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# Simplified nomograms based on platelet-associated models for survival prediction in Asian hepatocellular carcinoma patients after surgery

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ABSTRACT

*Background & aims:* Accumulating evidence showed platelets were closely related to hepatocellular carcinoma (HCC) prognosis. We here aimed to develop two simple-to-use nomograms based on the PLT-associated modified models to refine prognostic prediction of Asian HCC.

*Methods:* The nomograms were established using 684 eligible Asian patients who received curative resection for HCC, among which 456 and 228 were randomly assigned to the derivation and validation cohorts, respectively. Univariate and multivariate Cox analyses in the derivation set were used to identify the independent prognostic factors of the hepatectomy patients as the nomogram variables. We evaluated the discrimination and calibration of the nomograms by concordance indexes (C-index), calibration plots and Kaplan-Meier curves. The discrimination ability of the PLT-based nomograms was compared with the conventional staging systems using time-dependent receiver operating characteristic (ROC) curves.

*Results:* The nomogram for overall survival (OS) estimation was comprised of MPV/PC [mean platelet volume/platelet count], SII [systemic immune-inflammation index], NPS [neutrophil-platelet score], PAPAS [platelet count/age/ALP/AFP/AST index] and S index. And the nomogram for recurrence-free survival (RFS) prediction was of NPS, PAPAS and S index. The C-indexes of the OS nomogram in the derivation and validation sets were 0.704 and 0.707, and those of the RFS nomogram were 0.668 and 0.703. The calibration plots fitted well. The survival curves showed great discriminatory powers. The area under the curve (AUC) of our nomograms were significantly larger than that of the three conventional models ($P < 0.05$).

*Conclusions:* The two PLT-based nomograms were accurate in predicting the OS and RFS of Asian HCC patients after hepatectomy.

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most fatal global health issues, being ranked as the second major cause of cancer-related death and the sixth most common malignancy worldwide [1]. Although large improvement of therapeutic modalities has been seen over the years, the prognosis of HCC remains unsatisfactory [2,3]. In some studies, the five-year recurrence rate of HCC after resection reached over 75% [4]. This is mainly because of the high heterogeneity of the cancer itself and patients and the lack of effective preoperative assessment [5]. Therefore, it is imperative for an accurate predictive tool to stratify patients at different risk and guide personalized treatment and surveillance of each individual patient.

Though the role of platelets (PLT) in HCC has not been elucidated, the evidence of PLT involved in a series of tumor biological processes including the growth, metastasis and angiogenesis of HCC appears consistent [6,7]. Studies in vitro showed PLT and its lysates could stimulate the proliferation and invasion of HCC cells [6,8]. And preclinical studies demonstrated that anti-PLT therapy like aspirin could significantly inhibit HCC development and improve survival [9]. With respect to the tumorigenic mechanism of PLT, some researchers proposed that PLT interacted with cancer cells which facilitated hematogenous metastasis of HCC [10]. Moreover, PLT could produce several types of growth factors and cytokines, contributing to the tumor growth [11]. Based on all these evidence, it is reasonable to conclude that PLT might be a potential prognostic predictor of HCC.

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Consistent with experimental findings, clinical studies showed thrombocytosis was a risk factor of the survival of HCC [12]. However, small disparity exits that thrombocytopenia has been identified as an unfavorable indicator of HCC prognosis as well [13]. The reasons of this inconsistency are probably as follows: The poor outcome of the HCC patients with thrombocytosis is mostly the result of the direct stimulatory effect of PLT on tumor progression while the poor prognosis of those with thrombocytopenia mainly reflects the severity of the underlying disease like cirrhosis [14].

Due to the complexity of the pathophysiological environment of cancerous liver compared to the normal liver and the instability of the one-element model-PLT count as it can be easily influenced by various factors, it might be inappropriate and inaccurate to use the absolute value of PLT as the predictive tool alone [15]. Thus, increasing modified models based on PLT have been proposed in recent years exhibiting better performance than PLT count in prognostication of HCC [16]. As Asia accounts for more than half of the HCC cases worldwide [17], we here incorporated 19 PLT-associated compound prognostic indexes in order to construct robust and simple-to-use PLT-based nomograms which can improve the prognostic prediction and facilitate the management-decision in HCC patients from Asia after curative resection.

## 2. Patients and methods

### 2.1. Patients and study design

A retrospective study was performed based on the clinical data collected from a total of 1689 consecutive patients with HCC who underwent hepatectomy in three hospitals: the First Affiliated Hospital of Xi'an Jiaotong University from January 2005 to December 2016 (n = 1046), the Affiliated Hospital of Qinghai University from January 2011 to June 2017 (n = 361) and the Second Affiliated Hospital of Xi'an Jiaotong University (n = 282). Patients reviewed from the Second Affiliated Hospital of Xi'an Jiaotong University were from an ongoing study which began in January 2012. The inclusion criteria were: 1) age > 18 years; 2) preoperative Child-Pugh class A or B; 3) Tumor-node-metastasis (TNM) stage I, II or III according to the 8th edition of American Joint Committee on Cancer (AJCC) staging system [18]; 4) no anti-cancer treatment before surgery; 5) curative resection as defined in a previous study [19]; 6) histologically proven HCC. Patients who were lost to follow up or had incomplete clinical data were excluded. Eventually, 684 eligible patients were included in this study and were randomly allocated into two groups at a ratio of 2:1. The larger group containing 456 participants was considered as the derivation set and the smaller one of 228 patients was used as the validation set. This study was censored on December 31, 2017 and approved by the Institutional Ethics Committees of the three hospitals. Written informed consent was obtained from each patient for using their data in research.

### 2.2. PLT-associated models

For each patient, clinical data including baseline characteristics (e.g. gender and age, medical history), routine preoperative laboratory tests (e.g. liver and coagulation function, AFP [alpha-fetoprotein] level), presurgical imaging findings (e.g. tumor number and size, tumor capsule) and primary tumor features (e.g. microvascular invasion, resection margin) derived from the surgical specimens were collected [20]. 19 PLT-based models published by the previous studies which might be associated with HCC prognosis were investigated in our study. The formulation methods of the 19 existing models were presented in Table S1. Risk scores of these PLT-associated prognostic systems for all the participants were then calculated using the collected clinical data of their own.

**Table 1**
Demographic baseline characteristics of the patients with hepatocellular carcinoma in derivation and validation groups.

| Clinical characteristics[a] | Derivation group[b] (n = 456) | Validation group[b] (n = 228) | *P* value |
|---|---|---|---|
| Age, years | 53.2( ± 10.6) | 54.1( ± 12.3) | 0.321 |
| Gender | | | |
| male | 355 (77.9) | 179 (78.5) | 0.845 |
| female | 101 (22.1) | 49 (21.5) | |
| Hepatitis B | | | |
| yes | 303 (66.4) | 153 (67.1) | 0.863 |
| no | 153 (33.6) | 75 (32.9) | |
| Hepatitis C | | | |
| yes | 32 (7.0) | 22 (9.6) | 0.229 |
| no | 424 (93.0) | 206 (90.4) | |
| Child-Pugh class [c] | | | |
| A | 208 (90.4%) | 98 (89.1%) | 0.699 |
| B | 22 (9.6%) | 12 (10.9%) | |
| TNM staging | | | |
| III | 163 (35.7) | 74 (32.5) | 0.115 |
| II | 83 (18.2) | 57 (25.0) | |
| I | 210 (46.1) | 97 (42.5) | |
| Tumor number | | | |
| multiple | 70 (15.4) | 37 (16.2) | 0.766 |
| single | 386 (84.6) | 191 (83.8) | |
| Tumor size (cm) | 6.2( ± 3.8) | 6.3( ± 3.6) | 0.800 |
| Tumor capsule | | | |
| incomplete | 284 (62.3) | 131 (28.7) | 0.223 |
| complete | 172 (37.7) | 97 (71.3) | |
| Microvascular invasion | | | |
| presence | 145 (31.8) | 81 (35.5) | 0.328 |
| absence | 311 (68.2) | 147 (64.5) | |
| Liver cirrhosis | | | |
| yes | 230 (50.4) | 110 (48.2) | 0.589 |
| no | 226 (49.6) | 118 (51.8) | |
| Ascites | | | |
| yes | 59 (12.9) | 25 (11.0) | 0.458 |
| no | 397 (87.1) | 203 (89.0) | |
| Spleen diameter (mm) | 112.5( ± 22.0) | 110.8( ± 24.6) | 0.472 |
| Hypertension | | | |
| yes | 87 (19.1) | 43 (18.9) | 0.945 |
| no | 369 (80.9) | 185 (81.1) | |
| Diabetes mellitus | | | |
| yes | 45 (9.9) | 19 (8.3) | 0.516 |
| no | 411 (90.1) | 209 (91.7) | |
| AFP (ng/ml) | | | |
| > 400 | 142 (31.1) | 74 (32.4) | 0.708 |
| 20-400 | 112 (24.6) | 56 (24.6) | |
| ≤20 | 202 (44.3) | 98 (43.0) | |
| PLT ( × $10^9$/L) | | | |
| ≥300 | 18 (3.9) | 9 (3.9) | 0.105 |
| 150-300 | 175 (38.4) | 72 (31.6) | |
| < 150 | 263 (57.7) | 147 (64.5) | |
| ALT (U/L) | | | |
| > 40 | 220 (48.2) | 111 (48.7) | 0.914 |
| ≤40 | 236 (51.8) | 117 (51.3) | |
| AST (U/L) | | | |
| > 35 | 276 (60.5) | 152 (66.7) | 0.118 |
| ≤35 | 180 (39.5) | 76 (33.3) | |
| ALB (g/L) | | | |
| ≤35 | 117 (25.7) | 61 (26.8) | 0.758 |
| > 35 | 339 (74.3) | 167 (73.2) | |
| INR | | | |
| > 1.3 | 32 (7.0) | 23 (10.1) | 0.164 |
| ≤1.3 | 424 (93.0) | 205 (89.9) | |

Abbreviations: AFP, alpha-fetoprotein; PLT, platelet; ALT, alanine aminotransferase.
AST, aspartate aminotransferase; ALB, albumin; INR, international normalized ratio.

[a] Continuous variables are expressed as mean ( ± standard deviation, SD), categorical variables as absolute frequencies, n (%).

[b] The number of cirrhotic patients in the derivation and validation group is 230 and 110, respectively.

[c] Child-Pugh class is only for cirrhotic patients.

**Table 2**
Univariate and multivariate analyses of the candidate nomogram variables for overall and recurrence-free survival.

| Variables | Overall survival | | | | Recurrence-free survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| API (> 6/≤6) | 0.897 (0.682–1.180) | 0.438 | – | – | 0.804 (0.615–1.051) | 0.110 | – | – |
| MPV/PC (> 0.85/≤0.85) | 1.954 (1.409–2.709) | < 0.0001[a] | 1.785 (1.252–2.544) | 0.001[a] | 1.516 (1.117–2.059) | 0.008[a] | 1.296 (0.928–1.810) | 0.128 |
| Pohl score (1/0) | 1.046 (0.778–1.405) | 0.768 | – | – | 0.974 (0.726–1.306) | 0.860 | – | – |
| AARP (1/0) | 0.879 (1.596–1.296) | 0.515 | – | – | 0.923 (0.626–1.360) | 0.685 | – | – |
| COP-NLR (2/1/0) | 1.352 (1.037–1.762) | 0.026[a] | 0.819 (0.557–1.203) | 0.308 | 1.450 (1.125–1.869) | 0.004[a] | 0.884 (0.600–1.303) | 0.533 |
| SII (> 320/≤320) | 1.648 (1.244–2.184) | 0.001[a] | 2.064 (1.381–3.085) | < 0.0001[a] | 1.552 (1.179–2.043) | 0.002[a] | 1.447 (0.970–2.160) | 0.070 |
| NPS (2/1/0) | 1.643 (1.302–2.073) | < 0.0001[a] | 1.709 (1.246–2.344) | 0.001[a] | 1.972 (1.589–2.447) | < 0.0001[a] | 2.191 (1.594–3.012) | < 0.0001[a] |
| PLR (> 86/≤86) | 1.142 (0.866–1.507) | 0.346 | – | – | 1.211 (0.926–1.585) | 0.163 | – | – |
| CDS (> 6/≤6) | 1.224 (0.925–1.619) | 0.157 | – | – | 1.154 (0.876–1.520) | 0.307 | – | – |
| APRI (≥1.00/ < 1.00) | 0.987 (0.750–1.300) | 0.927 | – | – | 1.079 (0.824–1.411) | 0.581 | – | – |
| FIB-4 (> 2.82/≤2.82) | 1.221 (0.925–1.612) | 0.159 | – | – | 1.244 (0.947–1.635) | 0.117 | – | – |
| FibroQ (> 4.60/≤4.60) | 1.162 (0.879–1.536) | 0.292 | – | – | 1.079 (0.821–1.416) | 0.586 | – | – |
| Lok index (> 0.57/≤0.57) | 1.169 (0.885–1.545) | 0.270 | – | – | 1.083 (0.823–1.424) | 0.571 | – | – |
| GUCI (≥1.10/ < 1.10) | 1.067 (0.810–1.404) | 0.645 | – | – | 1.115 (0.852–1.459) | 0.427 | – | – |
| PAPAS (> 3.00/≤3.00) | 1.587 (1.187–2.123) | 0.002[a] | 1.793 (1.284–2.504) | 0.001[a] | 1.633 (1.236–2.158) | 0.001[a] | 1.897 (1.384–2.602) | < 0.0001[a] |
| King's score (> 20/≤20) | 0.995 (0.756–1.310) | 0.973 | – | – | 1.154 (0.882–1.510) | 0.297 | – | – |
| S index (> 0.39/≤0.39) | 1.546 (1.166–2.049) | 0.002[a] | 1.673 (1.192–2.347) | 0.003[a] | 1.692 (1.283–2.233) | < 0.0001[a] | 1.761 (1.265–2.449) | 0.001[a] |
| PSR (≤1200/ > 1200) | 1.061 (0.770–1.461) | 0.718 | – | – | 1.241 (0.900–1.710) | 0.188 | – | – |
| Forns index (> 9.50/≤9.50) | 1.122 (0.847–1.486) | 0.422 | – | – | 1.128 (0.851–1.494) | 0.402 | – | – |

Abbreviations: HR, hazard ratio; CI, confidence interval; API, age-platelet index; MPV, mean platelet volume; PC, platelet count; AARP, AAR-platelet count score; COP-NLR, combination of platelet count and neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; NPS, neutrophil-platelet score; PLR, platelet count-to-lymphocyte ratio; CDS, cirrhosis discriminant score; APRI, aspartate aminotransferase-to-platelet count ratio index; FIB-4, fibrosis index based on the four factors; FibroQ, fibro-quotient; GUCI, the Göteborg University Cirrhosis Index; PAPAS, platelet count/age/ALP/AFP/AST index; PSR, platelet count-to-spleen diameter ratio.

[a] Statistically significant.

### 2.3. Follow-up

Hepatectomy was performed by an open or laparoscopic approach depending on the difficulty of operation evaluated by surgeons. Patients were followed up every 3–6 months. The routine follow-up included liver function, serum AFP level and at least one imaging examination such as abdominal ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI). If patients were suspected of recurrence, contrast-enhanced CT or MRI, hepatic arteriography/portal venography if necessary, was conducted to validate the diagnosis. Overall survival (OS) was calculated from the date of surgery to the date of death of any cause or the last follow-up. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the date of recurrence or the date of the last follow-up or death for those with no recurrence.

### 2.4. Statistical considerations

For baseline clinical characteristics, continuous data were compared using the Student's *t*-test or Mann-Whitney *U* test while discrete data were compared via Chi-square test or Fisher exact test. 19 PLT-based risk models were considered as the candidate nomogram variables and screened through univariate and multivariate Cox regression analysis for the independent prognostic factors of OS and RFS ($P < 0.05$). Out of them, continuous variables were transferred into categorical ones using the median as the cut-off point before put into Cox models. Meanwhile, the hazard ratio (HR) with its 95% confidence interval (CI) of the categorical factors were also generated. The above variable comparisons and Cox analysis were carried out in SPSS 23.0 for windows (SPSS, Chicago, IL). The nomograms of OS and RFS were formulated based on the respective independent factors of OS and RFS using the package of "rms" in R, version 3.4.0 (http://www.r-project.org/). The concordance indexes (C-index) and the calibration plots of both the derivation and validation sets based on 500 bootstrap samples were used to assess the discrimination and calibration ability of the nomograms. According to the constructed nomogram, each participant would get a Nomo-score for risk stratification of death or recurrence. Patients were divided into different risk groups using the tertiles of the Nomo-scores as the cut-off points. Kaplan-Meier analyses and log-rank tests were conducted to compare the survival of different risk groups in GraphPad prism, version 7.0. We further compared the discrimination ability of our nomogram models and the previously proposed prognostic models of HCC including AJCC/TNM staging system, Barcelona Clinic Liver Cancer (BCLC) staging system and Cancer of the Liver Italian Program (CLIP) score. To make these comparisons, time-dependent receiver operating characteristic (ROC) curves of each model were plotted using the validation set and the corresponding time-dependent area under the curve (AUC) was also calculated via the R package "timeROC". In all the analyses of this study, $P < 0.05$ was adopted as the significant threshold.

## 3. Results

### 3.1. Clinical characteristics of the participants

The clinicopathological characteristics of the patients in the derivation and validation cohorts were summarized in Table 1. All the clinical variables were well matched between the two groups ($P > 0.05$). The median follow-up time was 39.5 months (range: 6.0–140.0 months) for the derivation set and 36.8 months (range: 6.0–123.0 months) for the validation set. The median OS for the derivation and validation cohorts were 20.2 months (inter-quartile range [IQR]: 20.6 months) and 19.6 months (IQR: 21.5 months), respectively. The 1-, 3- and 5-year OS rates were 79.0%, 52.0% and 29.0% for the derivation set, 74.7%, 48.6% and 28.1% for the validation set. The median RFS for the derivation and validation cohorts were 16.4 months (IQR: 19.1 months) and 16.0 months (IQR: 20.2 months), respectively. The 1-, 3- and 5-year RFS rates were 71.2%, 44.3% and 22.3% for the derivation set, 70.2%, 44.0% and 23.7% for the validation set.

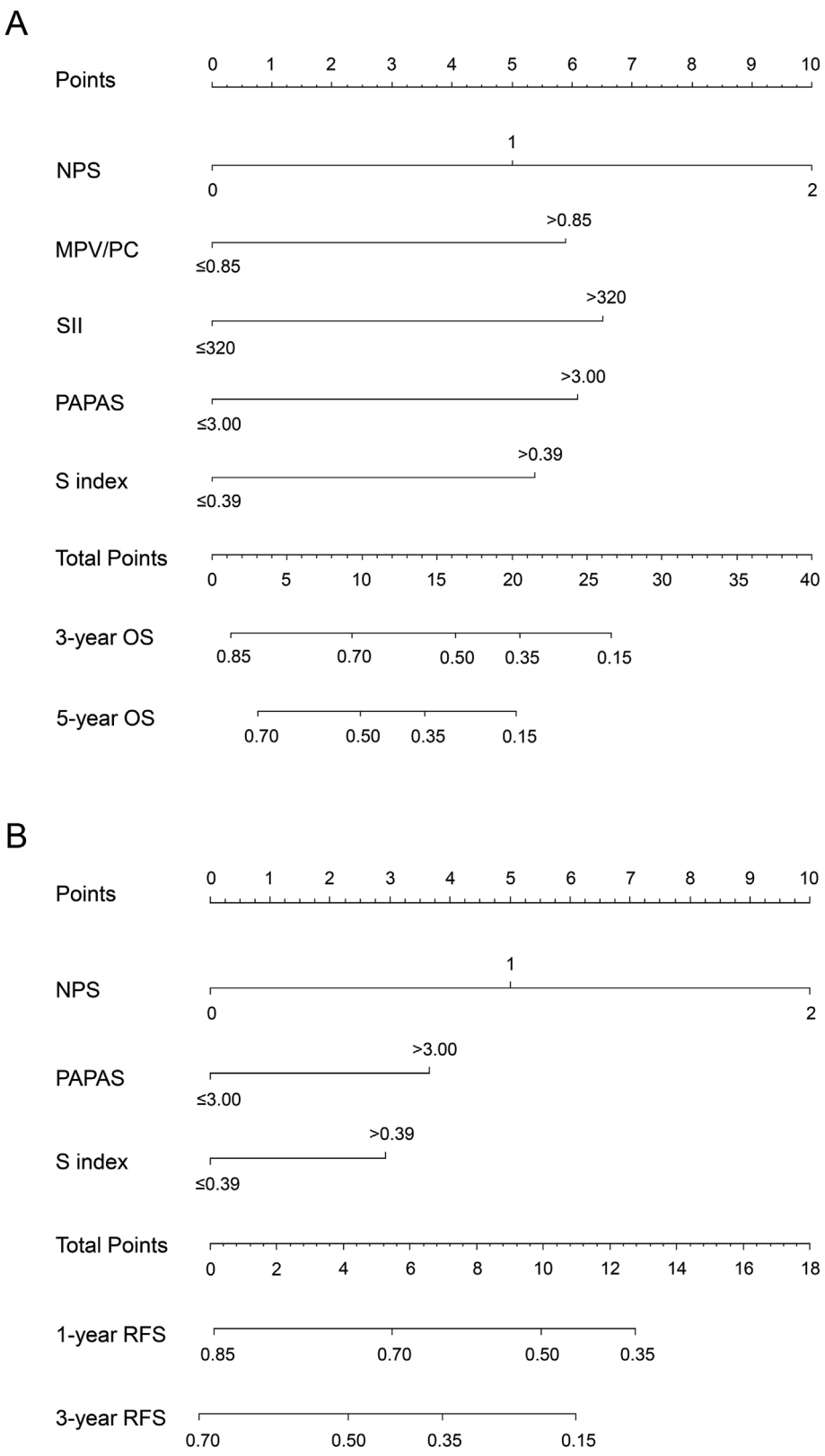


**Fig. 1. Simplified PLT-based nomograms for predicting the OS and RFS in hepatectomy patients with HCC.** To use the nomograms, draw a vertical line from the location on the axis of the variable itself which is determined by its value to the top axis named "Points". Add the points of all the variables of an individual patient up to get the total points. And find the location of the total points on the "Total Points" axis. Then draw another vertical line from the location to the two axes lower which represent the probabilities of 3- or 5-year OS (A) and 1- or 3-year RFS (B) of the patient. To ensure easy and quick access to the value of the PLT-associated variables, we have made a tiny tool (Supplementary file 1). With this tool, you can get the value of the variable as soon as you input the necessary indexes of the variable formula into our tool.

### *3.2. Construction of the PLT-based nomograms for OS and RFS*

Univariate and multivariate analyses were carried out to evaluate the correlation between 19 transformed categorical PLT-based variables and OS or RFS in the derivation set. The results showed five of them including MPV/PC [mean platelet volume/platelet count], SII [systemic immune-inflammation index], NPS [neutrophil-platelet score], PAPAS [platelet count/age/ALP/AFP/AST index] and S index were independent risk factors of OS and three including NPS, PAPAS and S index were independent factors of RFS (Table 2). The nomograms for OS (Fig. 1A) and RFS (Fig. 1B) prediction were formulated based on their respective independent factors.

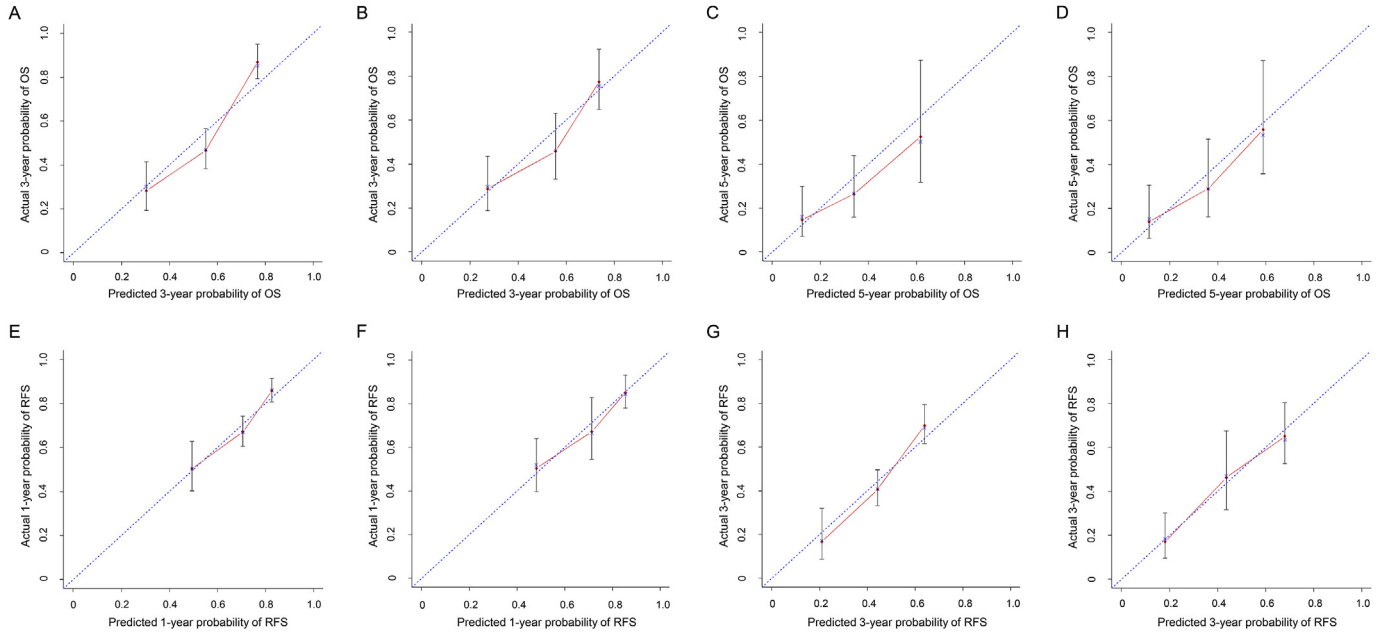


**Fig. 2. Calibration curves of the OS and RFS nomograms for predicting 3- (A & B), 5-year (C & D) OS and 1- (E & F), 3-year (G & H) RFS in the derivation (A, C, E & G) and validation (B, D, F & H) sets.** In each plot, the Actual observation and the nomogram-predicted probability were drawn on the y- and x-axes, respectively. The 45-degree dotted line stood for a complete agreement between the actual and predicted probabilities.

### 3.3. Validation of the constructed nomograms

The risk prediction ability of the resulting nomograms was internally validated in another cohort. For the estimation nomogram for OS, the C-indexes in the derivation and validation sets were 0.704 (95% CI: 0.666–0.742) and 0.707 (95% CI: 0.653–0.761), respectively. For the PLT-based nomogram for predicting RFS, the C-indexes in the derivation and validation sets were 0.668 (95% CI: 0.0.628–0.708) and 0.703 (95% CI: 0.649–0.757), respectively. The calibration plots in both derivation and validation cohorts showed good agreement between the actual observation and the predicted probability either of 3- (Figure 2A and B) and 5- year (Fig. 2C and D) OS or of 1- (Fig. 2E and F) and 3-year (Fig. 2G and H) RFS.

### 3.4. Discriminatory powers of the PLT-based nomograms

To further confirm the discriminatory accuracy of the constructed nomograms, Kaplan-Meier curves were depicted to compare the OS and RFS rates among the high-, intermediate- and low-risk patients. The cut-off points for risk stratification were consistent in the derivation and validation sets, determined to be 10.0 and 16.0 for OS, 3.5 and 7.0 for RFS. From the survival plots, our PLT-based nomograms showed clear different prognostic strata in either the derivation (Fig. 3A and B) or the validation cohort (Fig. 3C and D), with all the log-rank *P* values being less than 0.0001.

### 3.5. Comparisons of the predictive accuracy

The discrimination ability of the two PLT-based nomograms were compared with TNM stage, BCLC stage and CLIP score in predicting OS and RFS. From the time-dependent ROC curve analyses based on the validation set, our nomograms displayed better accuracy in OS and RFS prediction than the three competing models. The time-dependent AUC of the OS estimation nomogram for predicting 3- and 5-year OS were 0.758 (Fig. 4A) and 0.855 (Fig. 4B) which were significantly larger than that of any of the other three staging systems ($P < 0.05$). Similarly, the time-dependent AUC of the RFS estimation nomogram for predicting 1- and 3-year RFS were 0.714 (Figs. 4C) and 0.782 (Fig. 4D). There were also significant differences between the AUC of the RFS nomogram and the other three models ($P < 0.05$).

## 4. Discussion

In this study, we constructed two PLT-based nomograms for predicting the OS and RFS of hepatectomy patients using the clinical data from three medical centers in China. Our nomograms integrate the significantly independent variables-modified models associated with PLT, as one risk score (Nomo-score) system. Each variable in the nomogram generates its risk points according to its relation to the OS or RFS. This is like a second modification based on the first modification (modified models based on PLT count) which can be expected of higher accuracy in survival prediction. On the other hand, the OS and RFS nomograms, comprised of five and three factors, respectively, are easy-to-use. The values of all the nomogram variables can be quickly calculated from our tiny tool (Supplementary file 1) and the baseline indexes needed for calculation are all easily accessible routine tests as well which remarkably increases its clinical applicability in a wide range of health care systems. With the OS and RFS nomograms, Asian patients can be estimated for their risk of death in up to five years and recurrence in three years providing guidance for prevention treatment.

The five modified models formulating the OS or the RFS nomogram can be classified into three categories: self-modification (MPV/PC), inflammation-related (SII and NPS) and fibrosis- or cirrhosis-related (PAPAS and S index). In case of MPV/PC, it was found to be a useful predictive factor for HCC and liver cirrhosis by several published studies [21,22]. The previous results of the role of MPV/PC in HCC focused on its diagnostic value. While in this study, we investigated its prognostic value. Our results showed MPV/PC was significantly associated with the postsurgical OS and RFS of HCC patients (Cox univariate $P < 0.05$). In particular, as one of the OS nomogram variables, it was also the independent risk factor of the OS of HCC patients after resection (Cox multivariate $P < 0.05$). Anyway, our findings provided evidence for MPV/PC as a prognostic indicator in Asian hepatectomy patients with HCC, more studies needed for validation though.

The sustained inflammatory microenvironment of HCC has been demonstrated to be one of the fundamental elements for tumor

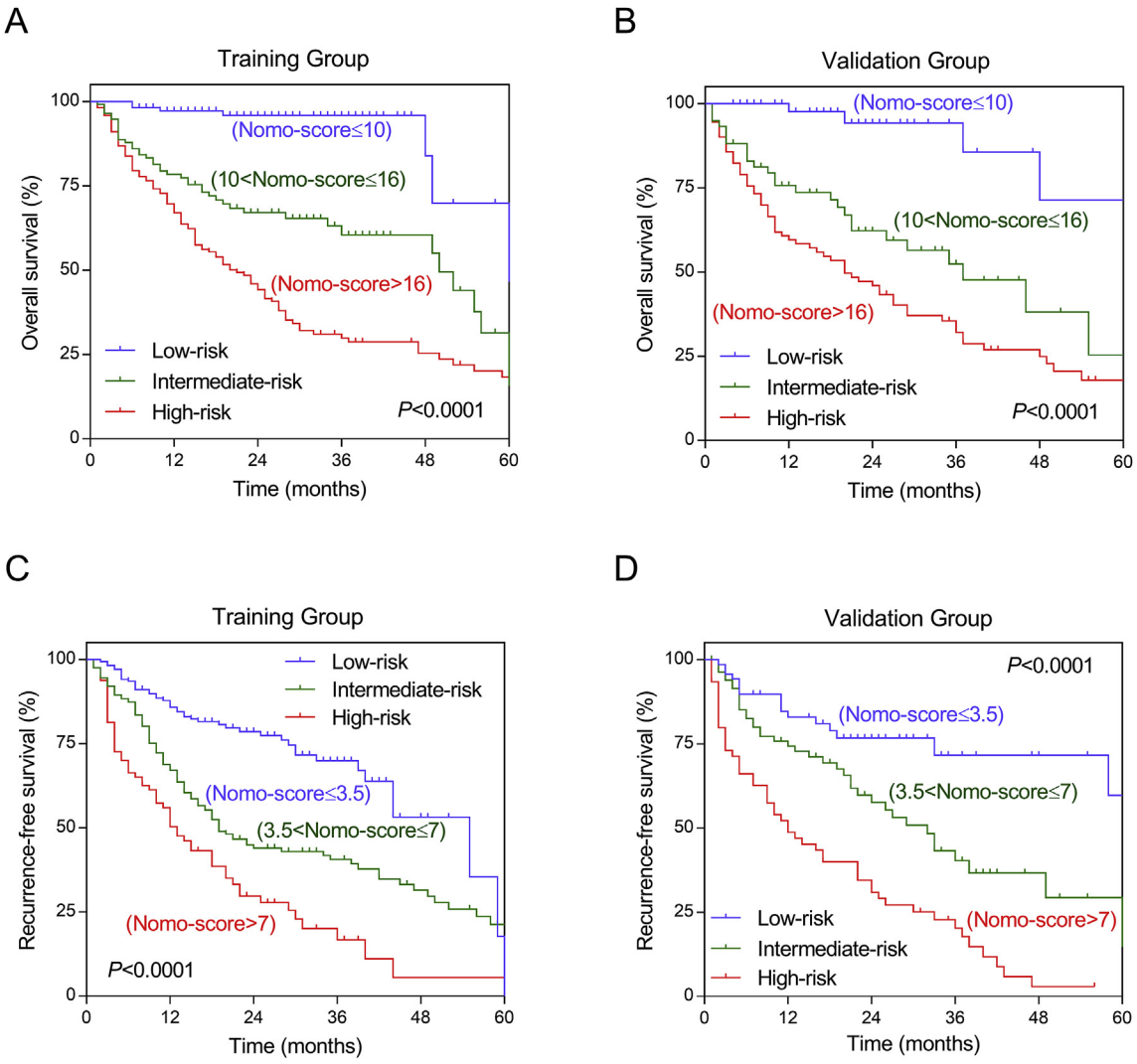


**Fig. 3. Kaplan-Meier curves of different risk groups stratified by the tertiles of the Nomo-scores derived from the OS and RFS nomograms.** The OS (A & B) and RFS (C & D) rates were compared both in the derivation (A & C) and validation (B & D) sets.

development, which is driven by various clinical factors including hepatitis B (HBV) or C (HCV) infection, alcohol abuse and nonalcoholic fatty liver disease [23]. Recent studies showed PLT functioned as a key player in HCC inflammation apart from its conventional role in vascular homeostasis [24]. It was found that PLT could cause the intrahepatic accumulation of virus-specific $CD8^+$ T cells and virus-nonspecific inflammatory cells in HBV-associated HCC, contributing to the maintenance of the inflammatory microenvironment [25]. Besides, PLT carries specific granules which can produce pro-inflammatory mediators under stimulation [26]. For instance, CD40 ligand released by activated PLT is a signal for the recruitment of inflammatory cells [27]. Built on these observations, several PLT-based prognostic systems associated with inflammation have been proposed for survival prediction in HCC patients [28,29]. In our nomograms, we enrolled two inflammation-related PLT-based models, SII and NPS. With respect to SII, it has been reported to be a useful prognostic predictor for HCC patients after curative resection in previous studies [29,30]. In this study, SII was also validated as the independently significant risk factor of the OS of HCC patients. Although it was not included in the RFS nomogram, Cox univariate analysis showed SII significantly correlated with the RFS of hepatectomy patients ($P < 0.05$). In terms of NPS, to the best of our knowledge, this was the first study involving the relations between NPS and the postoperative OS or RFS of HCC patients. Actually, NPS was raised as a survival predictor of patients presenting with colorectal cancer and increasing NPS was related to the poor survival of a variety malignancies including hepaticopancreaticobiliary cancers by Dr. Watt et al. in an earlier study [31]. Heroin, when we used this model, we changed the threshold of PLT from $400 \times 10^9$/L Dr. Watt et al. set in their study to $300 \times 10^9$/L as HCC patients were frequently accompanied thrombocytopenia [14]. Nonetheless, our results showed the new NPS was significantly associated with the OS and RFS of HCC patients after curative resection and further displayed superior predicting ability when it joined other variables in the OS and RFS nomograms supporting the notion that NPS was a potentially reliable prognostic indicator of the patients who underwent resection for HCC. Moreover, our findings based on SII and NPS gave clinical implications that severe preoperative inflammation might be a latent cardinal factor responsible for the unfavorable outcome of Asian HCC patients.

Most HCC occurs in cirrhotic livers. It has been demonstrated by numerous studies that liver cirrhosis or advanced fibrosis was a vital factor worsening the postsurgical survival of HCC patients [32,33]. Recent researches showed that administration of anti-PLT drugs like aspirin could significantly reduce liver fibrosis and improve survival in HCC patients, suggesting the pro-fibrotic role of PLT [9,24]. Additional studies revealed the possible mechanism that PLT might promote liver fibrosis through driving local inflammation [34,35]. These evidence naturally led to the speculation that PLT-associated estimation models for liver fibrosis might be the useful predictive tools for the prognosis of

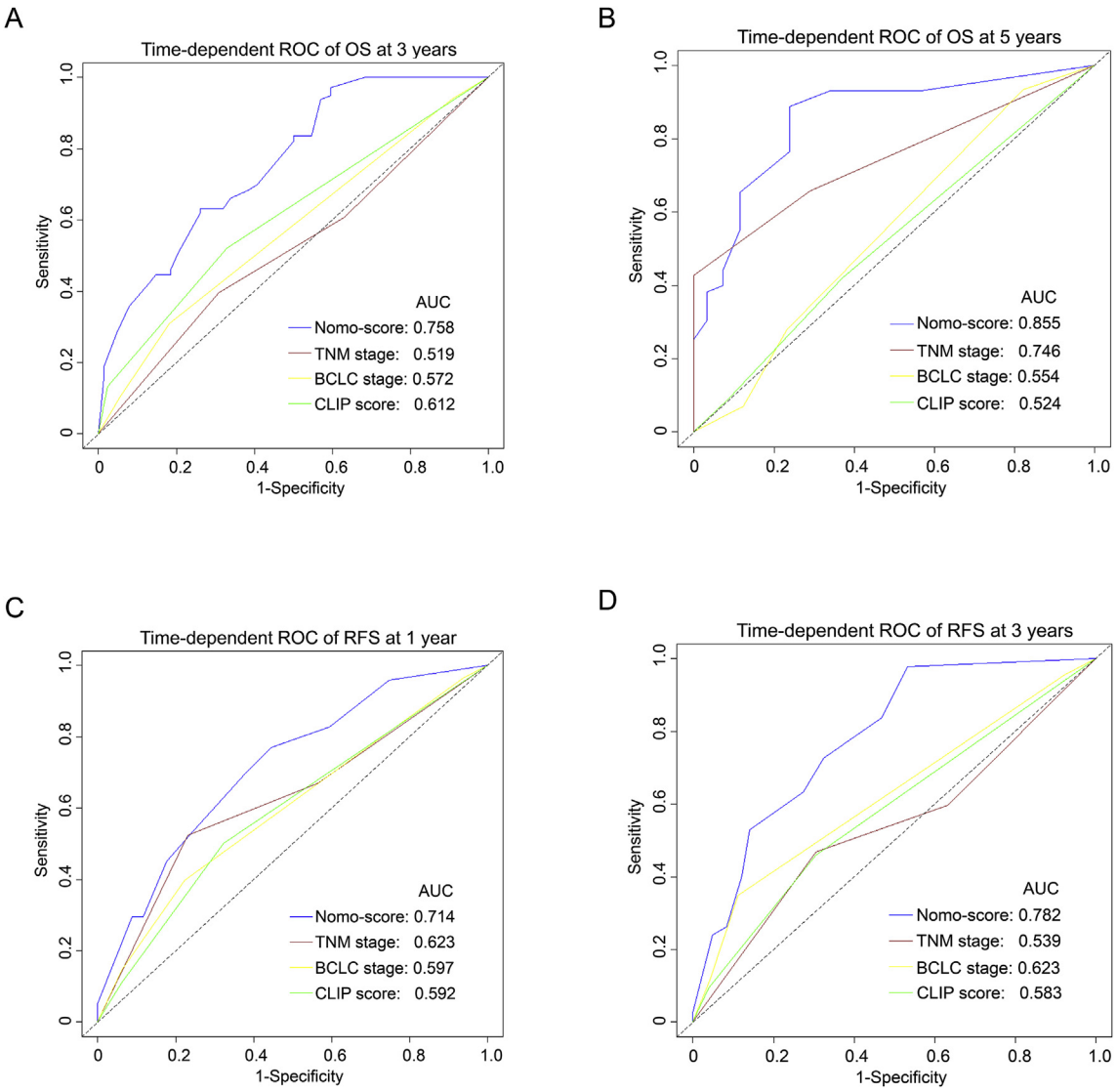


**Fig. 4. Time-dependent ROC curves of the OS and RFS in the validation cohort using our nomograms and three conventional staging systems.** For the OS or the RFS nomogram and TNM, BCLC, CLIP systems, the AUC generated from their time-dependent ROC curves for predicting the OS at 3 (A) and 5 (B) years or the AUC for predicting the RFS at 1 year (C) and 3 years (D) was presented.

HCC patients as well. And this hypothesis has been validated for several such compound indexes [16,36]. In our nomograms, we incorporated two PLT-based modified models previously used for fibrosis prediction [37,38]. One is PAPAS, the other is S index. Our study, for the first time, found that either PAPAS or S index was the independently significant risk factor of the OS and RFS of Asian HCC patients after surgery. Their prognostic value was further validated in the two nomograms.

The comparisons of the predictive power between our nomograms and three conventional staging systems showed that our models are infinitely superior to the others. The reasons might be that these stages mainly focus on the clinical characteristics of tumors like morphological traits [39]. For example, TNM stage is especially useful for tumor extension evaluation but inherently lack of predictive ability [40]. With respect to BCLC stage, some researchers raised that it was more of a clinical path for therapeutic choices rather than a tool for prognostic assessment [41]. In addition, BCLC staging system involves subjective component like performance status, which might lead to the varying tumor staging results from different doctors. Although CLIP score improves in predictive efficiency, it does not include evaluating indicator of the overall physical condition of patients and is incapable of assessing early-stage HCC [39,42]. Anyway, the constructed nomograms in this present study shows a remarkable prognostic prediction ability, our results needed further validation though.

Our study has several limitations. First, the retrospective study has an inherent selection bias. Second, although this is a multi-center study, all patients were Asian. And the rate of HBV infection in the overall group is 66.7% while the rate of HCV infection is only 7.9%. Therefore, validation of our nomograms in non-Asian populations with low HBV-infection rate are warranted. Last but not least, to ensure the feature of being simple-to-use, all the continuous variables were transformed into dichotomous variables for the nomogram construction using the median as the cut-off value. This modality of data processing may decrease robustness of the nomogram models and the cut-off value may also need further consideration. Despite all the limitations, our nomograms for survival prediction of HCC patients after surgery showed great discrimination and calibration ability even when compared with conventional models.

In conclusion, we here developed and validated two robust PLT-based nomograms for predicting the OS and RFS of the Asian patients who received curative resection for HCC. The combined application of the two simple-to-use nomograms can provide an accurate individualized estimation of recurrence and postoperative survival and

efficiently assist oncologists and surgeons in improving the surveillance of each HCC patient. Furthermore, our findings highlighted the prognostic value of PLT and provide extra evidence for the treatment of HCC and understanding of the possible mechanism of PLT in the development and progression of HCC.

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## Declaration of conflict of interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.07.008.

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