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ORIGINAL ARTICLE

Retrospective Study

Significance of platelet count and platelet-based models for hepatocellular carcinoma recurrence

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Abstract

AIM: To explore the effects of platelet count (PLT) and 11 platelet-based indices on postoperative recurrence of hepatocellular carcinoma (HCC).

METHODS: We retrospectively analyzed 172 HCC patients who were treated by partial hepatectomy. Preoperative data, including laboratory biochemical results, were used to calculate the 11 indices included in the analysis. We performed receiver operating characteristic curve analysis to determine the optimal cut-off values for predicting recurrence. Cumulative rates of HCC recurrence were calculated using Kaplan-Meier survival curves and differences were analyzed by log-rank tests. Multivariate analyses were performed to identify independent predictors of recurrence, early recurrence (within one year after surgery), and late recurrence in HCC. To obtain better prognostic models, PLT-based indices were analyzed separately after being expressed as binary and continuous variables. Two platelet-unrelated, validated HCC prognostic models were included in the analyses as reference indices. Additional analyses were performed after patients were stratified based on hepatitis B virus infection status, cirrhosis, and tumor size to investigate the significance of platelets in different subgroups.

RESULTS: In the study cohort, 44.2% (76/172) of patients experienced HCC recurrence, and 50.6% (87/172) died during a median follow-up time of 46 mo. PLT and five of the 11 platelet-related models were significant predisposing factors for recurrence ($P < 0.05$). Multivariate analysis indicated that, among the clinical parameters, presence of ascites, PLT $\geqslant 148 \times 10^9$/L, alkaline phosphatase $\geqslant$ 116 U/L, and tumor size $\geqslant$ 5 cm were independently associated with a

higher risk of HCC recurrence ($P < 0.05$). Independent and significant models included the aspartate aminotransferase/PLT index, fibrosis index based on the four factors, fibro-quotient, aspartate aminotransferase/PLT/γ-glutamyl transpeptidase/alpha-fetoprotein index, and the PLT/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase index. There were different risk factors between early and late recurrences, and PLT and these indices were more inclined to influence late recurrence. PLT was only predictive of recurrence in non-cirrhotic HCC patients, and was not influenced by tumor size, which was a critical confounder in our study.

CONCLUSION: PLT and PLT-based noninvasive models are effective tools for predicting postoperative recurrence, especially late recurrence. Larger cohorts are needed to validate our findings.

Key words: Alkaline phosphatase; Alpha-fetoprotein; Aspartate aminotransferase; Blood platelets; Hepatocellular carcinoma; Recurrence

Core tip: The high risk of postoperative recurrence is one of the greatest problems plaguing potential curative treatment for hepatocellular carcinoma (HCC). Although several prognostic models have been proposed for HCC, these indices mainly focus on non-modifiable tumor characteristics. In contrast, platelet count is an improvable variable, and there are numerous platelet-based models associated with cirrhosis and HCC formation. We found that platelet count and nearly half of the established platelet-related models were independently associated with postoperative recurrence. We also demonstrated different risk factors between early and late recurrences, with platelets more likely to influence late recurrence.

Pang Q, Zhang JY, Xu XS, Song SD, Qu K, Chen W, Zhou YY, Miao RC, Liu SS, Dong YF, Liu C. Significance of platelet count and platelet-based models for hepatocellular carcinoma recurrence. *World J Gastroenterol* 2015; 21(18): 5607-5621 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i18/5607.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i18.5607

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent neoplasm and the third most frequent cause of cancer mortality[1]. Major risk factors include excessive alcohol intake and infection with hepatitis C virus (HCV) and/or hepatitis B virus (HBV)[2], which represents the most prevalent etiology for HCC and cirrhosis. Thus, the majority of HCC patients are from areas where there is a high prevalence of HBV infection, such as Asia and Africa[2,3]. Although the diagnosis and treatment of HCC have dramatically improved, the prognosis remains unsatisfactory with an overall 5-year survival rate of 5%-6%[4]. One reason for this involves the high risk for postoperative recurrence. Although microvascular invasion has been implicated as a major factor[5,6], the majority of postoperative tumor recurrences are due to *de novo* cancers from the cirrhotic liver[5]. The identification of related predisposing risk factors will help to reduce recurrence rates.

Survival in HCC has been associated with platelet count (PLT)[7-9], which is also an independent predictor of hepatocarcinogenesis[10-12]. Platelets are involved in thrombosis, inflammatory responses, liver regeneration[13-15], and the regulation of angiogenesis[15,16]. PLTs are significantly decreased in cirrhotic patients[17], and can be used, along with several platelet-based noninvasive models, to detect hepatic cirrhosis in patients with HBV/HCV infection with high accuracy[18-21]. Thus, we hypothesized that platelets might play a crucial role in HCC relapse. However, few studies have reported the association between PLT/platelet-based indices and postoperative recurrence in HCC. Herein, we evaluated PLT and 11 platelet-related indices for predicting HCC recurrence. For these analyses, the Cancer of the Liver Italian Program (CLIP)[22], aspartate aminotransferase/alanine aminotransferase ratio (AAR)[23], and two platelet-unrelated prognostic models of HCC were used as references.

MATERIALS AND METHODS

Study population

A total of 172 histologically proven HCC patients over 18 years of age who were treated by hepatic resection at our hospital between December 2002 and July 2012 were enrolled in this study. Complete clinical, laboratory and follow-up information was available for all patients. Patients were excluded from the study due to: (1) coexistent hematologic diseases; (2) previous treatment for HCC; (3) intrahepatic cholangiocarcinoma; and (4) extrahepatic spread. This study was in compliance with the provisions of the 2013 version of the Declaration of Helsinki[24], and the protocol was approved by the Ethics Committee of our hospital.

Data collection

Electronic medical records were used to collect information concerning patient age, sex, etiology (HBV, HCV), cirrhosis status, ascites, preoperative laboratory data [levels of alanine aminotransferase, aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), PLT, prothrombin time (international normalized ratio), and alpha-fetoprotein (AFP)], operation notes, tumor characteristics (number, diameter of the largest lesion, vascular invasion), and pathologic reports. The primary outcome measure for the study was HCC recurrence. The secondary outcomes were early (within one year) and late

Table 1 Scoring of noninvasive models

Index	Formula
CLIP	Sum of: Child-Pugh: A = 0, B = 1, C = 2 Tumor morphology: Uninodular and extension ≤ 50% = 0, multinodular and extension ≤ 50% = 1, massive or extension ≥ 50% = 2 AFP: < 400 = 0, ≥ 400 = 1 Portal vein thrombosis: no = 0, yes = 1
Pohl	Positive: AAR > 1 and PLT < 150
AARP	Positive: AAR > 1 or PLT < 150
AAR	AST/ALT
API	Sum of: Age (yr): < 30 = 0, 30-39 = 1, 40-49 = 2, 50-59 = 3, 60-69 = 4, ≥ 70 = 5 PLT: ≥ 225 = 0, 200-224 = 1, 175-199 = 2, 150-174 = 3, 125-149 = 4, < 125 = 5
CDS	Sum of: PLT: > 340 = 0, 280–339 = 1, 220-279 = 2, 160-219 = 3, 100-159 = 4, 40-99 = 5, < 40 = 6 ALT/AST: > 1.7 = 0, 1.2-1.7 = 1, 0.6-1.1 = 2, < 0.6 = 3 PT: < 1.1 = 0, 1.1-1.4 = 1, > 1.4 = 2
APRI	AST × 100/PLT
FIB-4	Age × AST/PLT × $ALT^{1/2}$
FibroQ	10 × Age × AST × PT/ALT × PLT
Lok	Lok index = exp (log odds)/[1 - exp (log odds)] Log odds = -5.56-0089 × PLT + 1.26 × AAR + 5.27 × PT
GUCI	Normalized AST × PT × 100/PLT
APGA	Log (index) = 1.44 + 0.1490 × log (GGT) + 0.3308 × log (AST) - 0.5846 log × (PLT) + 0.1148 × log (AFP + 1)
PAPAS	Log (index + 1) = 0.025 + 0.0031 × age + 0.1483 × log (ALP) + 0.004 × log (AST) + 0.0908 × log (AFP + 1) - 0.028 × log (PLT)

AAR: Aspartate aminotransferase/alanine aminotransferase ratio; AARP: AAR-platelet count score; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/alpha-fetoprotein index; API: Age/platelet count index; APRI: Aspartate aminotransferase/platelet count ratio index; AST: Aspartate aminotransferase; CDS: Cirrhosis discriminant score; CLIP: Cancer of the Liver Italian Program; FIB-4: Fibrosis index based on the four factors; FibroQ: Fibro-quotient; GGT: γ-glutamyl transpeptidase; GUCI: Goteburg University Cirrhosis Index; PAPAS: Platelet count/age/ALP/AFP/AST index; PLT: Platelet count; PT: Prothrombin time. AFP (ng/mL); Age (year); ALT (U/L); AST (U/L); GGT (U/L); PLT (10^9/L); PT (international normalized ratio).

recurrences.

Noninvasive platelet scoring models

The following scoring models were used in this study: AAR; CLIP; AAR-PLT score[25]; Pohl *et al*[26] index; age/PLT index[27]; cirrhosis discriminant score[28]; AST/PLT ratio index[29]; fibrosis index based on the four factors (FIB-4)[30]; fibro-quotient (FibroQ)[31]; Lok *et al*[32] index; Goteburg university cirrhosis index[33]; AST/PLT/GGT/AFP index (APGA)[34]; and the PLT/age/ALP/AFP/AST index (PAPAS)[35]. Index scores were calculated based on the formulas presented in Table 1.

HCC diagnosis, treatment and follow-up

HCC was initially diagnosed by computed tomography, magnetic resonance imaging and/or ultrasound findings. All patients underwent hepatectomy by either anatomic or non-anatomic resection on the basis of preoperative hepatic function and tumor characteristics. HCC diagnosis was confirmed by pathology of resected tumor tissues.

After discharge, all patients were regularly followed at outpatient clinics, by either computed tomography or magnetic resonance imaging, physical examination, abdominal ultrasound, chest X-ray, and serologic tests (including liver function and AFP level). The same evaluations were performed as follow-ups every 3 mo for the first year, every 4 mo for the second year, and every 6 mo thereafter. Recurrence was determined based on the emergence of clinical, radiologic, and/or pathologic evidence of HCC. Patients who had recurrence received salvage treatments, including further hepatic surgery, percutaneous ablation, or transcatheter arterial chemoembolization, as appropriate.

Statistical analysis

All statistical analyses were performed using PASW Statistics for Windows (version 18.0 software; SPSS Inc., Chicago, IL, United States). Student's t and χ^2 tests were used to compare continuous and categorical variables, respectively. The receiver operating characteristic curve was calculated to determine the optimal cut-off point (with the highest cumulative value of the sum of specificity and sensitivity) of each variable for detecting recurrence. Cumulative recurrence rates were estimated by the Kaplan-Meier method and differences were analyzed by log-rank tests. All variables found to be significant ($P < 0.05$) were then entered into a multivariate analysis with Cox proportional hazard regression models. Normally distributed ($P > 0.05$ from a Kolmogorov-Smirnov test) continuous variables are expressed as mean ± standard deviation (SD), otherwise they are presented as median (range).

RESULTS

Patient characteristics

The study population consisted of 139 men and 33 women with an overall mean age of 53.5 ± 10.5 years. Of these, 121 patients were infected with HBV and 59 were cirrhotic. The median survival time after surgical resection was 52 mo, with 1-, 3- and 5-year overall survival rates of 74.1%, 54.4% and 46.6%, respectively. During a median follow-up of 46 mo, 50.6% (87/172) of the patients died and 44.2% (76/172) developed recurrence. Demographic data, serologic tests, tumor characteristics and index scores of patients stratified by recurrence are summarized in Table 2. Of all the variables, only tumor size and CLIP score were significantly different between recurrent and non-recurrent patients.

Determination of cut-off values for continuous variables

The receiver operating characteristic curve of PLT

Table 2 Characteristics of patients stratified according to recurrence status

Parameter	Recurrence (n = 76)	No recurrence (n = 96)	P value
Sex, male/female	63/13	76/20	0.537
Age, yr	54.6 ± 10.3	52.7 ± 10.6	0.231
Etiology, yes/no			
HBV	51/25	70/26	0.407
Cirrhosis	23/53	36/60	0.321
Ascites	11/65	6/90	0.073
Laboratory results in U/L			
ALT	49 (11-1315)	39 (7-1436)	0.291
AST	50 (16-1075)	40 (11-1493)	0.308
ALP	111 (30-732)	89 (36-867)	0.149
GGT	80 (12-623)	62 (14-914)	0.084
PLT as 10^9/L	136 (41-370)	117 (3-486)	0.055
PT (INR)	1.06 (0.82-1.63)	1.06 (0.73-1.62)	0.697
AFP, ≥ 200/< 200 ng/mL	38/32	36/50	0.122
Tumor			
Size, ≥ 5/< 5 cm	57/19	37/59	< 0.001
Type, multiple/single	18/58	14/82	0.128
Vascular invasion, yes/no	8/68	6/90	0.308
Noninvasive model score			
CLIP	1 (0-4)	1 (0-4)	0.027
Pohl, negative/positive	47/39	60/36	0.930
AARP, negative/positive	14/62	11/85	0.198
AAR	1.08 (0.13-3.29)	1.02 (0.09-4.85)	0.826
API	7 (1-10)	7 (2-10)	0.319
CDS	6 (2-9)	6 (3-9)	0.286
APRI	0.90 (0.16-19.71)	0.90 (0.17-55.71)	0.658
FIB-4	2.90 (0.51-17.98)	2.94 (0.40-81.57)	0.384
FibroQ	4.68 (0.48-22.82)	4.49 (0.14-108.25)	0.224
Lok index	0.56 ± 0.23	0.58 ± 0.22	0.600
GUCI	1.04 (0.14-19.32)	0.95 (0.17-83.56)	0.624
APGA	22.95 (6.03-89.35)	19.03 (5.81-92.94)	0.136
PAPAS	3.67 (1.52-9.40)	3.02 (1.67-5.75)	0.136
Survival in mo	23 (5-120)	87 (1-117)	0.003
Death, yes/no	69/7	18/78	< 0.001

AAR: Aspartate aminotransferase/alanine aminotransferase ratio; AARP: AAR-platelet count score; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/AFP index; API: Age/platelet count index; APRI: Aspartate aminotransferase/platelet count ratio index; AST: Aspartate aminotransferase; CDS: Cirrhosis discriminant score; CLIP: Cancer of the Liver Italian Program; FIB-4: Fibrosis index based on the four factors; FibroQ: Fibro-quotient; GGT: γ-glutamyl transpeptidase; GUCI: Goteburg University Cirrhosis Index; HBV: Hepatitis B virus; INR: International normalized ratio; PAPAS: Platelet count/age/ALP/AFP/AST index; PLT: Platelet count; PT: Prothrombin time. Values are expressed as mean ± SD, median (range), or n.

indicated that 148 × 10^9/L was a cut-off value, as it corresponded to the maximal sum of sensitivity plus specificity. Among the indices, only ALP [area under the curve (AUC) = 0.618, 95%CI: 0.528-0.708], CLIP (AUC = 0.636, 95%CI: 0.535-0.712), and PAPAS (AUC = 0.636, 95%CI: 0.548-0.724) were significant indicators for determining recurrence (P < 0.05) (Figure 1). A PAPAS cutoff of 2.41 presented a sensitivity of 85.5% and a specificity of 38.4%.

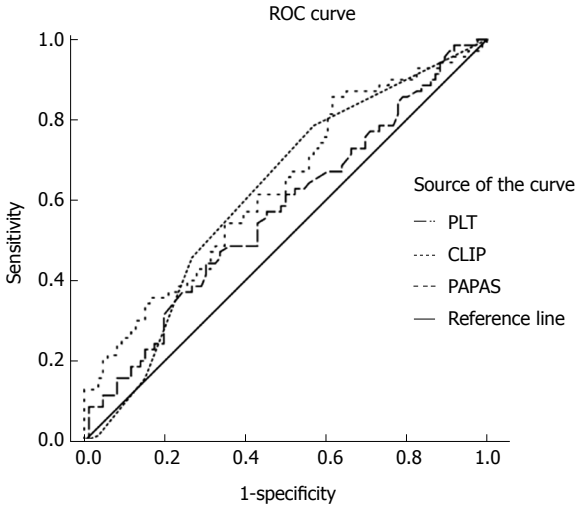


Figure 1 Predictive potentials for detecting recurrence. Receiver operating characteristic (ROC) curves for Cancer of the Liver Italian Program (CLIP) and platelet count/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase (PAPAS) indices and platelet count (PLT).

Predictors of tumor recurrence

Figure 2A and B show the Kaplan-Meier cumulative recurrence and survival curves of the entire patient cohort. A log-rank analysis demonstrated that patients with ascites, AST ≥ 55 U/L, ALP ≥ 116 U/L, GGT ≥ 144 U/L, PLT ≥ 148 × 10^9/L, AFP ≥ 96 ng/mL, and tumor size ≥ 5 cm had an elevated probability of postoperative recurrence (Table 3). Scatter plots reveal the relationship between PLT and recurrence and overall survival. In addition, the boxplots further reflect the relations between platelets and postoperative recurrence (Figure 2C) as well as survival (Figure 2D). Among the 13 noninvasive indices, CLIP ≥ 1, AAR ≥ 1.07, APRI ≥ 1.94, FIB-4 ≥ 4.30, FibroQ ≥ 6.36, APGA ≥ 26.9, and PAPAS ≥ 2.41 were significantly associated with a high risk of relapse. Figure 3 shows the Kaplan-Meier cumulative recurrence curves stratified according to PLT and five of these platelet-based indices.

Multivariate analysis of biochemical variables expressed as binary variables revealed that ascites, ALP, PLT, and tumor size were independent risk factors for recurrence (Figure 4A). Among the noninvasive indices, multivariate analysis performed after adjusting for the seven predictive factors showed that APRI, FIB-4, FibroQ, APGA, and PAPAS were independent predictors for recurrence (Figure 4B). The two platelet-unrelated indices, CLIP and AAR, were not independently associated with recurrence. Further assessment of the noninvasive indices expressed as continuous variables (with original scores that were not converted into binary data) revealed that only APGA and PAPAS were independently related to recurrence

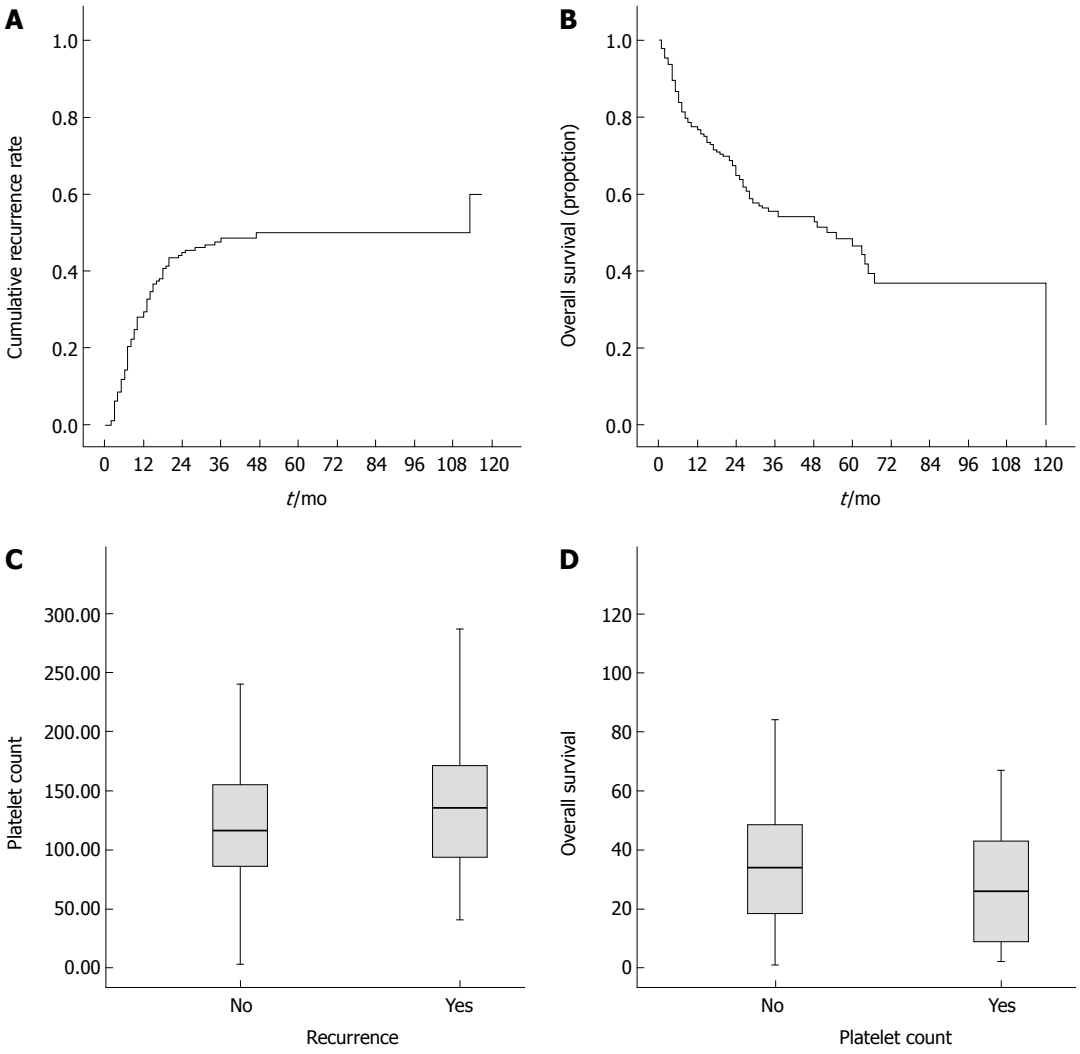


Figure 2 Survival and recurrence. Kaplan-Meier curves for cumulative recurrence (A) and overall survival (B). Boxplots comparing platelet count with recurrence (C) and overall survival (D).

(Figure 5).

Predictors of early or late recurrence

Forty-six of the cases of recurrence occurred within 1 year of surgery. Factors significantly contributing to this early recurrence included elder age, HBV negativity, tumor size ⩾ 5 cm, high AST, ALP, GGT and AFP levels, and elevated CLIP, APGA and PAPAS scores. Multivariate analysis showed that age, HBV infection, AFP, tumor size, and APGA were independent, valuable tools for predicting early recurrence (Figure 6). There were 30 late recurrences, and a log-rank test identified ascites, AST, ALP, GGT, PLT, tumor size, AAR, Lok index, and PAPAS score as associated factors. Among these, ALP, PLT, tumor size, Lok index, and PAPAS were significant independent predictors of late recurrence as determined by multivariate analysis.

Relationship between clinicopathologic features and PLT, APGA, and PAPAS status

As APGA and PAPAS were better tools to predict recurrence, we assessed their associations with several clinicopathologic features (Table 4). Patients with APGA ⩾ 26.9 or PAPAS ⩾ 2.41 had a significantly higher recurrence rate and larger tumors in comparison with patients with lower scores ($P < 0.05$).

Subgroup analysis according to presence of cirrhosis and tumor size

Previous studies showed that PLT and platelet-based indices were significantly associated with probable cirrhosis in patients with HBV/HCV. To clarify the subgroups of patients negatively influenced by preoperative PLT, APGA and PAPAS scores, patients were classified according to presence of cirrhosis irrespective of HBV infection. Interestingly, recurrence rates were significantly higher in non-cirrhotic patients with PLT ⩾ 148 × 10^9/L, APGA ⩾ 26.9 and PAPAS ⩾ 2.41 (*P*s < 0.05), but not in those with cirrhosis (Figure 7). In patients with cirrhosis, PLT values were not indicative of recurrence rates.

Tumor size was identified in our analyses as a

Table 3 Predictors of recurrence stratified according to recurrence time by Log-rank test

Variable	Recurrence, *P* value		
	Overall	Early	Late
Men	0.726	0.768	0.848
Age ⩾ 62 yr	0.080	0.006	0.530
HBV	0.143	0.046	0.875
Cirrhosis	0.259	0.134	0.957
Ascites	0.022	0.219	0.028
ALT ⩾ 44 U/L	0.086	0.118	0.429
AST ⩾ 55 U/L	< 0.001	0.005	0.001
ALP ⩾ 116 U/L	< 0.001	0.011	0.001
GGT ⩾ 144 U/L	< 0.001	0.004	0.007
PLT ⩾ 148 × 10^9/L	0.021	0.376	0.009
PT (INR) ⩾ 1.17	0.398	0.390	0.792
AFP ⩾ 96 ng/mL	0.003	0.005	0.246
AFP ⩾ 200 ng/mL	0.008	0.011	0.316
Tumor size ⩾ 5 cm	< 0.001	< 0.001	0.001
Multiple tumors	0.125	0.169	0.471
Vascular invasion	0.063	0.205	0.150
CLIP ⩾ 1	< 0.001	0.001	0.116
CLIP ⩾ 2	< 0.001	< 0.001	0.386
Positive Pohl	0.748	0.683	0.993
Positive AARP	0.181	0.120	0.861
AAR ⩾ 1.07	0.048	0.491	0.021
API ⩾ 6	0.771	0.402	0.575
CDS ⩾ 8	0.678	0.972	0.466
APRI ⩾ 1.94	0.022	0.053	0.213
APRI ⩾ 0.56	0.080	0.054	0.665
FIB-4 ⩾ 4.3	0.044	0.130	0.152
FibroQ ⩾ 6.36	0.025	0.131	0.084
Lok ⩾ 0.33	0.836	0.698	0.870
Lok ⩾ 0.70	0.078	0.592	0.026
GUCI ⩾ 2.24	0.050	0.318	0.050
GUCI ⩾ 0.65	0.125	0.088	0.757
APGA ⩾ 26.9	< 0.001	< 0.001	0.333
PAPAS ⩾ 2.41	< 0.001	0.002	0.034
PAPAS ⩾ 3.62	< 0.001	0.001	0.024

AAR: Aspartate aminotransferase/alanine aminotransferase ratio; AARP: AAR-platelet count score; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/AFP index; API: Age/platelet count index; APRI: Aspartate aminotransferase/platelet count ratio index; AST: Aspartate aminotransferase; CDS: Cirrhosis discriminant score; CLIP: Cancer of the Liver Italian Program; FIB-4: Fibrosis index based on the four factors; FibroQ: Fibro-quotient; GGT: γ-glutamyl transpeptidase; GUCI: Goteburg University Cirrhosis Index; HBV: Hepatitis B virus; INR: International normalized ratio; PAPAS: Platelet count/age/ALP/AFP/AST index; PLT: Platelet count; PT: Prothrombin time.

possible predictor of tumor recurrence. Therefore, we investigated whether this factor influenced PLT and platelet-based models. Results show that PLT, PAGA, and PAPAS were all useful indictors for patients with large and small tumors ($P < 0.05$) (Figure 8). Further analyses revealed that cirrhosis and tumor size were not associated, and non-cirrhotic patients had a higher rate of elevated PLT in comparison with cirrhotic patients (39.8% *vs* 27.1%).

DISCUSSION

The high risk of recurrence is viewed as one of the greatest concerns plaguing HCC treatment[5]. The recurrence probability after curative therapy was 44.2% in our current study, within the reported range of 50%-100%[36]. Thus, it is crucial to identify the predisposing factors for recurrence and improve them before treatment. The roles of PLT and platelet-relative models for evaluating such factors were highlighted in this retrospective evaluation of 172 patients. The results confirmed that tumor size, ascites, PLT and ALP were independent prognostic factors of overall recurrence. We identified APRI, FIB-4, FibroQ, APGA, and PAPAS as independent predictors of recurrence.

Due to portal hypertension, a decrease in thrombopoietin production[17,37], and capture by the liver[13], PLT significantly decreases in cirrhotic patients[17]. Numerous observational studies have shown that thrombocytopenia is a major risk factor for the development of cirrhosis[18,20,38]. Moreover, PLT is associated with HCC[39], and several platelet-based indices have been identified as predictors of HCC formation. Tamaki *et al*[40] reported that an FIB-4 > 3.25 independently increased the risk of developing HCC by a factor of 1.7. However, it is unclear whether platelets accelerate or impede HCC occurrence, as Sitia *et al*[41] suggested that management of immune-mediated chronic HBV in an animal model with antiplatelet drugs, such as aspirin and clopidogrel, could prevent hepatocarcinogenesis.

The association between platelets and survival in HCC remains inconsistent and disputable as well. Buergy *et al*[42] demonstrated that an elevated PLT level at the time of diagnosis was associated with a shorter survival in many solid tumors, including lung cancer, pancreatic adenocarcinoma, gastric cancer, and HCC. Nouso *et al*[43] recruited 157 HCC patients with Child-Pugh class C cirrhosis and found that a PLT level > 80 × 10^9/L was an independent predictor of poor overall survival. In contrast, additional studies highlighted that thrombocytopenia/low PLT level adversely affected survival in HCC patients who received liver resection[44-47]. However, few studies have focused on the influence of PLT on postoperative recurrence. Although Amano *et al*[45] showed that decreased PLT was associated with a higher risk of recurrence in HCC, our study indicated that patients with a PLT level ⩾ 148 × 10^9/L had a higher recurrence probability.

As prognosis of HCC remains far from satisfactory owing to the high incidence of tumor recurrence, several HCC prognostic models (such as CLIP[48-51]) have been proposed. However, these models mainly focus on non-modifiable tumor characteristics. Furthermore, tumor size and vascular invasion are not significant predictors of survival in HCC[52]. Thus, these models have certain limitations and there is an urgent need for effective, interventional models to evaluate the prognosis of HCC. In contrast, PLT is a correctable, inexpensive index and there are several established platelet-based models. However, the effects of

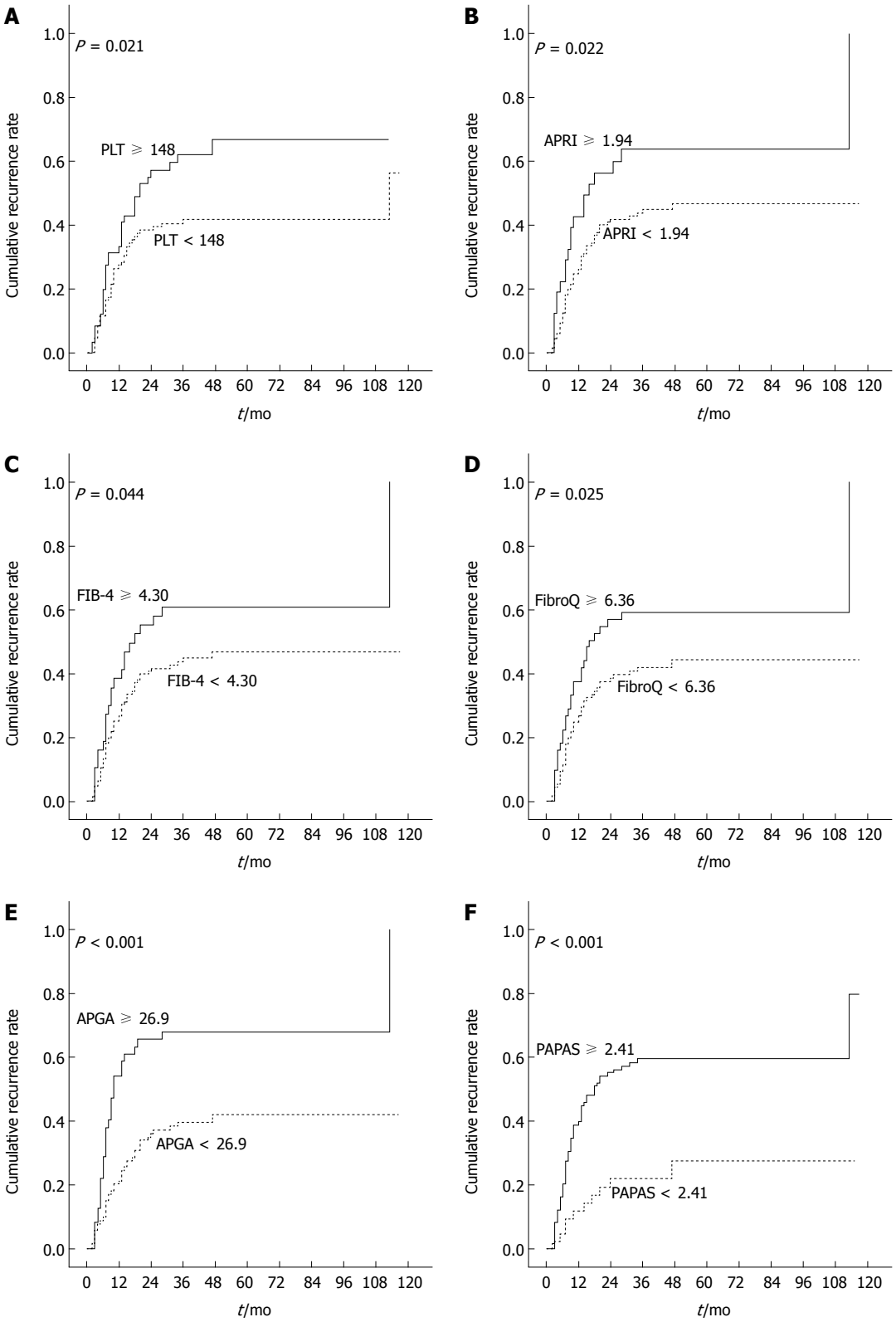


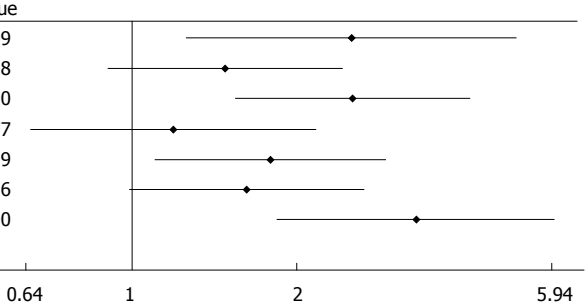
Figure 3 Cumulative recurrence. Kaplan-Meier curves of patients stratified according to A: Platelet count (PLT); B: Aspartate aminotransferase/platelet count ratio (APRI) index; C: Fibrosis index based on the four factors (FIB-4); D: Fibro-quotient (FibroQ); E: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/alpha-fetoprotein (APGA) index; F: Platelet count/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase (PAPAS) index.

these indices in predicting recurrence have not been extensively evaluated. This study demonstrates that nearly half of these indices were helpful predictors of recurrence, including APRI, FIB-4, FibroQ, APGA and PAPAS, which were more powerful prognostic tools than CLIP.

APRI is a valuable index for predicting survival, especially in patients with HBV infection or cirrhosis[7].

A

Variable	Crude HR (95%CI)	Crude *P* value	Adjusted HR (95%CI)	Adjusted *P* value
Ascites: Yes	2.61 (1.09-3.92)	0.027	2.52 (1.26-5.02)	0.009
AST: ⩾ 55 U/L	2.57 (1.63-4.41)	0.000	1.48 (0.91-2.43)	0.118
ALP: ⩾ 116 U/L	2.46 (1.56-3.88)	0.000	2.53 (1.55-4.15)	0.000
GGT: ⩾ 144 U/L	2.60 (1.56-4.33)	0.000	1.19 (0.65-2.16)	0.577
PLT: ⩾ 148 × 10^9/L	1.69 (1.07-2.66)	0.024	1.79 (1.10-2.90)	0.019
AFP: ⩾ 96 ng/mL	2.00 (1.24-3.22)	0.005	1.62 (0.99-2.66)	0.056
Tumor size: ⩾ 5 cm	4.15 (2.46-7.01)	0.000	3.31 (1.85-5.93)	0.000



B

Variable	Crude HR (95%CI)	Crude *P* value	Adjusted HR (95%CI)	Adjusted *P* value
CLIP: 1-6	2.64 (1.49-4.68)	0.001	1.40 (0.69-2.83)	0.347
CLIP: 2-6	2.51 (1.56-4.03)	0.000	1.12 (0.62-2.01)	0.703
AAR: ⩾ 1.07	1.56 (1.00-2.45)	0.053	0.81 (0.49-1.33)	0.396
APRI: ⩾ 1.94	1.79 (1.07-2.99)	0.026	1.89 (1.04-3.45)	0.037
FIB4: ⩾ 4.30	1.64 (1.00-2.67)	0.049	1.76 (1.01-3.05)	0.045
FibroQ: ⩾ 6.36	1.69 (1.06-2.70)	0.029	1.77 (1.05-3.00)	0.032
APGA: ⩾ 26.9	2.40 (1.49-3.86)	0.000	2.02 (1.22-3.36)	0.007
PAPAS: ⩾ 2.41	3.35 (1.71-6.55)	0.000	2.52 (1.25-5.08)	0.000
PAPAS: ⩾ 3.62	2.46 (1.53-3.95)	0.000	1.65 (0.99-2.75)	0.055

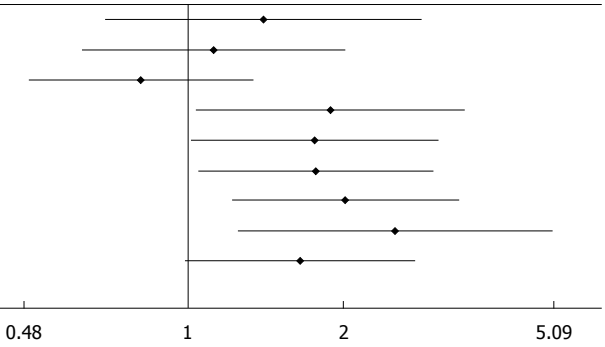


Figure 4 Multivariate analysis of prognostic indicators expressed as binary variables. A: Clinical and biochemical parameters; B: Noninvasive indices. AAR: Aspartate aminotransferase/alanine aminotransferase ratio; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/alpha-fetoprotein index; APRI: Aspartate aminotransferase/platelet count ratio index; AST: Aspartate aminotransferase; CLIP: Cancer of the Liver Italian Program; FIB-4: Fibrosis index based on the four factors; FibroQ: Fibro-quotient; GGT: γ-glutamyl transpeptidase; HR: Hazard ratio; PAPAS: Platelet count/age/alkaline phosphatase/alpha- fetoprotein/aspartate aminotransferase index; PLT: Platelet count.

Variable	Crude HR (95%CI)	Crude *P* value	Adjusted HR (95%CI)	Adjusted *P* value
CLIP	1.50 (1.22-1.84)	0.000	1.03 (0.78-1.36)	0.831
AAR	1.40 (0.93-2.12)	0.109	0.88 (0.59-1.31)	0.516
APRI	1.01 (0.96-1.07)	0.634	1.03 (0.94-1.14)	0.545
FIB4	1.00 (0.97-1.03)	0.784	0.98 (0.91-1.16)	0.626
FibroQ	0.99 (0.96-1.02)	0.528	0.97 (0.92-1.02)	0.241
APGA	1.02 (1.01-1.04)	0.001	1.02 (1.01-1.03)	0.004
PAPAS	1.55 (1.30-1.86)	0.000	1.36 (1.12-1.65)	0.002

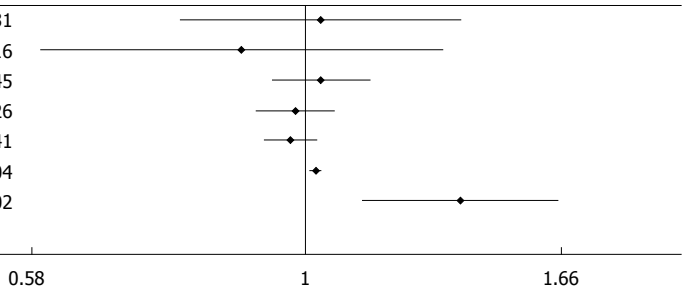


Figure 5 Multivariate analysis of noninvasive indices expressed as continuous variables. AAR: Aspartate aminotransferase/alanine aminotransferase ratio; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/alpha- fetoprotein index; APRI: Aspartate aminotransferase/platelet count ratio index; CLIP: Cancer of the Liver Italian Program; FIB-4: Fibrosis index based on the four factors; FibroQ: Fibro-quotient; HR: Hazard ratio; PAPAS: Platelet count/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase index.

In our study, we found that an APRI ⩾ 1.94 was independently associated with a high relapse risk. Although a prospective analysis by Seo *et al*[53] showed that API was an independent predictor of intrahepatic distance recurrence, our results found no such association. Our study also showed that an FIB-4 ⩾ 4.3 was an indictor of recurrence, consistent with reports of HCC risk for patients with HIV infection[54] and for prognosis in nonalcoholic fatty liver disease[55]. Moreover, our multivariate analyses identified APGA and PAPAS as superior indicators, which have been seldom used in other studies. However, our study had a limited number of patients, and more studies are needed to determine their prognostic value.

A meta-analysis of 11 studies by Choi *et al*[56] confirmed that portal hypertension increases

Variable	Crude HR (95%CI)	Crude *P* value	Adjusted HR (95%CI)	Adjusted *P* value
Early recurrence				
Age: ⩾ 62 yr	2.21 (1.22-4.00)	0.009	2.66 (1.39-5.09)	0.003
Non-HBV	1.80 (0.99-3.25)	0.053	2.34 (1.17-4.65)	0.016
AST: ⩾ 55 U/L	2.22 (1.25-3.97)	0.007	1.28 (0.68-2.44)	0.445
ALP: ⩾ 116 U/L	2.61 (1.16-3.69)	0.014	1.53 (0.85-2.77)	0.160
GGT: ⩾ 144 U/L	2.40 (1.28-4.51)	0.006	1.24 (0.60-2.54)	0.561
AFP: ⩾ 96 ng/mL	2.30 (1.25-4.23)	0.008	2.95 (1.44-6.05)	0.003
Tumor size:⩾ 5 cm	5.35 (2.49-11.49)	0.000	3.96 (1.80-8.81)	0.001
CLIP: 1-6	3.38 (1.51-7.58)	0.003	2.20 (0.86-5.66)	0.102
APGA: ⩾ 26.9	3.00 (1.67-5.40)	0.000	2.75 (1.45-5.19)	0.002
PAPAS: ⩾ 2.41	3.92 (1.55-9.94)	0.004	1.01 (0.31-3.28)	0.983
Late recurrence				
Ascites: Yes	2.61 (1.09-3.92)	0.027	2.51 (0.91-6.89)	0.074
AST: ⩾ 55 U/L	3.23 (1.57-6.62)	0.001	1.70 (0.78-3.70)	0.183
ALP: ⩾ 116 U/L	3.25 (1.58-6.69)	0.001	2.95 (1.38-6.33)	0.005
GGT: ⩾ 144 U/L	3.03 (1.29-7.13)	0.011	2.30 (0.93-5.69)	0.072
PLT: ⩾ 148 × 10^9/L	2.51 (1.22-5.15)	0.012	2.70 (1.29-5.64)	0.008
Tumor size:⩾ 5 cm	3.16 (1.50-6.66)	0.000	2.51 (1.16-5.42)	0.020
AAR: ⩾ 1.07	2.30 (1.10-4.79)	0.026	1.38 (0.60-3.21)	0.450
Lok: ⩾ 0.70	2.33 (1.08-5.04)	0.032	3.45 (1.25-9.56)	0.017
PAPAS: ⩾ 2.41	2.74 (1.03-7.31)	0.044	2.37 (1.00-5.59)	0.049

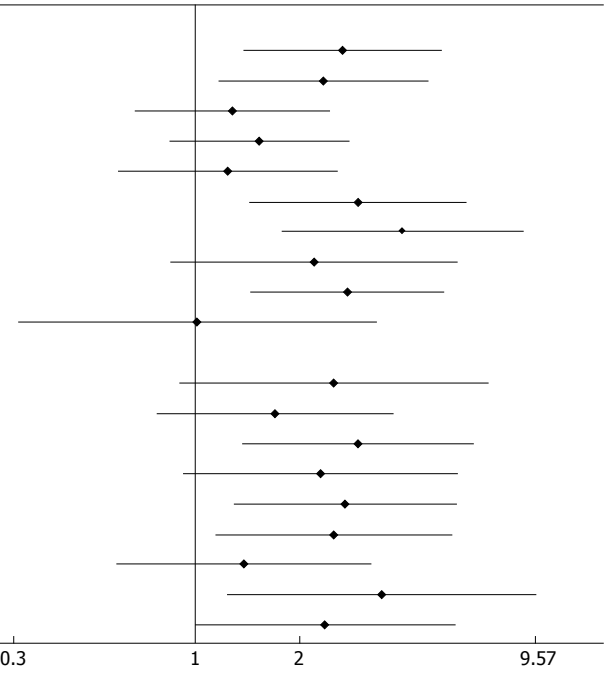
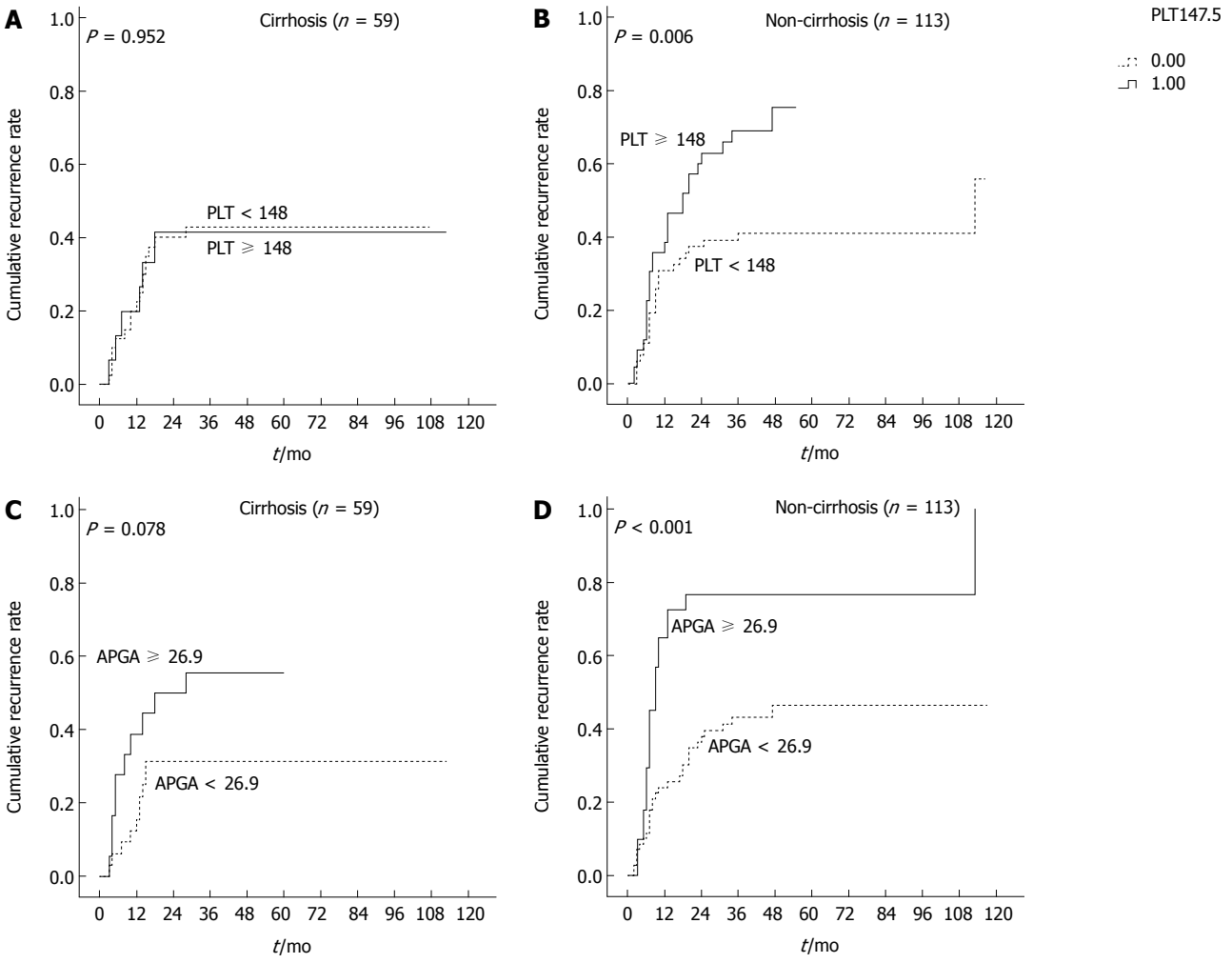


Figure 6 Predictors of early and late recurrences by multivariate analysis. AAR: Aspartate aminotransferase/alanine aminotransferase ratio; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/AFP index; AST: Aspartate aminotransferase; CLIP: Cancer of the Liver Italian Program; GGT: γ-glutamyl transpeptidase; HBV: Hepatitis B virus; HR: Hazard ratio; PAPAS: Platelet count/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase index; PLT: Platelet count.



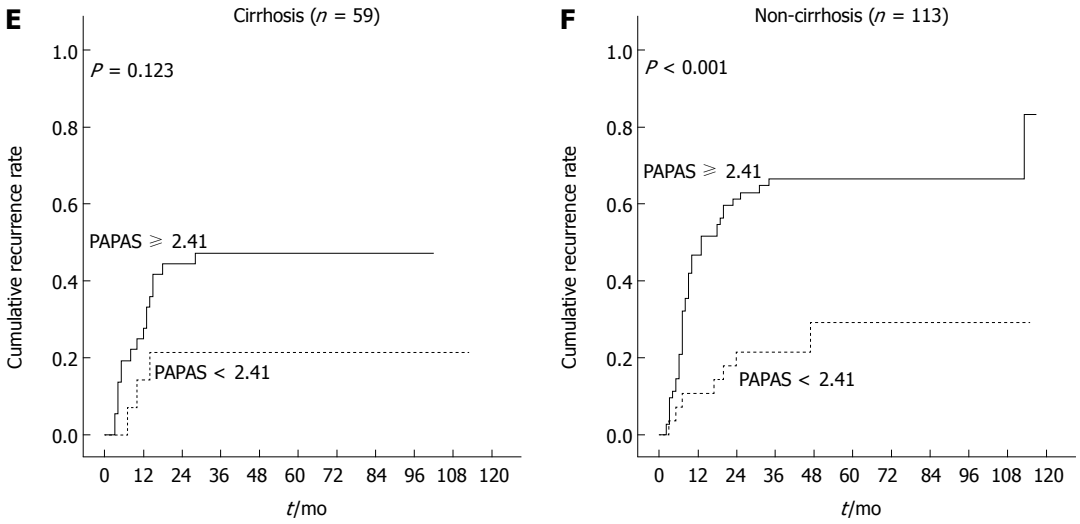
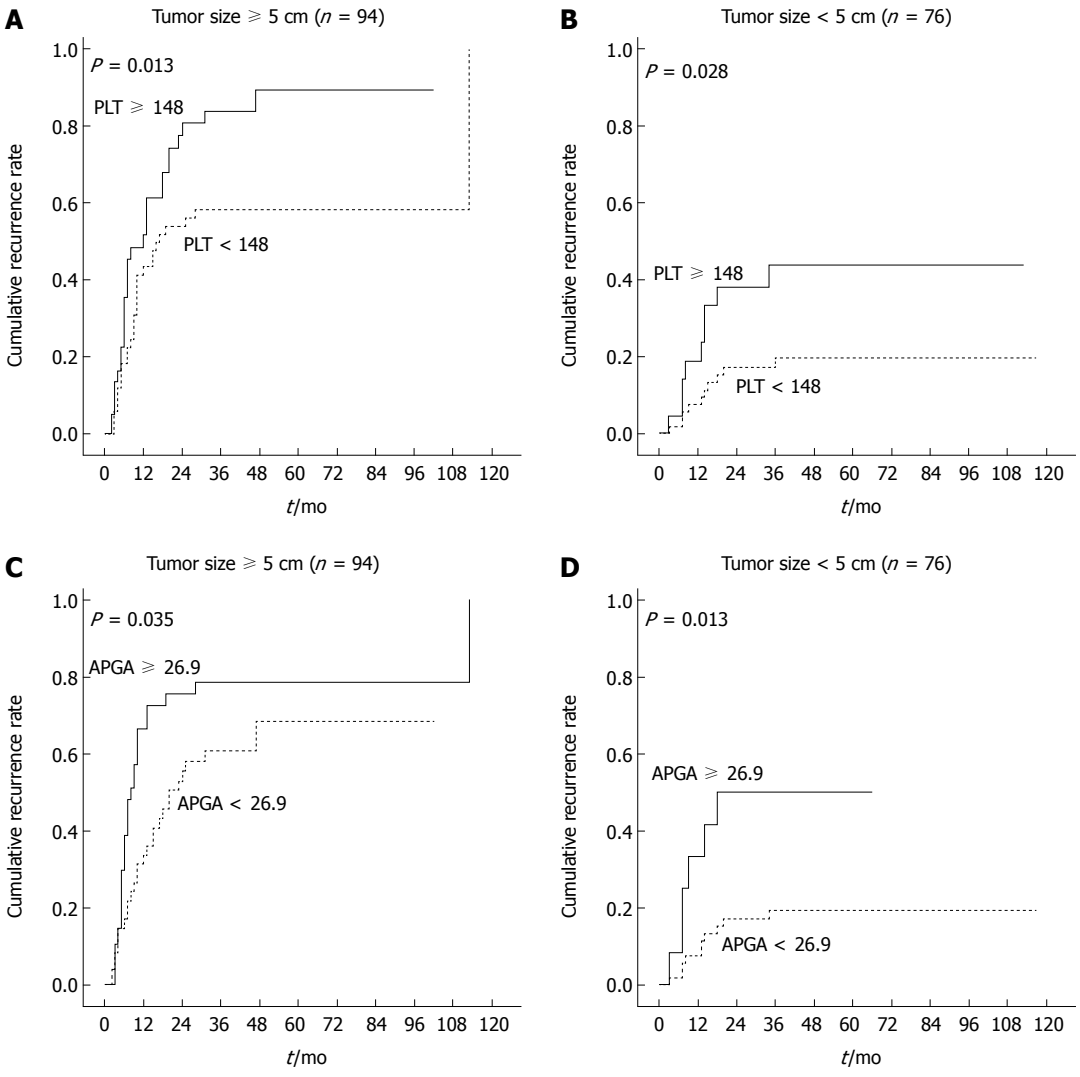


Figure 7 Cumulative recurrence curves of cirrhotic and non-cirrhotic patients. Kaplan-Meier curves of patients stratified according to A, B: Platelet count (PLT); C, D: Aspartate aminotransferase/PLT/γ-glutamyl transpeptidase/alpha-fetoprotein (APGA) index; E, F: PLT/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase (PAPAS) index.



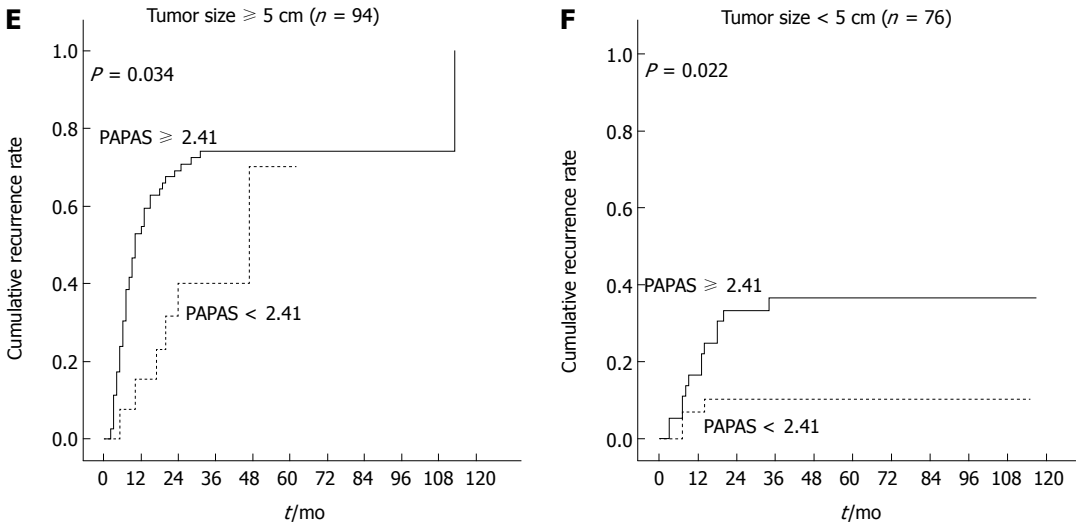


Figure 8 Cumulative recurrence curves of patients with large (⩾ 5 cm) and small (< 5 cm) tumors. Kaplan-Meier curves of patients stratified according to A, B: Platelet count (PLT); C, D: Aspartate aminotransferase/PLT/γ-glutamyl transpeptidase/alpha-fetoprotein (APGA) index; E, F: PLT/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase (PAPAS) index.

Table 4 Comparison of clinicopathologic features

Variable	PLT			APGA			PAPAS		
	< 148 × 10^9/L (*n* = 111)	⩾ 148 × 10^9/L (*n* = 61)	*P* value	< 26.9 (*n* = 105)	⩾ 26.9 (*n* = 51)	*P* value	< 2.41 (*n* = 43)	⩾ 2.41 (*n* = 113)	*P* value
HBV, yes/no	82/29	39/22	0.172	75/30	38/13	0.686	32/11	81/32	0.732
Sex, male/female	90/21	49/12	0.904	85/20	42/9	0.833	36/7	91/22	0.647
Median age in year	52.6	55.2	0.115	54	52.1	0.263	NA	NA	NA
Ascites, yes/no	8/103	9/52	0.113	12/93	4/47	0.489	5/38	11/102	0.958
Cirrhosis, yes/no	43/68	16/45	0.098	33/72	21/30	0.230	15/28	39/74	0.965
Tumor size, ⩾ 5/< 5 cm	55/56	39/22	0.070	51/54	38/13	0.002	14/29	75/38	< 0.001
Tumor type, multiple/single	19/92	13/48	0.499	19/84	11/40	0.606	4/39	26/87	0.052
Vascular invasion, yes/no	11/100	3/58	0.252	7/98	6/45	0.440	2/41	11/102	0.482
Recurrence, yes/no	43/68	33/28	0.052	39/66	31/20	0.005	10/33	60/53	0.001
Median survival in mo	37.5	29.5	0.050	37.3	27.9	0.026	43.4	30.8	0.006

APGA: Aspartate aminotransferase/platelet count/γ-glutamyl transpeptidase/alpha-fetoprotein index; HBV: Hepatitis B virus; NA: Not applicable; PAPAS: Platelet count/age/alkaline phosphatase/alpha-fetoprotein/aspartate aminotransferase index; PLT: Platelet count.

mortality, morbidity, complications and liver failure in HCC patients, and several studies demonstrated that thrombocytopenia, which reflects the degree of hypertension, induces similar outcomes[57-59]. Kubo *et al*[60] suggested that a low PLT in HCC patients with HCV was the only independent predictor of multicentric HCC. In addition, a decreased PLT level was significantly associated with elevated AFP levels[11,61,62], both of which are associated with HCC recurrence[63,64]. In contrast, serum PLT levels positively correlate with tumor size in HCC[39,65], and platelets can stimulate the growth and invasion of several HCC cell lines *in vitro*[66]. High PLT, such as in thrombocytosis, could also result in many adverse side effects, including deep vein thrombosis[67]. Thus, although thrombocytopenia and thrombocytosis are not contraindications for resection in HCC[44], it is still recommended to normalize serum PLT levels by prophylactic platelet transfusions or taking relevant agents before treatment.

There were some limitations in the current study. First and most important, although there was an adverse relationship between PLT and platelet-based indices, high levels of all predicted a high HCC recurrence. This dichotomy may due to the fact that although thrombocytopenia/low PLT has been identified as a crucial risk factor for HCC formation[10,11] and prognosis[44-47], it was identified as a favorable factor for HCC prognosis in our study and several others[42,43]. In addition, our limited study population included numerous variables that may have contributed to the discrepancy. Second, performances of the noninvasive indices for determining recurrence were all poor in our study. This could be due to the relatively small number of patients and a short follow-up period. Third, approximately three-quarters of the HCC cases in our cohort were caused by HBV infection, thus it is also necessary to validate our results in relation to HCV infection. Many of the formulas used in these indices were deduced in cohorts with[26-29,32,33] or partly with[23,31] HCV-infected individuals, or with

HCV/HIV coinfection[30]. On the other hand, detection of cirrhosis with these indices has been validated in patients with chronic HCV in numerous studies[68-71]. These findings suggest that these noninvasive models may demonstrate better prognostic value in patients with HCV-positive HCC. Fourth, PLT, APGA, and PAPAS were significant predictors in patients without cirrhosis, but not in patients with cirrhosis. The limited number of individuals within each subgroup may explain this result, and thus further study is need for verification.

This study was the first to explore the performances of 11 platelet-based indices for detecting postoperative recurrence in HCC. Furthermore, these indices were compared with CLIP and AAR, two models that are not associated with platelets. We demonstrated that several PLT-based models were more valuable than the two PLT-unrelated indices. Additionally, stratification of patients demonstrated that PLT was not affected by tumor size, which was a major confounder in our study population. Taken together, the data show that in patients with HCC, PLT and several platelet-based indices might be effective tools to assess postoperative relapse, especially late relapse. As these significant prognostic models were noninvasive, inexpensive, and easy to calculate, our findings will be helpful for surgeons assessing postoperative recurrence probability in HCC.

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COMMENTS

Background

The high risk of postoperative recurrence is one of the greatest problems plaguing potential curative treatment and hastening death for patients with hepatocellular carcinoma (HCC). It is essential to identify predisposing risk factors and endeavor to improve them before surgery. However, there are few variables currently available to accurately predict postoperative recurrence. Platelet count (PLT) is a simple parameter that has been closely associated with cirrhosis and HCC.

Research frontiers

PLT and platelet-based noninvasive indices have a high accuracy in detecting hepatic cirrhosis and HCC. The current study demonstrates that PLT and these indices are valuable tools to predict postoperative recurrence.

Innovations and breakthroughs

Several prognostic models for HCC have been established, mainly based on non-modifiable tumor characteristics. In contrast, PLT is improvable, and the authors highlight that PLT and platelet-based models are independently associated with recurrence, especially late recurrence (more than one year after liver resection). This study included PLT and 11 platelet-based models for assessing recurrence risk, which may be more useful in clinical application. Patients with a high PLT have a worse HCC prognosis, especially for those without cirrhosis.

Applications

By testing PLT and calculating several platelet-related indices before surgery, authors could estimate HCC recurrence probability after liver resection. These results may be used to reduce postoperative recurrence rate for patients by improving preoperative PLT.

Terminology

Platelets are involved in thrombosis, inflammatory responses, and liver regeneration *via* releasing several inflammatory mediators. PLT is a reflection of platelet function, with a normal range of 100 × 10^9/L-300 × 10^9/L.

Peer-review

The authors explored the complicated issue of predicting HCC recurrence and identified platelet-based indices as a possible tool. The results indicate that high platelet levels may predict recurrence, especially in non-cirrhotic patients.

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