



## Thrombocytopenia for prediction of hepatocellular carcinoma recurrence: Systematic review and meta-analysis

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**Author contributions:** Pang Q and Qu K contributed equally to this work; Pang Q, Dong YF and Liu C designed the study; Pang Q and Zhang JY performed the literature search; Pang Q, Qu K, Song SD extracted the data; Lin T, Xu XS and Tai MH contributed to quality evaluation for each study and drew the forest plots; Pang Q, Qu K and Zhang JY wrote the paper; and Bi JB, Liu SS, Lin T, Xu XS, Wan Y and Liu HC revised the paper.

Supported by National Natural Science Foundation of China, No. 81272644 and No. 81072051.

**Conflict-of-interest statement:** No potential conflicts of interest relevant to this article were reported.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at email: [liuchangdoctor@163.com](mailto:liuchangdoctor@163.com). Participants gave informed consent for data sharing. No additional data are available.

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Received: January 5, 2015  
Peer-review started: January 6, 2015  
First decision: February 13, 2015  
Revised: March 1, 2015  
Accepted: April 3, 2015  
Article in press: April 3, 2015  
Published online: July 7, 2015

### Abstract

**AIM:** To investigate the association between thrombocytopenia and relapse after treatment for hepatocellular carcinoma (HCC).

**METHODS:** We searched the PubMed, EMBASE, and Web of Science databases to obtain eligible studies. The hazard ratios (HRs) values and 95% confidence intervals (CIs) were pooled by random effects model. Subsequently, we estimated the heterogeneity, performed a sensitivity analysis, determined the publication bias, and performed subgroup and meta-regression analyses. Study quality was assessed by using the Oxford Center for Evidence Based Medicine tool.

**RESULTS:** We identified 18 eligible studies by retrieval (published during 2000-2014). Out of the 4163 patients with HCC who were recruited, 2746 (66.0%) experienced recurrence. In general, our meta-analysis suggested that low platelet count (PLT) before therapy significantly increased the probability of postoperative recurrence (HR = 1.53, 95%CI: 1.29-1.81). PLT was also valuable in the prediction of intrahepatic distant recurrence (HR = 1.49, 95%CI: 1.25-1.77). Subgroup

and meta-regression analyses identified various therapeutic modalities as the source of a high degree of heterogeneity. The pooled HR values showed no obvious change when a single study was removed, but otherwise, an opposite-effects model was used. In addition, no significant publication bias was detected.

**CONCLUSION:** Thrombocytopenia before treatment might be an inexpensive and useful predictor of postoperative recurrence in patients with HCC.

**Key words:** Hepatocellular carcinoma; Blood platelets; Thrombocytopenia; Recurrence; Prognosis

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**Core tip:** The probability of high postoperative recurrence is the greatest problem that affects the potential curative treatment of patients with hepatocellular carcinoma (HCC). No factors have been widely considered as useful predictors for postoperative recurrence in HCC. We analyzed 18 relevant studies to determine the significance of platelet count. We included 4163 patients with HCC and found that thrombocytopenia before therapy significantly increased the probability of postoperative recurrence as well as intrahepatic distant recurrence. We emphasize that thrombocytopenia is an inexpensive, helpful predictor of postoperative recurrence in patients with HCC.

Pang Q, Qu K, Bi JB, Liu SS, Zhang JY, Song SD, Lin T, Xu XS, Wan Y, Tai MH, Liu HC, Dong YF, Liu C. Thrombocytopenia for prediction of hepatocellular carcinoma recurrence: Systematic review and meta-analysis. *World J Gastroenterol* 2015; 21(25): 7895-7906 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i25/7895.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i25.7895>

## INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignancy with an increasing incidence worldwide. Chronic infections with several types of hepatitis viruses, especially hepatitis B virus (HBV) and hepatitis C virus (HCV), are well-recognized risk factors for HCC<sup>[1]</sup>. Between these two, HBV infection is a major etiological factor, and thus, the majority of patients with HCC reside in developing countries where HBV is prevalent<sup>[2]</sup>.

With the advancement in techniques, substantial progress has been made in the diagnosis and treatment of HCC over the past few decades. Current therapies primarily consist of liver resection, transplantation, radiofrequency ablation (RFA), and transcatheter arterial embolization (TACE). However, despite these treatments, the overall 5-year survival rate is 5%-6%, and therefore, the prognosis of HCC

is unsatisfactory<sup>[3]</sup>. Many factors are related to the prognosis of HCC<sup>[4,5]</sup>. Among these factors, high probability of postoperative recurrence is the greatest issue that affects the potential curative treatments for HCC<sup>[5]</sup>.

Platelet function in thrombosis, the inflammatory response, and liver regeneration *via* the release of several inflammatory mediators such as serotonin, platelet derived growth factor (PDGF), and transforming growth factor (TGF)- $\beta$ <sup>[6,7]</sup>. Abnormalities in platelets, either quantitative or functional, would result in a series of pathological changes and would subsequently lead to some disorders. Platelet count (PLT) and/or several platelet-based noninvasive models have been validated as valuable indices for the detection of liver cirrhosis<sup>[8-10]</sup>; a disorder that is strongly associated with the incidence and outcome of HCC. Moreover, thrombocytopenia has been proposed as a useful tool to identify carcinogenesis in basic liver diseases<sup>[11,12]</sup>, as well as to predict postoperative morbidity and mortality of patients with HCC<sup>[13]</sup>. Furthermore, our previous study and other reports have suggested that thrombocytopenia is related to poor survival of patients with liver cancer<sup>[14-16]</sup>.

However, whether or not preoperative thrombocytopenia might increase the risk of relapse in patients with HCC is unclear and controversial. Some studies found that thrombocytopenia was significantly associated with HCC recurrence, whereas others failed to show a significant association between thrombocytopenia and HCC recurrence. However, we previously suggested that a higher preoperative PLT might lead to a higher postoperative recurrence rate<sup>[16]</sup>. Here, we further summarize all of the relative articles in order to clarify this issue.

## MATERIALS AND METHODS

### Search strategy and selection criteria

A systematic search in the PubMed, EMBASE, and ISI Web of Science databases for studies published until 31 August 2014 was performed by two independent investigators (Pang Q and Zhang JY). Our core search consisted of the terms (PLT or platelet or platelets or thrombopenia or thrombocytopenia or thrombocytosis) and (recurrence or relapse) and (hepatocellular carcinoma or HCC or liver cancer or hepatic carcinoma or hepatic cancer). In addition, we manually retrieved the reference lists of relevant reviews and included those studies as well.

We included studies that met the following predetermined criteria: (1) published as an original article; (2) HCC was determined by pathology/imaging; (3) studied the relationship between PLT and HCC recurrence and reported the hazard ratios (HRs) and 95% confidence intervals (CIs), or provided sufficient data to calculate them; (4) PLT was expressed as a binary variable (with a lower or a higher category as a reference); and (5) recruited no fewer than 20 patients.

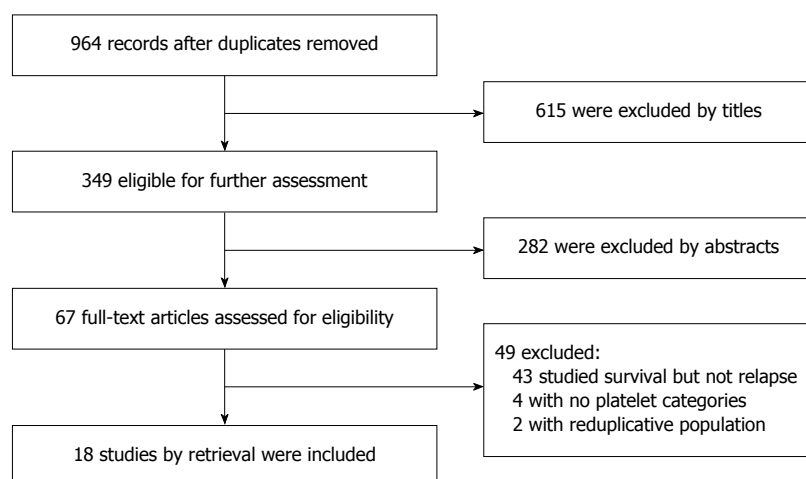


Figure 1 Flow chart of the search strategy and study selection.

The exclusion criteria were: (1) studies of secondary liver cancer or other liver diseases; (2) HCC was assessed by serum markers; (3) studies of the effect of PLT on survival but not on recurrence; (4) studies that only provided the *P* value or other conditions that could not be used to calculate HR and 95%CI values; (5) PLT was expressed as a continuous variable; and (6) conference abstracts or letters. If two or more publications recruited identical populations, we only included the one with the largest number of cases or the one with the most adjusted HR values.

#### Data abstraction

Based on the above selection criteria, two researchers (Pang Q and Qu K) independently evaluated the retrieved studies. The  $\kappa$  statistic was calculated to assess the variability between the observers, and all discrepancies were resolved by discussion. For each included study, we abstracted the following data with a standardized data-collection protocol: first author, publication year, country where the study population lived, gender distribution, method of treatment, total cases, recurrent cases, duration of follow-up, cut-off value of PLT, and adjusted (prior use) or crude HR value and 95%CI. The quality of each study was appraised using the Oxford Center for Evidence-based Medicine appraisal approach<sup>[17]</sup>. We followed the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines<sup>[18]</sup> for the reporting of this meta-analysis. All data were verified by one author (Pang Q).

#### Statistical analysis

If a study considered a lower PLT as a reference, we converted its HR value to an estimated value with a higher category as a reference (which reflected the influence of a low PLT on recurrence). We assessed the heterogeneity among the studies with the *Q* value and the  $I^2$  statistic value (25%, 50%, and 75% correspond to the cut-off points for low, moderate, and high degrees of heterogeneity, respectively). Heterogeneity

was considered to be statistically significant if *P* was < 0.10 for *Q* statistic, or  $I^2$  was > 50%; otherwise, no significant heterogeneity was observed. We calculated the pooled HR value for recurrence (or distant recurrence) by random-effects model. If high heterogeneity was found, we explored the potential source of heterogeneity by performing a subgroup analysis and meta-regression. Subsequently, we performed an influence analysis to evaluate whether any single study could markedly affect the result. Moreover, we compared the HR values that were pooled by a fixed-effect model and that were summed by a random-effects model. Eventually, publication bias was examined by funnel plots with Begg's and Egger's tests. The statistical methods of this study were reviewed by Dr. Kai Qu from the Department of Epidemiology, MD Anderson Cancer Center, University of Texas, and Prof. Ya-Feng Dong from the University of Kansas School of Medicine, United States.

We used STATA 12.0 software to analyze the data. A bilateral *P* value < 0.05 was indicated a significant difference.

## RESULTS

The flow chart that details our literature search and selection process is shown in Figure 1. Of the total 964 citations, we finally included 18 studies. There was good agreement between the two observers on which studies to include ( $\kappa$ : 0.940). No additional studies were found within the references of reviews and included studies. All 18 studies were published in English.

#### Characteristics of the included studies

The baseline values of the included studies in this meta-analysis are summarized in Table 1. Our meta-analysis consisted of 4163 patients, of which 2784 (66.9%) were men. During the mean or median follow-up period, which ranged from 12 to 151.2

**Table 1** Baseline characteristics of the studies included in the meta-analysis

Ref.	Year	Country	Cutoff (10 <sup>9</sup> /L)	Therapy	Adjusted HR	Recurrence type	Men	Women	Recurrence	Follow-up time (mo)	LoE
Saito <i>et al</i> <sup>[32]</sup>	2014	Japan	100	PH + RFA	No	Overall	38	13	39	39.9-46.6	4
Kaibori <i>et al</i> <sup>[19]</sup>	2013	Japan	150	PH	Yes	Overall	60	14	14	151.2	2a
Shiina <i>et al</i> <sup>[24]</sup>	2012	Japan	100	RFA	Yes	Distant	751	419	740	38.2	2b
Nishikawa <i>et al</i> <sup>[25]</sup>	2012	Japan	100	RFA	Yes	Distant	114	68	86	36.4	2b
Kao <i>et al</i> <sup>[26]</sup>	2012	Taiwan	100	RFA	Yes	Overall	162	96	163	28.5	2b
Miyatake <i>et al</i> <sup>[33]</sup>	2012	Japan	100	PH + PTA	Yes	Overall	260	135	277	42-46	2b
Ikeda <i>et al</i> <sup>[20]</sup>	2011	Japan	150	RFA	No	Overall	68	39	55	12	4
Amano <i>et al</i> <sup>[21]</sup>	2011	Japan	100	PH	No	Overall	127	24	107	49.2	4
Ishikawa <i>et al</i> <sup>[31]</sup>	2011	Japan	100	TACE	Yes	Distant	47	31	46	36.6	1b
Hagihara <i>et al</i> <sup>[34]</sup>	2011	Japan	100	PH + PTA	No	Overall	124	58	81	44.4	4
Nonaka <i>et al</i> <sup>[22]</sup>	2010	Japan	100	PH	No	Overall	42	22	32	12	4
Kang <i>et al</i> <sup>[23]</sup>	2009	Korea	100	PH	No	Overall	125	42	78	38	4
Fuke <i>et al</i> <sup>[28]</sup>	2008	Japan	100	RFA	Yes	Distant	80	37	90	29.1	2b
Nouso <i>et al</i> <sup>[27]</sup>	2008	Japan	100	RFA	No	Overall + distant	415	206	589	34.7	4
Jeong <i>et al</i> <sup>[35]</sup>	2007	Japan	100	PH + medical	Yes	Overall	65	19	50	32	2b
Tateishi <i>et al</i> <sup>[29]</sup>	2006	Japan	100	RFA	No	Overall	276	140	277	NR	4
Yamanaka <i>et al</i> <sup>[30]</sup>	2005	Japan	100	RFA	Yes	Distant	17	9	14	18	2b
Ikeda <i>et al</i> <sup>[36]</sup>	2000	Japan	100	PH + RFA	No	Overall	13	7	8	25	4

LoE: Level of evidence; NR: Not reported; PH: Partial hepatectomy.

mo, 2746 (66.0%) patients experienced recurrence. Sixteen studies adopted a cut-off value of  $100 \times 10^9/L$  for PLT while the remaining two<sup>[19,20]</sup> considered  $150 \times 10^9/L$  as the cut-off point. There was one individual inception cohort study with > 80% follow-up and this was assessed as level 1b using the Oxford Center for Evidence-based Medicine tool. Others were retrospective cohort studies and were identified as either level 2a/2b or 4. All studies were performed in Asia, and the effect of PLT on intrahepatic distant recurrence was estimated in six of them.

### Pooled HR values for all of the studies

After calculation of the summed effects, we demonstrated that low PLT before treatment significantly increased the risk of HCC recurrence (HR = 1.53, 95%CI: 1.29-1.81). The forest plot is shown in Figure 2. We observed a moderate degree of heterogeneity between studies ( $I^2 = 50.8\%$ ,  $P = 0.007$ ).

### Impact of thrombocytopenia on recurrence

Subsequently, we summed the 17 studies, which used a cutoff value of  $\times 100 \times 10^9/L$  for PLT and consisted of 4035 patients, in order to investigate the influence of thrombocytopenia on recurrence after treatment. Thrombocytopenia was found to be a useful tool for the prediction of recurrence in HCC (HR = 1.42, 95%CI: 1.27-1.60) (Table 2).

### Pooled HR value for patients who underwent liver resection, RFA

Different treatment modalities, which are given according to the tumor characteristics and stage, may influence the survival and risk of recurrence. Among these therapies, surgical resection is the primary curative treatment modality for HCC. Subsequently, we

explored the impact of PLT on patients who received partial hepatectomy. Overall, 231 of the 470 (49.1%) patients who underwent resection experienced recurrence. By pooling the four eligible studies<sup>[19,21-23]</sup>, we demonstrated a significant association between the preoperative PLT level and postoperative recurrence (HR = 4.46, 95%CI: 1.57-12.65), with a high degree of heterogeneity (Figure 3A).

Eight studies<sup>[20,24-30]</sup> recruited patients with HCC who underwent RFA. Of these included patients, 2014 of the 2897 (69.5%, about 1.42 times the number of patients who underwent resection) experienced recurrence during follow-up. Figure 3B indicates that PLT is still a useful indicator for the prediction of recurrence in patients who received RFA. There was no significant heterogeneity and the pooled HR value was 1.43 (95%CI: 1.24-1.65).

### Effect of PLT on distant recurrence

Recurrence is divided into local and intrahepatic distant recurrence. Only one study<sup>[27]</sup> in our meta-analysis estimated the association between thrombocytopenia and local recurrence. In contrast, six studies<sup>[24,25,27,28,30,31]</sup>, which consisted of 2193 patients (1541 had a relapse), reported the effect of PLT on distant recurrence. A cutoff point of  $100 \times 10^9/L$  for PLT was used in all six studies. This meta-analysis showed that thrombocytopenia was also a significant indicator for the prediction of distant recurrence (HR = 1.49, 95%CI: 1.25-1.77) (Figure 3C). Little heterogeneity ( $I^2 = 15.8\%$ ,  $P = 0.312$ ) was found among these studies.

### Effect of PLT on recurrence of HCV-related HCC

Etiology is another major factor that is associated with the prognosis of HCC. Most of our included studies calculated the HR value without a distinction among

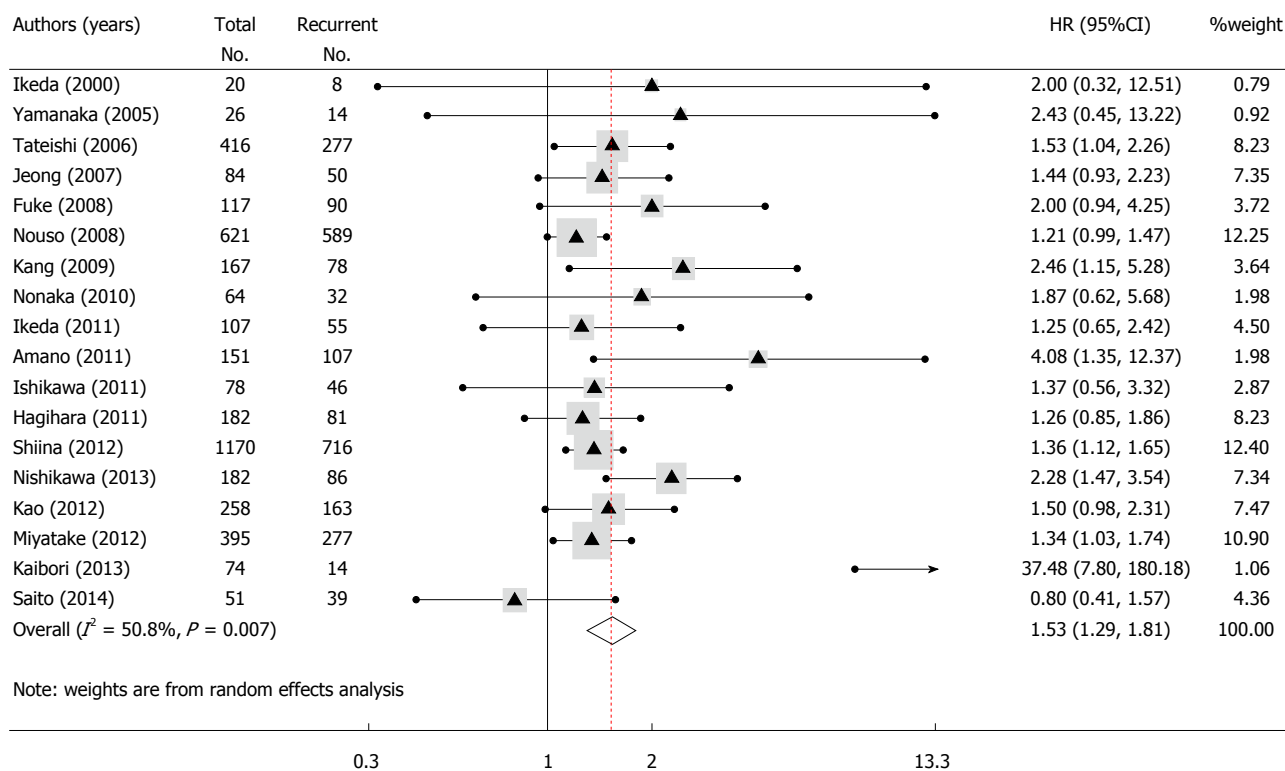


Figure 2 Effect of platelet count on hepatocellular carcinoma recurrence.

**Table 2** Effects of platelet count in different studies using the two effects model

	Random-effects model	Fixed-effect model
	HR (95%CI)	HR (95%CI)
All studies	1.53 (1.29-1.81)	1.41 (1.28-1.55)
Thrombocytopenia	1.42 (1.27-1.60)	1.39 (1.26-1.54)
Liver resection	4.46 (1.57-12.65)	3.48 (2.07-5.83)
RFA	1.43 (1.24-1.65)	1.39 (1.24-1.56)
Distant recurrence	1.49 (1.25-1.77)	1.45 (1.26-1.67)
HCV-HCC	1.33 (1.12-1.60)	1.33 (1.12-1.60)

RFA: Radiofrequency ablation; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

the various etiologies. Seven studies<sup>[28,30,32-36]</sup> only recruited patients with HCV-related HCC. Similarly, thrombocytopenia also had significant potential in the prediction of relapse in these patients (HR = 1.33, 95%CI: 1.12-1.60), and no significant between-study heterogeneity was observed ( $I^2 = 0\%$ ,  $P = 0.651$ ) (Figure 3D).

**Exploration of heterogeneity**

To explore the source of heterogeneity, we performed subgroup and meta-regression analyses. We analyzed the covariates that might be responsible for the potential heterogeneity. We had at least two studies in each subgroup and included treatment method; follow-up time ( $\geq 3$  or  $< 3$  years); whether adjustment for confounding factors was performed; type of recurrence (overall or distant recurrence); and the number of recruited patients. The results of our exploration are

shown in Table 3. We suggested that the treatment method might affect the pooled effect size ( $P < 0.05$  in subgroup and meta-regression analysis). All of the subgroups showed a significant association between PLT and recurrence except the one subgroup whose studies recruited patients who received palliative therapies<sup>[31,35]</sup> (TACE or medical therapy, HR = 1.43, 95%CI: 0.96-2.11). For all five covariates, no significant between-group differences (all  $P > 0.05$ ) were found when a multivariable meta-regression was performed.

**Sensitivity analysis and determination of publication bias**

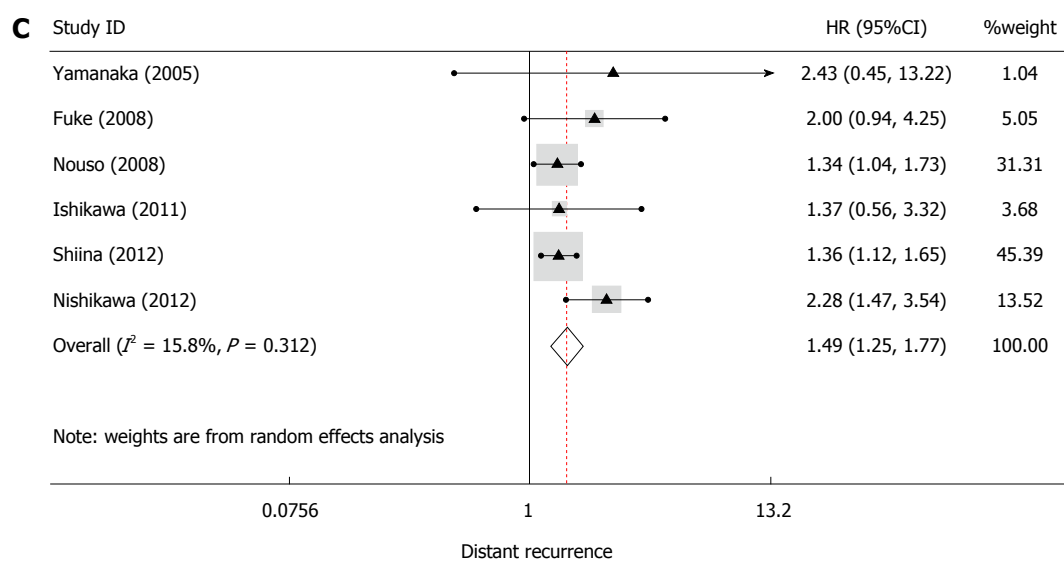
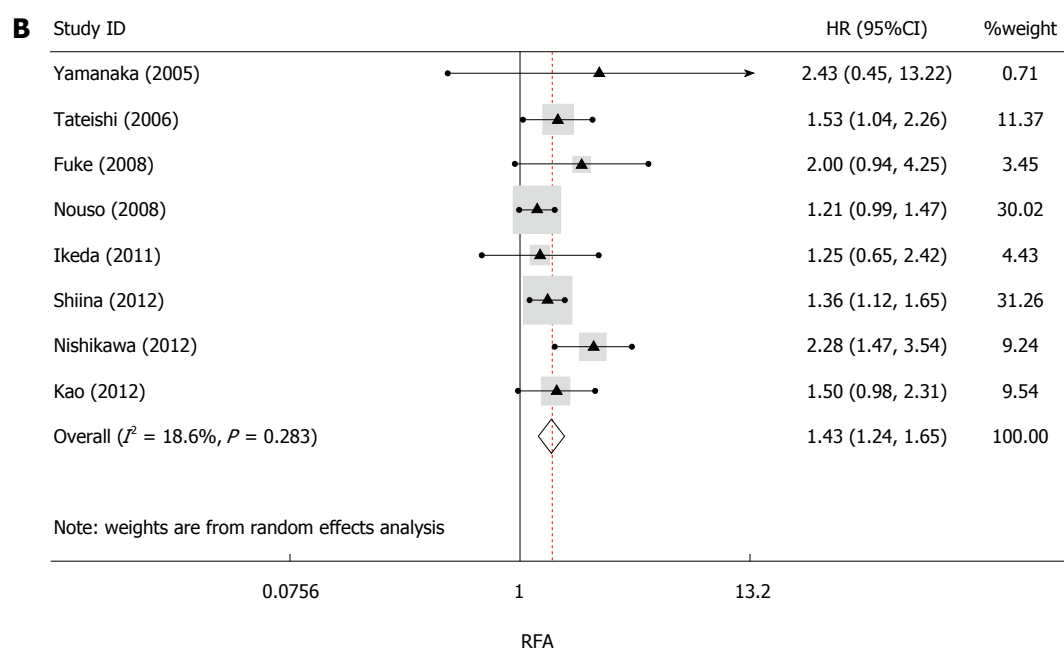
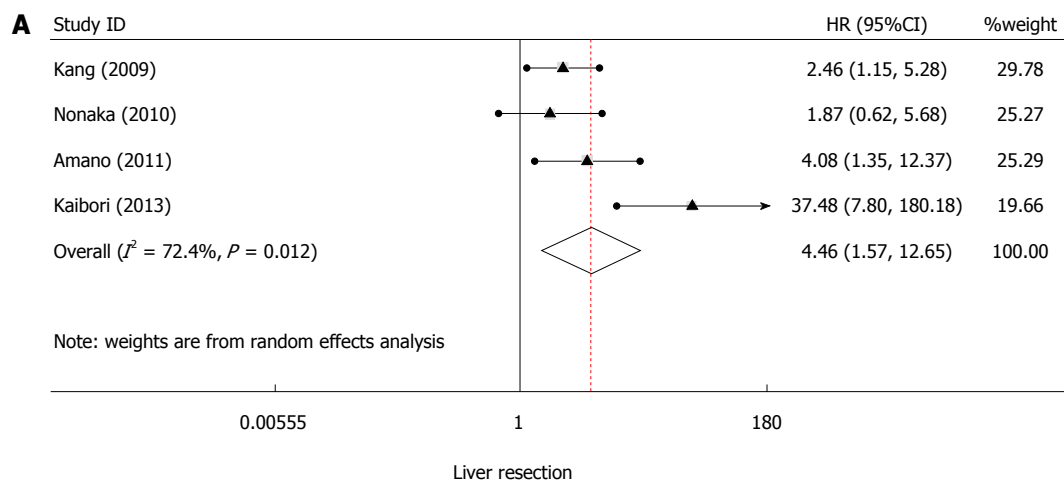
Furthermore, a sensitivity analysis was conducted to validate the certainty of our findings. When the opposite-effects model was used, the results did not significantly change (Table 2). Then, we performed an influence analysis and found that no single study affected the summary estimation (Figure 4).

Eventually, we constructed a funnel plot to detect the existence of publication bias, and the figure reflects the basic symmetry (Figure 5). Indeed, no significant evidence of publication bias was found ( $P$  values were 0.11 and 0.36 in Begg’s test and Egger’s test, respectively).

**DISCUSSION**

A high risk of recurrence is considered one of the greatest concerns with regard to the treatment of patients with HCC<sup>[5]</sup>. The postoperative recurrence rate





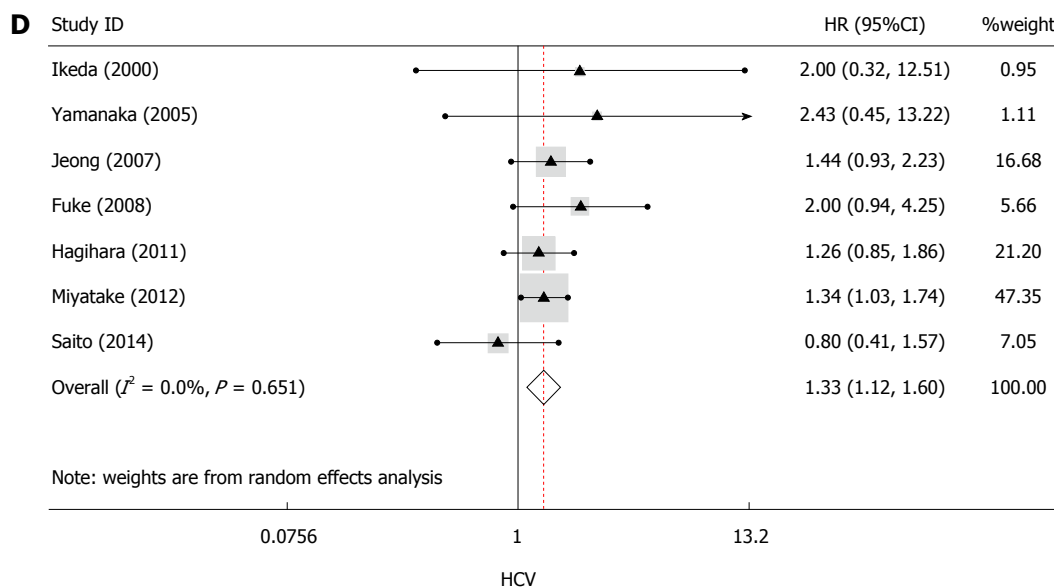


Figure 3 Effect of platelet count on hepatocellular carcinoma recurrence in patients who underwent liver resection (A) and RFA (B), on distant recurrence (C), and on recurrence in patients with hepatitis C virus-related hepatocellular carcinoma (D).

**Table 3 Subgroup and meta-regression analyses**

Covariates	Subgroup	No.	HR (95% CI)	Heterogeneity			Meta-regression	
				$P^a$	$I^2$	$P^b$	Crude $P$	Adjusted $P$
Treatment	Resection	4	4.46 (1.57-12.65)	0.012	72.4	0.005	0.048	0.212
	RFA	8	1.43 (1.24-1.65)	0.283	18.6			
	Resection+RFA	4	1.26 (1.03-1.55)	0.532	0			
	Others	2	1.43 (0.96-2.11)	0.916	0			
Follow-up (mo)	$\geq 36$	9	1.71 (1.25-2.35)	0.000	73.4	0.454	0.596	0.989
	$< 36$	9	1.35 (1.17-2.56)	0.859	0			
Confounder	Adjusted	9	1.70 (1.30-2.22)	0.004	64.1	0.198	0.345	0.863
	Unadjusted	9	1.37 (1.12-1.68)	0.225	24.6			
Recurrence type	Overall	13	1.51 (1.21-1.87)	0.005	57.6	0.351	0.720	0.999
	Distant	5	1.64 (1.25-2.14)	0.247	26.1			
Recruited No.	$\geq 150$	9	1.49 (1.26-1.69)	0.103	39.7	0.600	0.443	0.944
	$< 150$	9	1.78 (1.10-2.88)	0.007	61.8			

<sup>a</sup> $P$  value for  $Q$  statistic of between-study heterogeneity in each subgroup; <sup>b</sup> $P$  value for  $Q$  statistic of heterogeneity between the subgroups.

was reported to range from 50% to 100%<sup>[19]</sup>. To obtain a satisfactory prognosis in cases of HCC, it is crucial to determine the predisposing factors for recurrence and improve these factors before treatment. Platelets are associated with the prognosis of various solid tumors, including HCC<sup>[37]</sup>. However, the significance of platelets in the risk of recurrence of HCC remains unknown. This is the first time that an estimation by a quantitative summary of all relative studies has been performed. Our meta-analysis showed that patients with a low PLT before treatment had a significantly increased risk of postoperative relapse. In general, thrombocytopenia could increase the risk of recurrence by 53%. Specifically, thrombocytopenia was demonstrated to be a useful tool for the prediction of recurrence, no matter whether hepatic resection or RFA was performed for HCC.

Recurrence comprises both local and intrahepatic distant recurrence. The factors that influence the two

types of recurrence are different<sup>[27,28]</sup>. It is essential to identify the risk factors separately for the two types in order to prevent recurrence. However, few studies have differentiated local from intrahepatic distant recurrence. Only one study exclusively reported the local recurrence, and six studies exclusively estimated the distant recurrence in our meta-analysis. By pooling the latter studies, we found that thrombocytopenia was also significantly associated with distant recurrence.

Our results are important in that they provide crucial guidance for the estimation of the prognosis of patients with HCC. No significant difference was found between our use of the random-effects and fixed-effect models. The pooled HR values were not markedly affected by a single study, which indicated the robustness of our results. By subgroup and meta-regression analyses, we demonstrated that the various treatment modalities might be a source of heterogeneity.

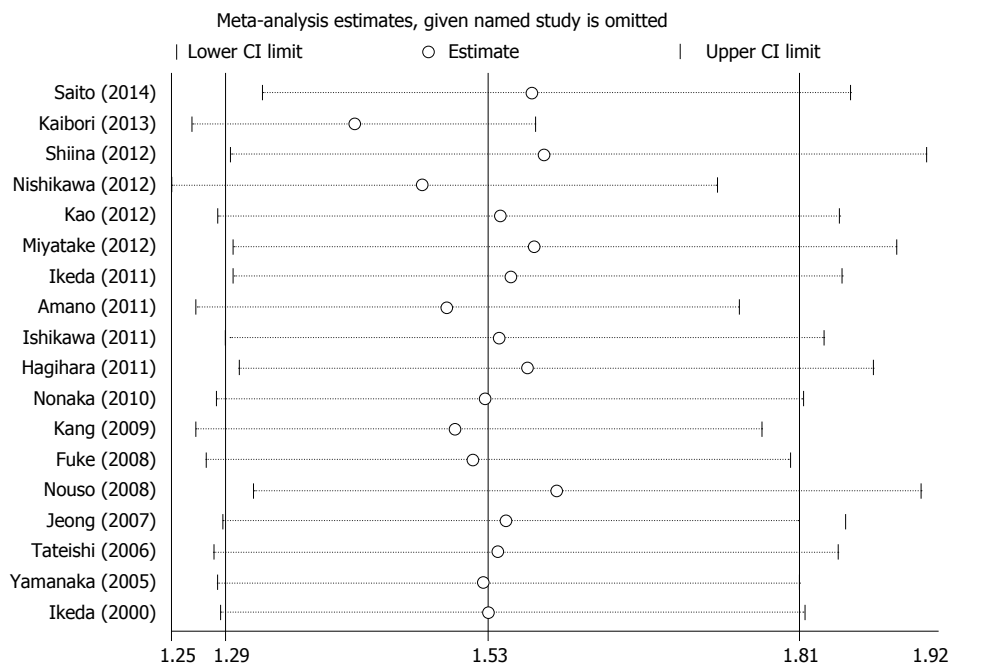


Figure 4 Influence analysis of our included studies.

This study did have some limitations. First, gender, age, Child-Pugh grade, and several other parameters that are important prognostic factors for HCC were not adjusted in this meta-analysis and several included studies were level 4. Whether or not the significance of PLT is independent of these confounders remains unknown. However, after pooling the adjusted HR values (Table 3), we suggest that platelets might be independently associated with postoperative relapse. Second, pathological examination is universally viewed as the gold standard for the diagnosis of HCC. However, to obtain more data, we did not exclude the studies that assessed HCC by imaging. Third, thrombocytopenia is strongly associated with the progression of liver cirrhosis and is considered an independent risk factor for multicentric HCC<sup>[38]</sup>. In other words, thrombocytopenia is only a surrogate marker or a confounding factor of multicentric carcinogenesis associated with liver cirrhosis. It is therefore necessary to evaluate the relationship between thrombocytopenia and recurrence of HCC in the cases with a corresponding amount of liver cirrhosis. However, because all the retrieved studies failed to stratify the patients with HCC according to the presence or degree of liver cirrhosis, we could not explain whether thrombocytopenia is independent of liver cirrhosis. Nevertheless, based on our previous report, in patients with HCC without cirrhosis, but not in those with cirrhosis, PLT was significantly associated with recurrence<sup>[16]</sup>. In another study, a lower PLT was also associated with a significantly worse prognosis in patients with HCC and cirrhosis<sup>[4]</sup>.

Due to portal hypertension, a decrease in thrombopoietin (TPO) production in the liver, and the capture of platelets by the liver<sup>[6]</sup>, PLT tends to decrease in

various liver diseases. Numerous studies have shown that thrombocytopenia is a major risk factor for the degree of cirrhosis, development of cirrhosis, as well as for carcinogenesis in patients with chronic hepatitis<sup>[8,39,40]</sup>. However, the exact mechanism of the effects of PLT in the prognosis of HCC is still unclear. Several clinical studies have demonstrated that thrombocytopenia could increase postoperative complications and morbidity, and could lead to the deterioration of liver function<sup>[41-43]</sup>. With the analysis of 202 patients with HCV-related HCC who underwent hepatectomy, Kubo *et al*<sup>[38]</sup> emphasized that PLT was the only independent predictor for multicentric HCC; in addition, PLT was significantly associated with the severity of active hepatitis and hepatic fibrosis (both  $P < 0.05$ ). A previous study also indicated that PLT was a useful predictor of portal vein invasion<sup>[44]</sup>. Additionally, a decreased PLT level was found to be significantly associated with an elevated  $\alpha$ -fetoprotein level<sup>[12,45,46]</sup>. Furthermore, patients with a lower preoperative PLT showed a significantly higher probability of cirrhosis, a higher level of bilirubin, a greater amount of bleeding, and a high level of indocyanine green retention at 15 min<sup>[23]</sup>. The above-mentioned factors were all related to recurrence in HCC<sup>[27,29]</sup>, and thus, these findings may help hepatologists explore the exact mechanism. By both *in vitro* and *in vivo* studies, Nozaki *et al*<sup>[47]</sup> proved that TPO could promote liver regeneration and improve cirrhosis *via* an increase in platelets. PDGF, which is mainly stored in platelets, is associated with tumor progression and prognosis in HCC<sup>[48]</sup>. These findings support the relationships between PLT and HCC recurrence. In addition to its influence on recurrence, our previous research and several other studies also showed that thrombocytopenia could result in poor



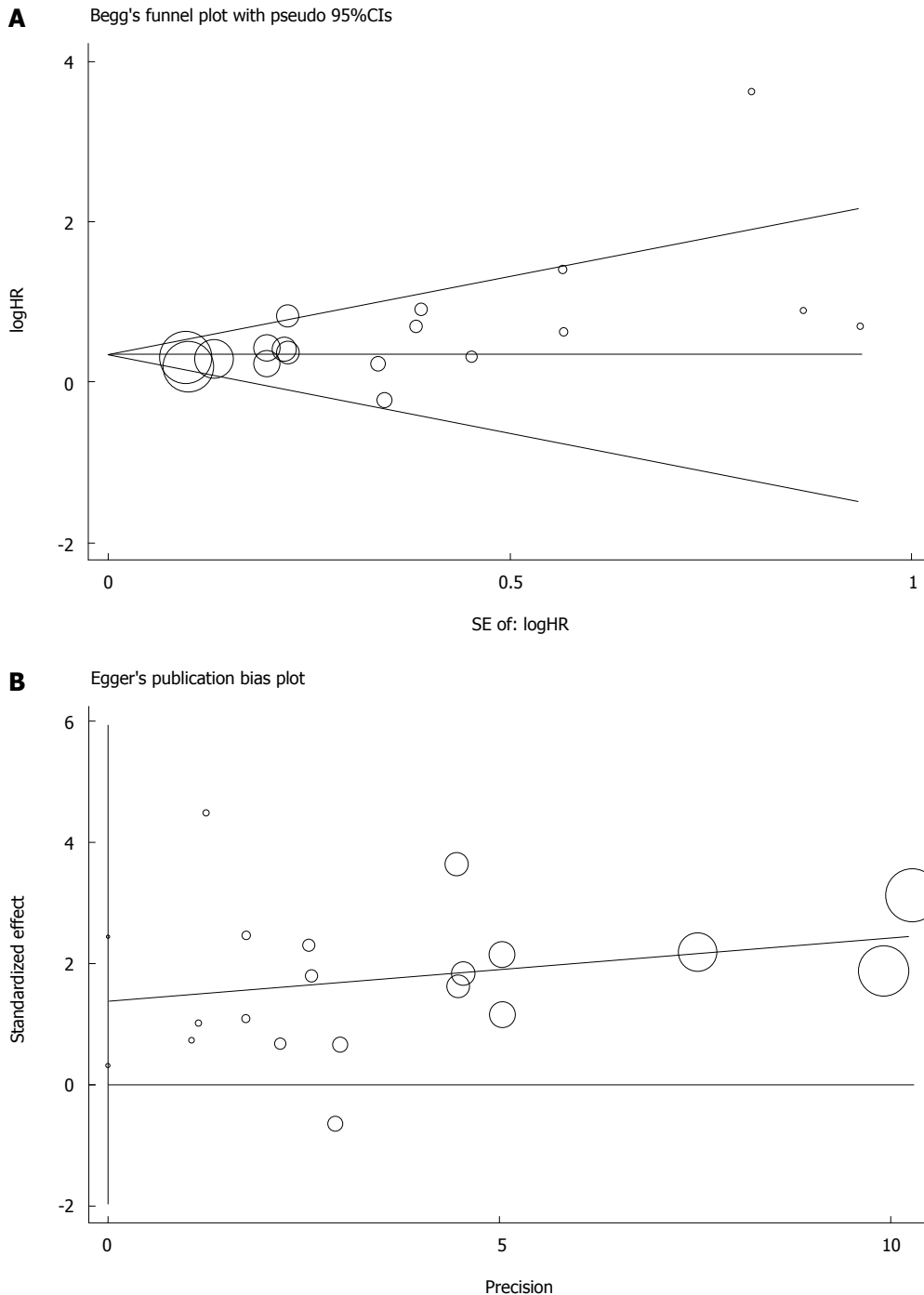


Figure 5 Begg's (A) and Egger's (B) plots of our included studies.

survival in patients with HCC<sup>[4,15,34]</sup>. However, data on the relationship between PLT and tumor stage or other crucial prognostic factors for HCC are lacking.

Additionally, thrombocytosis was found to be associated with the incidence of HCC as well<sup>[49]</sup> and could lead to an increase in the risk of death from HCC<sup>[37]</sup> and other cancers<sup>[50]</sup>. A positive correlation has been suggested between serum PLT and tumor size<sup>[49,51]</sup>. In *in vitro* studies, platelets are a stimulating factor for the growth and invasion of several HCC cell lines<sup>[52]</sup>, which further indicates the adverse effects of excessive platelets.

Therefore, it is believed that a huge gap in the cut-off values of PLT (such as  $400 \times 10^9/L$  vs  $100 \times 10^9/L$ ) may show opposite effects in the prognosis of HCC. Although thrombocytopenia and thrombocytosis are not contraindications for resection in patients with HCC<sup>[4]</sup>, it is still recommended to normalize the serum platelet level by prophylactic platelet transfusions or by taking agents before treatment. On the contrary, although sorafenib, interferon, or other chemotherapeutic/anticancer drugs might be effective in the delay and/or management of postoperative recurrence, they could lead to many complications

such as thrombocytopenia<sup>[32,33,53,54]</sup>. Therefore, for patients who are taking these drugs, a regular assessment of the platelet level in order to maintain the level within a normal range, is pivotal to obtain a favorable outcome.

In conclusion, our meta-analysis suggested that thrombocytopenia was a valuable, inexpensive predictor for recurrence in patients with HCC. Further experimental and clinical studies are needed to validate the results and to clarify the exact mechanism.

## ACKNOWLEDGMENTS

We thank Dr. Wei Chen, Yan-Yan Zhou and Run-Chen Miao in the Department of Hepatobiliary Surgery, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University for their support in this meta-analysis.

## COMMENTS

### Background

Hepatocellular carcinoma (HCC) is a common malignancy with an increasing incidence worldwide. No matter which treatments are given, the prognosis of HCC is poor. Many factors are related to the prognosis of HCC. Among these factors, a high postoperative recurrence rate is the greatest problem that influences potential curative treatments for HCC. It is crucial to seek several key risk factors that influence postoperative recurrence in HCC.

### Research frontiers

Thrombocytopenia is significantly associated with poor survival in HCC. However, whether or not a preoperative low platelet count could increase the risk of recurrence in patients with HCC remains uncertain. The authors endeavored to validate this issue in a meta-analysis.

### Innovations and breakthroughs

Several HCC prognostic models, which mainly focus on the tumor characteristics, have been proposed to assess postoperative survival. However, these models played a limited role in the prediction of recurrence. In contrast, the authors found that thrombocytopenia, a simple and inexpensive index, was significantly associated with a high probability of recurrence, including distant recurrence, in patients with HCC, no matter what treatments were given.

### Applications

Through a validation of this novel prognostic predictive parameter, this study may represent a future strategy for cancer prediction in the follow-up of patients with HCC.

### Terminology

Platelets are involved in thrombosis, inflammatory response, and liver regeneration via the release of several inflammatory mediators such as serotonin. The platelet count is a crucial reflection of platelet function, with a normal range of  $100 \times 10^9$  to  $300 \times 10^9/L$ . Thrombocytopenia occurs when the platelet count is  $< 100 \times 10^9/L$ .

### Peer-review

This is a prognostic meta-analysis and the manuscript is very well written.

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ISSN 1007-9327

