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RESEARCH

Elevated platelet distribution width and diabetes may serve as preoperative predictors of microvascular invasion in primary hepatocellular carcinoma

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Abstract

Background and objective Hepatocellular carcinoma (HCC) is one of the malignancies with increasing incidence globally, and microvascular invasion (MVI) is a crucial determinant of prognosis in patients. This study aimed to investigate platelet distribution width (PDW) and diabetes mellitus as indicators for predicting preoperative MVI in HCC, providing more accurate predictive tools for clinicians to guide treatment strategies and improve patient survival and quality of life.

Methods A retrospective study was conducted, including 1357 patients who underwent hepatectomy for HCC between January 2008 and December 2014 at the Eastern Hepatobiliary Surgery Hospital in China. Clinical, pathological, and radiological data, including PDW and diabetes status, were collected. Univariate and multivariate logistic regression analyses were performed to identify risk factors for MVI and establish a predictive model. The predictive performance of the model was evaluated through nomograms and internal validation.

Results Univariate analysis revealed significant associations between MVI and diabetes mellitus, presence of liver cirrhosis, prealbumin level, tumor diameter, number of tumors, HBV DNA viral load $>10^4$, and PDW ≥ 17. Multivariate logistic regression analysis identified diabetes mellitus, liver cirrhosis, prealbumin level, tumor diameter, number of tumors, HBV DNA viral load $>10^4$, and PDW ≥ 17 as independent risk factors for MVI. Based on these findings, a predictive model was established, demonstrating high predictive accuracy and stability in both the training and validation cohorts.

Conclusion This study confirmed PDW and diabetes mellitus as reliable indicators for predicting preoperative MVI in HCC and established a corresponding predictive model. Future research should further explore the underlying mechanisms and enhance clinical validation to advance the field of HCC treatment.

Keywords Hepatocellular carcinoma · Platelet distribution width · Diabetes mellitus · Microvascular invasion · Nomogram

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with a rising incidence and mortality rate that poses a significant global health burden (Wenjing et al. 2024). Among the various factors influencing HCC prognosis, microvascular invasion (MVI) has emerged as a critical determinant of poor outcomes, directly impacting both survival rates and recurrence risks (Sunyoung et al. 2019). Currently, the gold standard for MVI assessment relies on postoperative pathological examination (Lei et al. 2016). However, this approach is inherently limited by its latency, as it cannot provide timely guidance for preoperative treatment strategies, ultimately compromising patient

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prognosis. Therefore, the development of accurate preoperative MVI prediction methods is essential for optimizing personalized treatment plans, improving therapeutic outcomes, and enhancing the quality of life for HCC patients.

In recent years, the field of HCC research has witnessed significant advancements, particularly in the exploration of non-invasive preoperative prediction methods. While postoperative pathological examination remains the cornerstone of MVI diagnosis, its inability to inform preoperative decision-making has spurred the search for alternative approaches. Emerging evidence suggests that preoperative patient demographics and laboratory indices may hold promise as predictive tools, offering a potential pathway to overcome the limitations of traditional methods (Wang et al. 2024; Devillers et al. 2023; Shi et al. 2024). Emerging evidence suggests that preoperative patient demographics and laboratory indices may hold promise as predictive tools, offering a potential pathway to overcome the limitations of traditional methods. This shift towards preoperative prediction not only addresses a critical gap in clinical practice but also opens new avenues for improving patient outcomes through early intervention and tailored therapeutic strategies.Preoperative laboratory indices such as serum tumor markers and liver function tests can reflect the tumor burden and hepatic functional status of patients with liver cancer, providing valuable references for predicting patient outcomes. Imaging indices such as ultrasound, CT, MRI, etc., can visually display hepatic sclerosis, tumor size, and quantity, thereby providing important evidence for the diagnosis and staging of liver cancer (Huang et al. 2023; Ridder et al. 2022). Literature reports indicate a significant correlation between factors such as serum AFP levels, liver function test results, tumor size, and quantity with the occurrence of MVI, and the comprehensive application of these indices can improve the accuracy of MVI prediction (Zhao et al. 2013; Zhenchang et al. 2020).Meanwhile, radiomic markers based on CT imaging and machine learning algorithms have also been utilized for preoperative prediction of MVI (Sudeep et al. 2015; Jian et al. 2017; Yi-Quan et al. 2020) 。However, preoperative reports on the predictive value of platelet distribution width and diabetes risk for MVI are scarce.

Platelet distribution width is one of the indicators of platelet activation (Xia et al. 2018). Malignant tumors can activate platelets, causing them to adhere to tumor cells. Through a series of reactions, this process mediates the growth, invasion, and metastasis of malignant tumors, and also promotes the growth of blood vessels within malignant tumors (Pan et al. 2023). Therefore, there is a significant correlation between platelet distribution width and various malignant tumors, including non-small cell lung cancer (Cui et al. 2017), melanoma (Li et al. 2017), laryngeal carcinoma (Kara et al. 2019), gastric cancer (Saito et al. 2021), breast cancer (Takeuchi et al. 2017), etc., which provides certain auxiliary diagnostic and prognostic value for malignant tumors.

The relationship between diabetes and HCC has been extensively studied (Plaz Torres et al. 2022). The risk of HCC in diabetic patients is usually higher than that in non-diabetic individuals. This may be related to factors such as chronic liver disease, hepatic steatosis, and inflammatory reactions caused by diabetes (Shih-Wei et al. 2011). In addition, the liver function and metabolic status of diabetic patients may be closely related to the development of HCC.

Through this study, we hope to provide a new and effective method for the preoperative prediction of MVI in liver cancer patients. This will not only improve the diagnostic accuracy and treatment effectiveness for liver cancer patients but also provide scientific evidence for clinical decision-making, promoting progress and development in the field of liver cancer treatment. At the same time, this study will also provide useful references and guidance for future liver cancer research and clinical practice.

In summary, this study aims to predict the MVI of liver cancer patients through preoperative patient demographics and laboratory indicators, which holds significant clinical significance and practical value. We look forward to providing new insights and methods for the treatment and prognosis assessment of liver cancer patients through the conduct of this study.

Materials and methods

Patients

We retrospectively reviewed the medical records of all patients diagnosed with HCC who underwent liver resection at the Hepatic Surgery Department of the Eastern Hepatobiliary Surgery Hospital in China between January 2008 and December 2014. Inclusion criteria were as follows: (1) patients who underwent standard clinical resection; (2) confirmed by pathological diagnosis; (3) underwent imaging evaluation within 2 weeks before liver resection. Exclusion criteria were: (1) prior anticancer treatment; (2) history of malignancy; (3) insufficient clinical information; (4) extrahepatic metastasis; (5) unclear diagnosis of MVI. Finally, a total of 1357 patients with HCC were included. This study was a retrospective study approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital.

In this study, MVI was defined as the presence of tumor cells within the vascular spaces lined by endothelial cells, as confirmed by postoperative pathological examination. This

definition is consistent with the widely accepted criteria in the field of HCC research.

The 1357 patients were randomly assigned to either the training cohort or the validation cohort using the R version 4.3.1 (http://www.r-project.org/). The random assignment was performed to ensure an unbiased distribution of patient characteristics between the two cohorts, thereby enhancing the reliability of the model development and validation process. The cut-off value for PDW was determined using Receiver Operating Characteristic (ROC) curve analysis. A PDW value of 17.0 was identified as the optimal threshold, providing the best balance between sensitivity and specificity for predicting MVI in our study population.

Clinical, pathological, and imaging data acquisition

Patient data, including age, sex, smoking, alcohol consumption, antiviral therapy, family history of liver cancer, and diabetes, were collected from medical records. Laboratory blood tests were performed before liver resection, including PLT, PDW, HBsAg, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19−9, serum albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), prealbumin (PA), prothrombin time (PT), and HBV DNA. MVI results from postoperative pathological reports were also collected. Imaging data assessment included tumor size, capsule, ascites, liver cirrhosis, and tumor number.

Follow up

All patients were followed-up with monthly CT or MRI for 1 year. CT or MRI was carried out at an interval of once every 6 months thereafter. Tumor recurrence was suspected when there was a progressive elevation of serum AFP evidence and was diagnosed by dynamic CT scan or MRI.

Statistical analysis

Continuous variables are presented as means (standard deviation, SD) or medians, and comparisons are made using Student's t-test or the Mann-Whitney U test. Categorical variables are expressed as numbers (percentages) and compared using the chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for the presence of MVI. Each variable in the training set that was considered clinically relevant ($p<0.05$ in univariate analysis) entered into multivariate logistic regression analysis, and final independent risk factors for recurrence were determined by stepwise regression selection. Column charts were constructed based on available preoperative clinical-pathological data. Column charts, area under the receiver operating characteristic curve (AUC), calibration curve, and decision curve analysis (DCA) were performed using R version 4.3.1. All statistical tests were two-tailed, with $p<0.05$ considered statistically significant, using SPSS version 26.0.

Results

Clinical pathological characteristics

During the study period, a total of 1357 patients meeting the inclusion criteria were enrolled, with 949 and 408 patients assigned to the training and validation groups, respectively. The clinical pathological characteristics of the patients are presented in Table 1. Baseline clinical pathological data were comparable between the training and validation groups. In the training and validation groups, 73 (7.7%) and 34 (8.3%) patients were diagnosed with diabetes, respectively, while 432 (45.5%) and 166 (40.7%) patients had PDW values greater than 17. MVI identified by histopathology was observed in 447 (47.1%) and 193 (47.3%) patients, respectively.

The univariate and multivariate logistic regression analyses of MVI in the training group

All variables shown in Table 2 were included in the univariate logistic regression analysis to determine the independent risk factors for MVI. The results of the univariate analysis are shown in Table 3, which indicates that diabetes ($p=0.001$), presence of cirrhosis ($p=0.001$), PA ($p=0.035$), tumor diameter ($p<0.001$), multiple tumors ($p=0.007$), HBV DNA load > 104 ($p<0.001$), and PDW > 17 ($p<0.001$) were significantly associated with MVI. Subsequently, all the factors were included in the multivariate logistic regression analysis, and the results showed that diabetes [2.427 (1.390–4.238), $p<0.001$], presence of cirrhosis [1.608 (1.180–2.192), $p=0.001$], PA [0.998 (0.996-1.000), $p<0.001$], tumor diameter [1.085 (1.042–1.130), $p<0.001$], multiple tumors [2.009 (1.263–3.194), $p<0.001$], HBV DNA load > 104 [3.636 (2.535–5.217), $p<0.001$], and PDW > 17 [3.427 (2.566–4.576), $p<0.001$] were risk factors for MVI (Table 3).

Construction and evaluation of nomogram in the training cohort and its application for evaluation in the validation cohort

All variables used in this analysis were based on preoperative data. Tumor-related variables, including diameter, number, and encapsulation status, were assessed through

Table 1 Baseline clinical characteristics of patients

Variables	Training cohort ($n=949$)	Validation cohort ($n=408$)	p value
Age, Mean (SD), years	52.5(11.1)	51.6(10.7)	0.893
Gender			0.690
Female	158(16.6%)	64(15.7%)	
Male	791(83.4%)	344(84.3%)	
Alcohol consumption			0.689
No	697(73.4%)	295(72.3%)	
Yes	252(26.6%)	113(27.7%)	
Cigarette smoking			0.757
No	610(64.3%)	266(65.2%)	
Yes	339(35.7%)	142(34.8%)	
Antiviral therapy			0.717
No	886(93.4%)	384(94.1%)	
Yes	63(6.6%)	24(5.9%)	
Diabetes			0.742
No	876(92.3%)	374(91.7%)	
Yes	73(7.7%)	34(8.3%)	
Cirrhosis			0.950
Absent	316(33.3%)	137(33.6%)	
Present	633(66.7%)	271(66.4%)	
Hydroperitoneum			0.666
Absent	869(91.6%)	377(92.4%)	
Present	80(8.4%)	31(7.6%)	
PLT, Median(min, max), 10^9/L	146(12,1261)	152(27,435)	0.106
TBIL, Median(min, max), umol/L	13.3(3.6,551.5)	13.7(5.0,243.6)	0.356
DBIL, Median(min, max), umol/L	5(0.9,539.0)	5(0.9,197.7)	0.328
ALB, Median(min, max), g/L	41.2(1.2,472)	41.5(1.4,472.0)	0.271
PA, Median(min, max), g/L	220(0.1,524.0)	217(0.1,524.0)	0.185
ALT, Median(min, max), U/L	37.8(4.7,3059.2)	39.5(5.1,2895.0)	0.089
Blood glucose, Median(min, max), umol/L	4.9(0.7,494.0)	4.9(3.4,314.0)	0.721
CEA, Median(min, max), ng/ml	2.4(0.3,809.6)	2.3(0.3,293.6)	0.605
CA19-9, Median(min, max), ng/ml	20.7(0.6,1200.0)	22.8(0.6,1000.0)	0.258
AFP, ng/ml			0.855
≤20	364(38.4%)	154(37.7%)	
>20	585(61.6%)	254(62.3%)	
Tumor diameter*,Mean (SD), cm	6.2(3.9)	6.3(3.8)	0.709
Tumor number*			0.955
Single	834(87.9%)	359(88.0%)	
Multiple	115(12.1%)	49(12.0%)	
MVI			0.953
Absent	447(47.1%)	193(47.3%)	
Present	502(52.9%)	215(52.7%)	
Tumor capsule			0.966
Complete	281(29.2%)	116(28.4%)	
Incomplete or None	668(70.4%)	292(71.6%)	
Family history of HCC			0.337
Absent	913(96.2%)	397(97.3%)	
Present	36(3.8%)	11(2.7%)	
HBVDNA, IU/ml			0.787
$\leq 10^4$	707(74.5%)	301(73.8%)	
$>10^4$	242(25.5%)	107(26.2%)	
PDW			0.107
<17	517(54.5%)	242(59.3%)	
≥17	432(45.5%)	166(40.7%)	

TBIL, total bilirubin; DBIL, Direct bilirubin; ALB, albumin; TP, total protein; PA, prealbumin; ALT, alanine aminotransferase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen19-9;AFP, alpha fetoprotein; MVI, microvascular invasion.PDW, Platelet distribution width

*Preoperative images were obtained from contrast-enhanced Computed Tomography or contrast-enhanced magnetic resonance imaging

Table 2 Univariate logistic regression analysis of risk factors of MVI in the training cohort

Variable	B	SE	OR(95%CI)	*p* value
Gender, Male versus Female	-0.126	0.211	0.881(0.583–1.333)	0.55
Age, years	-0.010	0.007	0.990(0.977–1.003)	0.142
Diabetes, present versus absent	1.017	0.295	2.764(1.551–4.927)	0.001
Antiviral therapy, Yes versus No	0.322	0.300	1.380(0.767–2.484)	0.282
Cigarette smoking, Yes versus No	0.228	0.187	1.256(0.870–1.813)	0.224
Alcohol consumption, Yes versus No	0.153	0.200	1.165(0.788–1.724)	0.445
Family genetic history of HCC, Yes versus No	0.513	0.387	1.670(0.782–3.566)	0.185
Cirrosis, present versus absent	0.545	0.165	1.725(1.249–2.383)	0.001
Hydroperitoneum, present versus absent	-0.146	0.281	0.864(0.498-1.500)	0.604
PLT, 10^9/L	0.001	0.001	1.001(1.000-1.002)	0.223
TBIL, umol/L	0.008	0.011	1.008(0.988–1.029)	0.436
DBIL, umol/L	-0.009	0.013	0.991(0.965–1.017)	0.492
ALB, g/L	0.000	0.004	1.000(0.993–1.007)	0.989
PA, g/L	-0.002	0.001	0.998(0.996-1.000)	0.035
ALT, U/L	0.000	0.001	1.000(0.999–1.001)	0.633
Blood glucose, umol/L	0.005	0.007	1.005(0.991–1.018)	0.486
AFP, ng/ml, >20 versus ≤20	0.207	0.157	1.230(0.904–1.673)	0.188
CEA, ng/ml	-0.012	0.009	0.988(0.971–1.006)	0.199
CA199, ng/ml	0.001	0.001	1.001(1.000-1.003)	0.085
Tumor diameter, cm	0.081	0.022	1.084(1.039–1.132)	<0.001
Tumor number, Multiple versus Single	0.655	0.242	1.925(1.197–3.096)	0.007
Capsule, Complete versus Incomplete or None	-0.125	0.168	0.882(0.635–1.225)	0.454
HBVDNA, IU/L, $>10^4$ versus $\leq 10^4$	1.243	0.190	3.465(2.389–5.025)	<0.001
PDW, ≥17 versus <17	1.282	0.151	3.602(2.680–4.841)	<0.001

B, coefficient; SE, stand error; CI, confidence interval; OR, Odds ratio

Table 3 Multivariate logistic regression analysis of risk factors of MVI in the training cohort

Variable	B	SE	OR(95%CI)	*p* value
Diabetes, present versus absent	0.887	0.284	2.427(1.390–4.238)	<0.001
Cirrosis, present versus absent	0.475	0.158	1.608(1.180–2.192)	0.001
PA, g/L	-0.002	0.001	0.998(0.996-1.000)	0.012
Tumor diameter, cm	0.082	0.021	1.085(1.042–1.130)	<0.001
Tumor number, Multiple versus Single	0.698	0.237	2.009(1.263–3.194)	<0.001
HBVDNA, IU/L,$>10^4$ versus $\leq 10^4$	1.291	0.184	3.636(2.535–5.217)	<0.001
PDW, ≥17 versus <17	1.232	0.148	3.427(2.566–4.576)	<0.001

B, coefficient; SE, stand error; CI, confidence interval; OR, Odds ratio

preoperative radiological studies. These independently associated multivariate logistic regression factors were utilized to form the nomogram for predicting MVI risk (Fig. 1). (PA was adjusted and not included due to its minor contribution to the model). The model's calibration was evaluated, with a C-statistic of 0.746, DXY of 0.493, R (Sunyoung et al. 2019) of 0.238, discrimination index D of 0.195, unreliable index U of−0.002, and quality index Q of 0.198, indicating good predictive capability of the model (Fig. 2). Furthermore, in the training cohort, the nomogram exhibited robust predictive ability for MVI, with a C-index of 0.746. Additionally, the calibration plot depicted a consistent prediction of MVI probability with actual observed values, and decision curve analysis showed favorable net benefits at various threshold probabilities when using the nomogram in clinical practice (Fig. 3A, C and E). Upon internal validation, it was found that in the validation cohort, the AUC was 0.767, and calibration curve and DCA results were also highly satisfactory (Fig. 3B, D and F), indicating good predictive ability of the model.

Survival analysis of HCC patients under different MVI risk scores

Based on the risk model, the median probability of MVI was 53.1%. All patients were divided into low MVI risk and high MVI risk groups, comparing OS and RFS between the two groups of patients. Patients in the low MVI risk group had significantly better RFS ($P<0.0001$). In the high MVI risk group, patients' OS was significantly lower than those in the low MVI risk group ($P<0.0001$, Fig. 4).

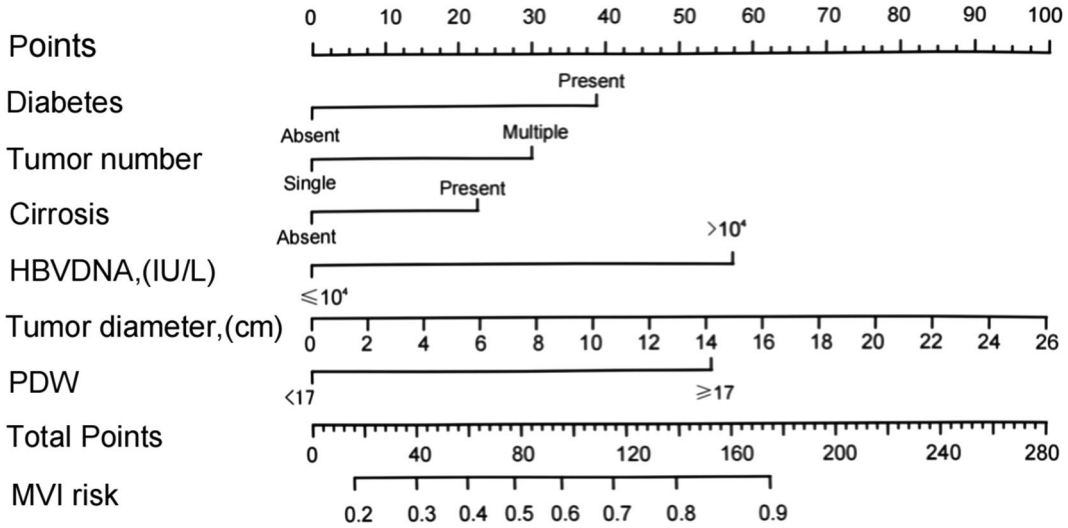

Fig. 1 Nomogram for MVI prediction

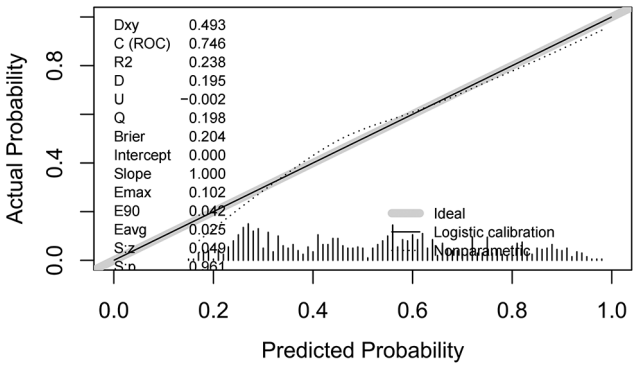

Fig. 2 Training group calibration curve and evaluation parameters

Discussion

HCC is a malignant tumor with a rising incidence globally, and MVI is one of the crucial factors affecting patient prognosis. Although traditional postoperative pathological assessment can identify the presence of MVI, its lagging nature limits its guiding role in preoperative treatment selection. This study investigates PDW and diabetes mellitus as indicators for predicting preoperative MVI in HCC, aiming to provide more accurate predictive tools for clinical guidance in treatment strategies, thereby improving patient survival rates and quality of life.

PDW is an indicator of platelet size and morphological heterogeneity, showing prognostic value in various malignant tumors. The results of this study indicate a significant correlation between PDW > 17 and MVI, suggesting a potential association between PDW and MVI in HCC. In previous studies, PDW > 16.8 has been identified as an indicator of poor prognosis in breast cancer (Yiru et al. 2018), and our previous research has also found PDW > 17.1 to be a risk factor for predicting recurrence within 3 years after HCC resection (Li et al. 2023), indicating PDW as a simple and reliable preoperative predictive indicator, offering new insights for clinical practice.

The potential mechanism by which PDW is associated with MVI in HCC may involve its reflection of platelet activation status. Activated platelets release pro-inflammatory cytokines and angiogenic factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which are known to promote tumor progression, angiogenesis, and microvascular invasion (Minciuna et al. 2024). Higher PDW levels indicate increased platelet heterogeneity and activation, potentially leading to enhanced tumor cell adhesion to the vascular endothelium and facilitating invasion into microvessels (Xu and Guo 2023). Moreover, platelet activation is linked to epithelial-mesenchymal transition (EMT), a key process in HCC metastasis and MVI formation.

Similarly, diabetes mellitus may promote MVI in HCC through multiple mechanisms. Chronic hyperglycemia and insulin resistance contribute to a pro-inflammatory and pro-fibrotic liver microenvironment, increasing the likelihood of tumor invasion into microvessels (Ye et al. 2024). Diabetes mellitus is also associated with increased oxidative stress and systemic inflammation, which can accelerate tumor progression. Furthermore, diabetic patients often exhibit platelet hyperreactivity and increased coagulation activity, creating a microthrombotic state that may enhance tumor-endothelium interactions and promote MVI formation (Ranucci et al. 2019; Minno et al. 2012). This prothrombotic environment may explain why diabetes mellitus is an independent risk factor for MVI in HCC, as confirmed in our study.

Diabetes mellitus has been shown to be associated with an increased incidence of HCC (Teng et al. 2023; Yang et

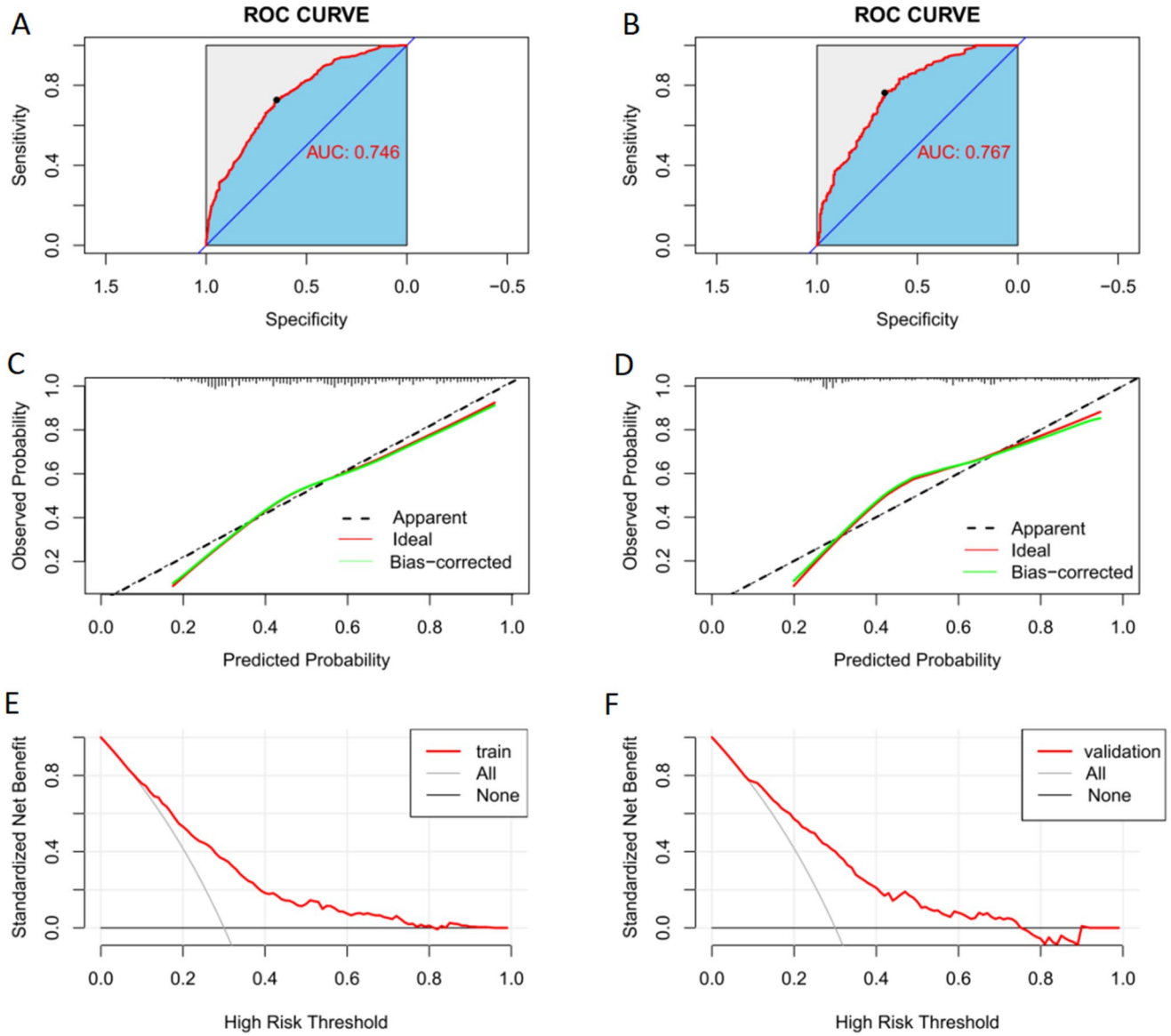

Fig. 3 MVI Predictive model evaluation, training group: ROC (**A**), calibration curve (**C**), DCA (**E**); validation group: ROC (**B**), calibration curve (**D**), DCA (**F**)

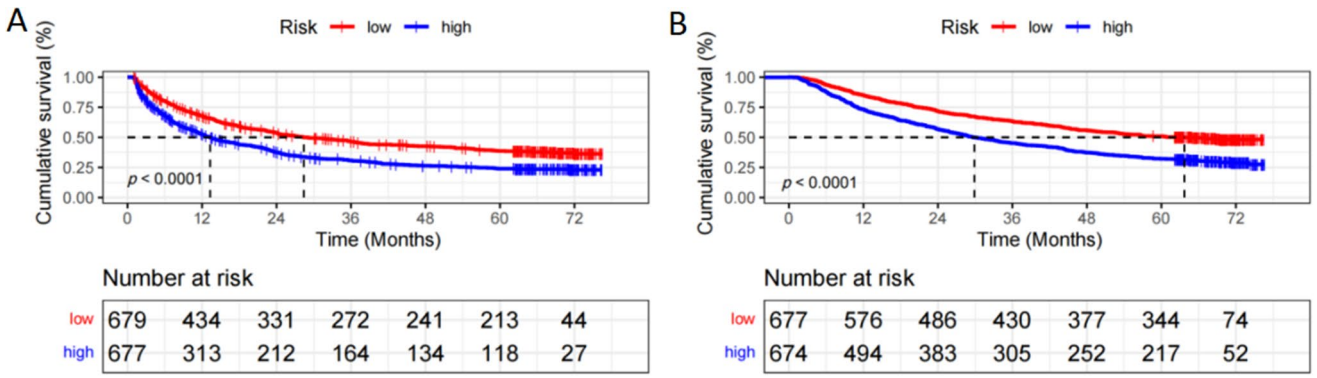

Fig. 4 Kaplan-Meier cumulative survival curves for patients in the high and low MVI risk groups. (**A**) RFS (**B**)OS

al. 2020). This study further confirms the close relationship between diabetes mellitus and MVI, with diabetes mellitus being one of the independent risk factors for MVI. This may be related to liver changes, steatosis, and inflammatory responses caused by diabetes mellitus, thereby affecting the development and invasion of HCC. Literature also reports that diabetes mellitus is characterized by platelet morphological and functional abnormalities and platelet hyperactivity, considered a prothrombotic state (Abd El-Ghany et al. 2021). Therefore, diabetic patients should receive more attention in HCC treatment, and clinicians should consider their unique physiological conditions when formulating treatment plans.

Through multivariate logistic regression analysis, we established a predictive model including PDW, diabetes mellitus, and other factors, visualized using a nomogram. This model demonstrated high predictive accuracy and stability in both the training and validation groups, providing a new method for accurate prediction of preoperative MVI. Deng et al. incorporated tumor size, AFP, and NLR indicators into the nomogram model for preoperative prediction of MVI risk (Deng et al. 2019). Chang et al.'s nomogram model included preoperative FIB-4, AFU, AFP levels, liver cirrhosis, and tumor margin irregularity to predict MVI (Chang et al. 2023). Additionally, the broad clinical application prospects of this model can help clinicians identify high-risk patients, formulate personalized treatment plans, and improve surgical success rates and patient survival rates.

Although this study has achieved certain results, there are still some limitations. Firstly, it is a single-center retrospective study, which may have certain selection biases, and further multicenter, large-sample prospective studies are needed to validate the results. Secondly, this study did not consider all possible factors that may affect MVI, such as liver function and inflammatory indicators, and future research can further improve predictive models. Moreover, this study did not explore the mechanistic relationship between PDW and diabetes mellitus in depth, which needs to be elucidated through more in-depth experimental research, particularly regarding the role of platelet activation, inflammatory cytokines, and coagulation factors in MVI development.

In conclusion, this study confirms PDW and diabetes mellitus as reliable indicators for predicting preoperative MVI in HCC and establishes corresponding predictive models, providing a new predictive tool for clinical practice. Future research should further explore their potential mechanisms through in vitro and in vivo studies, particularly focusing on the interactions between platelets, endothelial cells, and tumor cells in the context of MVI. Strengthening validation in clinical applications will also help promote progress and development in the field of HCC treatment.

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Author contributions Jia Jian'an conceived the project and wrote the manuscript. Wang Ling and Li Huiming designed the experiments, collected the study subjects, performed the experiments, and analyzed the data. Liu Jun, Rao Chunmei, Jiang Yuhuan prepared Tables 1, 2 and 3. All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The studies involving human participants were reviewed and approved by Ethics The study was conducted in accordance with the Declaration of Helsinki. Informed Consent was obtained from all individual participants included in the study.

Patient consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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