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Combined DeRitis ratio and alkaline phosphatase on the prediction of portal vein tumor thrombosis in patients with hepatocellular carcinoma

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Portal vein tumor thrombosis (PVTT) is one of the common complications of HCC and represents a sign of poor prognosis. PVTT signifies advanced liver cancer, deteriorating liver function, and heightened susceptibility to intrahepatic dissemination, systemic metastasis, and complications related to portal hypertension. It is important to seek novel strategies for PVTT arising from HCC. Portal vein tumor thrombus (PVTT) in hepatocellular carcinoma (HCC) represents a worse liver function, less treatment tolerance, and poor prognosis. This study aimed to investigate the diagnostic value of the combination of the DeRitis ratio (AST/ALT) and alkaline phosphatase (ALP) index (briefly named DALP) in predicting the occurrence risk of PVTT in patients with HCC. We performed a retrospective study enrolling consecutive patients with HCC from January 2017 to December 2020 in Hebei Medical University Third Hospital. ROC analysis was performed to estimate the predictive effectiveness and optimal cut-off value of DALP for PVTT occurrence in patients with HCC. Kaplan–Meier analysis revealed the survival probabilities in each subgroup according to the risk classification of DALP value. Univariate and multivariate Logistics regression analyses were applied to determine the independent risk for poor prognosis. ROC analysis revealed that the optimal cut-off value for DALP was 1.045, with an area under the curve (AUC) of 0.793 (95% CI 0.697–0.888). Based on the DALP classification (three scores: 0–2) with distinguishable prognoses, patients in the score 0 group had the best prognosis with a 1-year overall survival (OS) of 100%, whereas score 2 patients had the worst prognosis with 1-year OS of 72.4%. Similarly, there was a statistically different recurrence-free survival among the three groups. Besides, this risk classification was also associated with PVTT progression in HCC patients (odds ratio [OR] 5.822, P < 0.0001). Pathologically, patients in the score 2 group had more advanced tumors considering PVTT, extrahepatic metastasis, and ascites than those in score 0, 1 groups. Moreover, patients with a score of 2 had more severe hepatic inflammation than other groups. Combination of DeRitis ratio and ALP index presented a better predictive value for PVTT occurrence in patients with HCC, contributing to the tertiary prevention.

Keywords Hepatocellular carcinoma, Portal vein tumor thrombosis, DeRitis ratio, Alkaline phosphatase

Hepatocellular carcinoma (HCC) is a significant malignant tumor related to the digestive system. According to the Global Cancer Observatory (GLOBOCAN) in 2020, HCC ranks as the sixth most common malignancy and the third leading cause of cancer-related deaths worldwide, indicating a major global health challenge[1,2]. Particularly in China, HCC holds the fourth-highest incidence and the second-highest mortality rate among malignant

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tumors[3,4]. The main known risk factors associated with HCC include viral infections (chronic hepatitis B and C), metabolic disorders (diabetes and non-alcoholic fatty liver disease), toxic exposures (alcohol and aflatoxins), and abnormal immunity[5]. Unfortunately, the diagnosis of liver cancer at advanced stages leaves patients with limited treatment options and significantly poor survival rates.

Portal vein tumor thrombosis (PVTT), the most common form of microvascular invasion, is a frequent complication of HCC. Around 10–60% of patients diagnosed with PVTT have entered intermediate and advanced stages with the deterioration of liver function, which leads to intrahepatic and distant metastasis, contributing to merely around 2.7 months of the median survival time for HCC patients with PVTT (HCC-PVTT) after receiving supportive care[6,7]. Therefore, preventing PVTT occurrence in patients with HCC clinically represents tertiary prevention. Presently, PVTT is categorized into five grades by the Liver Cancer Study Group of Japan (LCSGJ) worldwide, including VP0, VP1, VP2, VP3, VP4. There is a significant decline in a grade-dependent manner in the overall survival rates of 1-year, 3-year, and 5-year patients. Previous studies have investigated the relationship between treatment and survival rates for patients with different grades of HCC-PVTT. However, a precise prediction of the initiation of PVTT in patients with HCC has yet been an unsolved problem[8–10]. Currently, the diagnosis of HCC-PVTT primarily relies on imaging techniques such as contrast-enhanced computer tomography (CT) and magnetic resonance imaging (MRI), lacking simple and cost-effective markers[11,12].

Growing evidence indicates that active viral replication-induced chronic inflammation increases the risk of liver cancer by creating a microenvironment that alters tissue homeostasis, cell proliferation, and genetic stability, which further enables tumors to originate, develop, and metastasize[13,14], suggestive of the compromised liver environment contributes to the PVTT and the metastasis of tumor cells. Meanwhile, liver damage caused by the persistent HBV/HCV infection triggers increases in liver enzyme levels, like as serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), especially for the DeRitis ratio (AST/ALT) in recent years[15–17], is significantly correlated with the severity of diseases and adverse outcomes. The DeRitis ratio is considered a reliable predictor of liver function damage, with an elevated ratio indicating tumor progression and deterioration of liver functional reserve. Studies have reported that the DeRitis ratio was greater than 1, representing severe liver inflammation, potentially contributing to the development of liver cancer and tumor metastasis[18,19]. Parallelly, as a hydrolytic enzyme primarily distributed in the liver, bone, and kidney, alkaline phosphatase (ALP) also plays an important role in the occurrence and development of HCC along positively correlated with poor prognosis. Moreover, recent literature also displays that ALP is considered an independent prognostic factor and the most predictive factor of HCC[20,21]. Potentially, combine of DeRitis ratio and ALP may be effective in the prediction of PVTT in patients with HCC[22,23]. Herein, we aim to establish a scoring system based on the combined DeRitis ratio and ALP to predict the occurrence risk of PVTT in patients with HCC.

Materials and methods

Participants and study design

In this retrospective study, patients with HCC admitted to Hebei Medical University Third Hospital from January 2017 to December 2020 were enrolled. This study conformed to the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Hebei Medical University Third Hospital (Approve Number: KS2023-068-1). Due to the study's retrospective nature, the requirement for informed consent was waived by the Ethics Committee of Hebei Medical University Third Hospital. The inclusion criteria for HCC patients were as follows: (a) newly diagnosed with HCC based on radiological diagnosis or pathological examination; (b) no history of radiotherapy, chemotherapy or anti-inflammatory treatment; (c) no other malignant tumors or related infectious diseases; and (d) complete clinical and pathological data. The exclusion criteria included: (a) simultaneous malignancies; (b) with secondary hepatic carcinoma; (c) incomplete clinical and follow-up data. Finally, 102 HCC patients (68 with and 34 without PVTT) were included in the current study (Fig. 1).

Clinicopathologic parameters and follow-up

Patient demographic information, including age and sex, and clinicopathological features, including liver function and tumor-related parameters, were obtained through a medical electronic record system. All the HCC patients were classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Size, number, neovascularization, and extrahepatic metastasis in tumors were evaluated by computed tomography (CT) scan or contrast-enhanced magnetic resonance imaging (MRI) and pathology examinations, respectively. Follow-up was defined as end up at the date (December 2023) of the final visit for patients alive or the date of death for patients with HCC before the final time.

Laboratory parameters and definitions

The laboratory data were obtained from the patients' first venous blood samples taken at admission. The outcome of in-hospital patients with HCC was gotten from medical records, including alanine transaminase, aspartate transaminase, alpha-fetoprotein, alkaline phosphatase, white blood cell count, neutrophil count, lymphocyte count, etc.

Combination of DeRitis ratio (AST/ALT) and alkaline phosphatase (ALP) index was briefly named DALP[24]. Based on the DALP classification, three subgroups were defined as: score 0, AST/ALT ≤ 1.045 and ALP ≤ 120.5 U/L; score 1, AST/ALT ≤ 1.045, ALP > 120.5 U/L and AST/ALT > 1.045, ALP ≤ 120.5 U/L; score 2, AST/ALT > 1.045 and ALP > 120.5 U/L.

Statistical analysis

Statistical analyses were carried out using SPSS version 25.0 (IBM, Armonk, New York, USA). Quantitative data was described by a mean (SD). Among them, independent sample *t* test was used for comparing normally

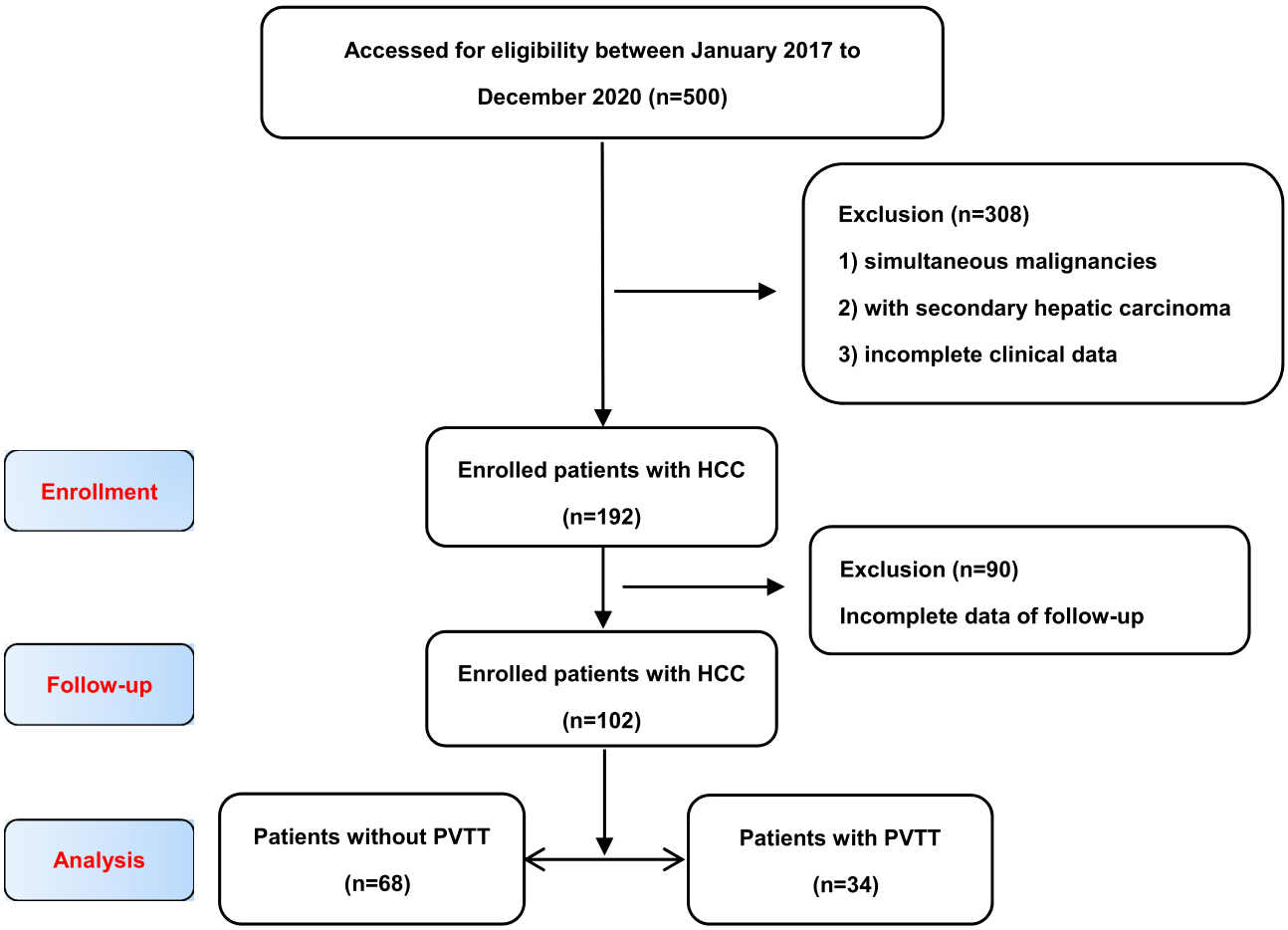

Fig. 1. Participant flow. *HCC* hepatocellular carcinoma, *PVTT* portal vein tumor thrombus.

distributed data, Mann–Whitney *U* test was used for comparing non-normal distributed data between two groups. Categorical variables were shown as numbers (frequency) and were compared using Chi-squared test or Fisher's exact tests. Survival curve was plotted using the Kaplan–Meier method with log-rank test. The multiple comparisons was adjusted by the Bonferroni correction. The optimal cut-off value of the DALP was determined by receiver operating characteristic (ROC) curve. Logistics regression analysis was utilized to identify independent risk factors. Significant variables in univariate analyses were brought into the multivariate model analysis. Multivariate analysis with the forward stepwise method was used to avoid the multicollinearity. Two-sided $P < 0.05$ was considered statistically significant ($P < 0.017$ after Bonferroni correction).

Results

Characteristics of patients with HCC

In total, 102 patients were included in the study (Fig. 1), and baseline characteristics were displayed in Table 1. The mean age was 55.8 ± 9.3 years, 87 patients were males (85.3%). 27 patients (26.5%) had ascites. Aspects of oncology features, 69 patients (67.6%) showed AFP > 20 ng/mL. 50 cases (49%) with tumor size > 5 cm, 52 cases (50.9%) with multiple tumors, 37 cases (36.3%) in BCLC-C or -D stages, and 34 patients (33.3%) had PVTT. After comparison, statistical variables between the PVTT group (n = 34) and the non-PVTT group (n = 68) included ascites, BCLC Stage, extrahepatic metastasis, Tumor size, TBIL, DBIL, DeRitis ratio, NEUT, WBC, PLT, PT, ALP, A/G (all $P < 0.05$, Table 1).

Patients in the PVTT group were typically diagnosed at the advanced stages of BCLC (C or even D stages), with a large tumor size and prone to extrahepatic metastasis. Moreover, the 1-year survival rate of patients with PVTT was apparently lower than that of patients in the none-PVTT group. Furthermore, they had significantly higher levels of TBIL, DBIL, DeRitis ratio, NEUT, WBC, PLT, PT, ALP, and DAPL compared to patients in the none-PVTT group (all $P < 0.05$), suggestive of higher levels of inflammation and altered coagulation function in the PVTT group compared to the none-PVTT group (Table 1).

Multivariate analysis of risk factors related to PVTT

To corroborate the independent risk factors impacting the occurrence of PVTT in patients with HCC, the above significant variables from Table 1 were included in the multivariate model with the forward stepwise method. The results of multivariate analysis revealed that WBC (OR 1.244, 95% CI 1.047–1.480, P = 0.013) and DALP

Variable	Total (n = 102)	None-PVTT (n = 68)	PVTT (n = 34)	P value
Male	87 (85.3%)	58 (85.3%)	29 (85.3%)	1.000
Age (years)	55.8 (9.3)	56.5 (9.2)	54.4 (9.6)	0.696
Obesity	49 (48.0%)	32 (47.1%)	17 (50.0%)	0.779
1-year death	11 (10.8%)	0 (0.0%)	11 (32.4%)	< 0.001
Diabetes	6 (5.9%)	4 (5.9%)	2 (5.9%)	1.000
Hypertension	30 (29.4%)	18 (26.5%)	12 (35.3%)	0.357
Alcohol	36 (35.3%)	22 (32.4%)	14 (41.2%)	0.379
Smoke	40 (39.2%)	25 (36.8%)	15 (44.1%)	0.473
Ascites	27 (26.5%)	12 (17.6%)	15 (44.1%)	0.004
AFP				0.073
≤ 20 ng/mL	33 (32.4%)	26 (38.2%)	7 (20.6%)	
> 20 ng/mL	69 (67.6%)	42 (61.8%)	27 (79.4%)	
BCLC stage				< 0.001
A	36 (35.3%)	36 (52.9%)	0 (0.0%)	
B	29 (28.4%)	29 (42.6%)	0 (0.0%)	
C + D	37 (36.3%)	3 (4.4%)	34 (100.0%)	
Extrahepatic metastasis	16 (15.7%)	3 (4.4%)	13 (38.2%)	< 0.001
Tumor number				0.123
Single	50 (49%)	37 (54.4%)	13 (38.2%)	
Multiple	52 (51%)	31 (45.6%)	21 (61.8%)	
Tumor size (cm)				0.025
≤ 5	52 (51%)	40 (58.8%)	12 (35.3%)	
> 5	50 (49%)	28 (41.2%)	22 (64.7%)	
TBIL (μmol/L)	52.85 (71.48)	42.15 (62.55)	74.24 (83.59)	0.002
DBIL (μmol/L)	32.43 (56.36)	25.21 (50.14)	46.86 (65.54)	0.002
TG (mmol/L)	1.28 (1.08)	1.06 (0.73)	1.71 (1.48)	0.086
TC (mmol/L)	3.94 (1.26)	3.95 (1.17)	3.89 (1.45)	0.454
AST (U/L)	98.17 (159)	59.60 (53.62)	175.32 (249.69)	0.002
ALT (U/L)	75.09 (177.5)	54.60 (52.25)	116.08 (297.18)	0.180
DeRitis ratio	1.48 (0.96)	1.24 (0.69)	1.97 (1.23)	0.001
HDL (mmol/L)	0.98 (0.43)	1.01 (0.41)	0.93 (0.48)	0.427
LDL (mmol/L)	2.27 (0.92)	2.36 (0.75)	2.09 (1.17)	0.196
NEUT (10^9/L)	3.88 (2.58)	3.31 (2.04)	5.04 (3.15)	0.001
WBC (10^9/L)	5.77 (3.09)	5.15 (2.60)	7.00 (3.64)	0.005
LYM (10^9/L)	1.30 (0.69)	1.30 (0.67)	1.28 (0.74)	0.652
MONO (10^{12}/L)	0.50 (0.39)	0.45 (0.29)	0.60 (0.53)	0.072
RBC (10^{12}/L)	4.11 (0.83)	4.12 (0.71)	4.10 (1.05)	0.910
HGB (g/L)	126.35 (21.85)	128.33 (21.24)	122.38 (22.83)	0.196
PLT (10^9/L)	126.43 (74.41)	110.98 (57.58)	157.34 (93.47)	0.018
PT (s)	14.07 (3.62)	13.36 (2.06)	15.49 (5.33)	0.010
TP (g/L)	65.81 (8.13)	65.76 (7.53)	65.90 (9.31)	0.934
ALB (g/L)	36.65 (7.25)	37.81 (6.43)	34.34 (8.30)	0.022
GLB (g/L)	28.90 (7.57)	27.87 (6.41)	30.96 (9.26)	0.060
A/G	1.37 (0.50)	1.43 (0.43)	1.25 (0.62)	0.028
ALP (U/L)	129.51 (78.3)	107.51 (52.43)	173.5 (100.95)	< 0.001
DALP				< 0.001
Score 0	32 (31.4%)	29 (42.6%)	3 (8.8%)	
Score 1	41 (40.2%)	31 (45.6%)	10 (29.4%)	
Score 2	29 (28.4%)	8 (11.8%)	21 (61.8%)	

Table 1. Characteristics and laboratory data of patients with HCC (n = 102). *AFP* Alpha-fetoprotein, *BCLC* Barcelona clinic liver cancer, *TBIL* total bilirubin, *DBIL* direct bilirubin, *TG* triglyceride, *TC* total cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase; DeRitis ratio, AST/ALT, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NEUT* neutrophil, *WBC* white blood cell, *LYM* lymphocyte, *MONO* monocytes, *RBC* red blood cell, *HGB* hemoglobin, *PLT* platelet, *PT* prothrombin time, *TP* total protein, *ALB* albumin, *GLB* globulin, *A/G* albumin/globulin, *ALP* alkaline phosphatase, *DAPL* DeRitis ratio, ALP.

(OR 5.822, 95% CI 2.717–12.477, P < 0.0001) were independent risk factors of PVTT, positively associated with their increase in patients with HCC (Table 2).

ROC curve analysis for the predictive value of DALP on PVTT

ROC curves analysis further showed that despite the AUC of DeRitis Ratio and ALP was 0.698 and 0.732, respectively, the AUC of the joint probability of DALP was 0.753 (95% CI 0.645–0.861), as well as the combined score of DALP was 0.793 (95% CI 0.697–0.888), as shown in Table 3. Visually shown in Fig. 2, the combined score of DALP had a significantly better predictive capability for the occurrence of PVTT in patients with HCC, compared to the combined probabilities of the two indicators or each marker.

DALP classification correlated with clinic pathological parameters

Next, HCC patients with different DALP scores were further classified into three groups (32 cases with a score of 0, 41 cases with a score of 1, and 29 cases with a score of 2). Of them, patients with score 2 exhibited significant characteristics of tumor invasiveness (including the presence of PVTT, BCLC-C, D stages, and extrahepatic metastasis) and ascites, together with the lowest levels of albumin and the A/G ratio. In contrast, patients with score 0 showed the highest proportion of early-stage BCLC and the highest levels of hemoglobin, as well as low

	β	SE	Wald χ^2	P value	OR	95% CI
Ascites				0.145		
AFP > 20/≤ 20 ng/mL				0.144		
Tumor size (cm): > 5/≤ 5				0.380		
TBIL (μmol/L)				0.775		
DBIL (μmol/L)				0.846		
TG (mmol/L)				0.075		
NEUT (10^9/L)				0.884		
WBC (10^9/L)	0.219	0.088	6.125	0.013	1.244	1.047–1.480
MONO (10^{12}/L)				0.815		
PLT (10^9/L)				0.622		
PT (s)				0.093		
A/G				0.715		
DALP (score 2 vs. 1 vs. 0)	1.762	0.389	20.518	< 0.001	5.822	2.717–12.477

Table 2. Multivariate logistic regression of risk factors for PVTT. *AFP* Alpha-fetoprotein, *TBIL* total Bilirubin, *DBIL* direct bilirubin, *TG* triglyceride, *NEUT* neutrophil, *WBC* white blood cell, *MONO* monocytes, *PLT* platelet, *PT* prothrombin time, *A/G* albumin/globulin, *ALP* alkaline phosphatase, *DAPL* DeRitis ratio and ALP.

Indicates	AUC	Cut-off value	Sensitivity%	Specificity%	P value
DeRitis ratio	0.698	1.045	82.4	52.9	0.001
ALP	0.732	120.5	70.6	77.9	< 0.001
DALP joint probability	0.753	0.306	70.6	76.5	< 0.001
DALP combined score	0.793	1.5	61.8	88.2	< 0.001

Table 3. ROC curve evaluation of different indicators for predicting PVTT.

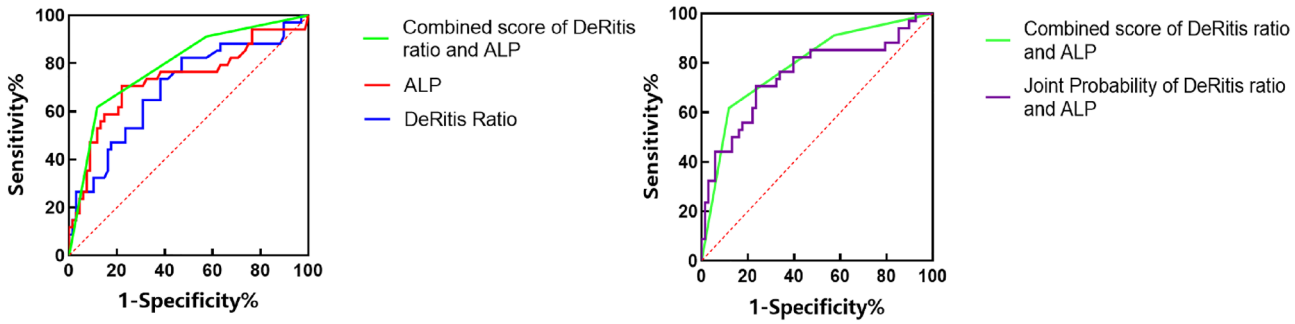

Fig. 2. ROC curves assessing the predictive ability of DALP in PVTT.

levels of TBIL, DBIL, and GLB (all P < 0.05, Table 4). These results suggested that a higher score of DALP was positively associated with advanced-stage HCC.

Survival curve analysis

Based on DALP score stratification, the results of survival analysis showed that patients with score 2 presented the poorest survival in terms of 1-year overall survival (score 0 vs. 1: P = 0.121, score 1 vs. 2: P = 0.019, score 0 vs. 2: P = 0.002) and recurrence-free survival (score 0 vs. 1: P = 0.843, score 1 vs. 2: P < 0.0001, score 0 vs. 2: P < 0.001) among three groups (Fig. 3).

Variable	Combined scoring based on serum DALP			P value			
	0 score (n = 32)	1 score (n = 41)	2 score (n = 29)	All	0 vs. 1	1 vs. 2	0 vs. 2
Male	31 (96.9%)	31 (75.6%)	25 (86.2%)	0.031	0.028	0.275	0.182
Age (years)	55.38 (8.90)	57.83 (8.78)	53.41 (10.23)	0.143			
Obesity	20 (62.5%)	15 (36.6%)	14 (48.3%)	0.095			
1-year death	0 (0.0%)	3 (7.3%)	8 (27.6%)	0.002*	0.251	0.050	0.001
Diabetes	2 (6.3%)	1 (2.4%)	3 (10.3%)	0.371			
Hypertension	8 (25.0%)	11 (26.8%)	11 (37.9%)	0.537			
Alcohol	15 (46.9%)	13 (31.7%)	8 (27.6%)	0.241			
Smoke	14 (43.8%)	15 (36.6%)	11 (37.9%)	0.844			
Ascites	3 (9.4%)	13 (31.7%)	11 (37.9%)	0.024*	0.022	0.589	0.008
AFP: > 20 ng/mL	19 (59.4%)	27 (65.9%)	23 (79.3%)	0.239			
BCLC stage				< 0.0001*	0.048	0.004	< 0.001
A	18 (56.3%)	14 (34.1%)	4 (13.8%)				
B	11 (34.4%)	14 (34.1%)	4 (13.8%)				
C + D	3 (9.4%)	13 (31.8%)	21 (72.4%)				
Extrahepatic metastasis	1 (3.1%)	7 (17.1%)	8 (27.6%)	0.021*	0.072	0.291	0.01
Multiple tumor	14 (43.8%)	19 (46.3%)	19 (65.5%)	0.183			
Tumor size (cm): > 5	11 (34.4%)	21 (51.2%)	18 (62.1%)	0.095			
PVTT	3 (9.4%)	10 (24.4%)	21 (72.4%)	< 0.001	0.096	< 0.001	< 0.001
TBIL (μmol/L)	28.76 (49.35)	55.13 (71.50)	76.20 (84.84)	< 0.001	0.012	< 0.001	0.522
DBIL (μmol/L)	15.74 (40.50)	33.34 (54.34)	49.56 (69.28)	< 0.001	0.007	0.558	< 0.001
TG (mmol/L)	1.24 (0.91)	0.97 (0.69)	1.76 (1.49)	0.006	0.196	0.005	0.599
TC (mmol/L)	4.26 (1.12)	3.79 (1.41)	3.78 (1.15)	0.163			
HDL (mmol/L)	1.00 (0.36)	0.95 (0.46)	1.01 (0.46)	0.812			
LDL (mmol/L)	2.37 (0.80)	2.33 (0.83)	2.08 (1.13)	0.470			
NEUT (10^9/L)	3.54 (1.84)	3.60 (2.59)	4.67 (3.14)	0.150			
WBC (10^9/L)	5.68 (2.56)	5.38 (3.04)	6.41 (3.65)	0.330			
LYM (10^9/L)	1.48 (0.79)	1.28 (0.70)	1.12 (0.48)	0.161			
MONO (10^{12}/L)	0.49 (0.37)	0.45 (0.23)	0.58 (0.56)	0.689			
RBC (10^{12}/L)	4.28 (0.70)	4.07 (0.92)	4.00 (0.84)	0.210			
HGB (g/L)	134.4 (17.72)	124.46 (21.65)	120.07 (24.16)	0.030	0.118	1.000	0.038
PLT (10^9/L)	113.54 (61.21)	113.12 (58.03)	159.48 (97.11)	0.099			
PT (s)	13.57 (1.90)	13.96 (3.98)	14.83 (4.46)	0.284			
TP (g/L)	64.61 (7.97)	66.30 (7.96)	66.44 (8.64)	0.882			
ALB (g/L)	39.38 (6.62)	37.18 (7.11)	32.89 (6.73)	0.001	0.805	0.013	0.001
GLB (g/L)	25.31 (6.12)	29.11 (6.39)	32.55 (8.86)	< 0.001	0.035	0.269	< 0.001
A/G	1.64 (0.47)	1.34 (0.39)	1.12 (0.54)	< 0.001	0.056	0.035	< 0.001

Table 4. Comparison of characteristics combined scoring based on serum DALP. *AFP* Alpha-fetoprotein, *BCLC* Barcelona clinic liver cancer, *TBIL* total bilirubin, *DBIL* direct bilirubin, *TG* triglyceride, *TC* total cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase; DeRitis ratio, AST/ALT, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NEUT* neutrophil, *WBC* white blood cell, *LYM* lymphocyte, *MONO* monocytes, *RBC* red blood cell, *HGB* hemoglobin, *PLT* platelet, *PT* prothrombin time, *TP* total protein, *ALB* albumin, *GLB* globulin, *A/G* albumin/globulin, *ALP* alkaline phosphatase, *DAPL* DeRitis ratio and ALP.

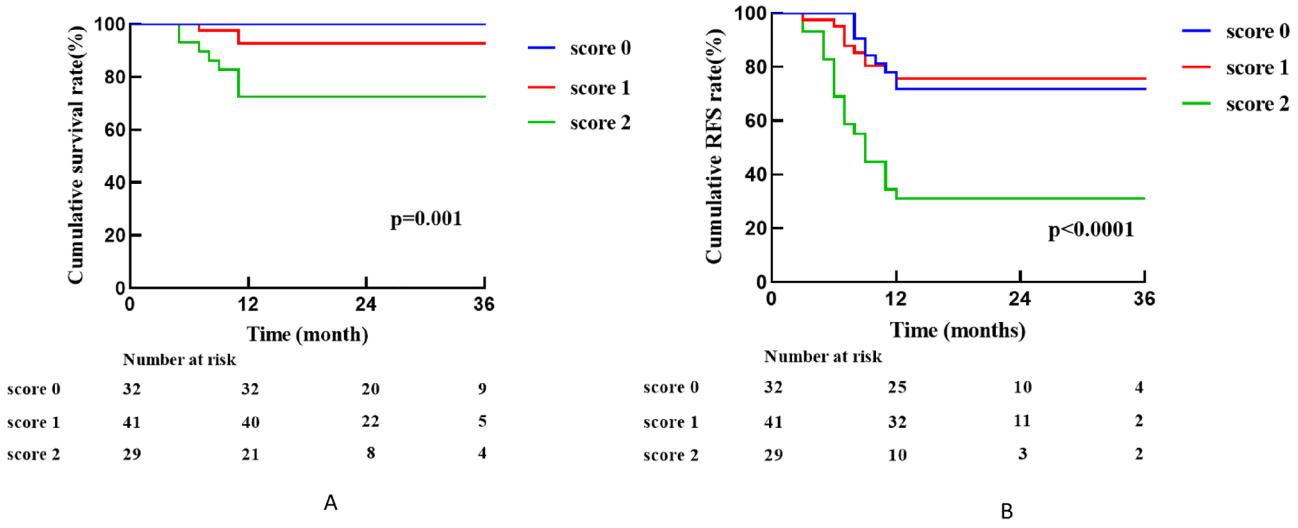

Fig. 3. Cumulative OS and RFS curves according to DALP score. (**A**) Cumulative OS curves of patients with HCC. (**B**) Cumulative RFS curves of patients with HCC. *OS* overall survival, *RFS* recurrence-free survival.

Discussion

PVTT is a common clinical manifestation of HCC and serves as a hallmark of advanced stages of the disease[6,7]. Currently, there is a scarcity of reliable methods or tools available for predicting the prognosis of HCC patients who have not yet developed PVTT. As key enzymes in metabolic processes, the serum levels of AST, ALT, and ALP are routinely assessed to evaluate liver function. Recent studies have highlighted the potential of inexpensive and readily accessible non-invasive biomarkers, such as the DeRitis ratio (AST/ALT) and ALP, as valuable prognostic indicators for predicting disease progression and long-term survival in HCC patients[20,25] and other diseases[26–30], irrespective of the etiology[31]. However, research on the association between baseline DeRitis ratio, ALP, and the development of PVTT in HCC patients is limited.

In this study, we established a simple scoring system based on the admission value of the combination of DeRitis ratio and ALP (DALP) to predict the occurrence of PVTT. ROC analysis revealed that this scoring system predicted PVTT occurrence better than using either marker alone (AUC 0.793, 95% CI 0.697–0.888, $P < 0.0001$), with the optimal cut-off value for the DeRitis ratio being 1.045. An DeRitis ratio > 1 often signifies severe liver inflammation as well as the occurrence and metastasis of liver cancer[18,19]. In our study, the optimal cut-off value of 1.045 for the DeRitis ratio was closely resembled the ratio of 1 used in prior research. Comparison of baseline characteristics between different DALP scores showed that the DALP score was associated with aggressive HCC, poor prognosis, and increased occurrence of PVTT. Univariate and multivariate analyses further confirmed that the DALP score is an independent risk factor for PVTT. Most importantly, the DALP score can be easily accessible, and its detection is affordable owing to the routine examination of AST, ALT, and ALP prior to clinical treatment. Therefore, we believe that the DALP score can serve as a new biomarker to accurately predict the development in HCC patients. Similarly, Liu et al.[32] reported that combining the DeRitis ratio with the neutrophil–lymphocyte ratio (NLR) was able to improve prognostic accuracy in HCC patients undergoing TACE. Additionally, Mo et al.[32,33] also developed a nomogram exhibited a superior predictive value of DeRitis ratio for the prognosis in HBV-related HCC patients.

The underlying pathophysiology mechanisms by which an elevated DALP score is associated with the occurrence of PVTT in HCC patients remains unclear. ALT is primarily found in the cytoplasm of hepatocytes, while AST is present in both the cytoplasm and mitochondria. When cellular and mitochondrial membrane integrity is compromised, both of them are released into the bloodstream, resulting in elevated serum levels. Due to the high energy demands for rapid proliferation, tumor cells often exhibit increased aerobic glycolysis, enhancing glucose uptake. AST plays a crucial role in the malate-aspartate shuttle pathway, and its activity, as well as the DeRitis ratio, is frequently elevated in cancer patients. Additionally, the hydrolytic enzyme ALP secreted by injured liver, bones, and intestine tissues acts as cell proliferation via a dephosphorylating mechanism. Particularly, it plays a pivotal role in promoting cancer cell proliferation, vascular invasion, and metastasis, significantly affecting the prognosis of cancer patients[26,34], like as HCC[35,36]. Given the above mechanisms, high tumor progression activity and impaired mitochondrial function may lead to increased AST/ALT release into the bloodstream, along with decreased clearance of AST/ALT as liver function deteriorates. Therefore, an elevated baseline DeRitis ratio and ALP levels comprehensively reflect tumor progression and deterioration of liver functional reserve.

However, there were some limitations in the present study. Firstly, this was a single-center retrospective and observational study, which means selection bias and incomplete clinical information. Secondly, HBV-related indicators (HBsAg titers, HBV DNA levels, positive or negative test results, HBV treatment) were not included in the current analysis and these aspects were reported associated with PVTT[37]. In addition, the sample size of patients with HCC complicated by PVTT was small, and the diagnosis of these patients relied solely on clinical imaging without a gold standard. Recent literatures have shown that neoplastic thrombosis-associated PIVKA-II

retains significant diagnostic capabilities for AFP-negative HCC patients, particularly among Asian populations. Combining PIVKA-II and AFP has been suggested as a potential new approach for surveillance[38–40]. Although our study did not include PIVKA-II data due to its absence in our database, the DALP scoring system also demonstrated good diagnostic performance for PVTT in HCC patients. In the future, larger-scale, multicenter, prospective studies are needed to incorporate these parameters to further validate their effectiveness.

Conclusion

Our study revealed significant risk factors associated with the occurrence of PVTT in patients with HCC and developed a prognostic DALP score classification, which could accurately predict PVTT, achieving early intervention and improving survival rate. These findings advocate for the active implementation of tertiary prevention strategies and hold promise for improving patient prognosis.

Data availability

Raw data for this study were generated at Hebei Medical University Third Hospital. Derived data supporting the findings of this study are available from the corresponding author upon request.

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Author contributions
S.Z. and M.D. conceived the research. S.Z., T.M., M.D., and Y.N. conceived the paper. T.M. and Y.N. organized the data collection and coordinated the field teams. Y.Z. and M.D. offered administrative and technical support. S.Z. analyzed the data. S.Z. and T.M. drafted the manuscript. All authors read and revised the manuscript and approved the submitted version of the paper.

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Competing interests
The authors declare no competing interests.

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