

Original Article

Prognostic role of elevated platelet count in patients with lung cancer: a systematic review and meta-analysis

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Received February 4, 2015; Accepted April 3, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: Recently, more and more studies have shown that platelet count (PLT) may be associated with the prognosis of lung cancer (LC). However, the prognostic role of PLT in lung cancer is still controversial. In the present study, we conducted a meta-analysis of all available English studies to evaluate the prognostic value of PLT in lung cancer. In order to investigate the association between PLT and overall survival (OS), the hazard ratio (HR) and its 95% confidence interval (CI) was evaluated. The odds ratio (OR) with its 95% confidence interval (CI) was used to assess the relationship between PLT and clinicopathological parameters. There were 12 studies (n = 5,884) were involved in this meta-analysis. The pooled results showed that elevated PLT was a negative predictor for OS and the pooled HRs was significant at 1.74 (95% confidence interval, 1.39-2.19). Elevated PLT was also significantly associated with advanced TNM stage (OR: 2.65, 95% CI: 1.77-3.97) and smoking history (OR: 2.70, 95% CI: 1.79-4.08). In addition, there was no significant correlation between elevated PLT and squamous cell carcinoma (OR: 1.54, 95% CI: 0.77-3.07). Our results demonstrated that elevated PLT denotes a poor prognosis in patients with LC.

Keywords: Platelet, meta-analysis, prognosis, lung cancer

Introduction

Lung cancer remains the most common malignant neoplasm worldwide [1]. Despite great improvements in diagnostic technologies, the prognosis of lung cancer (LC) patients remain poor due to local and distant metastasis are common [2]. Over the past decades, various studies have attempted to identify molecular biomarkers to predict the metastasis or recurrence of lung cancer [3, 4]. Disease stage and performance status are most widely accepted prognostic determinants [5]. Other prognostic factors have been commonly reported, mainly histology, gender, age, hemoglobin level, lactate dehydrogenase level (LDH), lymphocyte count, interleukin 6 level, and tumor characteristics [6]. However, none of these have been demonstrated to be sufficiently effective for clinical use. More recently, increased attention has been given to the association between malignancies and blood coagulation [7, 8]. A hypercoagulability state is one of the signs of a more aggressive disease, platelets actively promote cancer cell dissemination by protection of circulating cancer cells from immune surveillance, negotiation of cancer-cell arrest in the

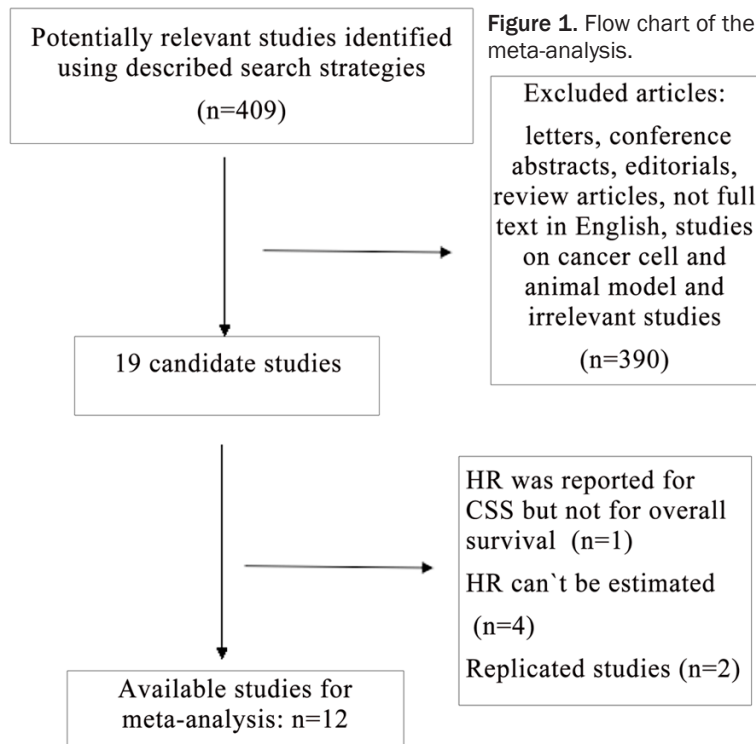
microvasculature, and stimulation of angiogenesis [9]. Several studies have demonstrated that elevated PLT correlates with a poor prognosis in numerous types of solid tumors, including esophageal carcinoma [10], gastric cancer [11, 12] and colorectal cancer [13]. The prognostic significance between elevated PLT and LC has also been reported [14]. However, according to their results, the current opinions about the correlation of PLT on patients' survival and tumor's clinicopathological variables remain controversial, we seek to conduct a meta-analysis to further evaluate the prognostic value of PLT in patients with LC.

Materials and methods

Search strategy

This meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines. We conducted a literature search of articles in PubMed and Embase with the terms "thrombocytosis", "platelet", "lung cancer" and "prognosis" or "outcome" up to June 2014 to identify relevant studies. Studies were included

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if they met the following criteria: (1) the diagnosis of LC was histopathologically confirmed (2) pretreatment PLT values were measured (3) they evaluated the potential association between pretreatment PLT and overall survival and (4) if studies' hazard ratios (HRs) were not directly reported, estimation of the HR could be reconstruct by other data. Articles were excluded based on the following criteria: (1) letters, conference abstracts, editorials, review articles, not full text in English, studies on cancer cell and animal model and irrelevant studies (2) missing key information such as hazard ratio (HR) and 95% confidence interval (CI) (3) literature written in language other than English. Two reviewers independently assessed the articles and relevant data from all of the publications. The literatures were examined independently by both. Any conflicts in data extraction or quality assessment were resolved by discussion between the two readers. We also searched references from the relevant literature, including all of the identified studies, reviews, and editorials.

Quality assessment

Quality of all the included studies was assessed according to 9-star Newcastle-Ottawa Quality Assessment Scale (NOS) [15] by two reviewers. This scale includes three aspects of evaluation:

selection, comparability, and outcome between the case group and control group. Studies that scored ≥ 6 were assigned as high-quality studies. Any disagreement was resolved by discussion.

Data extraction and conversion

We extracted data including: (1) first author's name, year of publication, country (region) of the population studied, sample size, proportion of patients with elevated platelet, demographic data regarding patient age, gender, follow-up period and smoking history (2) survival data including OS (3) cut-off value used to define "elevated PLT" (4) tumor data including pathologic type and TNM stage (5) HR of elevated PLT for OS

and their 95% CIs. The simplest method consisted of the direct collection of HR and their 95% CIs from the original literature, with an HR of > 1 being associated with a poorer outcome. When these data were not directly reported, we extracted the total number of observed deaths, and the number of patients in each group to calculate HR. When data was available only as Kaplan-Meier curves, data was extracted from the graphical survival plots, and then estimation of the HR was performed by the described method [16].

Statistical analysis

The heterogeneity of the combined HRs was evaluated using Cochran's Q test and Higgins' I-squared statistics. A p value less than 0.05 suggested significant heterogeneity among studies and the random-effects model (DerSimonian-Laird method) was performed to calculate the pooled HRs [17]. The fixed effects model was applied in the absence of between-study heterogeneity ($P \geq 0.05$). Sensitivity analyses and meta-regression analysis were performed to explore the reasons for heterogeneity among included studies. Publication bias was evaluated by the funnel plot and the Egger's bias indicator test [18]. Statistical analyses were performed by the statistical software Stata (version 12.0).

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Table 1. Summary table of the meta-analysis

Study Cohort	Study region	No (M/F, n)	NO. of elevated PLT (%)	Age (ys) (median and range)	Clinical stage	AC/SCC	Cutoff	Outcome	Follow-up (months) (median and range)	Hazard ratios	Treatment (predominant)	Smoking history yes/no
Aoe (2004)	Japan	482/129	98 (16.0)	64 (24-89)	I-IV	239/128	400 × 10 ⁹ /L	OS	NR	Reported	NR	NR
Du (2012)	China	195/63	151 (58.5)	53 (31-75)	IIIA-IV	163/95	400 × 10 ⁹ /L	OS	38 (3-86)	Reported	chemotherapy	NR
Yu (2012)	China	388/122	61 (11.9)	60 (37-82)	I-III	232/253	300 × 10 ⁹ /L	OS	NR	Reported	Surgery	354/156
Liu (2013)	China	615/268	138 (15.7)	63 (18-89)	I-IV	475/303	214.5 × 10 ⁹ /L	OS	NR	Reported	Surgery	NR
Maráz (2013)	Hungary	293/105	86 (21.6)	NR	I-IV	163/175	400 × 10 ⁹ /L	OS	62 (1-103)	Reported	Surgery	249/99
Luo (2012)	USA	56/54	37 (33.6)	(50-89)	I-IV	NR	300 × 10 ⁹ /L	OS	NR	Reported	NR	99/11
Barcala (2010)	Spain	35/446	103 (21.4)	66	I-IV	94/188	381 × 10 ⁹ /L	OS	NR	Estimated	NR	414/27
Adžić (2011)	Serbia	161/39	33 (16.5)	(42-78)	I-IV	55/140	420 × 10 ⁹ /L	OS	25 (1-84)	Estimated	Surgery	NR
Kim (2014)	Korea	149/50	15 (7.5)	65 (20-84)	I-III	107/75	400 × 10 ⁹ /L	OS	65 (0.7-102)	Reported	Surgery	136/63
Ji (2014)	China	168/66	20 (8.5)	NR	I	121/100	300 × 10 ⁹ /L	OS	NR	Reported	Surgery	154/80
Kim (2014)	Korea	558/296	59 (6.9)	66.3 (65.5-67)	IIIA-IV	203/384	450 × 10 ⁹ /L	OS	NR	Reported	MT	NR
Holgerson (2012)	Sweden	755/391	293 (25.5)	NR	I-IV	321/652	350 × 10 ⁹ /L	OS	NR	Reported	MT	1088/58

AC: adenocarcinoma; SCC: squamous carcinoma; OS: overall survival; NR: not reported; ys: years; MT: multiple therapy.

Table 2. Methodological quality assessment based on the NOS^a

Source	Selection				Comparability ^f	Outcome			Total ^j
	Representativeness ^b	Selection ^c	Exposure ^d	Demonstration ^e		Assessment ^g	Follow-Up ^h	Adequacy ⁱ	
Aoe (2004)	1	1	1	1	0	1	0	0	5
Du (2012)	1	1	1	1	1	1	1	0	7
Yu (2012)	1	1	1	1	1	1	0	0	6
Liu (2013)	1	1	1	1	1	1	0	1	7
Maráz (2013)	1	1	1	1	0	1	1	0	6
Luo (2012)	1	1	1	1	1	1	0	1	7
Barcala (2010)	1	1	1	1	1	1	0	1	7
Adžić (2011)	1	1	1	1	1	1	1	0	7
Kim (2014)	1	1	1	1	1	1	1	1	7
Ji (2014)	1	1	1	1	1	1	0	1	7
Kim (2014)	1	1	1	1	1	1	0	1	7
Holgerson (2012)	1	1	1	1	1	1	0	0	6

^aNewcastle-Ottawa Scale; ^bRepresentativeness of the Exposed Cohort (0,1); ^cSelection of the Non -Exposed Cohort (0,1); ^dAscertainment of Exposure (0,1); ^eDemonstration That Outcome of Interest Was Not Present at Start of Study (0,1); ^fComparability of Cohorts on the Basis of the Design or Analysis (0,1,2); ^gAssessment of Outcome (0,1); ^hWas Follow-Up Long Enough for Outcomes to Occur (0,1); ⁱAdequacy of Follow Up of Cohorts (0,1); ^jTotal: minimum equals 1; maximum equals 9 stars.

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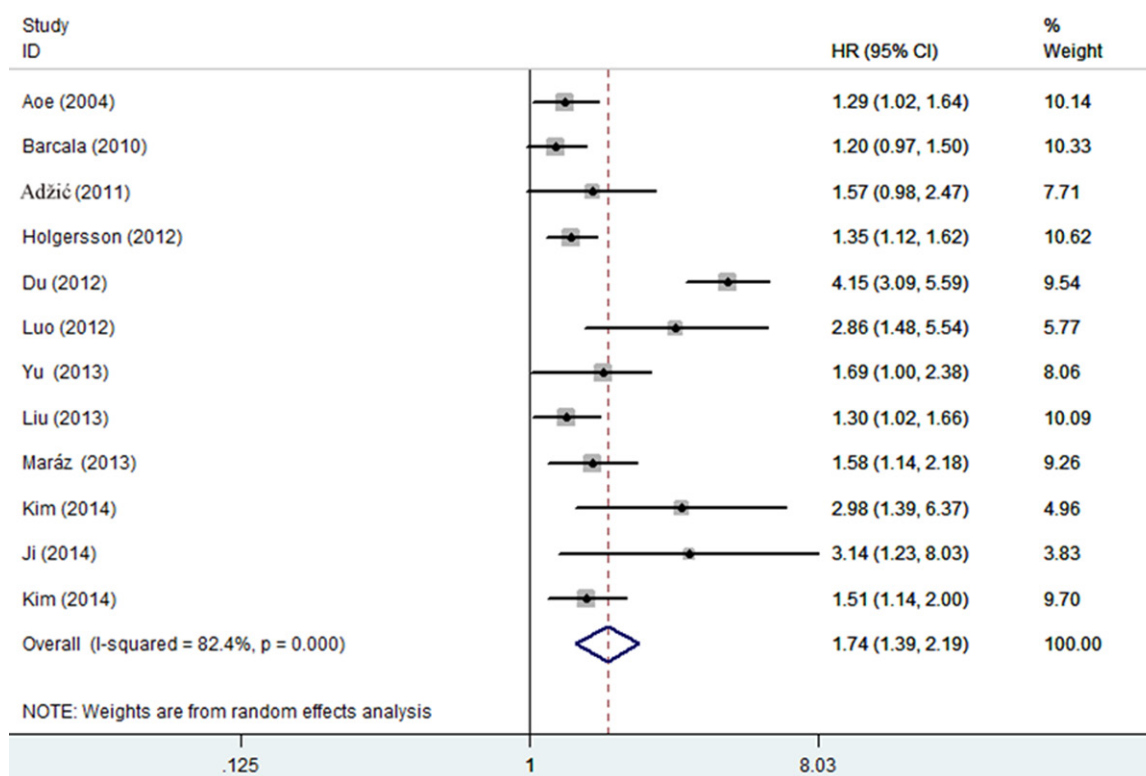


Figure 2. Forest plot of the association between high PLT and OS in LC. Each study was shown by the name of the first author and the HR with 95% CI arranged by publication year. The pooled HR and 95% CI were also presented (according to the random effects model).

Results

Data retrieval

After an initial search of PubMed and EMBASE, four hundred and nine potentially relevant articles for PLT were detected. Then 390 studies were excluded for being letters, conference abstracts, editorials, review articles, not full text in English, studies on cancer cell and animal model and irrelevant studies. As a result of further investigation, 2 studies were excluded as replicates [19, 20], 1 study was excluded as it reported HRs for cancer-specific survival (CSS) but not for overall survival [21] and 4 studies were excluded because HRs missing [22-25]. Finally, 12 reports were included for the current meta-analysis [26-37] (**Figure 1**).

Study characteristics

The main features of eligible studies are summarized in **Table 1**. We collected data from 12 studies including a total of 5,884 participants from China, Sweden, Hungary, Japan, Spain, Serbia, Korea and the United States. In the

twelve studies, there were six studies with cut-off values equal to or more than $400 \times 10^9/L$ and six studies with cut-off values less than $400 \times 10^9/L$. Five of these studies enrolled less than 300 patients and seven studies had more than 300 patients. The proportion of patients with elevated platelet applied in included studies was not consistent ranging from 6.9% to 58.5%. HR and 95% CI were reported directly in ten original literature of all the enrolled studies. There were 11 studies with NOS score ≥ 6 and 1 studies with NOS score < 6 (**Table 2**). In the two studies by Adžić et al and Barcala et al, HRs and their 95% CIs before treatment were calculated from Kaplan-Meier curves.

Meta-analysis of overall survival

In the twelve studies evaluating OS, the data indicated that elevated PLT predicted a worse outcome for LC with the pooled HR of 1.74 (95% CI: 1.39-2.19) but there was significant heterogeneity between studies (I-squared = 82.4%; $P < 0.001$) (**Figure 2**). Sensitivity analysis was performed by sequential omission of individual

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Table 3. Summary table of the subgroup meta analysis results

Analysis	N	Hazard ratio risk (95% CI)	Heterogeneity P value	I ² (%)
All studies	12	1.74 (1.39-2.19)	< 0.001	82.4
Geographical area				
Eastern countries	7	1.97 (1.34-2.88)	< 0.001	87.8
Western countries	5	1.38 (1.22-1.56)	0.122	45
Cut-off value				
Value ≥ 400 × 10 ⁹ /L	6	2.19 (1.18-4.06)	< 0.001	92.4
Value < 400 × 10 ⁹ /L	6	1.44 (1.25-1.67)	0.139	36.3
Sample size				
Sample size ≥ 300	7	1.35 (1.23-1.49)	0.693	0
Sample size < 300	5	2.81 (1.81-4.35)	0.017	67

studies to explore the heterogeneity, one study involved in the meta-analysis was found to have influence of the individual data set to the pooled HRs [28]. After excluding it, heterogeneity of included studies reduced significantly (I-squared = 36.5%; $P = 0.107$) and the pooled corresponding HR was 1.41 (95% CI, 1.28-1.54) which was not materially changed.

Subgroup analyses were performed and the results were summarized in **Table 3**. Subgroup analyses by ethnicity revealed that increased PLT was a negative predictor both in eastern countries [HR = 1.97, 95% CI: (1.34-2.88)] and western countries [HR = 1.38, 95% CI: (1.22-1.56)]. Stratification by sample size, we found the pooled HRs was a worse prognostic marker regardless of sample size with the pooled HRs [HR = 1.35, 95% CI: (1.23-1.49)] for sample size ≥ 300 and [HR = 2.81, 95% CI: (1.81-4.35)] for sample size < 300. When performing subgroup analyses stratified by cut-off value, we found that increased PLT was a negative predictor in LC patients with cut-off values < 400 × 10⁹/L [HR = 1.44, 95% CI: (1.25-1.67)] and patients with cut-off values ≥ 400 × 10⁹/L [HR = 2.19, 95% CI: (1.18-4.06)]. Then meta-regression was conducted by using variables as geographical area, cut-off value and sample size to explore the heterogeneity in further investigation. The results showed that sample size ($P = 0.001$) may contribute to the source of heterogeneity.

Meta-analysis about PLT and clinicopathological factors

To further identify the impact of PLT on LC prognosis as a biomarker, we investigated the asso-

ciation of elevated PLT with TNM stage, smoking history and histological type. The pooled estimates indicated that elevated PLT tended to be associated with advanced TNM stage (OR = 2.65, 95% CI: 1.77-3.97) with no significant heterogeneity (I² = 0.3%, $P = 0.367$) (**Figure 3A**). A fixed effect model revealed a significant association between elevated PLT and smoking history. The combined OR with no significant heterogeneity (I² = 5.9%, $P = 0.373$) indicated that elevated PLT had an evident association with smoker (OR = 2.70, 95% CI: 1.79-4.08) (**Figure 3B**). However, no significant association was observed between PLT and squamous carcinoma and the combined OR was 1.54 (95% CI: 0.77-3.07) with significant heterogeneity (I² = 70.5%, $P = 0.017$) (**Figure 3C**).

Publication bias

We applied a Begg's funnel plot to present the visual assessment of overt publication bias for the included studies and Egger's test adopted for the formal evaluation. As shown in **Figure 4**, the funnel plot was symmetrical. The P value of Egger's test was more than 0.1 which also indicated that there was no evidence for significant publication bias for OS.

Discussion

A great deal of predictors have been identified and applied for predicting LC outcomes in recent years, such as TNM stage, genetic factors, and inflammatory factors. Many blood coagulation markers can be detected in peripheral blood before treatment. PLT is a relatively cheap and convenient predictor. Our study found that elevated PLT has an unfavorable impact on OS in LC patients. Subgroup analyses revealed that elevated PLT was a significant prognostic marker for worse OS regardless of geographical area, sample size and cut-off value. Moreover, the pooled OR and its 95% CI showed that elevated PLT had significant association with TNM stage and smoking history in LC.

Recently, a variety blood coagulation markers have been identified and applied for predicting LC outcomes, such as D-dimer and fibrinogen

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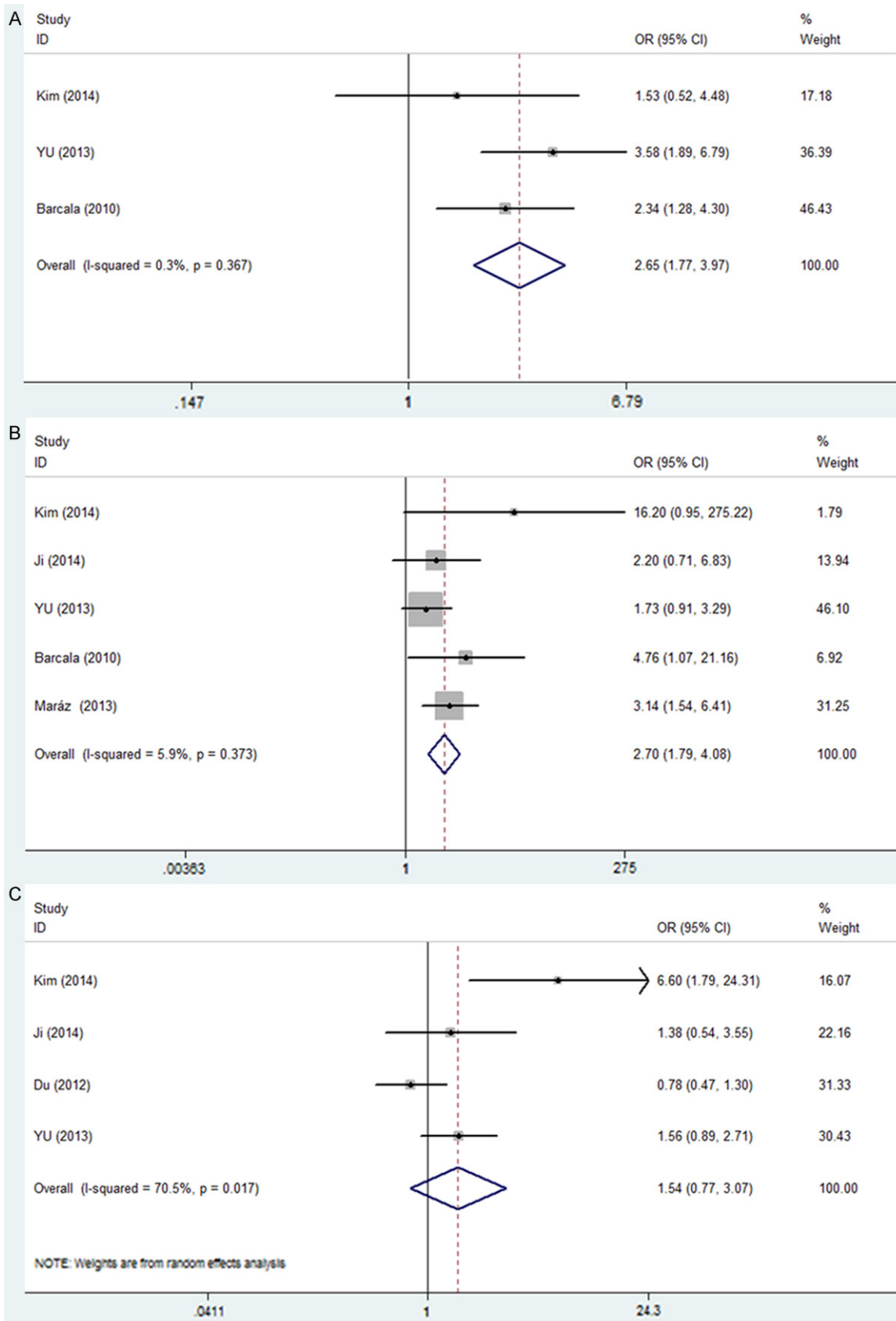


Figure 3. Forest plots showing results of studies on the association between elevated PLT and clinicopathological parameters. A. TNM stage (II-IV vs. I-III). B. Smoking history (yes vs. no). C. Pathological type (squamous carcinoma)

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vs. Non-squamous carcinoma). Each study is shown by the point estimate of the odds ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence intervals (CIs) for the OR.

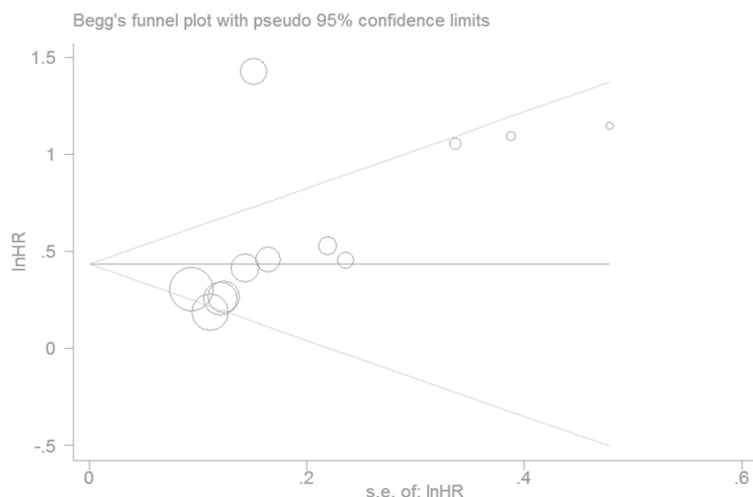


Figure 4. Funnel plots of studies included in the meta-analysis.

(FIB) which possess prognostic value in cancer population [38, 39]. However, D-dimer and FIB levels are not routinely examined as part of the pre-treatment assessment for LC patients in most hospitals, especially for those in backward areas with limited medical resources. In contrast, PLT can be easily measured from the widely available blood routine examination. Circulating tumor cells (CTCs) have also been identified as predictors of prognosis in LC patients [40], but the higher cost reduced its general clinical application. Accessibility and cost-effective analysis should be taken into consideration when selecting a laboratory prognostic biomarker. PLT, with the advantage of low economic cost and widely availability, was encouraged to be routinely tested for predicting survival outcome in LC patients.

PLT had found to be correlated with tumor metastasis and poor prognosis in malignant tumors including LC [14]. However, the precise reason for the association between elevated PLT and worse outcome for LC remains unknown. There are some possible mechanisms by which PLT is associated with worse outcome in cancer patients. Firstly, increased PLT may promote tumor cell growth and invasion. Plasma components stored in platelets can contribute to tumor growth and invasiveness of the cancer cells by releasing various cytokines, including vascular endothelial

growth factor (VEGF) and platelet-derived growth factor (PDGF), which has a significant role in regulating angiogenesis [41]. In addition, platelet promotes the formation of capillary-like structures by endothelial cells, via integrins mediating cell-cell adhesion [42]. Secondly, platelets interact with fibrin and tumor cells leading to the formation of platelet-fibrin-tumor cells which can evade immune surveillance and enhance tumor metastasis. It has been identified that inhibition of platelet activation significantly decreases the metastatic potential of tumor cells [43].

However, there were some limitations for this meta-analysis. Firstly, heterogeneity is a potential problem existed in this meta analysis due to the variation of patients' baseline characteristics, sample size and cutoff values. It is possible that the results of this meta-analysis could have been influenced by the heterogeneity. Subgroup and meta-regression was utilized to investigate the source of heterogeneity and the results showed that sample size might partially explain the source of inter-study heterogeneity. Taking into account such differences, we chose to apply a random model to minimize the confounding effect. Secondly, the cutoff value defining elevated PLT was set differently among studies, which may lead to between-study heterogeneity. Most studies used PLT equal to $400 \times 10^9/L$ as the cutoff, but it did not imply that cancer patients with an increased PLT less than $400 \times 10^9/L$ were not at increased risk, several other studies also demonstrated PLT ranges of $300 \times 10^9/L$ having prognostic significance in overall survival. Subgroup analyses stratified by cut-off values showed that the PLTs prognostic value was not affected substantially. Finally, PLT is often affected by several diseases which are linked to survival, such as severe hypertension, splenic disease and blood coagulation disorders and patients who had long-term taken aspirin or other acetylsalicylic acid drugs. For this reason, PLT cannot be considered as a "predictor" for LC survival unless

the included patients are free from other severe diseases related to PLT.

In conclusion, the evidence from this meta-analysis of published studies indicated that elevated PLT was a negative predictor for OS. Elevated PLT had significant association with TNM stage and smoking history in LC. The important role of PLT in cancer prognosis may promote its clinical utility. In view of the limitations of the present meta-analysis, further research with larger and worldwide sample sizes are expected to confirm our results.

Acknowledgements

We thank Ms Zhuqing Liu for her excellent technical support.

Disclosure of conflict of interest

None.

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