BMC Gastroenterology

RESEARCH ARTICLE

Open Access

Utility of mean platelet volume in differentiating intrahepatic cholangiocarcinoma from hepatocellular carcinoma

Xin Zhang[1†], Wen-Juan Huang[1†], Meng-Lin Zhang[1†], Wen Wang[1], Ye Niu[1], Rui-tao Wang[1*] and Zeng-yao Liu[2*]

Abstract

Background: Intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) are the most prevalent histologic types of primary liver cancer. HCC and ICC differ in treatment and prognosis, warranting an effective differential diagnosis between them. This study aimed to explore the clinical value of mean platelet volume (MPV) to discriminate between HCC and ICC.

Material/methods: We performed a retrospective analysis of ICC and HCC patients who were from the Harbin Medical University Cancer Hospital, China. Logistic regression analysis was used to identify the independent factors for the differentiation of HCC and ICC. A receiver operating characteristic curve was built to evaluate the diagnostic performance of the potential model. An independent validation study was performed to validate the diagnostic ability.

Results: ICC patients were detected in 146 out of 348 patients in the primary cohort. MPV levels were decreased in ICC patients compared with those in HCC patients. Logistic regression analysis revealed that MPV was an independent factor in distinguishing HCC from ICC. A combination of sex, hepatitis B surface antigen, MPV, alpha-fetoprotein, and carbohydrate antigen 19–9 demonstrated a good capability to differentiate HCC from ICC. Similar results were achieved in the validation cohort.

Conclusions: MPV may be a new marker to help distinguish ICC from HCC. Further validation studies are required.

Keywords: Intrahepatic cholangiocarcinoma, Hepatocellular carcinoma, Mean platelet volume

Introduction

Primary liver cancer (PLC) is the sixth most common cancer worldwide and the third-leading cause of cancer-related death [1]. The most common types of PLC are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), which account for roughly 95% of all PLC [2, 3]. HCC develops from hepatocytes, whereas ICC develops from biliary epithelium [4, 5]. Although HCC and ICC have overlapping etiological risk factors and clinical manifestations, the therapeutic strategies and prognoses between the two are distinct [2]. Therefore, it

†Xin Zhang, Wen-Juan Huang, and Meng-Lin Zhang contributed equally to this work

*Correspondence: ruitaowang@126.com; drliuzengyao@hrbmu.edu.cn

[1] Department of Internal Medicine, Harbin Medical University Cancer Hospital, Harbin Medical University, NO. 150 Haping ST, Nangang District, 150081 Harbin, China
[2] Department of Interventional Medicine, The First Affiliated Hospital of Harbin Medical University, NO. 23 Post Street, Nangang District, Harbin, Heilongjiang 150001, China

is a challenge to differential diagnosis between HCC and ICC.

At present, magnetic resonance imaging (MRI) and contrast-enhanced computerized tomography (CT) are the methods most commonly used to discriminate between the two subtypes, but ICC may mimic the radiological appearance of HCC on CT or MRI and lead to misdiagnosis [6–8]. Approximately 15% of histopathologically confirmed ICC patients who display a "wash-in and wash-out" enhancement pattern on contrast-enhanced CT were misdiagnosed as HCC [7]. Another study revealed that 7–19% of small ICC patients on MRI were misdiagnosed as HCC [9, 10]. Besides, due to the fact that some HCC cases may show the typical enhancement pattern of ICC on contrast-enhanced ultrasound (CEUS), the ability of CEUS to differentiate HCC from ICC is still controversial [11, 12]. Moreover, alpha-fetoprotein (AFP) and carbohydrate antigen 19–9 (CA19-9) are regarded as the blood biomarkers for distinguishing HCC from ICC. However, it is hard to make a distinction between small ICC and HCC in cirrhotic livers due to the low diagnostic sensitivity and specificity of these biomarkers [13, 14]. Elevated AFP is not uncommon in ICC. A series of studies observed that 10.3% of ICC patients had a serum AFP level of > 200 ng/mL [15]. The findings were also confirmed in the study by Zhou [16]. In addition, serum CA19-9 is a frequently used tumor marker for ICC diagnosis but has a low sensitivity and specificity of 53% and 63%, respectively [17, 18]. Thus, there is an urgent need to find new discriminative biomarkers in the clinic.

Platelets' roles in HCC growth have recently piqued the interest of researchers. Mean platelet volume (MPV), an indicator of platelet size, has been proposed as a parameter of platelet function and activation [19]. Furthermore, MPV can serve as a potential biomarker for the diagnosis and prognosis of various tumors, such as lung cancer, thyroid cancer, colorectal cancer, and laryngeal cancer [20–23]. Some reports have proved that MPV is useful as a diagnostic marker for AFP-negative HCC [24, 25]. However, no study to date has clarified the role of MPV in distinguishing ICC from HCC. The objective of this study was to evaluate whether MPV could discriminate between ICC and HCC.

Materials and methods

Patients

This study retrospectively reviewed the clinical data of patients histologically diagnosed with ICC or HCC at Harbin Medical University Cancer Hospital, China, between January 2017 and December 2019. Data from another independent cohort of ICC and HCC patients who were diagnosed at the First Affiliated Hospital of Harbin Medical University, from January 2018 to December 2020 was collected retrospectively. Our selection criteria in this study included the following: (1) patients were above 18 years old; (2) pathological diagnosis of HCC or ICC; (3) patients had a curative liver resection. Diagnostic criteria were based on the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition). The exclusion criteria included the following: (1) mixed hepatocellular-cholangiocellular carcinoma or other types of liver tumor (n = 36); (2) previous treatment history of HCC or ICC (n = 7); (3) no preoperative AFP or CA19-9 results (n = 6); (4) patients with a history of other cancers (n = 4), diabetes (n = 9), rheumatoid diseases (n = 2), cardiovascular diseases (n = 5), or medical treatment with anticoagulant, statins, or acetylic salicylic acid (n = 7).

The study was approved by the Institutional Ethics Committees of the two hospitals.

Data collection

All the data was collected from databases. The clinical medical data included demographics, comorbidities, preoperative routine blood tests, biochemistry tests, tumor marker tests, and imaging data. The information on blood tests was obtained from the test report from the Department of Clinical Laboratory. The platelet distribution width (PDW), MPV, and platelet count were directly obtained by an automated hematological analyzer (Sysmex XE-2100, Kobe, Japan).

Statistical analysis

The statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY). The Kolmogorov–Smirnov test was done to analyze the normally distributed variables. Non-normally distributed variables were expressed as the median and quartile. Logistic regression analysis was used to identify the independent factors for the differentiation of HCC and ICC. Receiver operating characteristic (ROC) analysis was used to determine the potential diagnostic performance of different models in differentiating ICC from HCC. $P < 0.05$ was considered statistically significant.

Results

All patients who underwent curative liver resection for ICC or HCC at two affiliated hospitals of Harbin Medical University were enrolled in the derivation set and validation set. The clinicopathological characteristics of patients are summarized in Table 1. Body mass index (BMI), hepatitis B surface antigen (HBsAg), cirrhosis, capsule, nodule diameter, white blood cell count (WBC), haemoglobin, platelet count, MPV, PDW, aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (γ-GGT), total bilirubin,

Table 1 The characteristics of the patients in derivation set and validation set

Variables	Derivation set	Validation set	*p* value
N	348	158	
Age (years)	55.8 ± 9.5	54.7 ± 10.4	0.246
BMI (kg/m^2)	24.3 ± 3.3	22.2 ± 2.5	**< 0.001**
Sex (Male, %)	250 (71.8)	102 (64.6)	0.099
HBsAg (%)	197 (56.6)	74 (46.8)	**0.041**
Hepatitis C (%)	19 (5.5)	4 (2.5)	0.143
Cirrhosis (%)	203 (58.3)	66 (41.8)	**0.001**
Tumor number (Multiple, %)	43 (12.4)	23 (14.6)	0.496
Capsule (Incomplete, %)	28 (8.0)	57 (36.1)	**< 0.001**
The largest nodule diameter (cm)	5.4 ± 3.1	6.5 ± 4.6	**0.007**
WBC (× 10^9/L)	6.04 ± 2.09	8.34 ± 4.09	**< 0.001**
Haemoglobin (g/L)	140.1 ± 15.9	124.7 ± 22.5	**< 0.001**
Platelet count (× 10^9/L)	182.7 ± 74.8	202.1 ± 99.8	**0.03**
MPV (fL)	14.5 ± 2.5	13.3 ± 2.1	**< 0.001**
PDW (%)	15.2 ± 2.3	13.2 ± 2.2	**< 0.001**
AST (U/L)	29 (22–43)	41 (26–77)	**< 0.001**
ALT (U/L)	30 (19–48)	56 (29–116)	**< 0.001**
γ-GGT (U/L)	65 (33–138)	96 (51–196)	**< 0.001**
Total bilirubin (μmol/L)	14.5 (11.2–18.2)	20.1 (14.3–37.1)	**< 0.001**
AFP (ng/mL)	6.08 (2.61–97.4)	6.23 (2.70–270.1)	0.818
CA19-9 (U/mL)	22.8 (11.3–50.5)	23.5 (12.2–59.4)	0.829
FIB-4	2.8 (1.7–4.7)	1.9 (1.1–3.0)	**0.014**
APRI	0.7 (0.4–1.4)	0.7 (0.3–1.2)	**< 0.001**
NLR	2.87 ± 1.76	4.03 ± 1.94	**< 0.001**

Data are expressed as means (SD) or percentage. SD, standard deviation; BMI, body mass index; HBsAg, hepatitis B surface antigen; WBC, white blood cell count; MPV, mean platelet volume; PDW, platelet distribution width; AST, aspartate transaminase; ALT, alanine transaminase; γ-GGT, γ-glutamyl transferase; AFP, alphafetoprotein; CA19-9, carbohydrate antigen 19–9; APRI, aspartate aminotransferase/platelet ratio index; FIB-4, fibrosis-4; NLR, neutrophil-to-lymphocyte ratio. Bold indicates statistically significant values ($P < 0.05$)

the aspartate aminotransferase/platelet ratio index (APRI), fibrosis-4 (FIB-4), and the neutrophil-to-lymphocyte ratio (NLR) in two groups were significantly different. However, no significant differences were observed between the derivation set and the validation set with regard to age, sex, hepatitis C, tumor number, AFP, and CA19-9 levels. The normal ranges for all the measured variables can be found in Additional file 1: Table S1.

Table 2 summarizes the characteristics of patients with ICC or HCC. In the derivation set, there were 348 patients, including 202 HCC patients and 146 ICC patients. In the validation set, 158 consecutive patients were studied, consisting of 107 HCC patients and 51 ICC patients. There were more males in the HCC group than in the ICC group. In the derivation cohort, statistical significance was observed in age, sex, HBsAg, hepatitis C, cirrhosis, tumor number, capsule, the largest nodule diameter, APRI, FIB-4, NLR, WBC, haemoglobin, platelet count, MPV, PDW, AST, ALT, γ-GGT, total bilirubin, AFP, and CA19-9 levels between the two groups (Table 2). Other parameters in the two groups were not significantly different.

Logistic regression analysis was performed to evaluate the risk factors for differentiation of HCC and ICC. In the derivation set, twenty-two variables, including age, sex, HBsAg, hepatitis C, cirrhosis, tumor number, largest nodule diameter, capsule, APRI, FIB-4, NLR, WBC, haemoglobin, platelet count, MPV, PDW, AST, ALT, γ-GGT, total bilirubin, AFP, and CA19-9 entered into the original model. Sex (female vs. male, OR, 3.645, 95%CI, 1.398–9.504, $P = 0.008$), HBsAg (positive vs. negative, OR, 2.747, 95% CI, 1.054–7.159, $P = 0.039$), cirrhosis (Yes vs. No, OR, 6.590, 95% CI, 2.648–16.398, $P < 0.001$), MPV (OR, 1.590, 95% CI, (1.171–2.159), $P = 0.003$), AST (OR, 1.002, 95% CI, 1.000–1.003, $P = 0.018$), AFP (OR, 0.974, 95% CI, (0.957–0.991), $P = 0.003$), and CA19-9 (OR, 1.069, 95% CI, (1.015–1.126), $P = 0.011$) were the independent risk factors for distinguishing HCC from ICC (Table 3). In the validation set, twelve variables, including age, sex, HBsAg, capsule, haemoglobin, platelet count, MPV,

Table 2 The characteristics of the patients with HCC or ICC

Variables	HCC	ICC	*p* value
Development set			
N	202	146	
Age (years)	54.3 ± 9.4	57.7 ± 9.3	**0.001**
BMI (kg/m^2)	24.2 ± 3.0	24.4 ± 3.7	0.487
Sex (Male, %)	163 (80.7)	87 (59.6)	**< 0.001**
HBsAg (%)	157 (77.7)	40 (27.4)	**< 0.001**
Hepatitis C (%)	17 (8.4)	2 (1.4)	**0.004**
Cirrhosis (%)	167 (82.7)	36 (24.5)	**< 0.001**
Tumor number (Multiple, %)	36 (17.8)	7 (4.8)	**< 0.001**
The largest nodule diameter (cm)	4.9 ± 3.3	6.0 ± 2.7	**0.002**
Capsule (Incomplete, %)	11 (5.4)	17 (11.6)	**0.036**
WBC (× 10^9/L)	5.46 ± 1.92	6.84 ± 2.04	**< 0.001**
Haemoglobin (g/L)	142.5 ± 14.5	136.8 ± 17.2	**0.001**
Platelet count (× 10^9/L)	166.1 ± 98.5	209.1 ± 79.0	**< 0.001**
MPV (fL)	10.9 ± 1.3	9.9 ± 1.5	**< 0.001**
PDW (%)	14.3 ± 2.5	14.8 ± 2.5	**0.032**
AST (U/L)	33 (24–45)	27 (20–40)	**0.002**
ALT (U/L)	33 (21–49)	26 (17–47)	**0.036**
γ-GGT (U/L)	58 (33–104)	80 (36–185)	**0.002**
Total bilirubin (μmol/L)	15.3 (11.8–20.1)	13.5 (10.2–16.8)	**0.001**
AFP (ng/mL)	19.4 (4.4–425.0)	3.2 (1.87–6.07)	**< 0.001**
CA19-9 (U/mL)	16.4 (9.5–31.1)	44.2 (20.2–470.2)	**< 0.001**
FIB-4	2.1 (1.4–3.2)	1.5 (1.1–2.4)	**< 0.001**
APRI	0.5 (0.3–1.0)	0.4 (0.2–0.6)	**< 0.001**
NLR	1.99 ± 1.36	3.58 ± 1.75	**0.001**
Validation set			
N	107	51	
Age (years)	52.7 ± 10.2	58.8 ± 9.6	**< 0.001**
BMI (kg/m^2)	22.0 ± 2.6	22.7 ± 2.3	0.082
Sex (male, %)	80 (74.8)	22 (43.1)	**< 0.001**
HBsAg (%)	63 (58.9)	11 (21.6)	**< 0.001**
Hepatitis C (%)	1 (0.9)	3 (5.9)	0.064
Cirrhosis (%)	50 (46.7)	16 (31.4)	0.067
Tumor number (Multiple, %)	18 (16.8)	5 (9.8)	0.242
The largest nodule diameter (cm)	6.4 ± 4.2	6.8 ± 5.6	0.636
Capsule (Incomplete, %)	32 (29.9)	25 (49.0)	**0.019**
WBC (× 10^9/L)	8.14 ± 3.58	8.75 ± 5.00	0.382
Haemoglobin (g/L)	121.8 ± 23.7	130.8 ± 18.7	**0.018**
Platelet count (× 10^9/L)	178.2 ± 91.5	252.3 ± 98.8	**< 0.001**
MPV (fL)	11.2 ± 1.0	10.3 ± 0.9	**< 0.001**
PDW (%)	13.2 ± 2.2	13.5 ± 2.0	0.431
AST (U/L)	38 (26–61)	55 (25–122)	0.062
ALT (U/L)	50 (30–87)	93 (27–169)	0.058
γ-GGT (U/L)	78 (42–137)	158 (66–413)	**< 0.001**
Total bilirubin (μmol/L)	18.2 (14.0–25.4)	47.0 (16.5–137.1)	**< 0.001**
AFP (ng/mL)	23.7 (4.7–482.4)	2.8 (1.6–3.7)	**< 0.001**
CA19-9 (U/mL)	16.7 (6.8–32.1)	96.6 (28.8–285.7)	**< 0.001**
FIB-4	2.0 (1.1–3.3)	1.6 (1.0–2.8)	**< 0.001**
APRI	0.7 (0.3–1.2)	0.7 (0.3–1.4)	0.132
NLR	3.96 ± 1.76	4.17 ± 1.32	0.548

Table 2 (continued)

Data are expressed as means (SD) or percentage. SD, standard deviation; BMI, body mass index; HBsAg, hepatitis B surface antigen; WBC, white blood cell count; MPV, mean platelet volume; PDW, platelet distribution width; AST, aspartate transaminase; ALT, alanine transaminase; γ-GGT, γ-glutamyl transferase; AFP, alphafetoprotein; CA19-9, carbohydrate antigen 19–9; APRI, aspartate aminotransferase/platelet ratio index; FIB-4, fibrosis-4; NLR, neutrophil-to-lymphocyte ratio. Bold indicates statistically significant values (P < 0.05)

Table 3 Logistic regression analysis of the risk factors for distinguishing HCC from ICC

Variables	β	OR (95% CI)	*p* value
Development set			
Sex (Male vs Female)	1.293	3.645 (1.398–9.504)	0.008
HBsAg (Positive vs Negative)	1.010	2.747 (1.054–7.159)	0.039
Cirrhosis (Yes vs No)	1.885	6.590 (2.648–16.398)	< 0.001
MPV (fL)	0.464	1.590 (1.171–2.159)	0.003
AST (U/L)	0.002	1.002 (1.000–1.003)	0.018
AFP (ng/mL)	− 0.026	0.974 (0.957–0.991)	0.003
CA19-9 (U/mL)	0.067	1.069 (1.015–1.126)	0.011
Validation set			
Sex (Male vs Female)	2.669	14.424 (2.795–74.439)	0.001
Haemoglobin (g/L)	− 0.058	0.944 (0.910–0.979)	0.002
MPV (fL)	1.388	4.007 (1.226–13.094)	0.022
Total bilirubin (μmol/L)	− 0.014	0.986 (0.973–0.999)	0.040
AFP (ng/mL)	0.007	1.007 (1.002–1.012)	0.008
CA19-9 (U/mL)	− 0.015	0.985 (0.972–0.998)	0.020

OR, odds ratio; CI, confidence interval. Abbreviations: see to Table 1

γ-GGT, total bilirubin, AFP, FIB-4, and CA19-9 were entered into the original model. Sex, AFP, CA19-9, haemoglobin, total bilirubin, and MPV were independently associated with the differentiation of HCC and ICC (Table 3).

We built a model incorporating five variables (sex, HBsAg, MPV, AFP, and CA19-9) to discriminate ICC from HCC. The sensitivity, specificity, positive predictive value, and negative predictive value are listed in Table 4. A ROC curve was built to evaluate the diagnostic performance of the potential model. ROC curves showed the sensitivity and specificity of the differential diagnosis of HCC versus ICC in the development set (Fig. 1) and validation set (Fig. 2). For the training set, the model demonstrated a powerful capability to differentiate ICC from HCC, with an area under the curve (AUC) value of 0.907. An independent validation study was performed to validate the diagnostic ability. For the validation set, the C-index was 0.931 (95% CI: 0.880–0.965), demonstrating sufficient accuracy in distinguishing ICC from HCC. The combination of these biomarkers exhibited a significantly larger AUC compared with MPV alone (P < 0.001) (Figs. 3, 4).

Table 4 Receiver operating characteristic curve analyses showing the utility of combined markers for differentiating between HCC and ICC

Model	Sensitivity	Specificity	PPV	NPV	AUC
Development set					
MPV	0.802	0.541	0.707	0.664	0.698 (0.646–0.746)
Combination	0.854	0.820	0.871	0.797	0.907 (0.870–0.935)
Validation set					
MPV	0.863	0.523	0.889	0.463	0.757 (0.683–0.822)
Combination	0.860	0.882	0.939	0.750	0.931 (0.880–0.965)

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; Combination, five variables (sex, HBsAg, MPV, AFP, and CA19-9) were included in the model

Discussion

This study is the first to observe that MPV plays a key role in distinguishing ICC from HCC. Moreover, the external validation cohort came to the same conclusion. These results indicate that MPV might exert distinct functions in the pathology of ICC and HCC.

The gold standard for the diagnosis of PLC is liver biopsy, but for tumors without a biopsy path or with a small diameter, biopsies are usually not available before surgery. Although many markers and techniques have been applied to help clinicians distinguish ICC from HCC [26–28], their clinical value is limited due to the lack of experienced radiologists and costly high-resolution equipment in some developing areas. In our study, we observed that MPV levels in ICC were significantly lower than those in HCC, both in the primary set and in the validation set. Furthermore, MPV may provide additional information to make a distinction between ICC and HCC.

The mechanisms underlying the association of MPV with differentiation are currently unclear. Some reports found that MPV levels in patients with HCC were significantly higher compared to patients with chronic hepatitis or healthy subjects [29]. The authors suggest that MPV could be a potential diagnostic marker for HCC in patients with chronic liver diseases. On the other hand, some studies detected that MPV and MPV-platelet count ratio were significantly higher in HCC patients and were useful for distinguishing AFP-negative HCC patients

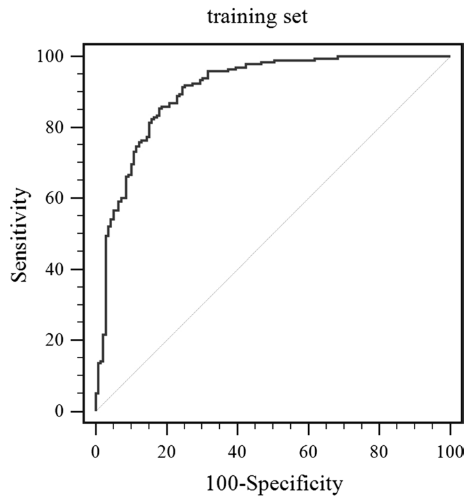

Fig. 1 ROC curve for the model showing the sensitivity and specificity of the differential diagnosis of HCC versus ICC in the training set

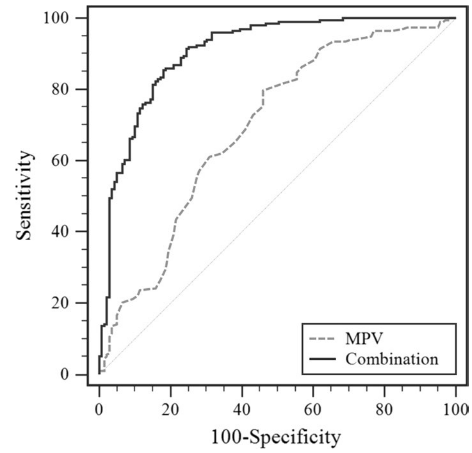

Fig. 3 ROC curve analysis showing the capability of the combination of MPV with other variables to differentiate ICC from HCC in the training set

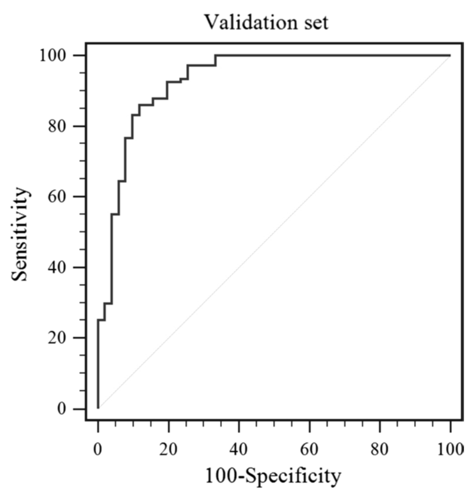

Fig. 2 ROC curve for the model showing the sensitivity and specificity of the differential diagnosis of HCC versus ICC in the validation set

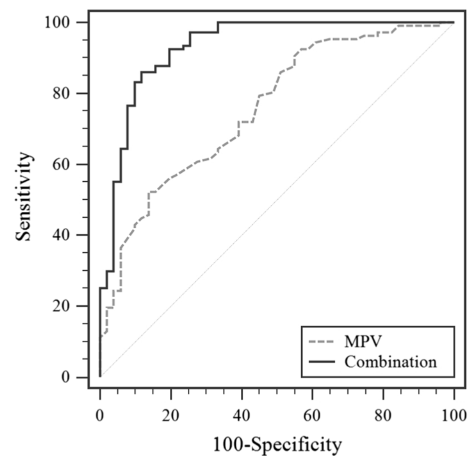

Fig. 4 ROC curve analysis showing the capability of the combination of MPV with other variables to differentiate ICC from HCC in the validation set

from healthy individuals [24]. Multiple lines of evidence demonstrate that most HCC develops in an inflammatory environment caused by viral hepatitis and alcoholic or nonalcoholic steatohepatitis [30]. Thrombocytopenia and increased MPV levels in HCC patients may result from decreased activity of thrombopoietin and bone marrow suppression associated with chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection and antiviral therapy application [31]. Relative to HCC, substantially less is known about the epidemiology of ICC. Although several ICC-specific risk factors have been identified, such as bile stasis and chronic inflammation of the biliary epithelium, the mechanisms by which they lead to the development of ICC are less clear [32]. Recently, a study revealed that platelets can bind with podoplanin via c-type lectin-like receptor 2 (CLEC-2) and that activated platelets promote liver protection and inhibit liver fibrosis after cholestatic liver injury [33]. Cholangiocarcinoma (CCA) is characterized by a reactive desmoplastic stroma containing enriched cancer-associated fibroblasts (CAFs) that express vascular endothelial growth factor A (VEGF-A) and vascular endothelial growth factor C (VEGF-C), resulting in expansion of the lymphatic vasculature and tumor cell intravasation [34]. Interestingly, previous studies confirmed that platelet-derived growth factor-D increased VEGF-C and VEGF-A production by stimulating CAFs [35].

Although our study observed a new biomarker to distinguish ICC from HCC, some limitations should be taken into consideration when interpreting the findings. Firstly, the heterogeneity of selected patients and statistical bias, such as the overfitting of the model, cannot be fully eliminated. Secondly, because many factors (such as comorbidities, lifestyle, drug usage, and physiology) could influence MPV levels [36], a stricter prospective trial should be designed to confirm the results before the clinical utility of this marker. Lastly, some preanalytical and analytical variables are responsible for the differences in MPV values. The venipuncture procedure, the anticoagulant used for blood collection, the temperature during measurement, different hematological analyzers and measuring methods are the common reasons for the imprecision of MPV evaluation. Standardization of these phases will contribute to a more accurate and reproducible measurement.

Conclusions

MPV may be a new marker to help distinguish ICC from HCC. Further validation studies are required.

Abbreviations

PLC: Primary liver cancer; ICC: Intrahepatic cholangiocarcinoma; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; CT: Computerized tomography; CEUS: Contrast-enhanced ultrasound; AFP: Alpha-fetoprotein; CA19-9: Carbohydrate antigen 19–9; MPV: Mean platelet volume; PDW: Platelet distribution width; ROC: Receiver operating characteristic; BMI: Body mass index; HBsAg: Hepatitis B surface antigen; WBC: White blood cell count; AST: Aspartate transaminase; ALT: Alanine transaminase; γ-GGT: γ-Glutamyl transferase; AUC: Area under the curve; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CLEC-2: C-type lectin-like receptor 2; CCA: Cholangiocarcinoma; CAFs: Cancer-associated fibroblasts; VEGF-A: Vascular endothelial growth factor A; VEGF-C: Vascular endothelial growth factor C; PDGF-D: Platelet-derived growth factor-D; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; APRI: Aspartate aminotransferase/platelet ratio index; FIB-4: Fibrosis-4; NLR: Neutrophil-to-lymphocyte ratio.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-022-02348-0.

Additional file 1. Table S1.

Acknowledgements

Not applicable.

Author contributions

RTW, ZYL, YN, and XZ: Conception and design. WJH, MLZ, WW, and XZ: Data collection and analysis. YN, WW, and ZYL: Interpretation of data. WJH, XZ, and MLZ: Drafted the manuscript. RTW, WJH, and XZ: Revised the manuscript. All of the authors have read and approved the final manuscript.

Funding

This work was supported by grants from the Harbin Medical University Cancer Hospital (JJZD2017-05).

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Harbin Medical University Cancer Hospital and the First Affiliated Hospital of Harbin Medical University Institutional Review Boards. All patients involved in the study gave written consent for this study.

Consent for publication

Not Applicable.

Competing interests

All authors declare no conflict of interest.

Received: 17 May 2021 Accepted: 24 May 2022
Published online: 06 June 2022

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Sia D, Villanueva A, Friedman SL, Llovet JM. Liver cancer cell of origin, molecular class, and effects on patient prognosis. Gastroenterology. 2017;152(4):745–61.
3. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.
4. Craig AJ, von Felden J, Garcia-Lezana T, Sarcognato S, Villanueva A. Tumour evolution in hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2020;17(3):139–52.
5. Saleh M, Virarkar M, Bura V, Valenzuela R, Javadi S, Szklaruk J, Bhosale P. Intrahepatic cholangiocarcinoma: pathogenesis, current staging, and radiological findings. Abdom Radiol (NY). 2020;45(11):3662–80.
6. Cheng N, Khoo N, Chung AYF, Goh BKP, Cheow PC, Chow PKH, Lee SY, Ooi LL, Jeyaraj PR, Kam JH, et al. Pre-operative imaging characteristics in histology-proven resected intrahepatic cholangiocarcinoma. World J Surg. 2020;44(11):3862–7.
7. Li R, Cai P, Ma KS, Ding SY, Guo DY, Yan XC. Dynamic enhancement patterns of intrahepatic cholangiocarcinoma in cirrhosis on contrast-enhanced computed tomography: risk of misdiagnosis as hepatocellular carcinoma. Sci Rep. 2016;6:26772.
8. Vigano L, Lleo A, Muglia R, Gennaro N, Sama L, Colapietro F, Roncalli M, Aghemo A, Chiti A, Di Tommaso L, et al. Intrahepatic cholangiocellular carcinoma with radiological enhancement patterns mimicking hepatocellular carcinoma. Updates Surg. 2020;72(2):413–21.
9. Huang B, Wu L, Lu XY, Xu F, Liu CF, Shen WF, Jia NY, Cheng HY, Yang YF, Shen F. Small intrahepatic cholangiocarcinoma and hepatocellular carcinoma in cirrhotic livers may share similar enhancement patterns at multiphase dynamic MR imaging. Radiology. 2016;281(1):150–7.
10. Ni T, Shang XS, Wang WT, Hu XX, Zeng MS, Rao SX. Different MR features for differentiation of intrahepatic mass-forming cholangiocarcinoma from hepatocellular carcinoma according to tumor size. Br J Radiol. 2018;91(1088):20180017.
11. Liu GJ, Wang W, Lu MD, Xie XY, Xu HX, Xu ZF, Chen LD, Wang Z, Liang JY, Huang Y, et al. Contrast-enhanced ultrasound for the characterization of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Liver Cancer. 2015;4(4):241–52.
12. Li F, Li Q, Liu Y, Han J, Zheng W, Huang Y, Zheng X, Cao L, Zhou JH. Distinguishing intrahepatic cholangiocarcinoma from hepatocellular

carcinoma in patients with and without risks: the evaluation of the LR-M criteria of contrast-enhanced ultrasound liver imaging reporting and data system version 2017. Eur Radiol. 2020;30(1):461–70.
13. Gao YX, Yang TW, Yin JM, Yang PX, Kou BX, Chai MY, Liu XN, Chen DX. Progress and prospects of biomarkers in primary liver cancer (Review). Int J Oncol. 2020;57(1):54–66.
14. Ejaz A, Cloyd JM, Pawlik TM. Advances in the diagnosis and treatment of patients with intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2020;27(2):552–60.
15. Liver Cancer Study Group of J: Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg* 1990, 211(3):277–287.
16. Zhou YM, Yang JM, Li B, Yin ZF, Xu F, Wang B, Liu P, Li ZM. Clinicopathologic characteristics of intrahepatic cholangiocarcinoma in patients with positive serum a-fetoprotein. World J Gastroenterol. 2008;14(14):2251–4.
17. Patel AH, Harnois DM, Klee GG, LaRusso NF, Gores GJ. The utility of CA 19–9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. Am J Gastroenterol. 2000;95(1):204–7.
18. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014;60(6):1268–89.
19. Handtke S, Thiele T. Large and small platelets-(When) do they differ? J Thromb Haemost. 2020;18(6):1256–67.
20. Zhu X, Chen Y, Cui Y. Absolute neutrophil count and mean platelet volume in the blood as biomarkers to detect lung cancer. Dis Markers. 2020;2020:1371964.
21. Yu YJ, Li N, Yun ZY, Niu Y, Xu JJ, Liu ZP, Liu T, Wang RT, Yu KJ. Preoperative mean platelet volume and platelet distribution associated with thyroid cancer. Neoplasma. 2017;64(4):594–8.
22. Fu S, Liu L, Zhang X, Liu ZP, Wang RT. Platelet indices in laryngeal cancer. Cancer Biomark. 2018;21(3):675–80.
23. Zhu X, Cao Y, Lu P, Kang Y, Lin Z, Hao T, Song Y. Evaluation of platelet indices as diagnostic biomarkers for colorectal cancer. Sci Rep. 2018;8(1):11814.
24. Luo CL, Rong Y, Chen H, Zhang WW, Wu L, Wei D, Wei XQ, Mei LJ, Wang FB. A logistic regression model for noninvasive prediction of AFP-negative hepatocellular carcinoma. Technol Cancer Res Treat. 2019;18:1533033819846632.
25. Wang T, Zhang KH. New blood biomarkers for the diagnosis of AFP-negative hepatocellular carcinoma. Front Oncol. 2020;10:1316.
26. Choi SY, Kim YK, Min JH, Kang TW, Jeong WK, Ahn S, Won H. Added value of ancillary imaging features for differentiating scirrhous hepatocellular carcinoma from intrahepatic cholangiocarcinoma on gadoxetic acid-enhanced MR imaging. Eur Radiol. 2018;28(6):2549–60.
27. Yang J, Zhang YH, Li JW, Shi YY, Huang JY, Luo Y, Liu JB, Lu Q. Contrast-enhanced ultrasound in association with serum biomarkers for differentiating combined hepatocellular-cholangiocarcinoma from hepatocellular carcinoma and intrahepatic cholangiocarcinoma. World J Gastroenterol. 2020;26(46):7325–37.
28. Iavarone M, Piscaglia F, Vavassori S, Galassi M, Sangiovanni A, Venerandi L, Forzenigo LV, Golfieri R, Bolondi L, Colombo M. Contrast enhanced CT-scan to diagnose intrahepatic cholangiocarcinoma in patients with cirrhosis. J Hepatol. 2013;58(6):1188–93.
29. Kurt M, Onal IK, Sayilir AY, Beyazit Y, Oztas E, Kekilli M, Turhan N, Karaman K, Akdogan M. The role of mean platelet volume in the diagnosis of hepatocellular carcinoma in patients with chronic liver disease. Hepatogastroenterology. 2012;59(117):1580–2.
30. van der Windt DJ, Sud V, Zhang H, Varley PR, Goswami J, Yazdani HO, Tohme S, Loughran P, O'Doherty RM, Minervini MI, et al. Neutrophil extracellular traps promote inflammation and development of hepatocellular carcinoma in nonalcoholic steatohepatitis. Hepatology. 2018;68(4):1347–60.
31. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int. 2017;37(6):778–93.
32. Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control. 2017;24(3):1073274817729245.
33. Maruyama S, Kono H, Furuya S, Shimizu H, Saito R, Shoda K, Akaike H, Hosomura N, Kawaguchi Y, Amemiya H, et al. Platelet C-Type lectin-like receptor 2 reduces cholestatic liver injury in mice. Am J Pathol. 2020;190(9):1833–42.
34. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557–88.
35. Cadamuro M, Brivio S, Mertens J, Vismara M, Moncsek A, Milani C, Fingas C, Cristina Malerba M, Nardo G, Dall'Olmo L, et al. Platelet-derived growth factor-D enables liver myofibroblasts to promote tumor lymphangiogenesis in cholangiocarcinoma. J Hepatol. 2019;70(4):700–9.
36. Korniluk A, Koper-Lenkiewicz OM, Kaminska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019;2019:9213074.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.