(0.24-1.76)	1	(0.00-4.64)
Chemotherapy												
Yes	4	(1.74-6.26)	6	(2.81-9.19)	182	NA	182	NA	8	(2.87-1.32)	11	(2.75-19.25)
No	1	(0.71-1.30)	1	(0.53-1.47)	93	(15.69-170.31)	NA	NA	2	(1.60-2.40)	4	(2.72-5.29)
T stage												
early stage	2	(0.15-3.85)	4	(1.11-6.89)	NA		NA		6	(0.56-11.45)	26	(0.61-51.39)
advanced stage	1	(0.33-1.68)	2	(1.00-2.99)	11	(0.00-35.60)	20	(0.00-44.75)	2	(1.19-2.85)	4	(2.05-5.95)
N stage												
N0	1	(0.48-1.52)	2	(0.61-3.39)	NA		NA		3	(1.844-4.156)	5	(1.912-8.088)
N1	0	NA	1	(0.00-4.51)	20	(2.11-37.89)	20	(2.11-37.89)	5	(0.868-9.132)	5	(1.012-8.988)

NA: not applicable.

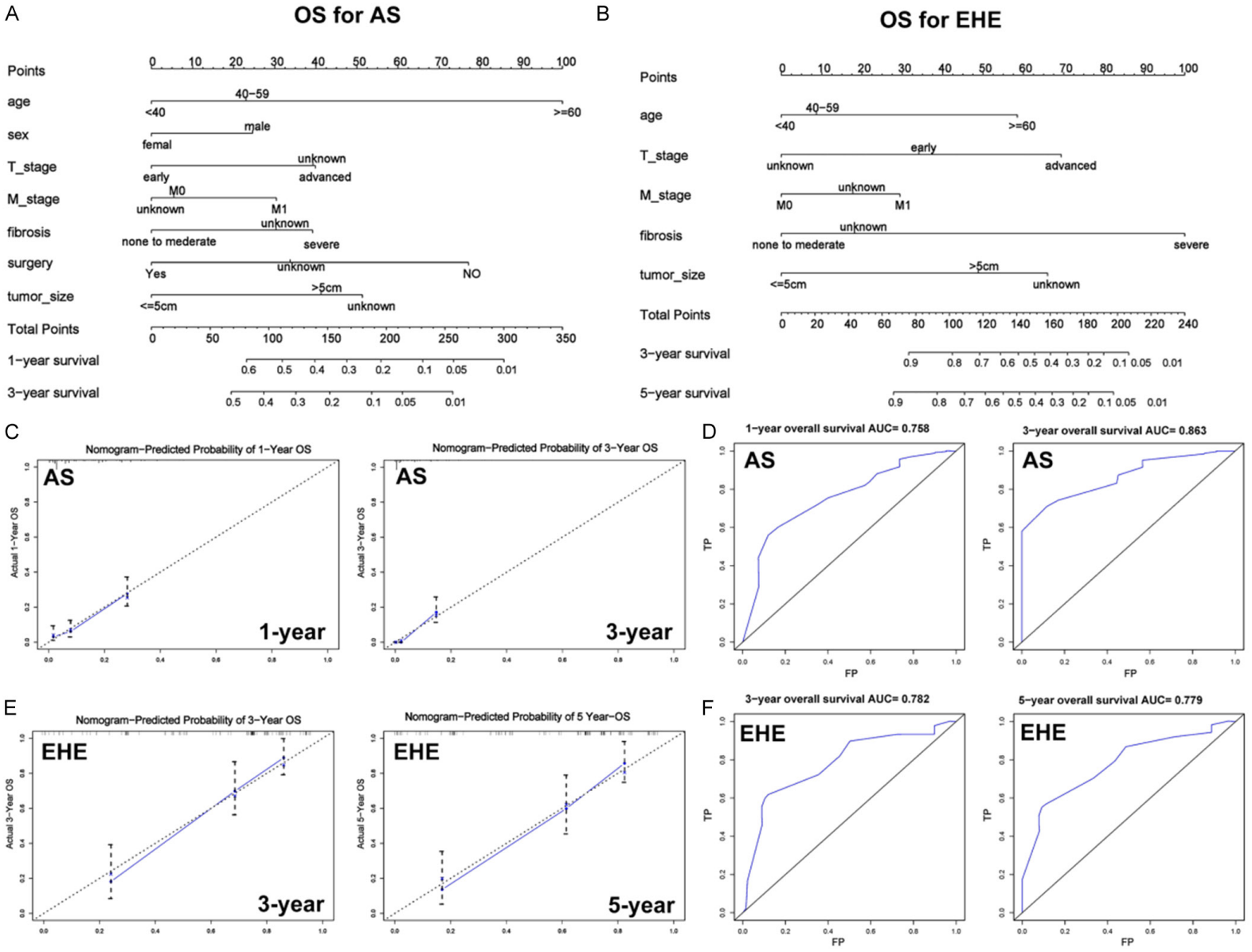

Figure S3. The establishment and evaluation of predictive nomogram models for overall survival (OS) in patients within AS and EHE cohort. A and B: The nomogram models. C and D: The calibration and area under the receiver operating characteristic curve (AUC) for patients with AS. E and F: The calibration and area under the receiver operating characteristic curve (AUC) for patients with EHE.