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Mean platelet volume predicts survival in patients with hepatocellular carcinoma and type 2 diabetes

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ABSTRACT

Background: Patients with hepatocellular carcinoma (HCC) having pre-existing type 2 diabetes (T2DM) have a poorer prognosis than those without T2DM. Moreover, accumulating evidence reveals that activated platelets play a crucial role in tumor and T2DM. The mean platelet volume (MPV) indicates platelet activation and is altered in malignancies. The present study aimed to investigate the clinical significance of MPV in patients with HCC having T2DM.

Methods: This retrospective study performed between January 2010 and December 2013 included 331 patients with HCC (165 with T2DM and 166 without T2DM). The overall survival was compared, and the predictors of overall survival were analyzed.

Results: The patients with T2DM had lower MPV levels than those without T2DM. Furthermore, the MPV levels significantly differentiated T2DM from non-T2DM. In addition, for patients with T2DM, the overall survival was significantly shorter in patients with low MPV levels than in those with high MPV levels. Multivariate analysis identified decreased MPV as an independent prognostic factor for overall survival only in patients with T2DM, but not in those without T2DM.

Conclusion: Reduced MPV was a prognostic factor for poor outcome in patients with HCC and T2DM.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and one of the leading causes of cancer-associated mortality [1]. The epidemiological evidence revealed that the presence of type 2 diabetes (T2DM) significantly increased the risk of developing HCC [2]. Recent reports demonstrated a high prevalence of T2DM in patients with liver cancer [3]. In addition, patients with HCC and pre-existing T2DM have a poorer prognosis than those without

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T2DM [4]. Therefore, identifying novel biomarkers for prognosis in patients with HCC and T2DM is critical to the development of more effective and targeted therapies.

Platelets have a key role in hemostasis, host immunity, and inflammatory responses [5]. Accumulating evidence showed the pro-metastatic role of platelets in cancer [6]. Tumor cells activate platelets, and platelets mediate tumor cell proliferation, angiogenesis, and dissemination [7]. The mean platelet volume (MPV) reflects the platelet size and indicates platelet activation in clinical practice [8]. Altered MPV levels were reported in various types of cancer, such as gastric cancer, ovarian cancer, lung cancer, breast cancer, and HCC [9–13]. Moreover, the MPV level was significantly higher in patients with T2DM than in those without T2DM [14]. However, studies focusing on the MPV levels in patients with HCC and T2DM are scarce.

Therefore, the present study aimed to investigate the clinical relevance of MPV in patients with HCC and T2DM.

2. Methods

2.1. Study population

A retrospective study was conducted at Harbin Medical University Cancer Hospital (Harbin, China) from January 2010 to December 2013. A total of 331 patients with HCC who underwent surgery were included (165 with T2DM and 166 without T2DM). Hepatic resection was performed using an open approach in all patients. All patient records were obtained from the hospital database, and patients were histologically confirmed with HCC by two experienced pathologists (Xiao-mei Li and Hong-xue Meng). Patients fulfilling the following criteria were eligible for enrollment: (1) solitary tumor of any size without vascular invasion; (2) Barcelona Clinic Liver Cancer (BCLC) stage 0 or A; (3) absence of portal hypertension; and (4) without distant metastasis at diagnosis. The following exclusion criteria were predefined: (1) patients receiving percutaneous ablation, preoperative chemotherapy, or radiotherapy; (2) hematological disorders; and (3) medical treatment with anticoagulant, statins, and acetylic salicylic acid. Diagnosis of T2DM was based on the American Diabetes Association criteria: (1) fasting plasma glucose (FPG) $\geq$7.0 mmol/L or casual glucose $\geq$11.1 mmol/L; (2) current treatment with a hypoglycemic agent; and (3) a 2-h postglucose level (after a 75-g oral glucose tolerance test) $\geq$11.1 mmol/L for the patients with impaired fasting glucose [15]. Recurrence-free survival (RFS) was defined as the interval between surgery and the first confirmed recurrence. Overall survival (OS) was defined as the date of surgery to the day of death or the last follow-up. Follow-up evaluations were performed every 3 months. The follow-up was completed on December 31, 2016. Patients were censored if they were alive at the last follow-up or died from a cause other than HCC. The median follow-up duration was 36 months. Three patients were lost to follow-up. The patient selection flowchart was provided in Fig. 1.

The following clinical features and laboratory findings of patients were collected for analysis: age, sex, body mass index (BMI), smoking status, drinking status, total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), albumin, FPG, alpha-fetoprotein (AFP), white blood cell (WBC) count, hemoglobin, platelet count, MPV, platelet distribution width, hepatitis B surface antigen (HBsAg), liver cirrhosis, tumor differentiation, tumor number, tumor size, T2DM duration, and T2DM medication.

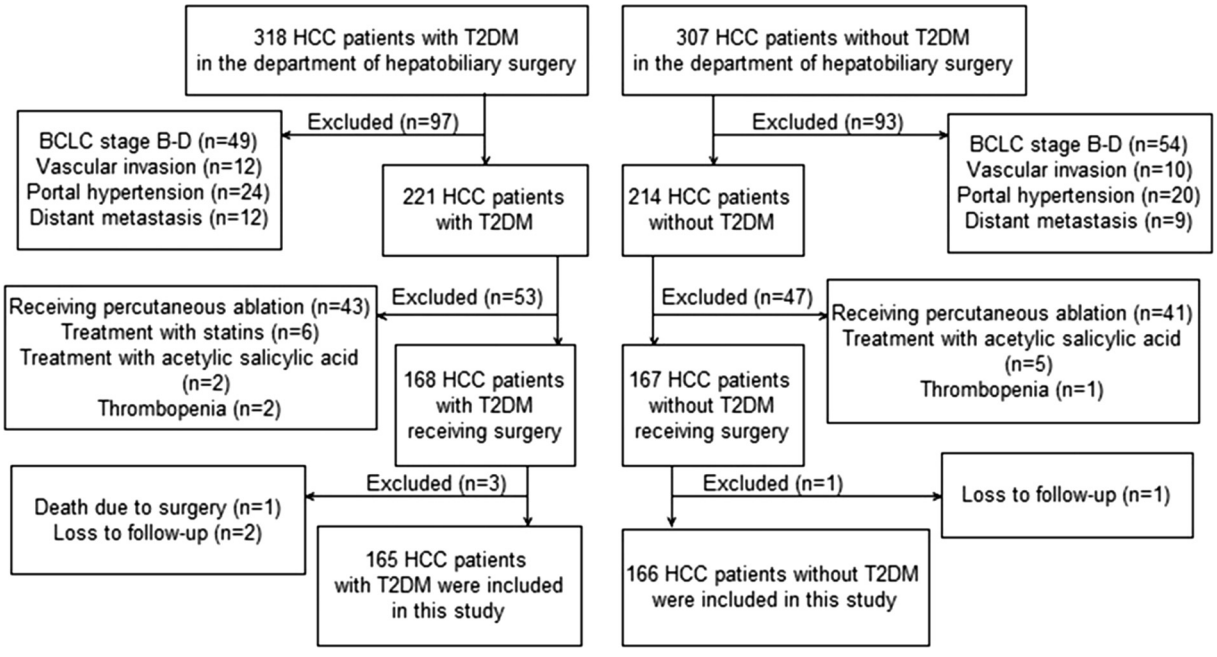

Fig. 1 – HCC patients selection flowchart.

Table 1 – Clinical characteristics of the HCC patients according to T2DM status.

Variables	With T2DM	Without T2DM	P value
N	165	166	
Age (years)	57.0 ± 7.9	52.9 ± 9.6	<0.001
Sex (male, %)	135 (81.8)	126 (75.9)	0.188
BMI (kg/m^2)	25.4 ± 3.3	23.9 ± 3.1	<0.001
Smoker (n, %)	65 (39.4)	61 (36.7)	0.620
Drinking (n, %)	45 (27.3)	41 (24.7)	0.593
WBC ($\times 10^9$/L)	5.70 ± 1.97	5.24 ± 1.79	0.025
Hemoglobin (g/dl)	137.3 ± 21.7	136.7 ± 18.0	0.784
Platelet count ($\times 10^9$/L)	140.4 ± 70.8	150.2 ± 75.6	0.227
MPV (fL)	9.9 ± 1.5	10.5 ± 1.8	0.002
PDW (%)	17.1 ± 1.7)	17.1 ± 2.2	0.861
FPG (mmol/L)	7.90 (6.08–11.13)	5.00 (4.69–5.30)	<0.001
TBIL (μmol/L)	16.8 (12.5–22.2)	12.4 (9.6–17.7)	<0.001
AST (U/L)	40 (30–61)	25 (18–41)	<0.001
ALT (U/L)	48 (32–75)	22 (17–34)	<0.001
GGT (U/L)	118 (66–254)	22 (36–104)	<0.001
Albumin (g/L)	40.0 ± 5.6	41.4 ± 4.9	0.015
AFP (ng/ml)	19.2 (5.1–293.1)	22.0 (6.3–313.4)	0.382
Age (years)			0.007
≤55	68 (41.2)	93 (56.0)	
>55	97 (58.8)	73 (44.0)	
AFP (ng/ml)			0.297
>20	82 (49.7)	92 (55.4)	
≤20	83 (50.3)	74 (44.6)	
HbsAg			0.812
Negative	35 (21.2)	37 (22.3)	
Positive	130 (78.8)	129 (77.7)	
Liver cirrhosis			0.463
With	105 (63.6)	112 (67.5)	
Without	60 (36.4)	54 (32.5)	
Tumor size	0.005		
≥5 cm	69 (41.8)	95 (57.2)	
<5 cm	96 (58.2)	71 (42.8)	
Tumor number			< 0.001
Single	109 (66.1)	141 (84.9)	
Multiple	56 (33.9)	25 (15.1)	
Tumor differentiation			0.706
Poor	33 (20.0)	36 (21.7)	
Moderate/high	132 (80.0)	130 (78.3)	
T2DM duration (years)	3.4 (0–5.0)	–	
Metformin, n (%)	7 (4.2)	–	

Data are expressed as means (SD) or median (IQR). BMI, body mass index; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; FPG, fasting plasma glucose; AFP, alpha fetoprotein; WBC, white blood cell; MPV, mean platelet volume; PDW, platelet distribution width.

The study protocol was approved by the Ethics Review Board of Harbin Medical University Cancer Hospital. Formal patient consent was not required for this study.

2.2. *Statistical analysis*

All statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., IL, USA). Data were presented as mean (standard deviation), median (interquartile range), or percentages. Two-tailed t tests (for normally distributed continuous variables) or Mann–Whitney *U* tests (for skewed distributed continuous variables) and Pearson chi-square tests (for categorical variables) were used to assess the differences between the two groups. Survival analyses were conducted using the Kaplan–Meier method, followed by the log-rank test. Univariate Cox proportional hazard regression analysis was used to assess all factors affecting the OS, whereas all factors with a *P* value no more than 0.10 were used in the multivariate Cox proportional hazard regression model. The optimal cut-off value for MPV was determined with time-dependent receiver operating characteristic (ROC) curve using the R package survival ROC (version 3.5.2). The two-sided *P* values less than 0.05 were considered to be statistically significant.

3. Results

3.1. *Patient characteristics*

A total of 331 patients with HCC, aged 24–79 years (median age, 56.0 years), were included in the study (165 patients with T2DM and 166 without T2DM). The mean age of patients

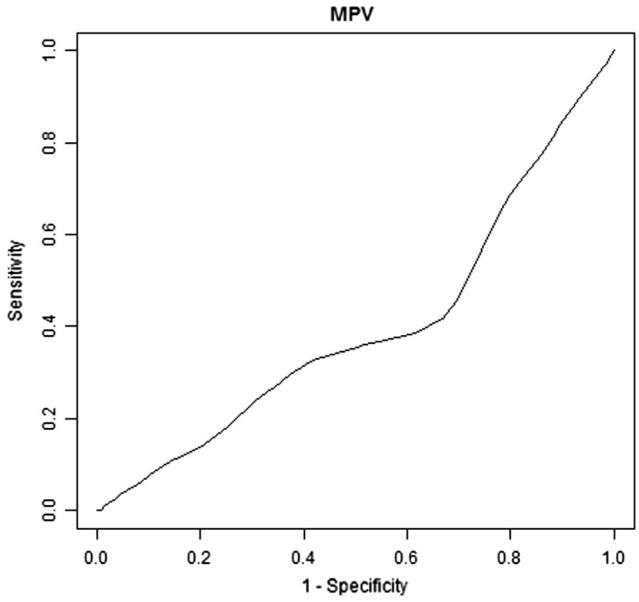

Fig. 2 – Receiver operating characteristic curve of MPV. Optimized cutoff value was determined for MPV using the standard ROC curve analysis.

without T2DM and with T2DM was 52.9 ± 9.6 and 57.0 ± 7.9 years, respectively. The baseline characteristics of patients with and without T2DM are presented in Table 1. Patients with T2DM were older and had higher BMI, WBC count, FPG, TBIL, AST, ALT, and GGT levels, and lower MPV and albumin levels. AFP, HbsAg status, liver cirrhosis, and tumor differentiation in the two groups showed no difference. Larger tumor size and multiple lesions were more often present in patients with T2DM.

3.2. *Prognostic values of MPV for HCC survival*

According to the ROC curve analysis, the optimal cut-off value of 9.4 had a 58.3% sensitivity and 66.7% specificity for survival rate (area under the curve = 0.616, 95% confidence interval = 0.537–0.690, $P = 0.021$) (Fig. 2).

Among patients with T2DM, 46 (27.9%) had death events after a median follow-up of 36 months. Patients with MPV ≤ 9.4 fL exhibited significantly shorter RFS and OS compared with those with MPV > 9.4 fL (61.2% vs 79.6%, $P = 0.007$). The Kaplan–Meier RFS and OS curves of reduced versus elevated MPV showed a significant separation (Fig. 3). Among patients without T2DM, 41 (24.7%) had death events after a median follow-up of 36 months. Patients with

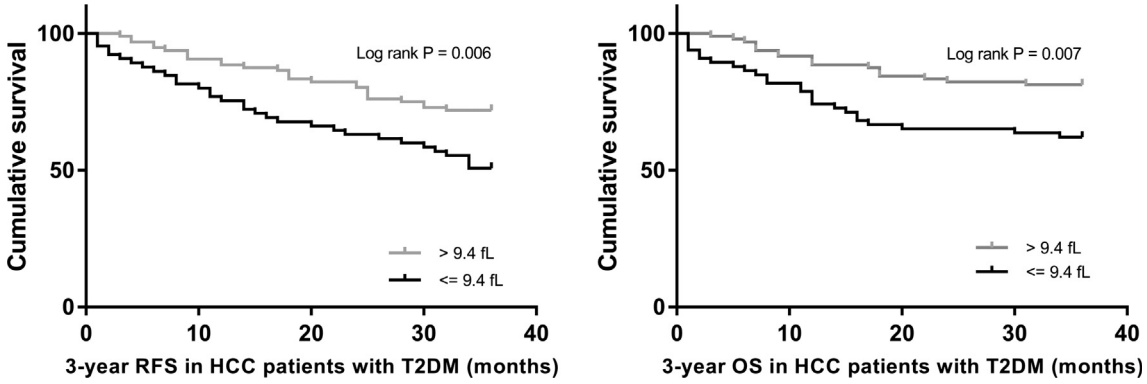

Fig. 3 – Kaplan–Meier survival curves for RFS and OS in patients with HCC and T2DM based on the MPV level. RFS and OS rates were significantly lower in patients with MPV ≤ 9.4 fL than in those with MPV > 9.4 fL.

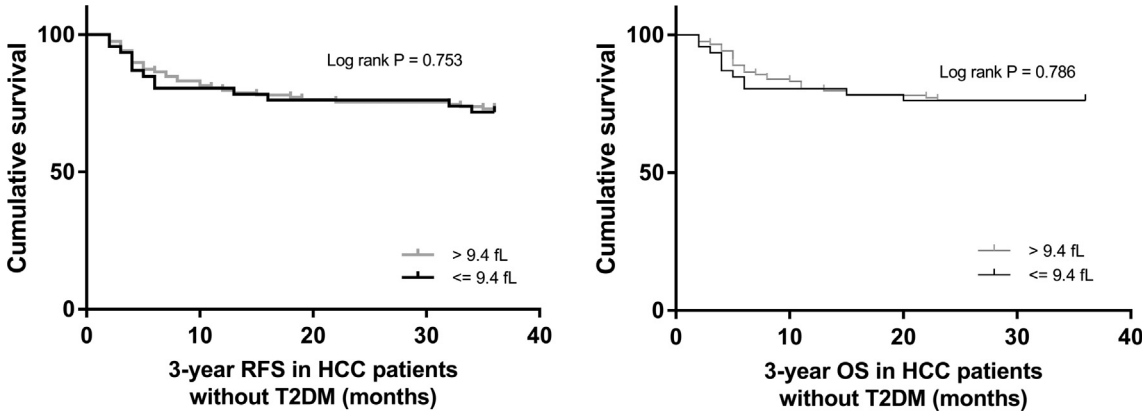

Fig. 4 – Kaplan–Meier survival curves for RFS and OS in patients with HCC but without T2DM based on the MPV level. RFS and OS rates were not significantly lower in patients with MPV ≤ 9.4 fL compared with those with MPV > 9.4 fL.

Table 2 – Multivariable logistic regression analysis on baseline variables associated with T2DM.

Variables	β	OR (95% CI)	P-value
Age (years)	1.085	1.044–1.127	<0.001
BMI (kg/m^2)	1.148	1.044–1.262	0.004
WBC (×10^9/L)	1.254	1.056–1.491	0.010
MPV (fL)	0.773	0.635–0.941	0.010
TBIL (μmol/L) (log-value)	1.688	0.880–3.236	0.115
AST (U/L) (log-value)	1.390	0.825–2.343	0.216
ALT (U/L) (log-value)	7.631	4.086–14.253	<0.001
GGT (U/L) (log-value)	1.736	1.191–2.530	0.004
Albumin (g/L)	0.945	0.891–1.001	0.054

MPV ≤ 9.4 fL did not exhibit shorter RFS and OS compared with those with MPV > 9.4 fL (75.6% vs 74.5%, $P = 0.786$). The Kaplan–Meier RFS and OS curves of reduced versus elevated MPV did not show a significant difference (Fig. 4).

3.3. *Risk factors for distinguishing T2DM from non-T2DM*

Logistic regression analysis was performed to evaluate the risk factors for distinguishing T2DM from non-T2DM in patients with HCC. The risk factors were significantly associated with differentiation in the regression analysis included age, BMI, MPV, WBC count, ALT, and GGT (Table 2). Notably, MPV was a significant factor in the multivariate model ($\beta = 0.773$; $P = 0.010$).

3.4. *Association of MPV with OS*

The clinicopathological data were used in the Cox regression models of OS. For patients without T2DM, the GGT, WBC, platelet count, AFP, tumor size, tumor number, and tumor differentiation were significant in the univariate analyses (Table 3). For patients with T2DM, the AST, ALT, GGT, AFP, tumor differentiation, T2DM duration, and MPV values were significant in the univariate analyses (Table 4). The significant factors in the univariate analysis were entered into multivariate Cox proportional regression to test the independent factors. The results revealed that tumor size and tumor differentiation were independent prognostic factors for OS in patients without T2DM (Table 3). GGT, AFP, tumor differentiation, T2DM duration, and MPV values were independent prognostic factors for OS in patients with T2DM (Table 4).

4. Discussion

This study showed that patients with HCC and T2DM had lower MPV levels compared with those without T2DM. MPV was found to be significantly associated with differentiation of T2DM from non-T2DM. In addition, decreased MPV was found to be an independent risk factor that influenced the prognosis in patients with HCC having T2DM.

The prevalence of HCC has increased in developing countries [16]. Established risk factors for liver cancer included chronic infection with hepatitis viruses and heavy alcohol use. Several prospective studies and meta-analyses revealed a higher risk of liver cancer incidence and mortality among patients with diabetes [17]. A recent report demonstrated that T2DM resulted in a three-fold increased risk of HCC and was associated with a worse prognosis for patients with HCC, independent of cirrhosis [18]. However, some reports failed to find the association between T2DM and HCC [19,20]. These conflicting data might be the result of small sample sizes, ethnic differences, differences in baseline characteristics of the study population, and differences in antineoplastic therapy.

Table 3 – Univariate and multivariate analysis of overall survival in patients with HCC but without T2DM.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years) (>55 versus ≤55)	1.245 (0.675–2.297)	0.483		
Sex (male versus female)	0.853 (0.427–1.702)	0.651		
BMI (kg/m^2)	1.052 (0.954–1.161)	0.306		
Smoking status (Yes versus No)	0.976 (0.517–1.844)	0.941		
Drinking status (Yes versus No)	0.982 (0.482–2.003)	0.961		
HbsAg (positive versus negative)	0.721 (0.361–1.438)	0.353		
Liver cirrhosis (with versus without)	0.899 (0.471–1.714)	0.747		
TBIL (μmol/L) (log-value)	1.356 (0.771–2.385)	0.290		
AST (U/L) (log-value)	1.087 (0.686–1.723)	0.722		
ALT (U/L) (log-value)	0.797 (0.423–1.501)	0.482		
GGT (U/L) (log-value)	1.596 (1.116–2.284)	0.011	1.345 (0.900–2.010)	0.148
Albumin (g/L)	1.025 (0.964–1.091)	0.424		
FPG (mmol/L) (log-value)	2.183 (0.138–34.617)	0.580		
Hemoglobin (g/dl)	1.008 (0.990–1.026)	0.391		
WBC (×10^9/L)	1.230 (1.043–1.452)	0.014	1.171 (0.946–1.450)	0.147
Platelet count (×10^9/L)	1.003 (1.000–1.006)	0.061	0.999 (0.994–1.004)	0.714
AFP (ng/ml) (>20 versus ≤20)	1.962 (1.016–3.790)	0.045	1.209 (0.579–2.526)	0.613
Tumor size (cm) (≥5.0 versus <5.0)	5.249 (2.206–12.490)	< 0.001	3.191 (1.260–8.078)	**0.014**
Tumor number (multiple versus single)	0.801 (0.314–2.042)	0.642		
Tumor differentiation (moderate/high versus poor)	3.504 (1.886–6.511)	<0.001	2.423 (1.186–4.951)	**0.015**
MPV (fL)	0.855 (0.707–1.034)	0.106		

Number in bold font indicates a significant P values.

Table 4 – Univariate and multivariate analysis of overall survival in patients with HCC and T2DM.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years) (>55 versus ≤55)	1.214 (0.667–2.209)	0.525		
Sex (male versus female)	0.909 (0.385–2.144)	0.827		
BMI (kg/m^2)	1.050 (0.964–1.144)	0.264		
Smoking status (Yes versus No)	0.821 (0.460–1.467)	0.505		
Drinking status (Yes versus No)	1.016 (0.558–1.849)	0.958		
HbsAg (positive versus negative)	1.283 (0.599–2.750)	0.522		
Liver cirrhosis (with versus without)	1.138 (0.614–2.108)	0.682		
TBIL (μmol/L)	1.271 (0.845–1.914)	0.250		
AST (U/L) (log-value)	1.899 (1.275–2.829)	0.002	1.570 (0.800–3.081)	0.190
ALT (U/L) (log-value)	1.661 (1.089–2.533)	0.018	1.120 (0.607–2.068)	0.716
GGT (U/L) (log-value)	1.573 (1.156–2.141)	0.004	1.568 (1.062–2.316)	**0.026**
Albumin (g/L)	0.987 (0.939–1.038)	0.622		
FPG (mmol/L) (log-value)	1.066 (0.524–2.168)	0.860		
AFP (ng/ml) (>20 versus ≤20)	2.402 (1.296–4.451)	0.005	2.607 (1.379–4.926)	**0.003**
Hemoglobin (g/dl)	0.991 (0.979–1.003)	0.146		
WBC (×10^9/L)	1.009 (0.875–1.163)	0.907		
Platelet count (×10^9/L)	1.002 (0.999–1.006)	0.218		
Tumor size (cm) (≥5.0 versus <5.0)	1.550 (0.869–2.762)	0.138		
Tumor number (multiple versus single)	1.257 (0.695–2.272)	0.449		
Tumor differentiation (moderate/high versus poor)	2.098 (1.119–3.935)	0.021	2.217 (1.068–4.603)	**0.033**
MPV (fL) (≤9.4 versus >9.4)	2.176 (1.214–3.900)	0.009	2.463 (1.346–4.505)	**0.003**
T2DM duration (years)	1.068 (1.015–1.123)	0.011	1.071 (1.013–1.133)	**0.016**
Metformin (yes versus no)	0.439 (0.060–3.184)	0.415		

Number in bold font indicates a significant P values.

Further, clarifying the relationship between HCC and T2DM might have significant clinical implications for preventing and treating HCC.

However, the underlying mechanisms connecting these two diseases are poorly understood. Platelet activation plays a crucial role in the development of both T2DM and HCC. A complex interplay between platelet-induced tumor growth and tumor cell-induced platelet activation exists [21]. Activated platelets inhibit HCC cell differentiation and promote tumor progression via platelet–tumor cell binding [22]. Furthermore, platelet releasates promote the proliferation of HCC cells by suppressing the expression of Kruppel-like factor 6 [23]. Clinical studies found that the platelet-derived endothelial cell growth factor is an angiogenic factor, which is found to be increased in patients with HCC [24]. Moreover, a recent report confirmed that the platelet-derived growth factor receptor alpha overexpression is a prognostic biomarker independent of the liver fibrosis status in HCC [25]. In addition, the anti-platelet therapy delays immune-mediated hepatocarcinogenesis and improves survival in a mouse model of chronic hepatitis B [26]. However, the association between T2DM and systemic inflammation may increase platelet reactivity and accelerate the development of vascular disease. Clinical reports confirmed that MPV is a predictive marker for glycemic control deterioration, stroke, and coronary artery disease in patients with T2DM [27,28]. Moreover, accumulating evidence indicated that platelets are able to modulate the function of immune cells via the direct release of growth factors and proinflammatory chemokines [29]. The present study indirectly confirmed the findings of the aforementioned studies using a simple platelet marker.

The mechanisms to explain the association between MPV and survival remain unclear. Inflammation may be responsible for the association. Activated platelets play an essential role in inflammation and cancer. MPV is an early parameter of activated platelets and associated with inflammatory conditions. In low-grade inflammatory conditions, such as dyslipidemia and hypertension, higher MPV levels are observed. Moreover, MPV is also increased in patients with T2DM, especially in the presence of microvascular complications [30]. An increase in MPV is one of the risk factors for macrovascular complications, such as myocardial infarction, ischemic stroke, and venous thromboembolism [27]. However, solid tumors with bone marrow metastasis are more likely to have low MPV levels [31]. In addition, low MPV level is associated with poor prognosis in renal cell carcinoma and invasive bladder cancer [32,33]. The biggest difference between previous studies and the present study was the study population. Diabetes was excluded in the previous studies investigating the association between MPV and cancer prognosis [32–34]. Previous studies confirmed that diabetes was independently associated with poor survival in patients with HCC [35]. Furthermore, dysregulated glucose metabolism, which concurs with a chronic proinflammatory condition, promotes tumor initiation and progression in patients with T2DM and HCC [36]. The release rate of smaller platelets from the bone marrow increased because of the interference of excessive proinflammatory cytokines with megakaryopoiesis [37]. Thus, lower MPV values might have resulted from an enhanced consumption of larger platelets in inflammatory states [8].

This study had several limitations. First, it was a retrospective study and the sample size was limited. Second, no data from the mechanistic view were included. Finally, this was a preliminary study; therefore, multicenter studies are needed to confirm the results.

In summary, reduced MPV was a prognostic factor for poor outcome in patients with HCC and T2DM.

Conflicts of interest

None.

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