The Prognostic Value of Platelet Count in Patients With Hepatocellular Carcinoma

Qing Pang, MD, PhD, Kai Qu, MD, Jing-Yao Zhang, MD, Si-Dong Song, PhD, Su-Shun Liu, MD, Ming-Hui Tai, PhD, Hao-Chen Liu, MD, and Chang Liu, MD, PhD

Abstract: Thrombocytopenia has been acknowledged to be a crucial risk factor for cirrhosis formation and hepatocarcinogenesis in chronic liver diseases. However, to date, the association between platelet count (PLT) and the prognosis of hepatocellular carcinoma (HCC) remains inconsistent and controversial. The aim of the present study was to determine whether PLT could be used as a useful predictor of survival in patients with HCC.

We performed systematic review in online databases, including PubMed, EmBase, and Web of Science, from inception until 2014. Studies were included if a statistical relationship was investigated between PLT and survival for HCC, and hazard ratio (HR) and 95% confidence intervals (CIs) for overall survival (OS) or recurrence-free survival (RFS) were provided. The quality of each included study was assessed by Newcastle–Ottawa scale score. To synthesize these studies, a random-effects model or a fixed-effects model was applied as appropriate. Then, we calculated heterogeneity, performed sensitivity analysis, tested publication bias, and did subgrouped and meta-regression analysis.

Finally, we identified 33 eligible articles (published from 1998 to 2014) involved 5545 patients by retrieval. A low level of preoperative PLT was found to be significantly associated with a poor survival of HCC. Irrespective of the therapy used, the pooled HRs for OS and RFS were 1.41 (95% CI, 1.14–1.75) and 1.44 (95% CI, 1.13–1.83), respectively. Specifically, in patients who underwent liver resection, the pooled HRs for OS and RFS were 1.67 (95% CI, 1.22–2.27) and 1.44 (95% CI, 1.04–1.99), respectively. Furthermore, patients with preoperative thrombocytopenia (PLT < 100 × 10^9/L) had a worse OS (HR: 1.73, 95% CI, 1.29–2.32) and RFS (HR: 1.57, 95% CI, 1.31–1.87) in comparison with patients without thrombocytopenia. All our findings showed no significant changes due to the removal of any study or the use of an opposite-effects model, and there was no significant publication bias. The limitations of this meta-analysis were nonuniform cut-off values of PLT, high between-study heterogeneities, potential confounders, and a bias of publication year.

A low preoperative PLT level results in an unfavorable outcome in HCC: PLT is a simple, inexpensive, and useful predictor of survival in patients with HCC.

Abbreviations: HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, MPV = mean platelet volume, OS = overall survival, PLT = platelet count, RFA = radiofrequency ablation, RFS = recurrence-free survival, TACE = transcatheter arterial chemoembolization.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer deaths worldwide. HCC is frequently secondary to infections with hepatitis viruses, such as hepatitis B virus (HBV) or hepatitis C virus (HCV). Because HBV infection is considered a primary risk factor for cirrhosis and HCC, 80% of HCC cases occur in areas with a high prevalence of HBV, especially in Asia-Pacific and sub-Saharan Africa regions. Alcohol use and obesity are also risk factors for HCC.

Despite dramatic improvements in diagnosis and treatment with improved surgical techniques and perioperative care over the past few decades, the prognosis of HCC is still poor, with an overall 5-year survival rate of approximately 5% to 6%. It is necessary for hepatologists to explore the factors affecting the outcomes of patients with HCC. Previous studies have shown that age, the presence of liver cirrhosis, a later stage, a high Child-Pugh grade, a tumor of ≥5 cm, tumor multiplicity, the presence of satellites, a high AFP level, noncurative therapy, etc., result in a significant decrease in the survival of HCC patients.

Platelets, the levels of which normally range from 100 to 300 × 10^9/L in adults, are involved in the inflammatory response by releasing several cytokines, such as platelet-derived growth factors and transforming growth factor-β. Moreover, platelets are able to transport these substances to specific sites and play roles in angiogenesis, wound healing, liver regeneration, etc. Numerical and functional abnormalities of platelets result in a series of physiological/pathological changes, serious complications, and even several disorders. Most cases of HCC are accompanied by liver cirrhosis, which is primarily caused by chronic liver inflammation. Liver cirrhosis could ultimately lead to portal hypertension and hypersplenism and cause a subsequent decrease in platelet count (PLT). Furthermore, PLT, and many noninvasive indices that regard PLT as a critical component, have been proven to be significant diagnostic indicators for predicting liver fibrosis and cirrhosis. Studies have demonstrated that the PLT level is an independent...
predictor of liver-related death\textsuperscript{15} and HCC occurrence,\textsuperscript{15–17} and it plays a decisive role in the choice of therapy in HCC.\textsuperscript{18}

However, whether the PLT level before treatment affects the long-term survival of HCC patients is controversial. We ever considered that a low PLT level results in a worse prognosis in HCC patients who received liver resection.\textsuperscript{19} However, several studies demonstrated that a high PLT level was associated with shorter survival or found no statistically significant association between them. Herein, we summed all relevant meta-analyses and investigated the prognostic role of PLTs in the outcome of HCC patients.

METHODS

Search Strategy and Selection Criteria
Two independent investigators (PQ and ZJY) performed a systematic search using the PubMed, EmBase, and ISI Web of Science databases (from inception to July 31, 2014) with no language restrictions. Our core search consisted of the terms (PLT OR platelet OR thrombocythemia OR thrombopenia OR thrombocytopenia OR “blood platelets” OR platelets) AND (prognosis OR prognostic OR survival OR mortality OR death) combined with the terms (“hepatocellular carcinoma” OR HCC OR “liver cancer” OR “hepatic carcinoma” OR “hepatic cancer” OR hepatoma). In addition, we contacted authors if full text or crucial data were not available. We retrieved the reference lists from relevant literature reviews and included the articles manually. We used EndNote X7 software to search and manage citations.

We included studies that met the following criteria: published as an original article; HCC was confirmed by pathology and (or) imaging; studied the relationship between PLTs and the survival of HCC patients, reporting hazard ratios (HRs) and 95\% confidence intervals (CIs) for overall survival (OS) or recurrence-free survival (RFS) or providing sufficient data to calculate these values or the possibility of contacting authors to obtain these data; expressed the PLT level as a binary (with the lower or higher category as a reference) or continuous variable; and included a total of \( \geq 20 \) patients. We excluded the following studies: studied benign liver disease or secondary liver cancer; diagnosed HCC by serum markers; had a maximal follow-up time of less than 1 year or only reported survival during hospitalization; only provided \( P \) values, or other conditions were present that did not permit the calculations of the effect size or 95\% CI; and conference abstracts or unpublished studies. For 2 or more articles involving overlapping populations, we included the one that recruited the largest number of cases or calculated the most adjusted HR values.

Data Abstraction
According to the selection criteria, 2 investigators (PQ and SSS) independently evaluated the retrieved studies for inclusion. Differences between the 2 investigators were estimated by a consistency check, and discrepancies between them were solved by discussion. For each included study, we abstracted the following information with a standardized data-collection protocol: the last name of the first author, publication year, region where the population resided, method of treatment, demographic data (gender and age), duration of follow-up, Child-Pugh grade, PLT cut-off value, HR value and 95\% CI and confounders that had been adjusted. Meanwhile, the qualities of the studies were assessed by modified NOS (Newcastle–Ottawa scale) scores\textsuperscript{20} with a maximum score of 9. We defined curative therapy as liver resection, transplantation, and RFA. Other therapies, such as TACE, were classified as palliative treatments. We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines\textsuperscript{21} for the present meta-analysis. All data were double-checked by 1 investigator (PQ).

Statistical Methods of Meta-Analysis
The data from the studies considering patients with lower PLT levels as a reference group were converted to HR estimations that reflected the impact of lower PLT levels (with the higher category as a reference) on HCC. HR values for OS and RFS in all included studies, in studies involving patients who underwent partial hepatectomy, and in studies that recruited individuals who underwent RFA were merged separately. We assessed heterogeneity between studies with the Q value and I\(^2\) statistic value (25\%, 50\%, and 75\% corresponded to the cut-off points for low, moderate, and high degrees of heterogeneity). A fixed-effect model was used for data showing statistically significant heterogeneity if \( P < 0.1 \) as determined by the Q statistic or I\(^2\) > 50\%; otherwise, we considered that there was no obvious heterogeneity and used a random-effects model. We performed subgroup analysis and meta-regression analysis to explore the potential sources of heterogeneity. We analyzed

FIGURE 1. Flow diagram of search strategy and study selection.
those covariates that may have contributed to the potential heterogeneity, and at least 3 studies were included in each subgroup, for which the PLT cut-off level, treatment method, follow-up time, number of recruited patients, survival analysis (adjusted or unadjusted HR), area, and Child-Pugh grade were assessed. In addition, we performed influence analyses to evaluate whether the results could be markedly affected by a single study. We compared the calculated summary effect sizes using fixed-effects and random-effects models. Finally, publication bias was examined using funnel plots with Begg and Egger test.

We used STATA 12.0 software to analyze the data. A bilateral $P$-value of less than 0.05 was considered indicative of a statistically significant difference.

### RESULTS

The flow diagram of our literature search and selection process is shown in Figure 1. Of the 920 total citations, we identified 33 publications which were published from 1998 to 2014. Agreement between observers with regard to which studies to include was good (kappa $= 0.937$). No additional articles were included from the reference review. All studies used in our meta-analysis were published in English except for one that was published in Korean.$^{22}$

Characteristics of Included Studies that Expressed PLT as Binary Variable

| Refs. | Area | Therapy | Gender (M/W) | Age (Year) | Follow-Up (Month) | Child-Pugh Grade | Cut-Off (10$^9$/L) | Survival Analysis NOS |
|-------|------|---------|--------------|------------|-------------------|------------------|-------------------|----------------------|
| Chung et al$^{32}$ | Korea | RFA | 80/27 | 58 | 19.5 | A76/B31 | – | AOS/ARFS 7 |
| Guo et al$^{36}$ | China | NR | 172/56 | 55.41 | NR | NR | NR | AOS 6 |
| Ishizuka et al$^{37}$ | Japan | Resection | 285/72 | NR | 27.5 | NR | NR | – | AOS 7 |
| Kometchou et al$^{38}$ | France | RFA | 175/60 | 65 | 27 | A200/B35 | – | UOS/URFS 5 |
| Li et al$^{39}$ | China | Sorafenib | 179/26 | 58 | 3.3 | A64/B99/C42 | – | AOS 8 |
| See et al$^{40}$ | Korea | RFA | 168/78 | 57 | 19.7 | A221/B25 | – | UOS 5 |
| Tatische et al$^{41}$ | Japan | RFA | 191/112 | 67.5 | 2.3 | A213/B75/C6 | – | UOS 6 |
| Tsuchiya et al$^{52}$ | Korea | Resection | 38/10 | 66.7 | 25.8 | NR | NR | – | UFS 5 |

AOS = adjusted HR for OS, ARFS = adjusted HR for RFS, NR = not reported, and NOS = Newcastle–Ottawa scale, PLT = platelet count, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, UOS = unadjusted HR for OS, URFS = unadjusted HR for RFS.

### Table 1. Baseline Characteristics for Studies Included in Meta-Analysis

| Refs. | Area | Therapy | Gender (M/W) | Age (Year) | Follow-Up (Month) | Child-Pugh Grade | Cut-Off (10$^9$/L) | Survival Analysis NOS |
|-------|------|---------|--------------|------------|-------------------|------------------|-------------------|----------------------|
| Chung et al$^{23}$ | Japan | Resection | 127/24 | N/A | 49.2 | A129/B22 | 100 | AOS/ARFS 6 |
| Arimura et al$^{24}$ | Japan | TACE | 95/45 | 63.3 | NR | A77/B48/C15 | 80 | UOS 4 |
| Brau et al$^{25}$ | America | Resection, RFA | 287/2 | 61.3 | NR | A113/B134/C42 | 100 | UOS 6 |
| Camma et al$^{26}$ | Italy | RFA | 131/71 | 66.8–67.4 | 19.2 | A165/B37 | 100 | AOS 8 |
| Hashimoto et al$^{27}$ | Japan | Resection | 120/29 | 61.7 | 42 | A/B/C | 120 | AOS/ARFS 9 |
| Hiroishi et al$^{28}$ | Japan | RFA, TACE | 11/9 | 68.8 | 3-29 | A12/B8 | 100 | ARFS 6 |
| Ikeda et al$^{29}$ | Japan | TACE | 122/46 | 63-64 | 30-34 | A86/B82 | 75 | UOS 5 |
| Kang et al$^{30}$ | Korea | Resection | 125/42 | 51.2–52.3 | 38 | A | 100 | ARFS 9 |
| Kao et al$^{31}$ | Taiwan | RFA | 162/96 | 67.8 | 28.5 | A226/B32 | 100 | UOS 6 |
| Kim et al$^{32}$ | Korea | TACE | 39/13 | 57 | 5 | A16/B23/C13 | 150 | AOS 6 |
| Kobayashi et al$^{33}$ | Japan | Resection | 146/53 | 62 | 39.6 | A | 100 | ARFS 7 |
| Kobayashi et al$^{34}$ | Japan | Resection | 186/80 | 65.3 | 45.2 | A236/B30 | 100 | ARFS 7 |
| Miyatake et al$^{35}$ | Japan | Resection | 260/135 | 58 | 42-46 | A317/B74/C4 | 100 | UOS/AOS 7 |
| Nishizaki et al$^{36}$ | Japan | TACE | 56/15 | 65 | NR | A43/B28 | 120 | UOS 5 |
| Nishikawa et al$^{37}$ | Japan | RFA | 217/151 | 69.9 | 36 | A70/B162/C100/D36 | 100 | AOS/ARFS 8 |
| Nouso et al$^{38}$ | Japan | RFA, TACE | 116/41 | 59-66 | NR | C157 | 80 | UOS/AOS 7 |
| Ochiai et al$^{39}$ | Japan | Resection | 208/76 | 64.6 | 36 | A273/B11 | 110 | UOS/URFS 6 |
| Roayaie et al$^{40}$ | America/Italy | Resection | 95/37 | 63.1 | 37.5 | A | 150 | AOS 7 |
| Santi et al$^{41}$ | Italy | Resection, RFA, TACE | 457/192 | 67-68 | 38.6 | A477/B172 | 100 | AOS 9 |
| Taketomi et al$^{42}$ | Taiwan | Resection, RFA, TACE | 167/43 | 60.66 | 26.6 | A158/B+C52 | 150 | AOS 7 |
| Tseng et al$^{43}$ | Taiwan | Resection, RFA, TACE | 49/39 | 65.8 | NR | NR | NR | 100 | AOS 6 |
| Tong et al$^{44}$ | Taiwan | Resection, RFA | 48/34 | 55.1–63.5 | NR | A | 100 | UFS 4 |
| Wu et al$^{45}$ | Taiwan | RFA | 104/57 | 67.5 | 38.1 | A/B | 100 | UOS 5 |
| Wu et al$^{46}$ | China | Resection | 79/7 | NR | NR | A/B | 100 | AOS 8 |
| Xie et al$^{47}$ | China | RFA, TACE | 408/79 | 53.5 | NR | NR | 97 | UOS 5 |

PLT as continuous variable (per 1 × 10$^9$/L increase)

| Refs. | Area | Therapy | Gender (M/W) | Age (Year) | Follow-Up (Month) | Child-Pugh Grade | Cut-Off (10$^9$/L) | Survival Analysis NOS |
|-------|------|---------|--------------|------------|-------------------|------------------|-------------------|----------------------|
| Chung et al$^{22}$ | Korea | RFA | 80/27 | 58 | 19.5 | A76/B31 | – | AOS/ARFS 7 |
| Guo et al$^{36}$ | China | NR | 172/56 | 55.41 | NR | NR | NR | AOS 6 |
| Ishizuka et al$^{37}$ | Japan | Resection | 285/72 | NR | 27.5 | NR | NR | – | AOS 7 |
| Kometchou et al$^{38}$ | France | RFA | 175/60 | 65 | 27 | A200/B35 | – | UOS/URFS 5 |
| Li et al$^{39}$ | China | Sorafenib | 179/26 | 58 | 3.3 | A64/B99/C42 | – | AOS 8 |
| See et al$^{40}$ | Korea | RFA | 168/78 | 57 | 19.7 | A221/B25 | – | UOS 5 |
| Tatische et al$^{41}$ | Japan | RFA | 191/112 | 67.5 | 2.3 | A213/B75/C6 | – | UOS 6 |
| Tsuchiya et al$^{52}$ | Korea | Resection | 38/10 | 66.7 | 25.8 | NR | NR | – | UFS 5 |

AOS = adjusted HR for OS, ARFS = adjusted HR for RFS, NR = not reported, and NOS = Newcastle–Ottawa scale, PLT = platelet count, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, UOS = unadjusted HR for OS, URFS = unadjusted HR for RFS.
(4250 men and 1295 women) with a mean or median follow-up of 5 to 46 months. The PLT cut-off values ranged from 75 to 150 \times 10^9/L, which were near the cut-off point for thrombopenia (100 \times 10^9/L). The qualities of the studies were moderate to high (the range of NOS scores was 4–9, with a mean of 6.52). Four studies were performed in western regions, and the others were conducted in eastern countries. Twenty-one and 9 studies reported HR values for OS and RFS, respectively. Ten studies estimated the influence of PLTs on the prognosis of patients who underwent liver resection, and 5 studies involved patients with RFA.

### Pooled HR Value for All Studies

After calculating the total effect size using a random-effects model, we found that a low PLT level before treatment indicated a poor prognosis. The forest plot is shown in Figure 2, and the pooled estimator was stratified by survival (OS and RFS). The 21 studies that analyzed OS had a pooled HR value of 1.41 (95% CI, 1.14–1.75), with a moderate degree of between-study heterogeneity ($I^2 = 74.9\%, P = 0.000$). The pooled HR value for RFS was 1.44 (95% CI, 1.04–1.99, $n = 9$ studies), and this value also showed a moderate degree of heterogeneity ($I^2 = 60.6\%, P = 0.009$).

### Pooled HR Values for Patients Who Underwent Liver Resection or RFA

Next, we explored the impact of PLTs in patients who received partial hepatectomy. The forest plot is presented in Figure 3A, and the results were also stratified by survival. We demonstrated that the merged HR value for OS was 1.67 (95% CI, 1.22–2.27, $I^2 = 58.8\%, P = 0.024, n = 7$ studies). For RFS, the HR value was 1.44 (95% CI, 1.04–1.99, $I^2 = 72.1\%, P = 0.003, n = 6$ studies). Both values showed significant heterogeneity between studies; thus, a random-effects model was used. For patients who underwent RFA, 1 study provided a risk estimate for RFS, and 5 studies estimated OS rates. As shown in Figure 3B, the influence of low PLT on the OS of these patients was great, with a pooled HR value of 1.96 (95% CI, 1.51–2.53, $I^2 = 0\%, P = 0.533$).

### Independent Significance of PLTs in HCC

To explore the independent role of PLTs in the prognosis of patients with HCC, we further analyzed the studies that provided an adjusted (entered into Cox multivariate analysis) HR value for survival. By summarizing the 13 relevant studies, we found that a low preoperative PLT was an independent indicator of a poor OS (HR: 1.63, 95% CI, 1.41–1.94, $I^2 = 0\%, P = 0.533$) (Figure 3C).

### Effects of Thrombocytopenia (PLTs < 100 \times 10^9/L) on Survival of HCC Patients

Thrombocytopenia is a crucial predictor of cirrhosis and HCC. For 12 studies that used a PLT cut-off value of 100 \times 10^9/L,
we estimated the significance of thrombocytopenia on the survival of HCC patients. As expected, patients with preoperative thrombocytopenia had a worse OS (HR: 1.73, 95% CI, 1.29–2.32) and RFS (HR: 1.57, 95% CI, 1.31–1.87) in comparison with those without thrombocytopenia (Figure 3D).

Exploration of Risk Estimation for Per-Unit (1 x 10\(^9\)/L) Increase in PLTs

Nine publications presented the HR as a per-unit increase in PLTs, and 1 of them was excluded as duplicated data. In summary, 1288 men and 441 women were recruited for meta-analysis with a median NOS score of 6 (ranging from 5 to 8) (Table 1). The pooled HR values calculated using a random-effects model showed that the PLT level was not statistically associated with OS or RFS when it was expressed as a continuous variable (Figure 4).

Exploration of Heterogeneity

From the above analyses, we found that the pooled HR value for OS (in all studies with the PLT level as a binary variable) produced the highest heterogeneity with the largest number of studies (21 studies). To explore the source of this heterogeneity, we performed subgroup analysis and meta-regression analysis. The covariates analyzed included the PLT cut-off value (100, >100, or <100), treatment method (curative vs. palliative), follow-up time (>3 years vs. <3 years), whether an adjustment for confounders was performed (adjusted vs. unadjusted), the number of included patients (>200 vs. <200), Child-Pugh grade (studies with more patients with grade A than with B + C (A > B + C) vs. A < B + C or more than 80% of patients with A vs. A < 80%), and area (west vs. east). The results of our analysis are shown in Table 2. We suggested that different PLT cut-off values, treatment methods, follow-up times, and Child-Pugh grades might have affected the pooled effect size (all P < 0.05 for the Q statistic of between-group analysis and/or P < 0.05 for univariate meta-regression).

The PLT level significantly influenced the prognosis of the patients treated with curative therapy, with an HR value of 1.78 (95% CI, 1.44–2.19). However, for the patients who received palliative treatment, no statistically significant association was found between the PLT level and survival. For the 3 covariates...
showing a $P < 0.10$ in univariate meta-regression, no significant between-group differences (all $P > 0.05$) were found as shown by multivariate meta-regression.

**Sensitivity Analysis and Test of Publication Bias**

Sensitivity analysis was conducted to assess the consistency of the above results. We compared the use of the random- and fixed-effects models for analysis of the studies and found that there were no obvious differences between them (Table 3). Then, impact analysis was carried out for both the OS and RFS studies, and the results suggested that no single study affected the pooled estimates (Figure 5).

Finally, we constructed a funnel plot to detect the existence of publication bias, and the results indicated basic symmetry.

**TABLE 2.** Subgroup Analysis (by Random-Effects Model) and Meta-Regression Analysis for OS Studies

| Covariates          | Subgroup | No. | HR (95% CI) | P     | I²    | Q value | P     | Crude P | Multiple P |
|---------------------|----------|-----|-------------|-------|-------|---------|-------|---------|------------|
| Cut-off (10^9/L)    | >100     | 6   | 1.21 (0.75–1.96) | 0.001 | 76.7  | 7.04    | 0.030 | 0.828   | 0.398 |
|                     | 100      | 11  | 1.73 (1.29–2.32) | <0.001 | 75.9  | 0.19    | 69.7  |         |            |
|                     | <100     | 4   | 1.04 (0.67–1.60)  | 0.019 | <0.01 | 43.4    | 24.14 | <0.001  | 0.031  | 0.131 |
| Treatment           | Curative | 12  | 1.78 (1.44–2.19)  | 0.054 | 43.4  | 24.14   | <0.001 | 0.031   | 0.131  |
|                     | Palliative | 4   | 0.94 (0.59–1.49)  | 0.027 | 67.3  |         |       |         |            |
|                     | Both     | 5   | 1.10 (0.68–1.79)  | <0.001 | 85.2  |         |       |         |            |
| Follow-up (months)  | ≥36      | 9   | 1.50 (1.23–1.82)  | 0.172 | 30.8  | 16.68   | <0.001 | 0.207   | 0.929  |
|                     | <36      | 5   | 1.61 (1.21–2.15)  | 0.163 | 38.8  |         |       |         |            |
|                     | NA       | 7   | 1.14 (0.67–1.95)  | <0.001 | 86.7  |         |       |         |            |
| Confounders         | Adjusted | 13  | 1.49 (1.13–1.95)  | <0.001 | 75.6  | 0.35    | 0.554 | 0.585   | NA       |
|                     | Unadjusted | 8   | 1.31 (0.89–1.94)  | <0.001 | 76.8  |         |       |         |            |
| Number              | ≥200     | 10  | 1.42 (1.08–1.85)  | <0.001 | 73.0  | 0.12    | 0.729 | 0.955   | NA       |
|                     | <200     | 11  | 1.43 (0.99–2.07)  | <0.001 | 78.4  |         |       |         |            |
| Child-Pugh          | A > 80%  | 9   | 1.62 (1.29–2.03)  | 0.041 | 50.3  | 32.55   | <0.001 | 0.010   | 0.241  |
|                     | A < 80%  | 7   | 0.88 (0.62–1.33)  | 0.001 | 73.1  |         |       |         |            |
| Child-Pugh          | A > B + C| 12  | 1.39 (1.09–1.76)  | <0.001 | 68.9  | 21.72   | <0.001 | 0.160   | NA       |
|                     | A < B + C| 4   | 0.91 (0.53–1.55)  | 0.003 | 78.2  |         |       |         |            |
| Area                | East     | 17  | 1.46 (1.14–1.87)  | <0.001 | 73.0  | 2.15    | 0.143 | 0.661   | NA       |
|                     | West     | 4   | 1.28 (0.77–2.14)  | <0.001 | 83.7  |         |       |         |            |

CI = confidence interval, OS = overall survival, HR = hazard ratio, and NA = not available.
FIGURE 5. Influence analyses of the overall survival (A) and recurrence-free survival (B) studies in meta-analysis.

**TABLE 3.** Effects of Platelet Count in Different Studies Using the 2-Effects Model

| Studies            | Overall Survival (HR, 95% CI)                  | Recurrence-Free Survival (HR, 95% CI) |
|--------------------|------------------------------------------------|---------------------------------------|
|                    | Fixed-Effects Model | Random-Effects Model | Fixed-Effects Model | Random-Effects Model |
| All studies        | 1.28 (1.16–1.42)    | 1.41 (1.14–1.75)    | 1.43 (1.24–1.66)    | 1.44 (1.13–1.83)    |
| Liver resection    | 1.58 (1.31–1.91)    | 1.67 (1.22–2.27)    | 1.38 (1.16–1.63)    | 1.44 (1.04–1.99)    |
| RFA                | 1.96 (1.51–2.53)    | 1.96 (1.51–2.53)    | 1.76 (1.29–2.40)    | 1.76 (1.29–2.40)    |
| Thrombocytopenia   | 1.43 (1.25–1.63)    | 1.73 (1.29–2.32)    | 1.57 (1.31–1.87)    | 1.57 (1.31–1.87)    |
| Adjusted HR        | 1.49 (1.31–1.69)    | 1.63 (1.30–2.04)    | 1.65 (1.41–1.94)    | 1.65 (1.41–1.94)    |

CI = confidence interval, HR = hazard ratio, RFA = radiofrequency ablation, HCV = hepatitis C virus, and HCC = hepatocellular carcinoma.
included studies and populations, various treatment methods, various time of follow-up, as well as various Child-Pugh stages in each subgroup. All of these confounders have been identified as potential sources of heterogeneity and thus could lead to conflicting effect sizes in the 3 subgroups. Finally, although we searched databases from their available dates of inception, the studies we eventually included all published in or after 1998. As a consequence, it was almost inevitable that there would be a bias of publication year in this meta-analysis.

What roles does PLT play in the occurrence, development, and outcome of HCC and HCC-related diseases? It has been suggested that alterations in the PLT level occur throughout the entire process of HCC development, from the original inflammation and subsequent liver cirrhosis to the ultimate formation of cancer. Due to portal hypertension and some other factors, such as a decrease in thrombopoietin production in the liver and the capture of platelets by the liver, the PLT level is generally low during each stage in HCC-related diseases. The assessment of the PLT has profound significance for guiding the early diagnosis, estimating the prognosis, and directing the treatments of patients with various liver diseases. Nozaki and coworkers have performed in vitro and in vivo studies and have proved that thrombopoietin promotes liver regeneration and improves liver cirrhosis by increasing the PLT level, indirectly implying that a decrease in this level would result in the poor prognosis of patients with liver disease.

In addition to its influence on long-term survival, a decrease in the PLT level could increase the hospital mortality as well as short-term mortality of HCC patients. The underlying molecular mechanism is still unknown. Based on some clinical studies, we found that a low PLT level increased the risk of the occurrence of some complications and the risk of HCC recurrence, both in patients who received liver resection and in those who underwent RFA. Kubo et al have recruited 202 patients who received hepatectomy for HCV-related HCC, suggesting that only the PLT level is an independent predictor of mult-centric HCC, and that it is significantly associated with the severities of active hepatitis and hepatic fibrosis (both \( P < 0.05 \)). A previous study has also indicated that the PLT level is a predictor of portal vein invasion. In addition, a decreased PLT level has been significantly associated with an elevated AFP level and abnormal liver function. These findings may aid in the elucidation of the potential mechanism underlying the influence of the PLT level on HCC patient outcome, but more studies are needed to determine the exact mechanism.

In addition to the PLT level, several platelet-based models have been validated as useful predictors of HCC. Shen et al and Hung et al have reported that a higher aspartate aminotransferase/platelet ratio index (APRI) is significantly associated with worse survival in HCC, which is consistent with our findings. Kinoshita et al have found that an elevated platelet-to-lymphocyte ratio (PLR) is related to poor OS in HCC, which seems contradict our results. However, in contrast with the data reported by Kinoshita et al, Pinato et al have noted that patients with a PLR of >300 have a median survival time of...
22 months compared to 8.0 months in patients whose PLR is <300. Thus, to date, the prognostic significance of PLR in HCC remains uncertain and controversial.

The activation of platelets is determined not only by the PLT level but also by mean platelet volume (MPV). Alterations in the MPV may be involved in some pathological processes of liver diseases. Cho et al. have found that the mean MPV level is significantly different between patients with HBV/HCC and controls. Subsequently, this group has indicated that the MPV/PLT ratio demonstrates a superior diagnostic capability for HCC compared with MPV alone. Previous studies have also found that MPV is an independent predictor of the severities of liver fibrosis and liver inflammation. However, studies reporting the association between MPV and HCC patient outcome are scanty.

In conclusion, there is a close relationship between the PLT level and survival in patients with HCC. However, to determine the influence of platelet activity (including the PLT level and MPV) on HCC and the underlying mechanism, more experimental and clinical studies are needed.

ACKNOWLEDGMENT

The authors gratefully acknowledge Lei Zhou from Harvard University in the United States for polishing the manuscript.

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–2917.
2. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris). 2010;58:273–277.
3. Chong RJ, Abdullah MS, Hossain MM, et al. Rising incidence of primary liver cancer in Brunei Darussalam. Asian Pac J Cancer Prev. 2013;14:3473–3477.
4. Buonaguro L, Petrizio A, Tagliamonte M, et al. Challenges in cancer vaccine development for hepatocellular carcinoma. J Hepatol. 2013;59:907–903.
5. Santi V, Trevisani F, Gramenzi A, et al. Semiannual surveillance is superior to annual surveillance in patients with cirrhosis and hepatocellular carcinoma. Hepatol. 2010;53:291–297.
6. Roayaie S, Obeidat K, Sposito C, et al. Retention of hepatocellular cancer ≤2 cm: results from two Western centers. Hepatology. 2013;57:1426–1435.
7. Mao YM, Luo ZY, Li B, et al. Prospective study on the survival of HCC patients treated with transcatheter arterial lipiodol chemoembolization. Asian Pac J Cancer Prev. 2012;13:1039–1042.
8. Choi HI, Kim DG, Na GH, et al. Clinical outcome in patients with hepatocellular carcinoma after living-donor liver transplantation. World J Gastroenterol. 2013;19:4737–4744.
9. Worms MA, Bossett T, Victor A, et al. Prognostic factors and outcomes of patients with hepatocellular carcinoma in non-cirrhotic liver. Scand J Gastroenterol. 2012;47:718–728.
10. Kondo R, Yano H, Nakashima O, et al. Accumulation of platelets in the liver may be an important contributory factor to thrombocytopenia and liver fibrosis in chronic hepatitis C. J Gastroenterol. 2013;48:526–534.
11. Udell JA, Wang CS, Tinnmouth J, et al. Does this patient with liver disease have cirrhosis? JAMA. 2012;307:832–842.
12. Lannerstedt H, Konopski Z, Sandvik L, et al. Combining transient elastography with FIB-4 enhances sensitivity in detecting advanced fibrosis of the liver. Scand J Gastroenterol. 2013;48:93–100.
31. Kao WY, Chiou YY, Hung HH, et al. Younger hepatocellular carcinoma patients have better prognosis after percutaneous radiofrequency ablation therapy. *J Clin Gastroenterol.* 2012;46:62–70.

32. Kim SJ, Choi IK, Park KH, et al. Serum vascular endothelial growth factor per platelet count in hepatocellular carcinoma: correlations with clinical parameters and survival. *Jpn J Clin Oncol.* 2004;34:184–190.

33. Kobayashi M, Ikeda K, Kawamura Y, et al. High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. *Cancer.* 2009;115:571–580.

34. Kobayashi T, Itamoto T, Tashiro H, et al. Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy. *J Hepatobiliary Pancreat Sci.* 2011;18:689–699.

35. Miyatake H, Kobayashi Y, Iwasaki Y, et al. Effect of previous interferon treatment on outcome after curative treatment for hepatitis C virus-related hepatocellular carcinoma. *Dig Dis Sci.* 2012;57:1092–1101.

36. Nizetki T, Sumie S, Torimura T, et al. Serum vascular endothelial growth factor as a predictor of response and survival in patients with advanced hepatocellular carcinoma undergoing hepatic arterial infusion chemotherapy. *J Gastroenterol.* 2012;47:686–695.

37. Nishikawa H, Osaki Y, Iguchi E, et al. Radiofrequency ablation for hepatocellular carcinoma: the relationship between a new grading system for the ablative margin and clinical outcomes. *J Gastroenterol.* 2013;48:951–965.

38. Nosu K, Ito Y, Kuwaki K, et al. Prognostic factors and treatment effects for hepatocellular carcinoma in Child C cirrhosis. *Br J Cancer.* 2008;99:1116–1115.

39. Ochiai T, Ogino S, Ishimoto T, et al. Prognostic impact of hepatectomy for patients with non-hepatitis B, non-hepatitis C hepatocellular carcinoma. *Anticancer Res.* 2014;34:4399–4410.

40. Taketomi A, Shimada M, Shirabe K, et al. Natural killer cell activity in patients with hepatocellular carcinoma: a new prognostic indicator after hepatectomy. *Cancer.* 1998;83:58–63.

41. Tseng PL, Wang JH, Tung HD, et al. Optimal treatment increased survival of hepatocellular carcinoma patients detected with community-based screening. *J Gastroenterol Hepatol.* 2010;25:1426–1434.

42. Wong KM, Yeh ML, Chuang SC, et al. Survival comparison between surgical resection and percutaneous radiofrequency ablation for patients in Barcelona Clinic Liver Cancer early stage hepatocellular carcinoma. *Indian J Gastroenterol.* 2013;32:253–257.

43. Wu WC, Chiou YY, Hung HH, et al. Prognostic significance of computed tomography scan-derived splenic volume in hepatocellular carcinoma treated with radiofrequency ablation. *J Clin Gastroenterol.* 2012;46:789–795.

44. Wu ZF, Xu Z, Li WS, et al. Impact of occult hepatitis B virus infection on outcome after resection for non-B non-C hepatocellular carcinoma. *J Surg Res.* 2015;193:153–160.

45. Xie H, Wang H, An W, et al. The efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization for primary hepatocellular carcinoma in a cohort of 487 patients. *PLoS One.* 2014;9:e89081.

46. Guo X, Chen M, Ding L, et al. Application of Cox model in coagulation function in patients with primary liver cancer. *Hepato-gastroenterology.* 2011;58:326–330.

47. Ishizuka M, Kubota K, Kita J, et al. Duration of hepatic vascular inflow clamping and survival after liver resection for hepatocellular carcinoma. *Br J Surg.* 2011;98:1284–1290.

48. N’Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology.* 2009;50:1475–1483.

49. Li X, Chen ZH, Ma XK, et al. Neutrophil-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. *Tumour Biol.* 2014;35:11057–11063.

50. Lee JY, Kim W, Kwon JH, et al. Noninvasive fibrosis indices predict intrahepatic distant recurrence of hepatocellular carcinoma following radiofrequency ablation. *Liver Int.* 2013;33:884–893.

51. Tateishi R, Shinya S, Akahane M, et al. Frequency, risk factors and survival associated with an intrahepatebral recurrence after radiofrequency ablation for hepatocellular carcinoma. *PLoS One.* 2013;8:e59040.

52. Tsuchiya M, Kono H, Matsuda M, et al. Protective effect of Juzen-taiho-to on hepatocarcinogenesis is mediated through the inhibition of Kupffer cell-induced oxidative stress. *Int J Cancer.* 2008;123:2503–2511.

53. Buergy D, Wenz F, Groden C, et al. Tumor-platelet interaction in solid tumors. *Int J Cancer.* 2012;130:2747–2760.

54. Akuta N, Suzuki F, Kobayashi M, et al. Correlation between hepatitis B virus surface antigen level and alpha-fetoprotein in patients free of hepatocellular carcinoma or severe hepatitis. *J Med Virol.* 2014;86:131–138.

55. Nozaki R, Murata S, Nowatari T, et al. Effects of thrombopoietin on growth of hepatocellular carcinoma: is thrombopoietin therapy for liver disease safe or not? *Hepatol Res.* 2013;43:610–620.

56. Yang T, Zhang J, Lu JH, et al. Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. *World J Surg.* 2011;35:2073–2082.

57. Zhao WC, Zhang HB, Yang N, et al. Preoperative predictors of short-term survival after hepatectomy for multinodular hepatocellular carcinoma. *World J Gastroenterol.* 2012;18:3272–3281.

58. Shinya S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol.* 2012;107:569–577quiz 578.

59. Minata M, Kudo M, Harada KH, et al. Expression of E-cadherin and vascular endothelial growth factor in noncancerous liver is associated with recurrence of hepatocellular carcinoma after curative resection. *Oncology.* 2013;84(Suppl. 1):88–92.

60. Taketomi A, Kitagawa D, Itoh S, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute’s experience with 625 patients. *J Am Coll Surg.* 2007;204:580–587.

61. Kaibori M, Kubo S, Nagano H, et al. Clinicopathological features of recurrence in patients after 10-year disease-free survival following curative hepatic resection of hepatocellular carcinoma. *World J Surg.* 2013;37:820–828.

62. Kao WY, Chiou YY, Hung HH, et al. Serum alpha-fetoprotein response can predict prognosis in hepatocellular carcinoma patients undergoing radiofrequency ablation therapy. *Clin Radiol.* 2012;67:429–436.

63. Kubo S, Tanaka H, Shuto T, et al. Correlation between low platelet count and multicentricity of hepatocellular carcinoma in patients with chronic hepatitis C. *Hepatol Res.* 2004;30:221–225.

64. Hagiwara S, Kudo M, Kawasaki T, et al. Prognostic factors for portal venous invasion in patients with hepatocellular carcinoma. *J Gastroenterol.* 2006;41:1214–1219.

65. Chen TM, Huang PT, Tsai MH, et al. Predictors of alpha-fetoprotein elevation in patients with chronic hepatitis C, but not hepatocellular carcinoma, and its normalization after pegylated interferon alfa 2a-rivavirin combination therapy. *J Gastroenterol Hepatol.* 2007;22:669–675.
66. Kobeisy MA, Morsy KH, Galal M, et al. Clinical significance of elevated alpha-foetoprotein (AFP) in patients with chronic hepatitis C without hepatocellular carcinoma in upper EGYPT. *Arab J Gastroenterol.* 2012;13:49–53.

67. Shen SL, Fu SJ, Chen B, et al. Preoperative aspartate amino transferase to platelet ratio is an independent prognostic factor for hepatitis B-induced hepatocellular carcinoma after hepatic resection. *Ann Surg Oncol.* 2014;21:3802–3809.

68. Hung HH, Su CW, Lai CR, et al. Fibrosis and AST to platelet ratio index predict post-operative prognosis for solitary small hepatitis B-related hepatocellular carcinoma. *Hepatol Int.* 2010;4:691–699.

69. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. *Br J Cancer.* 2012;107:988–993.

70. Pinato DJ, Stebbing J, Ishizuka M, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). *J Hepatol.* 2012;57:1013–1020.

71. Cho SY, Lee A, Lee HJ, et al. Mean platelet volume in Korean patients with hepatic diseases. *Platelets.* 2012;23:648–649.

72. Cho SY, Yang JJ, You E, et al. Mean platelet volume/platelet count ratio in hepatocellular carcinoma. *Platelets.* 2013;24:375–377.

73. Ceylan B, Mete B, Fincanci M, et al. A new model using platelet indices to predict liver fibrosis in patients with chronic hepatitis B infection. *Wien Klin Wochenschr.* 2013;125:453–460.

74. Ceylan B, Fincanci M, Yardimci C, et al. Can mean platelet volume determine the severity of liver fibrosis or inflammation in patients with chronic hepatitis B? *Eur J Gastroenterol Hepatol.* 2013;25:606–612.