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Early identification of hepatocellular carcinoma patients at high-risk of recurrence using the ADV score: a multicenter retrospective study

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Abstract

Background Postoperative recurrence is a vital reason for poor 5-year overall survival in hepatocellular carcinoma (HCC) patients. The ADV score is considered a parameter that can quantify HCC aggressiveness. This study aimed to identify HCC patients at high-risk of recurrence early using the ADV score.

Methods The medical data of consecutive HCC patients undergoing hepatectomy from The First Affiliated Hospital of Nanjing Medical University (TFAHNJMU) and Nanjing Drum Tower Hospital (NJDTH) were retrospectively reviewed. Based on the status of microvascular invasion and the Edmondson-Steiner grade, HCC patients were divided into three groups: low-risk group (group 1: no risk factor exists), medium-risk group (group 2: one risk factor exists), and high-risk group (group 3: coexistence of two risk factors). In the training cohort (TFAHNJMU), the R package nnet was used to establish a multi-categorical unordered logistic regression model based on the ADV score to predict three risk groups. The Welch's T-test was used to compare differences in clinical variables in three predicted risk groups. NJDTH served as an external validation center. At last, the confusion matrix was developed using the R package caret to evaluate the diagnostic performance of the model.

Results 350 and 405 patients from TFAHNJMU and NJDTH were included. HCC patients in different risk groups had significantly different liver function and inflammation levels. Density maps demonstrated that the ADV score could best differentiate between the three risk groups. The probability curve was plotted according to the predicted results of the multi-categorical unordered logistic regression model, and the best cut-off values of the ADV score were as

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follows: low-risk ≤ 3.4 log, 3.4 log < medium-risk ≤ 5.7 log, and high-risk > 5.7 log. The sensitivities of the ADV score predicting the high-risk group (group 3) were 70.2% (99/141) and 78.8% (63/80) in the training and external validation cohort, respectively.

Conclusion The ADV score might become a valuable marker for screening patients at high-risk of HCC recurrence with a cut-off value of 5.7 log, which might help surgeons, pathologists, and HCC patients make appropriate clinical decisions.

Keywords Hepatocellular carcinoma, ADV score, Microvascular invasion, Edmondson-steiner grade, Recurrence, Prediction model

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor in China, with the second highest mortality rate of all malignant tumors after lung cancer [1]. Globally, although the incidence and mortality of most cancers are decreasing, those of HCC is still increasing, making it the fourth most common cause of cancer-related death worldwide [2]. Surgical resection is the curative treatment of choice for early-stage HCC patients with good liver reserve function. However, the overall 5-year postoperative recurrence rate is as high as 70% [3]. Therefore, for HCC patients scheduled to undergo hepatectomy, early identification of those at high-risk for recurrence and appropriate clinical decision-making are crucial to improving prognosis and 5-year survival. Efficient biomarkers are needed in this process to guide precision therapy.

Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) are now commonly used tumor biomarkers for HCC [4]. Serum levels of both are strongly associated with the tumor biology of HCC. Previous studies showed that AFP-positive (≥20 ng/mL) patients had a more advanced tumor stage and a suppressive immune microenvironment (including accumulation of tumor-associated macrophages and depletion of different T-cell subsets) compared to AFP-negative patients [5]. Meanwhile, the overproduction of DCP was associated with proliferation, vascular invasion, and intrahepatic metastasis in HCC [6, 7]. This suggested that AFP and DCP are not only diagnostic biomarkers but also capable of responding to the inter-tumor heterogeneity of HCC. Moreover, long noncoding RNAs (lncRNAs) [8], many signaling pathways (e.g., Wnt-β-catenin, Hedgehog, and Hippo) [9], and toll-like receptor-4 (TLR4) single-nucleotide polymorphisms (SNPs) [10] have been proven vital in HCC occurrence and progression, which demonstrated that HCC is a liver mass with complex nature. Thus, the complex nature and heterogeneity of HCC are essential factors for the differences in treatment sensitivity and prognosis of different HCC patients [11].

High-risk recurrence characteristics of patients undergoing hepatectomy include poor tumor differentiation, micro- and macrovascular invasion, number of tumors greater than 3, and tumor size greater than 5 cm [12]. As gadoxetic acid-enhanced magnetic resonance imaging (MRI) improved the diagnostic efficacy of small HCC (<1 cm) [13], combined with abdominal contrast-enhanced computed tomography (CT) allowed more accurate preoperative assessment of macrovascular invasion (tumor invasion of portal or hepatic vein branches), tumor number, and tumor size. Hence, another vital aspect of early identification of those at high-risk of recurrence may be the prediction of microvascular invasion (MVI) and differentiation status of HCC. The degree of differentiation of HCC is now commonly defined by the Edmondson-Steiner (E-S) grade [14], whereas MVI refers to the presence of HCC cells in the lumen of the endothelium-lined vessels found under the microscope [15]. Many studies have confirmed that E-S grade III-IV and MVI are independent risk factors for poorer disease-free survival (DFS) and overall survival (OS) in HCC [16, 17]. However, E-S grade and MVI are variables that need to be carefully evaluated by pathologists after hepatectomy. Previous studies have established many preoperative models for predicting MVI or E-S grade, including radiomics [17–19]. To the best of our knowledge, no study has yet developed a model to predict these two high-risk recurrence factors simultaneously.

ADV score is an integrated scoring system derived from AFP level, DCP level, and tumor volume (TV). A multicenter study from Korea evaluated the ability of the ADV score to predict prognosis in HCC patients undergoing liver transplantation (LT). The results demonstrated that the ADV-5 log had a comparable prognostic impact with the Milan criteria, and they were both independent risk factors for recurrence-free survival (RFS) and OS [20]. Besides, a study including 9,200 patients who underwent hepatectomy also reported that ADV-5 log significantly affected HCC recurrence and 3-year mortality [21]. Thus, the ADV score may be an effective biomarker reflecting HCC heterogeneity and stratifying prognosis. Since the TV in the ADV score considers both the size and number of HCC [22], its greatest advantage may be that one convenient metric includes four prognostically relevant variables.

As mentioned above, advances in imaging have made the diagnosis of HCC combined with macrovascular invasion more accurate. Hence, this study aimed to investigate whether the ADV score could predict both MVI and E-S grade III-IV to provide a new biomarker and theoretical basis for the early identification of HCC patients at high-risk of recurrence.

Patients and methods

Study design and patients

The medical data of consecutive HCC patients undergoing hepatectomy from The First Affiliated Hospital of Nanjing Medical University (TFAHNJMU, from January 2020 to August 2023) and Nanjing Drum Tower Hospital (NJDTH, from January 2020 to December 2023) were retrospectively reviewed. Because of the unidentifiable patient information and the nature of the retrospective study, the institutional review boards of TFAHNJMU and NJDTH waived the requirement for written informed consent. This study followed the 1964 Declaration of Helsinki and its later amendments. Patients were included in this study if they met the following criteria: non-recurrent HCC patients; no preoperative local or systemic therapy; complete clinicopathologic data; and no history of other malignancies.

Data collection and calculation formulas

All patients' laboratory test data were obtained within one week before the hepatectomy, which included hepatitis markers, tumor markers, blood routine examination, liver function test, and coagulation test. In addition, we included six inflammatory markers and three serum liver fibrosis diagnostic models, and their calculation formulas were described in the previously published articles [23, 24]. The presence of liver cirrhosis was documented based on the most recent preoperative imaging reports. Table 1 presented all included variables.

ADV score

The ADV score=$\log_{10}$[AFP (ng/mL) × DCP (mAU/mL) × TV (mL)]. Tumor sizes from pathology reports were collected and used to calculate the TV. TV=4/3×π×a × b × c (a, b, and c=length of the three meridians of HCC in the pathology report). If multiple tumors are present, the total TV is the TV of the largest tumor multiplied by the number of tumors [22].

Pathological examination

Two experienced pathologists analyzed all hepatectomy specimens independently, and any disagreements were resolved after discussion. The degree of differentiation of HCC was defined by E-S grade [14]. Typical pathological images of the E-S grade were shown in Fig. S1. MVI refers to the presence of HCC cells in the lumen of the endothelium-lined vessels found under the microscope [15]. Typical pathological images of M0, M1, and M2 were presented in Fig. S2. Moreover, the number of tumors was recorded as solitary or multiple.

Statistical analysis and model development

Based on the status of MVI and the E-S grade, HCC patients were divided into three groups: low-risk group (group 1: no risk factor exists), medium-risk group (group 2: one risk factor exists), and high-risk group (group 3: coexistence of two risk factors). The Kruskal-Wallis test and χ^2 test were used to compare whether there were differences between the three groups for continuous and categorical variables. Subsequently, density maps were used to show the distribution situation of lgAFP, lgDCP, lgTV, and the ADV score in different risk groups [25].

In the training cohort (TFAHNJMU), the R package nnet (version 7.3–18) was used to establish a multi-categorical unordered logistic regression model based on the ADV score to predict three risk groups [26]. Then, the Welch's T-test was used to compare differences in clinical variables in three predicted risk groups. At last, the R package caret (version 6.0–94) was used to develop the confusion matrix, aiming to evaluate the diagnostic performance of the model in the training and external validation (NJDTH) cohort [27]. In the subgroup analyses, the paired T-test was used to compare whether the ADV score performed better in some populations (cirrhotic vs. non-cirrhotic patients and chronic hepatitis B [CHB] vs. chronic hepatitis C [CHC] patients). All statistical analyses were completed using the R software (version 4.2.2).

Results

Patients

350 and 405 patients from TFAHNJMU and NJDTH who met the criteria were included in this study. Fig. S3 presented the detailed flowchart for patient selection. According to the postoperative pathology report, in the training cohort, there were 85, 124, and 141 patients in the low-risk, medium-risk, and high-risk groups, respectively. At the same time, in the external validation cohort, there were 150, 175, and 80 patients in risk groups 1, 2, and 3, respectively. Furthermore, 298 (training: 129 of 350, 36.9%; external validation: 169 of 405, 41.7%; p=0.197) of all included patients had liver cirrhosis.

Evaluation indicator screening

The comparison of clinicopathology characteristics between different risk groups in the training cohort was presented in Table 1. The results showed that demographic characteristics (age and sex) did not differ significantly between groups, while four HCC biology markers (AFP, DCP, TV, and the ADV score) were significantly

Table 1 Comparison of clinicopathology characteristics among the training cohort

Variables	Risk Group 1 (*N* = 85)	Risk Group 2 (*N* = 124)	Risk Group 3 (*N* = 141)	*P*
Age, years	60.4 ± 12.8	61.5 ± 10.1	58.8 ± 10.2	0.117
Gender Male, n (%) Female, n (%)	68 (80.0%) 17 (20.0%)	98 (79.0%) 26 (21.0%)	115 (81.6%) 26 (18.4%)	0.873
Liver cirrhosis Absent, n (%) Present, n (%)	60 (70.6%) 25 (29.4%)	79 (63.7%) 45 (36.3%)	82 (58.2%) 59 (41.8%)	0.170
MVI Absent, n (%) Present, n (%)	85 (100.0%) 0 (0.0%)	89 (71.8%) 35 (28.2%)	0 (0.0%) 141 (100.0%)	**< 0.001**
E-S Grade I-II, n (%) III-IV, n (%)	85 (100.0%) 0 (0.0%)	35 (28.2%) 89 (71.8%)	0 (0.0%) 141 (100.0%)	**< 0.001**
Tumor number Solitary, n (%) Multiple, n (%)	79 (92.9%) 6 (7.1%)	116 (93.5%) 8 (6.5%)	120 (85.1%) 21 (14.9%)	**0.043**
TV, mL	49.1 ± 110.0	63.9 ± 103.0	154.0 ± 239.0	**< 0.001**
HbsAg Negative, n (%) Positive, n (%)	29 (34.1%) 56 (65.9%)	41 (33.1%) 83 (66.9%)	36 (25.5%) 105 (74.5%)	0.279
HCVAb Negative, n (%) Positive, n (%)	79 (92.9%) 6 (7.1%)	117 (94.4%) 7 (5.6%)	132 (93.6%) 9 (6.4%)	0.916
AFP, ng/mL	127.0 ± 308.0	348.0 ± 867.0	636.0 ± 1658.0	**0.006**
DCP, mAU/mL	1463.0 ± 4372.0	1761.0 ± 7104.0	6359.0 ± 10642.0	**< 0.001**
ADV score	4.1 ± 1.9	5.2 ± 1.9	6.8 ± 2.1	**< 0.001**
RDW, %	13.1 ± 0.8	13.3 ± 1.3	13.2 ± 1.1	0.377
NE, $\times 10^9$/L	3.0 ± 1.4	3.0 ± 1.3	3.0 ± 1.5	0.981
LYM, $\times 10^9$/L	1.5 ± 0.5	1.7 ± 0.6	1.5 ± 0.7	**0.025**
M, $\times 10^9$/L	0.5 ± 0.9	0.5 ± 0.2	0.5 ± 0.2	0.627
PLT, $\times 10^9$/L	144.0 ± 63.5	158.0 ± 81.1	152.0 ± 63.3	0.390
ALT, U/L	31.4 ± 21.5	40.2 ± 46.7	40.2 ± 28.3	0.130
AST, U/L	32.7 ± 21.7	38.6 ± 36.2	45.2 ± 31.0	**0.012**
GGT, U/L	54.7 ± 49.1	68.9 ± 73.5	94.5 ± 95.6	**0.001**
TB, μmol/L	15.4 ± 7.9	14.6 ± 7.3	15.5 ± 6.8	0.572
ALB, g/L	39.5 ± 3.9	38.8 ± 4.2	38.5 ± 4.2	0.177
PT, seconds	12.6 ± 3.1	12.4 ± 1.0	12.5 ± 0.9	0.602
INR	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.126
GLR[†]	41.2 ± 35.1	52.2 ± 79.8	78.7 ± 91.2	**0.001**
ALRI[†]	26.9 ± 29.0	28.1 ± 26.5	39.4 ± 40.2	**0.005**
ANRI[†]	14.8 ± 24.4	17.4 ± 23.5	18.2 ± 18.4	0.517
NLR[†]	2.4 ± 1.7	2.0 ± 1.0	2.4 ± 1.8	0.073
PLR[†]	109.0 ± 56.8	105.0 ± 61.5	118.0 ± 57.2	0.193
MLR[†]	0.4 ± 0.3	0.3 ± 0.1	0.4 ± 0.2	**0.045**
APRI[#]	0.8 ± 1.1	0.9 ± 1.1	0.9 ± 0.8	0.747
FIB-4[#]	3.2 ± 2.8	3.3 ± 2.8	3.3 ± 2.1	0.947
GPR[#]	0.5 ± 0.4	0.6 ± 1.1	0.9 ± 0.7	0.135

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as numbers of patients with percentages in parentheses. [†]Inflammatory markers. [#]Serum liver fibrosis diagnostic models

MVI, microvascular invasion; E-S, Edmondson-Steiner; TV, tumor volume; HBsAg, hepatitis B virus surface antigen; HCVAb, hepatitis C virus antibodies; AFP, alpha fetoprotein; DCP, des-γ-carboxy prothrombin; RDW, red blood cell distribution width; NE, neutrophil; LYM, lymphocyte; M, monocyte; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; TB, total bilirubin; ALB, albumin; PT, prothrombin time; INR, international normalized ratio; GLR, γ-glutamyl transferase to lymphocyte ratio; ALRI, aspartate aminotransferase to lymphocyte ratio index; ANRI, aspartate aminotransferase to neutrophil ratio index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; APRI, aspartate transaminase to platelet ratio index; FIB-4, fibrosis-4; GPR, γ-glutamyl transferase to platelet ratio

different and progressively higher with increasing levels of risk. Besides, the degree of hepatic function impairment (AST and GGT) and the level of inflammation (ALRI, MLR, and GLR) were positively associated with risk groups. Finally, density maps demonstrated that the ADV score could best differentiate between the three risk groups Fig. 1.

Model development and evaluation

Therefore, we selected the ADV score to establish the model to predict risk groups of HCC patients. The probability curve was plotted according to the predicted results of the multi-categorical unordered logistic regression model Fig. 2. Notably, the best cut-off values of the ADV score were as follows: low-risk ≤ 3.4 log, 3.4 log < medium-risk ≤ 5.7 log, and high-risk > 5.7 log (intersections of curves in Fig. 2).

Subsequently, two cohorts of patients were categorized into three groups based on the optimal cut-off values (ADV group). Similar to actual risk groups, HCC patients in different ADV groups had significantly different liver function and inflammation levels. First, patients in ADV group 3 had lower levels of ALB and higher levels of AST and GGT Fig. 3. Second, patients in ADV group 1 had lower inflammation levels than patients in groups 2 and 3 Fig. 4. These results initially proved the reliability of the ADV score.

Eventually, the confusion matrix was used to evaluate the diagnostic performance of the established model in different risk groups (Table 2). Most importantly, the sensitivities of the ADV score predicting the high-risk group (group 3) were 70.2% (99/141) and 78.8% (63/80) in the training and external validation cohort, respectively. It was suggested that HCC patients with an ADV score > 5.7 log might be at the highest risk for recurrence. In the meantime, high specificities of diagnosing low-risk groups (88.7% and 86.3%) suggested that HCC patients with an ADV score > 3.4 log had a high probability of MVI or E-S grade III-IV. The subgroup analyses revealed that the ADV score had similar overall diagnostic performance among different populations (cirrhotic vs.

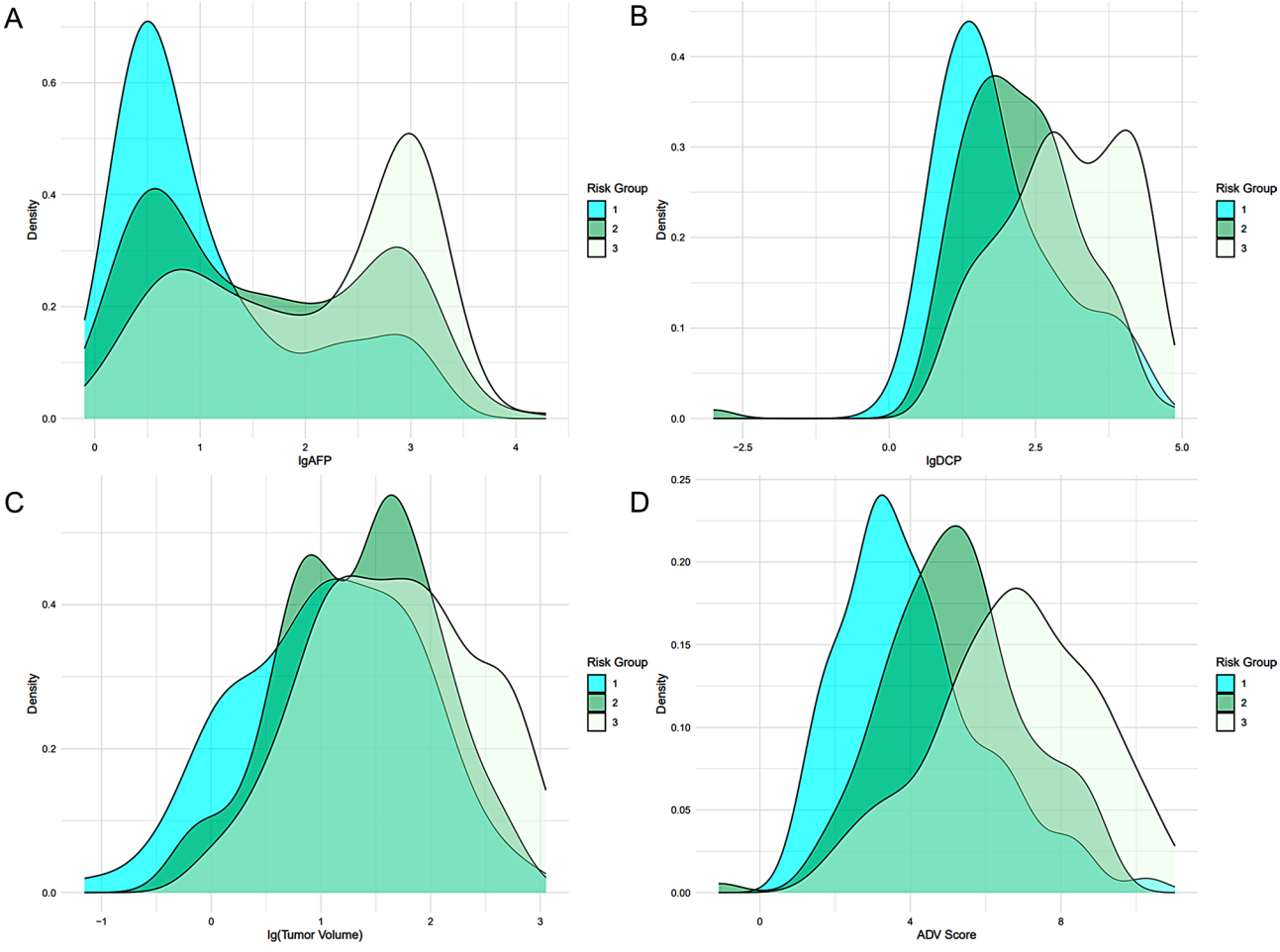

Fig. 1 Density maps of lgAFP **(A)**, lgDCP **(B)**, lgTV **(C)**, and the ADV score **(D)** in different risk groups. AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; TV, tumor volume

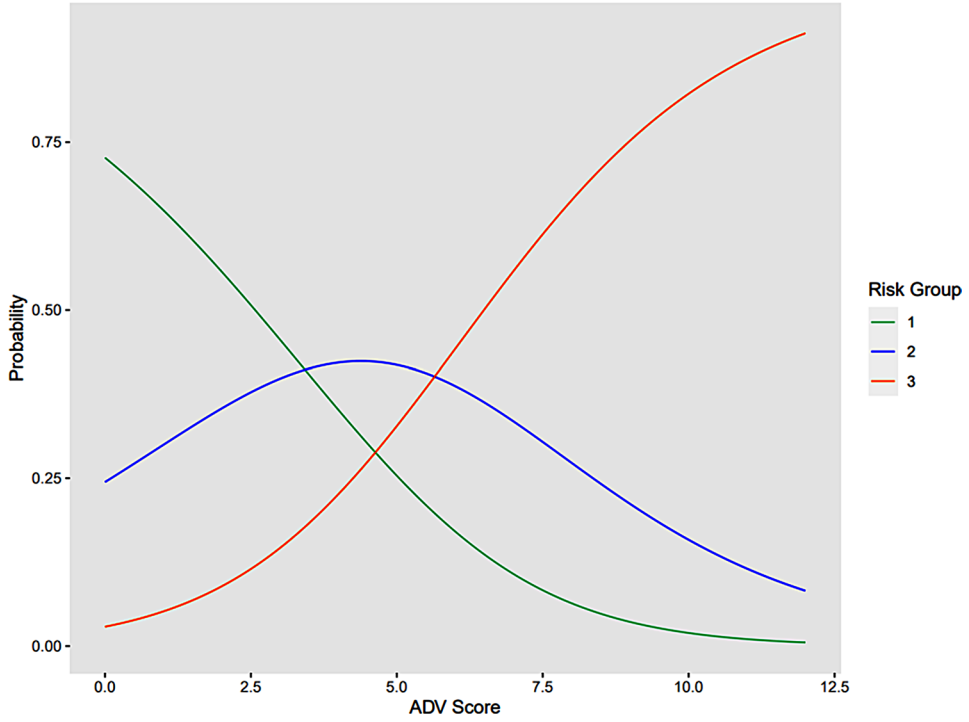

Fig. 2 The probability curve based on the predicted results of the multi-categorical unordered logistic regression model

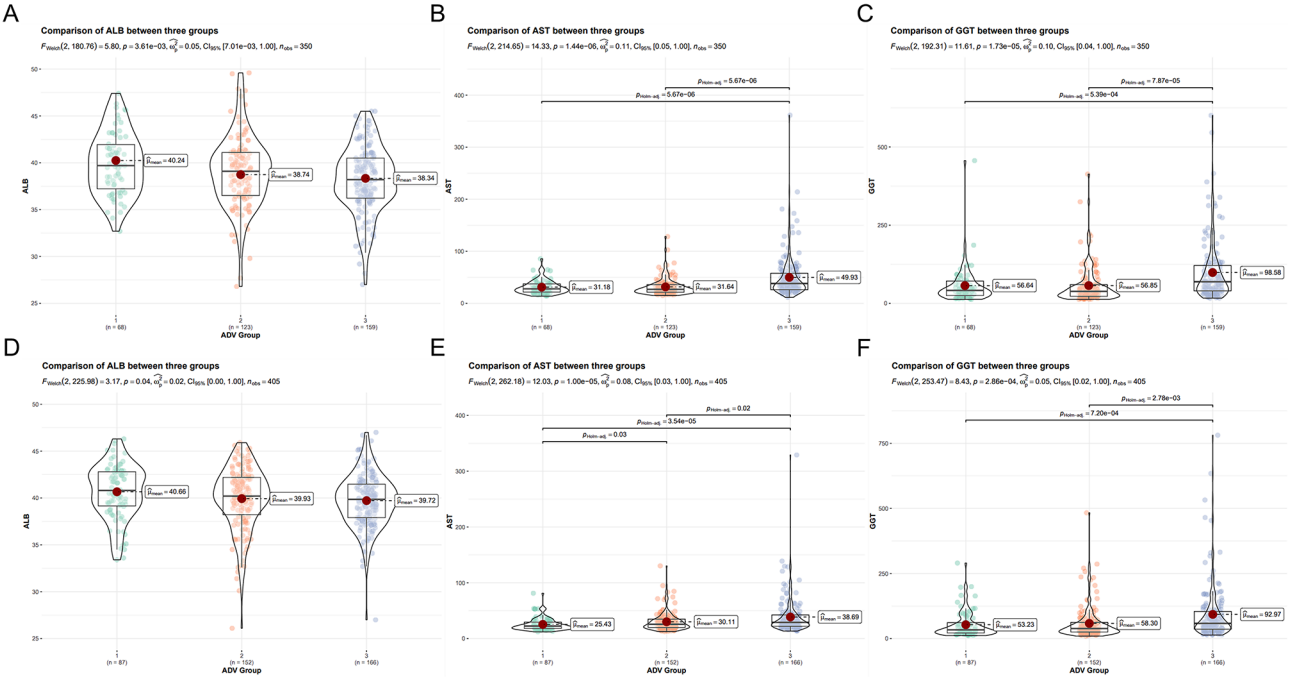

Fig. 3 Significant different liver function variables (ALB, AST, and GGT) in patients with different ADV groups in training **(A-C)** and external validation cohorts **(D-F)**. ALB, albumin; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase

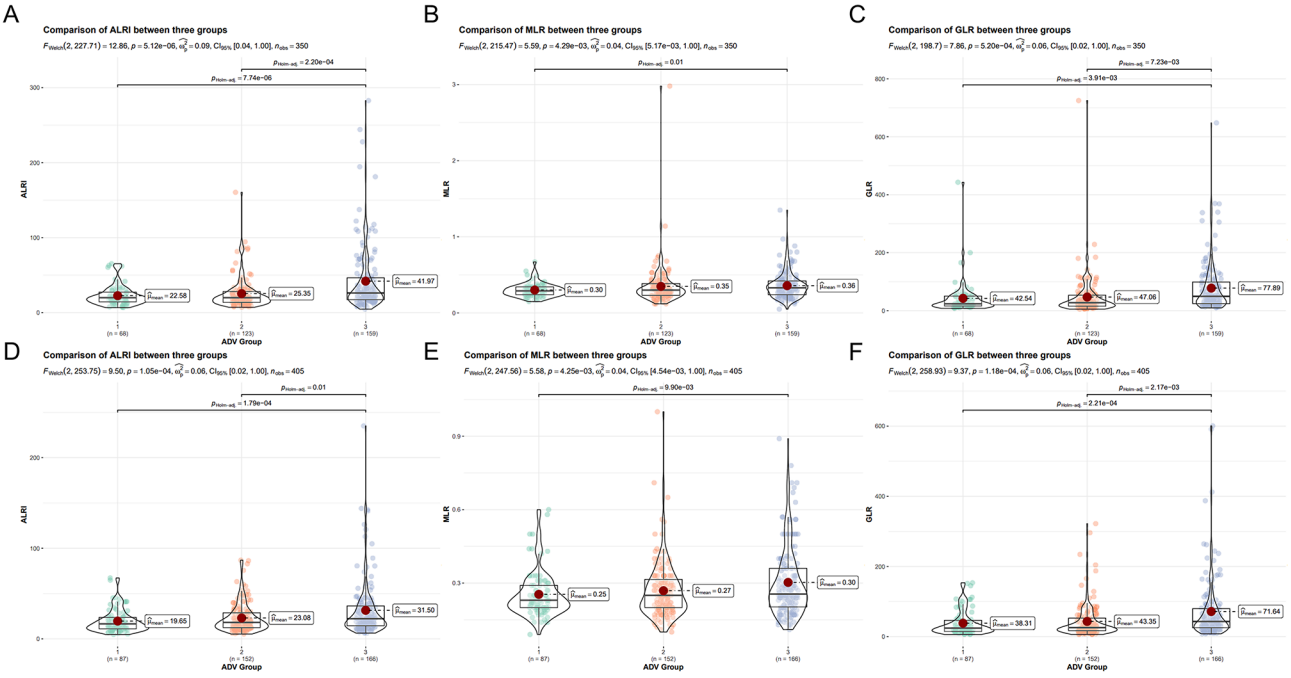

Fig. 4 Significant different inflammation variables (ALRI, MLR, and GLR) in patients with different ADV groups in training **(A-C)** and external validation cohorts **(D-F)**. ALRI, aspartate aminotransferase to lymphocyte ratio index; MLR, monocyte to lymphocyte ratio; GLR, γ-glutamyl transferase to lymphocyte ratio

Table 2 Diagnostic performance of the ADV score for predicting different risk groups

	Risk Group 1	Risk Group 2	Risk Group 3
Training cohort			
Sensitivity (%)	44.7 (38/85)	46.8 (58/124)	70.2 (99/141)
Specificity (%)	88.7 (235/265)	73.0 (165/226)	69.4 (145/209)
Accuracy (%)	78.0 (273/350)	63.7 (223/350)	69.7 (244/350)
External validation cohort			
Sensitivity (%)	36.0 (54/150)	34.9 (61/175)	78.8 (63/80)
Specificity (%)	86.3 (220/255)	63.0 (145/230)	67.1 (218/325)
Accuracy (%)	67.7 (273/405)	50.9 (223/405)	69.4 (281/405)

non-cirrhotic patients and CHB vs. CHC patients; Table S1 and S2).

Discussion

The ADV score is considered a parameter that can quantify HCC aggressiveness [28]. Table 3 provides an overview of published articles reporting the application of the ADV score in HCC [20–22, 28–36]. Results demonstrated that the ADV score could prognostically stratify HCC patients undergoing hepatectomy or LT. However, it is worth noting that almost all studies were from Korea (except for one study cooperating with Japan) [21]. This suggests that studies from different centers and regions are needed to validate the generalizability of the ADV score. This study categorized HCC patients into three groups based on two risk factors, with group 3 being the population to focus on in clinical practice. Early identification of the group 3 was the most essential objective of this study. Predicting MVI or E-S grade alone can be done using previously published models [17–19], as they were not distinguished in group 2.

AFP is a traditional biomarker for HCC, and its combination with ultrasound is still recommended as the primary strategy for screening HCC [12]. Nevertheless, due to the complex nature and inter-tumor heterogeneity of HCC, AFP alone is insufficient to diagnose it and predict its clinical course [37]. Recently, many studies have shown that DCP is vital in detecting HCC (including HCC≤3 cm), monitoring treatment outcomes and recurrence, and assessing prognosis [38, 39]. High levels of AFP and DCP are poor prognostic indicators for HCC patients [4]. Although differences in race, cohort size, and other aspects of different research might contribute to the differences in their cut-off value. For instance, Zhang Y et al. [40] reported that preoperative AFP>400 ng/mL increased the risk of HCC recurrence after hepatectomy by approximately 2-fold. Meanwhile, another retrospective study revealed that the hazard ratio (HR) for the effect of DCP>40 mAu/mL on HCC recurrence was 1.479 based on the multivariate analysis [41]. Similar to previous studies, this study used the tumor size from the pathology report to calculate the TV. Since the pathology index can only be obtained postoperatively, this is one of the limitations of this study. Our intention was to preoperatively identify independent risk factors for recurrence early, helping surgeons decide on treatment and

Table 3 An overview of the application of the ADV score in HCC

Ref.	Procedure	Cases	Cut-off value	Predicted event	Efficiency	The ADV score of 1log interval[†]	
						DFS	OS
Hwang S et al., 2016 [29]	hepatectomy	1727	5log	recurrence survival	HR = 1.57, $p < 0.001$ HR = 2.17, $p < 0.001$	< 0.001	/
Hwang S et al., 2018 [30]	hepatectomy	526	7log	recurrence survival	HR = 1.29, $p < 0.001$ HR = 1.33, $p = 0.001$	0.001	< 0.001
Ha SM et al., 2018 [31]	hepatectomy	35	4log	recurrence survival	HR = 2.20, $p = 0.095$ HR = 2.13, $p = 0.062$	/	/
Jung DH et al., 2019 [28]	hepatectomy	1572	4log	recurrence	HR = 1.31, $p = 0.004$	0.117	0.106
Park GC et al., 2020 [32]	hepatectomy	1390	10log	survival	HR = 5.00, $p < 0.001$	/	< 0.001
Hwang S et al., 2021 [33]	hepatectomy	147	9log	recurrence survival	HR = 1.85, $p = 0.002$ HR = 2.13, $p = 0.001$	< 0.001	0.042
Hwang S et al., 2021 [34]	LDLT	625	4log 6log	survival	c-index = 0.7 c-index = 0.66	< 0.001	< 0.001
Hwang S et al., 2021 [22]	LDLT	843	5log	recurrence survival	c-index = 0.63 c-index = 0.63	< 0.001	< 0.001
Hwang S et al., 2021 [35]	hepatectomy	100	8log	recurrence survival	HR = 1.40, $p = 0.098$ HR = 1.45, $p = 0.120$	0.873	0.017
Hwang S et al., 2022 [36]	LDLT	100	5.4log	recurrence survival	HR = 3.56, $p < 0.001$ HR = 5.58, $p < 0.001$	/	/
Kang WH et al., 2023 [21]	hepatectomy	9200	5log	recurrence	AUROC = 0.577	< 0.001	< 0.001
Park GC et al., 2023 [20]	LT	1599	5log	recurrence survival	AUROC = 0.705 AUROC = 0.728	0.021	< 0.001

[†]HCC patients were stratified according to the interval of 1log ADV score, then DFS and OS were compared

HCC, hepatocellular carcinoma; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; LDLT, living donor liver transplantation; c-index, index of concordance; AUROC, area under the receiver operating characteristic curve; LT, liver transplantation

management strategies. However, with the development of imaging technology, it is now clinically possible to perform preoperative 3-dimension (3D) reconstruction of the liver based on contrast-enhanced CT and calculate the TV (the user interface of the software of our department is shown in **Fig. S4**). We believe a close relevance exists between CT-based TV and pathology-based TV [35]. In future prospective studies, the CT-based TV will be used to further verify the dependability of the ADV score.

There is a strong association between two high-risk factors for recurrence, MVI and HCC poor differentiation. Qu C et al. [42] certified that the risk of MVI in patients with E-S grade III-IV was approximately 2.97 times higher than that of patients with good differentiation ($p < 0.001$). Another retrospective study found the presence of MVI in 35% of patients with poor differentiation, compared with only 14.6% of patients with E-S grade I-II ($p < 0.001$) [43]. Preoperative prediction of MVI risk can help guide therapeutic decisions in HCC patients with good hepatic reserve function who are scheduled to undergo surgery. First, for patients with HCC ≤ 3 cm or within the Milan criteria at high-risk of MVI, hepatectomy provided better 5-year recurrence and OS rates compared with radiofrequency ablation [44]. Second, for HCC patients within the Milan or up-to-7 criteria, predicted high-risk patients undergoing LT had a better long-term prognosis than those undergoing hepatectomy [45, 46]. Third, wide margins (margin distance ≥ 1 cm) and anatomic hepatectomy significantly prolonged DFS and OS in predicted MVI-positive HCC patients [47]. Fourth, intraoperative radiotherapy can be performed where available [48].

Our results demonstrated significant differences in hepatic function and inflammation levels among the three groups of patients differentiated by the ADV score (**Figs. 3 and 4**). Notably, previous studies indicated high preoperative levels of AST (>40 U/L) and GGT (≥60 U/L) as independent risk factors for the presence of MVI [49, 50]. At the same time, the decision tree and permutation test screened AST from numerous clinical parameters, which was significantly associated with E-S grade III-IV [19]. ALB was a relatively important variable influencing HCC recurrence and overall mortality [51]. The pro-inflammatory microenvironment of the cirrhotic liver is important in the development of most HCC [52]. ALRI, MLR, and GLR are prognostic indicators of inflammation capable of reflecting systemic inflammatory status, and they are significantly associated with early recurrence and long-term survival of HCC after hepatectomy [23, 53, 54]. In addition, Zhang H et al. [55] certified that GLR > 56 could be used for risk prediction of MVI. Meanwhile, HCC patients with E-S grade III-IV were reported to have higher ALRI levels than patients

with E-S grade I-II ($p=0.029$) [43]. The above results supported the reliability of the ADV score in predicting the risk of MVI and E-S grade.

Recent evidence suggested a benefit of adjuvant therapy in patients at high-risk of recurrence [12]. A phase III randomized study from China confirmed that postoperative adjuvant hepatic arterial infusion chemotherapy with 5-fluorouracil and oxaliplatin (HAIC-FOLFOX) significantly improved DFS in HCC patients with MVI [56]. Although the American Association for the Study of Liver Diseases (AASLD) still does not recommend neoadjuvant therapy for HCC patients undergoing hepatectomy outside of a clinical trial setting [12], the research teams of Ho WJ et al. [57] and Kaseb AO et al. [58] reported that preoperative neoadjuvant systemic therapy was feasible. Exploring effective neoadjuvant therapeutic options is an important future research direction to improve the prognosis of HCC patients after surgery. In a clinical trial setting, we considered predicted high-risk patients (presence of MVI & E-S grade III-IV) to be the candidates of the intention-to-treat (ITT) population. A randomized, placebo-controlled study published in 2015 showed that adjuvant therapy with sorafenib after hepatectomy in HCC patients did not improve RFS [59]. Notably, MVI was present in only 32% and 33% of patients in sorafenib and placebo groups, respectively. Is the appropriate ITT population the key to successful clinical trials in HCC? If the ITT population of the STORM trial was all patients with MVI or E-S grade III-IV, nobody can guarantee that sorafenib will not improve the prognosis of these patients. Since high-grade evidence needs to be obtained through multicenter randomized controlled trials (RCTs) with long-term follow-up, this requires significant human and financial resources. Thus, selecting the appropriate ITT population is crucial to enhance the RCTs' success rate. Patients with a high ADV score (>5.7 log) may be the ideal ITT population for neoadjuvant therapy.

This study used the ADV score to predict MVI and E-S grade status, which differs from previous articles focusing on HCC recurrence or overall survival (Table 3). Combining what is discussed above, the ADV score may be helpful in clinical decision-making in the following aspects, which were not proposed in previous studies. First, surgeons should choose a better surgical strategy for eradicating HCC lesions and MVI. Selecting predicted high-risk patients for neoadjuvant therapy in a clinical trial setting can be considered. Second, careful examination of pathology specimens by experienced pathologists is required to determine the accurate E-S grade because the E-S grades are categorized according to the size and morphology of HCC cells. Meanwhile, the "7-point method" is recommended for diagnosing MVI when sampling HCC specimens [60]. Third, for hepatitis B virus (HBV)-related HCC patients, standardized antiviral therapy should be administered preoperatively and postoperatively to reduce the incidence of MVI and improve prognosis [61, 62]. Finally, all predicted high-risk patients should cooperate with the doctor's treatment and receive more frequent follow-up visits.

Although an independent external validation cohort verified the diagnostic efficacy of the ADV score, this study still has several limitations. As mentioned above, pathology-based TV was used to calculate the ADV score. Since this is a retrospective cross-sectional study, selection bias is unavoidable, and follow-up data are lacking to investigate the impact of the ADV score on the long-term survival of HCC patients. Few non-HBV-related HCC patients were included due to the realities in China. Lastly, prospective studies are lacking in validating the ADV score's performance.

Conclusion

In conclusion, high-risk groups had more severe hepatic function impairment and higher levels of inflammation. The ADV score could best differentiate between risk groups, a valuable marker for screening patients at high-risk of HCC recurrence with a cut-off value of 5.7 log, which might help surgeons, pathologists, and HCC patients make appropriate clinical decisions.

Supplementary Information

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Supplementary Material 1

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Author contributions

Study concept and design: KW, XLX, and GWJ. Analysis and interpretation of data: SYC, ZYZ, and CBC. Generation of tables and figures: WWL, JSL, JWX, CLZ, YHY, ZGX, and HYW. Drafting of the manuscript: ZYZ, SYC, and CBC. Critical revision of the manuscript: KW, XLX, and GWJ. All authors read and approved the final version of the manuscript.

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Data availability

The datasets used in this study are available from corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate

The institutional review boards of The First Affiliated Hospital of Nanjing Medical University and The Affiliated Drum Tower Hospital of Nanjing University Medical School approved this retrospective study and waived the

requirement for written informed consent. All included patients' personal information is strictly confidential. This study followed the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
2. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589–604.
3. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261(5):947–55.
4. Zhou Z, Liu J, Xu X. A commentary on 'Prothrombin induced by vitamin K Absence-II versus alpha-fetoprotein in detection of both resectable hepatocellular carcinoma and early recurrence after curative liver resection: a retrospective cohort study' (Int J Surg. 2022;105:106843). Int J Surg. 2023;109(11):3656–3658.
5. He H, Chen S, Fan Z, Dong Y, Wang Y, Li S, et al. Multi-dimensional single-cell characterization revealed suppressive immune microenvironment in AFP-positive hepatocellular carcinoma. Cell Discov. 2023;9(1):60.
6. Inagaki Y, Tang W, Makuuchi M, Hasegawa K, Sugawara Y, Kokudo N. Clinical and molecular insights into the hepatocellular carcinoma tumour marker des-γ-carboxyprothrombin. Liver Int. 2011;31(1):22–35.
7. Yang Y, Li G, Lu Z, Liu Y, Kong J, Liu J. Progression of Prothrombin Induced by Vitamin K Absence-II in Hepatocellular Carcinoma. Front Oncol. 2021;11:726213.
8. Shah M, Sarkar D. HCC-Related lncRNAs: roles and mechanisms. Int J Mol Sci. 2024;25(1):597.
9. Xue Y, Ruan Y, Wang Y, Xiao P, Xu J. Signaling pathways in liver cancer: pathogenesis and targeted therapy. Mol Biomed. 2024;5(1):20.
10. Androutsakos T, Bakasis AD, Pouliakis A, Gazouli M, Vallilas C, Hatzis G. Single nucleotide polymorphisms of toll-like receptor 4 in Hepatocellular Carcinoma-A single-center study. Int J Mol Sci. 2022;23(16):9430.
11. Xu LX, He MH, Dai ZH, Yu J, Wang JG, Li XC, et al. Genomic and transcriptional heterogeneity of multifocal hepatocellular carcinoma. Ann Oncol. 2019;30(6):990–7.
12. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922–65.
13. Huang P, Zhou C, Wu F, Xiao Y, Qian X, Wang Y, et al. An improved diagnostic algorithm for subcentimeter hepatocellular carcinoma on gadoxetic acid-enhanced MRI. Eur Radiol. 2023;33(4):2735–45.
14. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer. 1954;7(3):462–503.
15. Hwang YJ, Bae JS, Lee Y, Hur BY, Lee DH, Kim H. Classification of microvascular invasion of hepatocellular carcinoma: correlation with prognosis and magnetic resonance imaging. Clin Mol Hepatol. 2023;29(3):733–46.
16. Zhou L, Rui JA, Wang SB, Chen SG, Qu Q. Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. Eur J Surg Oncol. 2011;37(6):521–5.
17. Xu X, Zhang HL, Liu QP, Sun SW, Zhang J, Zhu FP, et al. Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. J Hepatol. 2019;70(6):1133–44.
18. Lei Z, Li J, Wu D, Xia Y, Wang Q, Si A, et al. Nomogram for Preoperative Estimation of Microvascular Invasion Risk in Hepatitis B Virus-Related Hepatocellular Carcinoma within the Milan Criteria. JAMA Surg. 2016;151(4):356–63.
19. Mao Y, Wang J, Zhu Y, Chen J, Mao L, Kong W, et al. Gd-EOB-DTPA-enhanced MRI radiomic features for predicting histological grade of hepatocellular carcinoma. Hepatobiliary Surg Nutr. 2022;11(1):13–24.
20. Park GC, Hwang S, You YK, Choi Y, Kim JM, Joo DJ, et al. Quantitative prediction of Posttransplant Hepatocellular Carcinoma Prognosis using ADV score: validation with Korea-Nationwide Transplantation Registry Database. J Gastrointest Surg. 2023;27(7):1353–66.
21. Kang WH, Hwang S, Kaibori M, Kim JM, Kim KS, Kobayashi T, et al. Validation of quantitative prognostic prediction using ADV score for resection of hepatocellular carcinoma: A Korea-Japan collaborative study with 9200 patients. J Hepatobiliary Pancreat Sci. 2023;30(8):993–1005.
22. Hwang S, Song GW, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Quantitative prognostic prediction using ADV score for Hepatocellular Carcinoma following living Donor Liver Transplantation. J Gastrointest Surg. 2021;25(10):2503–15.
23. Mao S, Yu X, Shan Y, Fan R, Wu S, Lu C. Albumin-Bilirubin (ALBI) and Monocyte to lymphocyte ratio (MLR)-Based Nomogram Model to Predict Tumor recurrence of AFP-Negative Hepatocellular Carcinoma. J Hepatocell Carcinoma. 2021;8:1355–65.
24. Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut. 2016;65(8):1369–76.
25. Lu S, Xu L, Liang B, Wang H, Wang T, Xiang T, et al. Liver function derangement in patients with severe fever and Thrombocytopenia Syndrome. J Clin Transl Hepatol. 2022;10(5):825–34.
26. Oladele RO, Otu AA, Balogun OJ, Babalola OM, Nwosu AO, Iyabo Osaigbovo I, et al. Standardization of aspergillus IgG diagnostic cutoff in nigerians. Ther Adv Infect Dis. 2021;8:20499361211050158.
27. Chalmer MA, Hansen TF, Olesen J. Nosographic analysis of osmophobia and field testing of diagnostic criteria including osmophobia. Cephalalgia. 2019;39(1):38–43.
28. Jung DH, Hwang S, Lee YJ, Kim KH, Song GW, Ahn CS, et al. Small Hepatocellular Carcinoma with low tumor marker expression benefits more from Anatomical Resection Than Tumors with Aggressive Biology. Ann Surg. 2019;269(3):511–9.
29. Hwang S, Song GW, Lee YJ, Kim KH, Ahn CS, Moon DB, et al. Multiplication of Tumor volume by two tumor markers is a Post-resection Prognostic Predictor for Solitary Hepatocellular Carcinoma. J Gastrointest Surg. 2016;20(11):1807–20.
30. Hwang S, Joh JW, Wang HJ, Kim DG, Kim KS, Suh KS, et al. Prognostic prediction models for resection of large Hepatocellular Carcinoma: a Korean Multicenter Study. World J Surg. 2018;42(8):2579–91.
31. Ha SM, Hwang S, Park JY, Lee YJ, Kim KH, Song GW, et al. Validation of the OncoHepa test, a multigene expression profile test, and the tumor marker-volume score to predict postresection outcome in small solitary hepatocellular carcinomas. Ann Surg Treat Res. 2018;95(6):303–11.
32. Park GC, Hwang S, Park YH, Choi JU, Korean Liver Cancer Study Group. Validation of prognostic impact of ADV score for resection of hepatocellular carcinoma: analysis using Korea Liver Cancer Registry Database. Ann Surg Treat Res. 2020;98(5):235–46.

33. Hwang S, Moon DB, Kim KH, Ahn CS, Song GW, Jung DH, et al. Prognostic accuracy of the ADV score following resection of Hepatocellular Carcinoma with Portal Vein Tumor thrombosis. J Gastrointest Surg. 2021;25(7):1745–59.
34. Hwang S, Song GW, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Salvage living donor liver transplantation for hepatocellular carcinoma recurrence after hepatectomy: quantitative prediction using ADV score. J Hepatobiliary Pancreat Sci. 2021;28(11):1000–13.
35. Hwang S, Kim KH, Moon DB, Ahn CS, Ha TY, Song GW, et al. Prediction of post-resection prognosis using the ADV score for huge Hepatocellular Carcinomas ≥ 13 cm. J Liver Cancer. 2021;21(1):45–57.
36. Hwang S, Lee KJ, Moon DB, Song GW, Jung DH, Kim YK, et al. Prognostic impact of serum soluble PD-1 and ADV score for living donor liver transplantation in patients with previously untreated hepatocellular carcinoma. Ann Surg Treat Res. 2022;102(1):46–54.
37. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the study of the liver. EASL Clinical Practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
38. Kim DY, Toan BN, Tan CK, Hasan I, Setiawan L, Yu ML, et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. Clin Mol Hepatol. 2023;29(2):277–92.
39. Wang MD, Sun LY, Qian GJ, Li C, Gu LH, Yao LQ, et al. Prothrombin induced by vitamin K Absence-II versus alpha-fetoprotein in detection of both resectable hepatocellular carcinoma and early recurrence after curative liver resection: a retrospective cohort study. Int J Surg. 2022;105:106843.
40. Zhang Y, Kuang S, Shan Q, Rong D, Zhang Z, Yang H, et al. Can IVIM help predict HCC recurrence after hepatectomy? Eur Radiol. 2019;29(11):5791–803.
41. Imaoka Y, Ohira M, Kobayashi T, Honmyo N, Hamaoka M, Onoe T, et al. Impact of Geriatric Nutritional Risk Index after initial hepatectomy for Hepatocellular Carcinoma: a Retrospective Cohort Study with the Hiroshima Surgical Study Group of Clinical Oncology (HiSCO). J Gastrointest Surg. 2023;27(6):1152–8.
42. Qu C, Huang X, Liu K, Li K, Tan B, Qu L, et al. Effect of hepatitis B virus DNA replication level and anti-HBV therapy on microvascular invasion of hepatocellular carcinoma. Infect Agent Cancer. 2019;14:2.
43. Zhou Z, Cao S, Chen C, Chen J, Xu X, Liu Y, et al. A Novel Nomogram for the preoperative prediction of Edmondson-Steiner Grade III-IV in Hepatocellular Carcinoma patients. J Hepatocell Carcinoma. 2023;10:1399–409.
44. Bai S, Yang P, Xie Z, Li J, Lei Z, Xia Y, et al. Preoperative estimated risk of Microvascular Invasion is Associated with Prognostic differences following liver resection Versus Radiofrequency ablation for early Hepatitis B Virus-Related Hepatocellular Carcinoma. Ann Surg Oncol. 2021;28(13):8174–85.
45. Yang P, Teng F, Bai S, Xia Y, Xie Z, Cheng Z, et al. Liver resection versus liver transplantation for hepatocellular carcinoma within the Milan criteria based on estimated microvascular invasion risks. Gastroenterol Rep (Oxf). 2023;11:goad035.
46. Chan SC, Fan ST, Chok KS, Cheung TT, Chan AC, Fung JY, et al. Survival advantage of primary liver transplantation for hepatocellular carcinoma within the up-to-7 criteria with microvascular invasion. Hepatol Int. 2011;6(3):646–56.
47. Zhang XP, Xu S, Lin ZY, Gao QL, Wang K, Chen ZL, et al. Significance of anatomical resection and resection margin status in patients with HBV-related hepatocellular carcinoma and microvascular invasion: a multicenter propensity score-matched study. Int J Surg. 2023;109(4):679–88.
48. Wang L, Liu Y, Rong W, Wu F, Yu W, Liu K, et al. The role of intraoperative electron radiotherapy in centrally located hepatocellular carcinomas treated with narrow-margin (< 1 cm) hepatectomy: a prospective, phase 2 study. Hepatobiliary Surg Nutr. 2022;11(4):515–29.
49. Xu T, Ren L, Liao M, Zhao B, Wei R, Zhou Z, et al. Preoperative Radiomics analysis of contrast-enhanced CT for Microvascular Invasion and Prognosis Stratification in Hepatocellular Carcinoma. J Hepatocell Carcinoma. 2022;9:189–201.
50. Wang Y, Meng B, Wang X, Wu A, Li X, Qian X, et al. Noninvasive urinary protein signatures combined clinical information associated with microvascular invasion risk in HCC patients. BMC Med. 2023;21(1):481.
51. Liang Y, Wang Z, Peng Y, Dai Z, Lai C, Qiu Y, et al. Development of ensemble learning models for prognosis of hepatocellular carcinoma patients underwent postoperative adjuvant transarterial chemoembolization. Front Oncol. 2023;13:1169102.
52. O'Rourke JM, Sagar VM, Shah T, Shetty S. Carcinogenesis on the background of liver fibrosis: implications for the management of hepatocellular cancer. World J Gastroenterol. 2018;24(39):4436–47.
53. Casadei Gardini A, Foschi FG, Conti F, Petracci E, Vukotic R, Marisi G, et al. Immune inflammation indicators and ALBI score to predict liver cancer in HCV-patients treated with direct-acting antivirals. Dig Liver Dis. 2019;51(5):681–8.
54. Li S, Xu W, Liao M, Zhou Y, Weng J, Ren L, et al. The significance of Gamma-Glutamyl transpeptidase to lymphocyte count ratio in the early postoperative recurrence monitoring and prognosis prediction of AFP-Negative Hepatocellular Carcinoma. J Hepatocell Carcinoma. 2021;8:23–33.
55. Zhang H, Zhou Y, Li Y, Qin W, Zi Y, Liu Y, et al. Predictive value of gamma-glutamyl transpeptidase to lymphocyte count ratio in hepatocellular carcinoma patients with microvascular invasion. BMC Cancer. 2020;20(1):132.
56. Li SH, Mei J, Cheng Y, Li Q, Wang QX, Fang CK, et al. Postoperative adjuvant hepatic arterial infusion Chemotherapy with FOLFOX in Hepatocellular Carcinoma with Microvascular Invasion: a Multicenter, Phase III, Randomized Study. J Clin Oncol. 2023;41(10):1898–908.
57. Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, et al. Neoadjuvant Cabozantinib and Nivolumab converts locally Advanced HCC into Resectable Disease with enhanced Antitumor Immunity. Nat Cancer. 2021;2(9):891–903.
58. Kaseb AO, Hasanov E, Cao HST, Xiao L, Vauthey JN, Lee SS, et al. Perioperative Nivolumab monotherapy versus nivolumab plus ipilimumab in resectable hepatocellular carcinoma: a randomised, open-label, phase 2 trial. Lancet Gastroenterol Hepatol. 2022;7(3):208–18.
59. Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015;16(13):1344–54.
60. Sheng X, Ji Y, Ren GP, Lu CL, Yun JP, Chen LH, et al. A standardized pathological proposal for evaluating microvascular invasion of hepatocellular carcinoma: a multicenter study by LCPGC. Hepatol Int. 2020;14(6):1034–47.
61. Wang Z, Duan Y, Zhang J, Lv Y, Wu S, Cheng M, et al. Preoperative antiviral therapy and microvascular invasion in hepatitis B virus-related hepatocellular carcinoma: a meta-analysis. Eur J Pharmacol. 2020;883:173382.
62. Li Z, Lei Z, Xia Y, Li J, Wang K, Zhang H, Wan X, et al. Association of Preoperative Antiviral Treatment with incidences of Microvascular Invasion and Early Tumor recurrence in Hepatitis B Virus-Related Hepatocellular Carcinoma. JAMA Surg. 2018;153(10):e182721.

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