Prognostic value of platelet count in lung cancer: a systematic review and meta-analysis

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Abstract
Background: The prognostic value of pretreatment elevated platelet count remains controversial in lung cancer patients. We performed the present meta-analysis to determine the precise role of it in these patients.

Methods: We performed a multiple search strategy in PubMed database, EMBASE and Cochrane Library to identify eligible studies. Disease-free survival (DFS)/Progress-free survival (PFS)/Time to progress (TTP) and Overall survival (OS) were used as outcomes with hazard ratio (HR) and its 95% confidence intervals (CIs). Heterogeneity among studies and publication bias were also evaluated.

Results: A total of 39 studies including 16696 lung cancer patients were eligible in the analysis. Overall, the pooled analysis showed that pretreatment elevated platelet count was associated with poorer OS (HR = 1.47, 95%CI: 1.31-1.66, P<0.001) and poorer DFS/PFS/TTP ((HR=1.63, 95%CI: 1.28-2.09, P<0.001) in patients with lung cancer compared with normal platelet count. In subgroup analyses, pretreatment elevated platelet count was also associated with poorer OS and DFS/PFS/TTP in most subgroups. There was no evidence of publication bias.

Conclusions: This meta-analysis revealed that pretreatment elevated platelet count was an independent predictor of OS and DFS/PFS/TTP in lung cancer patients. Large scale prospective studies and a validation study are warranted.

Background
According to the Global Cancer Statistics 2018, Lung cancer is the most commonly cancer (11.6% of total cancer cases) and the leading cause of cancer lethality (18.4% of the total cancer deaths) worldwide. Non-small cell lung cancer (NSCLC), the leading type of lung cancer, account for 80% of all. Although various therapies like surgery, radiotherapy, chemotherapy, target therapy, and the rising immunization therapy have emerged, they exhibit limited effect for lung cancer and the prognosis of patients remains unsatisfactory, with five-year survival rates of 6.3% for small cell lung cancer (SCLC) and 18.2% for NSCLC. Compared to treating advanced cancer, prevention is much better. Therefore, it is important to investigate novel prognostic factors to improve treatment therapies.
In 1960s, RICHARD B.et al have suggested that the platelet was correlated with cancers. Tumor cells could secret platelet agonists to induce platelet aggregation and result in thrombocytosis by producing thrombopoietic cytokine like interleukin-1 (IL-1), IL-3, IL-11, and particularly tumor-derived IL-6. Many studies have shown thrombocytosis played a role in cancer genesis and development. Increasing evidence has indicated that platelet count correlates with prognosis in various malignancies such as lung, renal, gastric, colorectal and hepatocellular cancer and is considered as a hallmark of cancer. Additionally, the platelet count is convenient to perform, less expensive, and easily available. However, the current opinions about the correlation between platelet count and lung cancer prognosis are controversy. Some studies identify that platelet count is a poor prognosis in NSCLC, while some suggest that platelet count has no association with lung cancer. Therefore, we conduct this meta-analysis to further investigate the prognostic value of platelet count on the survival in lung cancer patients.

Methods
Search strategy
A comprehensive search was conducted by searching database including PubMed database, EMBASE and Cochrane Library, using the follow terms: (((((“lung cancer”) OR NSCLC) OR non-small cell lung cancer OR carcinoma of lungs) OR lung carcinoma)) And (((((“Thrombocytosis”) OR thrombocytosis) OR thrombocythemia) OR platelet count) OR blood platelets) OR platelets) OR platelet)) AND (((((“Prognosis”) OR prognosis) OR prognostic) OR survival) OR mortality).

Selection criteria
The including criteria were as follows: (1) the diagnosis of lung cancer was pathologically confirmed; (2) platelet count was measured preoperation; (3) hazard ratios (HRs) and their 95% confidence intervals (CIs) for platelet count can be obtained; (4) the cut-off value of thrombocytosis was reported; (5) the relationship between OS or DFS/PFS/TTP was evaluated.

Exclusion criteria
Articles were excluded if they meet the following criteria: (1) studies were reviews, case reports, letters, editorials, or conference abstracts; (2) articles not written in English; (3) studies with duplicate
data; (4) missing key information for evaluating the HR and its 95% CI; (5) studies based on cancer cells and animal models and irrelevant studies. The candidate articles were assessed by two reviewers independently. Any disputes were resolved through their discussion.

Data extraction and quality assessment
Two reviewers independently extract data and complete quality assessment from the selected literature. We extracted data including: the first author name, year of publication, sample size, the gender of patients, histological type, lymph nodes metastasis, recurrence, the cut-off value of thrombocytosis, venous thromboembolism, follow-up time, and primary outcome. The Newcastle-Ottawa Scale (NOS) scoring system was used to assess the quality of selected articles. Two reviewers independently evaluated the quality of each included study. The judges include three aspects of evaluation: selection, comparability, and outcome between the case group and control group. Studies with NOS scores ≥ 6 were considered as high-quality studies.

Statistical analysis
The meta-analysis was conducted by STATA 12.0 software (Stata Corp., College Station, TX, USA). HRs and corresponding 95% CI were used to analyse the association between platelet count and lung cancer. The Cochrane’s Q test and I² statistic were used to evaluate the heterogeneity among the included studies. I² >50% or the P-value<0.05 defined heterogeneity in the studies, and a random-effect model was adopted. Otherwise, a fixed-effect model was used. Moreover, subgroup analysis was conducted to detect the potential source of heterogeneity. A P value less than 0.05 indicated statistically significance. Publication bias was evaluated by Begg’s test and Egger’s regression test. Additionally, a sensitive analysis was performed to check the stability of the results.

Results
Study characteristics
A flow diagram demonstrating the search procedure was illustrated in Figure 1. After the original search, 2395 records were retrieved from electronic databases. Firstly, we removed the duplications, and 1178 were left. Among them, another 1112 items were also excluded by titles and abstracts examination. Next, the remaining 66 full texts were left for eligibility. Of these, 27 studies were
excluded on account of duplicate date and incomplete data. Ultimately, 39 studies including a total of 16696 participants met the criteria and were enrolled in this meta-analysis 17-19,26-61. Simultaneously in data extraction, if the study provides both univariate analysis and multivariate analysis results, we take the results of multivariate analysis, because multivariate analysis excluded the correlated confounding factors, which are more accurate.

The characteristics of patients included are presented in Table 1. All included studies were published between 1976 and 2017. As in Table 1, 39 studies were included in the meta-analysis, 29 studies with NSCLC, 2 studies with SCLC, and 8 studies include all types. Twenty-two studies were performed in Asians and 16 in Caucasians, while one study did not report the race. In terms of the cut-off value of platelet count, 7 studies conducted a cut-off value of <300, while 18 studies took 300–400 as cut-off point, and the remaining 13 studies considered ≥400 as the cut-off point. There were 39 studies evaluating the association between OS and platelet count, while 8 studies evaluated the DFS/PFS/TTP outcome. All of the 39 studies reported the HR and 95% CI directly. Additionally, the quality of the studies was assessed by NOS as shown in Table 2.

Meta-analysis

OS

All of 39 studies including 16696 patients provide data on the prognostic role of the platelet count on OS in lung cancer. The results indicate that elevated platelet count was associated with poorer OS in lung cancer patients (HR = 1.47, 95%CI: 1.31-1.66, P<0.001, Fig. 2A). Then we conducted the subgroup analysis to further investigate and the results were summarized in Table 3. In the subgroup stratified by ethnicity, we observed that elevated platelet count predicted poor OS in Asian populations (HR = 1.54, 95%CI: 1.32-1.8, P<0.001) while that in non-Asians had no significance (P = 0.063). Based on the clinic stage, an significant association between elevated platelet count and OS was found not only in stage I-III (HR = 1.52, 95%CI:1.22–1.89, P<0.001), but also in stage >III (HR = 1.7, 95%CI: 1.26–2.29, P<0.001). The obvious association between elevated platelet count and OS was observed when integrating the data from 28 studies which OS was evaluated with multivariate analysis (HR = 1.47, 95%CI: 1.31-1.66, P<0.001). In terms of the cut-off value, the subgroup analysis
confirmed that increased platelet count was a negative predictor in patients with cut-off values<300 (HR = 1.64, 95%CI: 1.25–2.15, P<0.1), and with cut-off values>400 (HR = 1.73, 95%CI: 1.35–1.61, P<0.001). Additionally, high platelet count still predict worse OS in patients with lung cancer, regardless of subtype of lung cancer (SCLC or NSCLC).

**DFS/PFS/TTP**

The meta-analysis of DFS/PFS/TTP, which contained 13 studies with 7183 patients, indicated that the cancer patients with high platelet count had significantly shorter DFS/PFS/TTP compared those with low platelet count (HR = 1.62, 95%CI: 1.33–1.98, P<0.001, Fig. 2B). Random-effect model was used. The subgroup analysis was performed and the results were shown in Table 3. The results suggested that in the subgroup analysis such as Asian populations (P<0.001), multivariate analysis subgroup (P<0.001), stage III-IV disease subgroup (P<0.001), 300≤cut-off value<400 subgroup (P<0.001), cut-off value>400 subgroup (P = 0.383), elevated platelet count was a negative predictor.

In three subgroups, patients with pretreatment elevated platelet count had similar DFS/PFS/TTP compared with patients with normal platelet count: stage I-III disease subgroup (P = 0.097), patients whose quality score <6 (P = 0.114), platelet count >400 (P = 0.383), platelet count <300 (P = 0.584).

**Publication bias and sensitivity analysis**

As shown in Figure 3, the funnel plot was symmetrical. Based on the Begg’s test (P = 0.866) and Egger’s regression test (P = 0.376), no significant publication bias was found.

Furthermore, we performed a sensitivity analysis to evaluate the reliability of our results. The corresponding pooled HR values was not significantly impacted, indicating the robustness of our conclusions (Fig. 4).

**Discussion**

Cancer is undoubtedly one of the most serious public health problems. In the past few years, neuron-specific enolase, carcino-embryonic antigen, squamous cell carcinoma associated antigen and gastrin-releasing peptide precursor fragments have played an important role in the clinical diagnosis of lung cancer. However, their specificity and sensitivity in diagnosis are still not satisfactory. Therefore, the exploration of new lung cancer markers is of great significance for clinicians to realize
early detection and early treatment.

In recent years, it has been observed that some systemic inflammation indicators like neutrophil-to-lymphocyte ratio (NLR)\textsuperscript{62}, platelet-to-lymphocyte ratio (PLR)\textsuperscript{63}, Glasgow prognostic score (GPS)\textsuperscript{64}, PI (Prognostic Index) and PNI (Prognostic Nutritional Index) \textsuperscript{65} played an important role in tumor genesis and development, which can be considered as predictors of prognosis. Since the 1960s, RICHARD B had observed that platelet count elevated in patients with cancers compared to those with nonmalignant diseases\textsuperscript{5}. Accumulating evidence suggesting that elevated platelet is associated with various cancers such as colorectal cancer, lung cancer, endometrial carcinoma and so on\textsuperscript{12,66,67}.

Platelet sustains proliferative signaling, resists cell death, and induces tumor angiogenesis\textsuperscript{68}. Also, platelet activates TGF-\(\beta\)/Smad and NF-\(\kappa\)B pathways, further promoting tumor migration and invasion\textsuperscript{69}. Moreover, as the immune cell\textsuperscript{70}, platelet releases TGF-\(\beta\), reducing the expression of NKG2D, weakening the role of NK cells\textsuperscript{71}. Platelet could be the prognosis predictor used in clinic.

Recently, several studies confirming the prognostic value of platelet count in lung cancer have been carried out, however the results were inconsistent. Therefore, we conduct the meta-analysis to determine the precise role.

We combine the outcomes of 39 studies with 16696 patients, suggesting that elevated platelet count is a poor predictor of OS and DFS/PFS/TTP in lung cancer patients. In our subgroup analysis, elevated platelet count is significantly associated with poor OS and DFS/PFS/TTP in diverse subgroups like in Asian populations, in stage I-III, and stage III-IV, in lung cancer patients whose score>6. However, the result is not significant in lung cancer patients score<6. The cut-off value of platelet count is disunity. We found the elevated platelet count was significantly associated with poor OS and DFS/PFS/TTP when cut-off value of PLT was between 300 and 400, while the cut-off value of PLT >400 does not have relationship with poor DFS/PFS/TTP. Taken together, the cut-off value between 300 and 400 can separate patients well by OS and DFS/PFS/TTP, and should be used as a prognostic biomarker in clinic use., which was more precise than the findings of the previous meta-analysis\textsuperscript{72}. Compared to the
previous meta-analysis\textsuperscript{72}, our results is more comprehensive and accurate. On the one hand, we take 39 articles into the meta-analysis, which include more new and important studies, increasing analytical capability of the analysis. On the other hand, more detailed subgroup analysis was performed. Except for the race and cut-off value, we also investigate the prognostic role of platelet count in different tumor stage, histology and quality score. Additionally, we discuss the association between PLT and OS and DFS/PFS/TTP, while the previous meta-analysis only studied the significance in OS.

However, there are some limitations of this study deserving mentioning. Firstly, the studies included in our meta-analysis are retrospective studies, more likely to have selection bias. Secondly, although publication bias and sensitivity analysis have confirmed the credibility, heterogeneity still existed in this meta-analysis due to several factors such as patients’ characteristics, sample size, adjuvant therapy, which did not include in our analysis. Moreover, the cut-off value for definition of the elevated platelet count differed among the studies. Most of the studies used 300–400 as cut-off value, while several others use <300 or >400 as cut-off value of platelet count to assess the prognosis, which might lead to between-study heterogeneity. Last but not least, platelet count could be affected by several factors such as thrombosis, hypertension, splenic diseases, blood coagulation disorders, myeloproliferative disease, infection and drugs. Therefore, platelet count cannot play the role of prognosis if patients have these diseases above.

Conclusions
In conclusion, our meta-analysis reveals that pretreatment elevated platelet count is related to poor OS and DFS/PFS/TTP in lung cancer patients, and is an independent prognostic predictor of lung cancer patients. Considering the limitations, large scale prospective studies and a validation study are warranted to test our results.

Declarations

Abbreviations
DFS: Disease-Free Survival
PFS: Progress-Free Survival
TTP: Time To Progress
OS: Overall Survival
HR: Hazard Ratio
CIs: Confidence Intervals
NSCLC: Non-Small Cell Lung Cancer
SCLC: Small Cell Lung Cancer
NOS: Newcastle-Ottawa Scale
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
GPS: Glasgow prognostic score
PI: Prognostic Index
PNI: Prognostic Nutritional Index

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Not applicable
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Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
Hai Zhong, Yuan Yuan and Yingying Qian were involved in the study design, literature search, review of the articles, extraction of the data, statistical analysis and writing of the manuscript. Liang Ye and Qian Li contributed in the study design, literature search, review of the articles, interpretation of the data and revision of the manuscript. Surong Fang and Wei Gu participated in the study design, interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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References

1. Bray, F, Ferlay, J, Soerjomataram, I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.2019; 68:394-424.

2. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 23:3175-3185.

3. Moro-Sibilot D, Smit E, de Castro Carpeño J, et al. Outcomes and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study. Lung cancer (Amsterdam, Netherlands). 2015; 88:215-222.

4. Paesmans M, Sculier JP, Libert P, et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1995; 13:1221-1230.

5. RICHARD B. DAVIS, ATHANASIOS THEOLOGIDES, B. J. KENNEDY. Comparative Studies of Blood Coagulation and Platelet Aggregation in Patients with Cancer and Nonmalignant Diseases. Ann. Intern. Med.1969 Jul;71(1). DOI 10.7326/0003-4819-71-1-67.

6. Wang, Y, Reheman, A, Spring, C. et al. Plasma fibronectin supports hemostasis and regulates thrombosis. J Clin Invest. 2014;124:4281-4293.

7. Bastida E, Ordinas A. Platelet contribution to the formation of metastatic foci: the role of cancer cell-induced platelet activation. Haemostasis. 1988; 18:29-36.

8. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. The New England journal of medicine. 2012; 366:610-618.

9. Lin RJ, Afshar-Kharghan V, Schafer Al. Paraneoplastic thrombocytosis: the secrets of tumor self-promotion. Blood. 2014; 124:184-187.

10. Baranyai Z, Krzystanek M, Jósa V, et al. The comparison of thrombocytosis and platelet-lymphocyte ratio as potential prognostic markers in colorectal cancer. Thrombosis and haemostasis.
Sasaki K, Kawai K, Tsuno NH, Sunami E, Kitayama J. Impact of preoperative thrombocytosis on the survival of patients with primary colorectal cancer. World Journal of Surgery. 2012; 36: 192-200.

X, Z, Y, R. Prognostic role of elevated platelet count in patients with lung cancer: a systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine. 2015; 8: 5379-5387.

Bensalah K, Leray E, Fergelot P, et al. Prognostic value of thrombocytosis in renal cell carcinoma. The Journal of Urology. 2006; 175: 859-863.

Wang YH, Kang JK, Zhi YF, et al. The pretreatment thrombocytosis as one of prognostic factors for gastric cancer: A systematic review and meta-analysis. International Journal of Surgery (London, England). 2018; 53: 304-311.

YY, W., X., Z., YY, Q., JQ, Q., FQ, L. Mean platelet volume/platelet count ratio in colorectal cancer: a retrospective clinical study. BMC Cancer. 2019; 19: 314.

Scheiner B, Kirstein M, Popp S, et al. Association of Platelet Count and Mean Platelet Volume with Overall Survival in Patients with Cirrhosis and Unresectable Hepatocellular Carcinoma. Liver Cancer. 2019; 8: 203-217.

Qiu, M. Z, Xu, R. H, Ruan, D. Y, et al. Incidence of anemia, leukocytosis, and thrombocytosis in patients with solid tumors in China. Tumour Biology: the Journal of the International Society for OncoDevelopmental Biology and Medicine. 2010; 31: 633-641.

S, L., W, E., H, J., S, P, J. C. Prognostic Significance of Host-related Biomarkers for Survival in Patients with Advanced Non-Small Cell Lung Cancer. Journal of Cancer. 2017; 8: 2974-2983.

Gonzalez Barcala, F. J, Garcia Prim, J. M, Moldes Rodriguez, M, et al. Platelet count: association with prognosis in lung cancer. Medical Oncology (Northwood, London, England). 2010; 27: 357-362.

Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25, 603-605.

Julian PTH Higgins, Simon G Thompson, Jonathan J Deeks, Douglas G Altman. Measuring inconsistency in meta-analyses. Cochrane Database Syst Rev 2018 08 20;8,
E, K., D, R. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. Statistical methods in medical research, 2012; 21: 409-426.

SE, B, IR, G. A comparison of statistical methods for meta-analysis. Statistics in medicine. 2001; 20: 825-840.

M, E., G, D. S., M, S, C, M. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed.). 1997; 315: 629-634.

J, W., Z, S., W, Y, Y, C. Elevated Serum Concentration of Chitinase 3-Like 1 is an Independent Prognostic Biomarker for Poor Survival in Lung Cancer Patients. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2016; 38: 461-468.

Møller Pedersen, L, Milman, N. Prognostic significance of thrombocytosis in patients with primary lung cancer. European Respiratory Journal. 1996; 9: 1826-1830.

G, C., RA, W., A, A., WP, S, KJ, O. B. Prognostic significance of platelet and microvessel counts in operable non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands). 2000;29: 169-177.

Suzuki M, Iizasa T, Ko E, et al. Serum endostatin correlates with progression and prognosis of non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands). 2002; 35: 29-34.

Swinson, D, E, Jones, J, L, Richardson, D, et al. Carbonic anhydrase IX expression, a novel surrogate marker of tumor hypoxia, is associated with a poor prognosis in non-small-cell lung cancer. J Clin Oncol. 2003; 21: 473-482.

Hong, X, Xu, Q, Yang, Z, et al. The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5 year follow-up. Lung cancer (Amsterdam, Netherlands). 2003; 39: 303-313.

Ünsal, E., Atalay, F., Atikcan, S, Yilmaz, A. Prognostic significance of hemostatic parameters in patients with lung cancer. Respiratory Medicine. 2004; 98:93-98.

Aoe K, Hiraki A, Ueoka H, et al. Thrombocytosis as a useful prognostic indicator in patients
with lung cancer. Respiration; international review of thoracic diseases. 2004; 71: 170-173.

33 Mandrekar, S. J, Schild, S. E, Hillman, S. L, et al. A prognostic model for advanced stage nonsmall cell lung cancer. Pooled analysis of North Central Cancer Treatment Group trials. Cancer. 2006; 107: 781-792.

34 Sylvain Pre´vost , Luc Boucher, Pierre Larive´e, Robert Boileau, Francxois Be´nard. Bone Marrow Hypermetabolism on 18F-FDG PET as a Survival Prognostic Factor in Non–Small Cell Lung Cancer. J. Nucl. Med.2006 Apr;47(4)

35 Altiay, G, Ciftci, A, Demir, M, et al. High plasma D-dimer level is associated with decreased survival in patients with lung cancer. Clin Oncol (R Coll Radiol). 2007;19:494-498.

36 Tomita, M., Shimizu, T., Hara, M., Ayabe, T, Onitsuka, T. Prognostic impact of thrombocytosis in resectable non-small cell lung cancer. Interact Cardiovasc Thorac Surg. 2008; 7: 613-615.

37 J, L., YJ, C., GL, N, A, D. Predictors of survival in patients with non-small cell lung cancer. Oncology nursing forum. 2012; 39:609-616.

38 Holgersson, G, Sandelin, M, Hoye, E Bergstrom, S Henriksson, R Ekman, S, et al. Swedish lung cancer radiation study group: the prognostic value of anaemia, thrombocytosis and leukocytosis at time of diagnosis in patients with non-small cell lung cancer. Med Oncol. 2012; 29: 3176-3182.

39 Yu, D., Liu, B., Zhang, L, Du, K. Platelet count predicts prognosis in operable non-small cell lung cancer. Exp Ther Med. 2013; 5: 1351-1354.

40 Liu, H. B, Gu, X. L, Ma, X. Q, et al. Preoperative platelet count in predicting lymph node metastasis and prognosis in patients with non-small cell lung cancer. Neoplasma. 2012; 60:203-208.

41 Du, Gangjun, Yang, Yingming, Zhang, Yaping, et al. Thrombocytosis and immunohistochemical expression of connexin 43 at diagnosis predict survival in advanced non-small-cell lung cancer treated with cisplatin-based chemotherapy. Cancer Chemotherapy and Pharmacology. 2013; 71: 893-904.

42 ANIKÓ MARÁZ , JÓZSEF FURÁK , ZOLTÁN VARGA , ZSUZSANNA KAHÁN , LÁSZLÓ TISZLAVICZ , LÁSZLÓ TISZLAVICZ .Thrombocytosis Has a Negative Prognostic Value in Lung Cancer. Anticancer Res.2013 Apr;33(4)

43 Li, Y., Miao, L. Y., Xiao, Y. L., Cai, H. R, Zhang, D. P. Elevated platelets enhance cancer cell
migration, promote hematogenous metastasis and associate with a poor prognosis in advanced non-small cell lung cancer cases. Asian Pac J Cancer Prev. 2014; 15: 139-143.

44 Zhang, T, Jiang, Y, Qu, X, et al. Evaluation of preoperative hematologic markers as prognostic factors and establishment of novel risk stratification in resected pN0 non-small-cell lung cancer. PLoS One 9, e111494, 2014, doi:10.1371/journal.pone.0111494.

45 Zhu, J. F, Cai, L, Zhang, X. W, et al. High plasma fibrinogen concentration and platelet count unfavorably impact survival in non-small cell lung cancer patients with brain metastases. Chin J Cancer. 2014; 33:96-104.

46 Kim M, Chang H, Yang HC, et al. Preoperative thrombocytosis is a significant unfavorable prognostic factor for patients with resectable non-small cell lung cancer. World J Surg Oncol 2014 Feb 12;12.DOI 10.1186/1477-7819-12-37

47 Kim KH, Park TY, Lee JY, et al. Prognostic significance of initial platelet counts and fibrinogen level in advanced non-small cell lung cancer. J Korean Med Sci. 2014; 29: 507-511.

48 Wu G, Yao Y, Bai C, et al. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thorac Cancer. 2015; 6:275-287.

49 Zhang W, YuC, Huang B, et al. Correlation between bone metastasis and thrombocytosis in pulmonary adenocarcinoma patients. Oncol Lett. 2015; 9: 762-768.

50 Ji, Y., Sheng, L., Du, X., Qiu, G, Su, D. Elevated platelet count is a strong predictor of poor prognosis in stage I non-small cell lung cancer patients. Platelets. 2015;26: 138-142.

51 ZhangH,Zhang L,Zhu K, et al. Prognostic Significance of Combination of Preoperative Platelet Count and Neutrophil-Lymphocyte Ratio (COP-NLR) in Patients with Non-Small Cell Lung Cancer: Based on a Large Cohort Study. PloS one 10, e0126496 (2015).

52 J, G., T, Z., S, Z. H, P, W.-P. Patients With Advanced Non-Small Cell Lung Cancer Requiring Inpatient Medical Oncology Consultation: Characteristics, Referral Patterns, and Outcomes. Clinical lung cancer. 2016; 17: 292-300.

53 Hong X, Xu Q,Yang Z, et al. The value of prognostic factors in Chinese patients with small cell
lung cancer: A retrospective study of 999 patients. The clinical respiratory journal . 2018;12:433-447.

54 Boddu, P., Villlines, D, Aklilu, M. Paraneoplastic Leukocytosis and Thrombocytosis as Prognostic Biomarkers in Non-small Cell Lung Cancer. Zhongguo Fei Ai Za Zhi. 2016;19:725-730.

55 Wu G,Yao Y,Bai C, et al. Combination of platelet count and lymphocyte to monocyte ratio is a prognostic factor in patients undergoing surgery for nonsmall cell lung cancer. Thorac Cancer2015 May;6(3)DOI 10.1111/1759-7714.12178.

56 M, O., S, I., Y, O, K, U. Platelet count and mean platelet volume are associated with not only bone, soft tissue, and lymph node metastases but also with malignant pleural effusion in lung cancer patients. Neoplasma. 2017; 64: 140-147.

57 M, O., S, I., Y, O, K, U. Platelet count and mean platelet volume are associated with not only bone, soft tissue, and lymph node metastases but also with malignant pleural effusion in lung cancer patients. Neoplasma. 2017; 64: 140-147.

58 Gao L, Zhang H, Zhang B, Zhang L, Wang C. Prognostic value of combination of preoperative platelet count and mean platelet volume in patients with resectable non-small cell lung cancer. Oncotarget2017 Feb 28;8(9)DOI 10.18632/oncotarget.14921.

59 Wang YQ, Zhi QJ, Wang XY,Yue DS,L K, Jiang RC.Prognostic value of combined platelet, fibrinogen, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with lung adenosquamous cancer. Oncol Lett. 2017; 14: 4331-4338.

60 HolgerssonG,BergqvistM,Nilssonj,Thureson M, Harmenberg J,Bergstrom S.The Prognostic Value of Pre-Treatment Leukocytosis in Patients with Previously Treated, Stage IIIB/IV Non-Small Cell Lung Cancer Treated with the IGF-1R Pathway Modulator AXL1717 or Docetaxel; a Retrospective Analysis of a Phase II Trial. Asian Pacific journal of cancer prevention : APJCP. 2017; 18: 1555-1560.

61 Holgersson G,Bergstrom S, Hallqvist A, et al. The prognostic value of pre-treatment thrombocytosis in two cohorts of patients with non-small cell lung cancer treated with curatively intended chemoradiotherapy. Neoplasma. 2017;64:909-915.

62 XB, G., T, T., XJ, T, XJ, Z. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. Scientific reports 5, 12493 2015.
63 H, Z., L, G., B, Z., L, Z, C, W. Prognostic value of platelet to lymphocyte ratio in non-small cell lung cancer: a systematic review and meta-analysis. *Scientific reports* **6**, 22618. 2016. DOI[10.1038/srep22618

64 Laird BJ, Kaasa S, McMillan DC, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2013; **19**: 5456-5464.

65 Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *European journal of cancer (Oxford, England : 1990)*. 2011; **47**: 2633-2641.

66 D, N., E, Y,Z, L. Pretreatment thrombocytosis predict poor prognosis in patients with endometrial carcinoma: a systematic review and meta-analysis. *BMC cancer* **19**, 73. 2019; doi[10.1186/s12885-018-5264-y.

67 Rao XD, Zhang H, Xu ZS, Cheng H, Shen W, Wang XP. Poor prognostic role of the pretreatment platelet counts in colorectal cancer: A meta-analysis. *Medicine* **97**, e10831 2018; doi[10.1097/MD.0000000000010831.

68 XR, X., GM, Y, H, N. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. *Blood*. 2018;**131**:1777-1789.

69 M, L., S, B, RO, H. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. *Cancer cell*. 2011; **20**: 576-590.

70 XR, X, Zhang D, Oswald BE, et al. Platelets are versatile cells: New discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. *Critical reviews in clinical laboratory sciences*. 2016; **53**:409-430.

71 Bauer S, Groh V, Wu J, et al. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. *Science (New York, N.Y.)*. 1999; **285**: 727-729.

72 Zhang X, Ran Y. Prognostic role of elevated platelet count in patients with lung cancer_ a systematic review and meta-analysis. Int J Clin Exp Med.2015 Apr 15;8(4):5379-87.
Tables
Table 1. The basic characteristics of included studies in the meta-analysis

| Author            | Year | Country     | Cases | Tumor type | Clinical stage | Cut-off value | Outcome | OS |
|-------------------|------|-------------|-------|------------|----------------|---------------|---------|----|
| Pedersen LM       | 1996 | Denmark     | 1115  | NSCLC+SCLC | I-IV           | 400           | OS      | M  |
| Cox G             | 2000 | UK          | 175   | NSCLC      | I-IIIA         | 320           | OS      | M  |
| Suzuki M          | 2002 | Japan       | 99    | NSCLC      | I-IV           | 231           | OS      | M  |
| Swinson DE        | 2003 | United Kingdom | 175 | NSCLC      | I-IIIA         | 314           | OS      | M  |
| Bremnes RM        | 2003 | Norway      | 436   | SCLC       | -              | 150           | OS      | M  |
| Unsal E           | 2004 | Turkey      | 58    | NSCLC+SCLC | I-IV           | 400           | OS      | M  |
| Aoe K             | 2004 | Japan       | 611   | NSCLC+SCLC | I-IV           | 400           | OS      | M  |
| Prévost S         | 2006 | Canada      | 120   | NSCLC      | Not Report     | 340           | OS      | M  |
| Tomita M          | 2008 | Japan       | 240   | NSCLC      | I-IV           | 400           | OS      | M  |
| Gonzalez Barcala FJ | 2010 | Spain      | 365   | NSCLC+SCLC | I-IV           | 258           | OS      | M  |
| Gonzalez Barcala FJ | 2010 | Spain      | 294   | NSCLC+SCLC | I-IV           | 381           | OS      | M  |
| Luo J             | 2012 | USA         | 110   | NSCLC      | I-IV           | 300           | OS      | M  |
| Holgersson G      | 2012 | Sweden      | 823   | NSCLC      | I-IV           | 350           | OS      | M  |
| Yu D              | 2013 | China       | 510   | NSCLC      | I-III          | 300           | OS,DFS  | M  |
| Maráz A           | 2013 | Hungary     | 398   | NSCLC+SCLC | I-IV           | 400           | OS      | M  |
| Kim KH            | 2014 | Korea       | 854   | NSCLC      | III-IV         | 450           | OS      | M  |
| Author  | Year | Country  | No.  | Disease | Stage | OS,DFS | Sex |
|---------|------|----------|------|---------|-------|--------|-----|
| Kim M   | 2014 | Korea    | 199  | NSCLC   | I-III | 400    | M   |
| Ji Y    | 2014 | China    | 234  | NSCLC   | I     | 300    | M   |
| Zhu JF  | 2014 | China    | 275  | NSCLC   | IV    | 300    | M   |
| Hong X  | 2016 | China    | 999  | SCLC    | -     | 300    | M   |
| Gotfrit J | 2016   | Canada  | 223  | NSCLC   | IIIB-IV | 400 | M   |
| Boddu P | 2016 | USA      | 571  | NSCLC   | I-IV  | 450    | M   |
| Liu W   | 2017 | China    | 1120 | NSCLC   | I-IIIA | 300  | M   |
| Wang YQ | 2017 | China    | 134  | NSCLC   | I-IIIA | 289  | M   |
| Holgersson G | 2017 | Sweden  | 222  | NSCLC   | III   | 350    | M   |
| Holgersson G | 2017 | Sweden  | 99   | NSCLC   | IIIB-IV | 350  | M   |
| Cui MM  | 2017 | China    | 270  | NSCLC   | I-III | Not Report | OS | M |
| Ohuchi M | 2017 | Japan    | 146  | NSCLC+ SCLC | I-IV | 244  | OS | M |
| Mandrekar SJ | 2006 | Canada+ USA | 1053 | NSCLC | IIIB-IV | 375  | OS,TTP | U |
| Altiay G | 2007 | Turkey   | 78   | NSCLC+ SCLC | III-IV | 400  | OS | U |
| Qiu MZ  | 2010 | China    | 430  | NSCLC   | I-IV  | 400    | OS | U |
| Liu HB  | 2013 | China    | 883  | NSCLC   | I-IV  | 300    | OS | U |
| Du G    | 2013 | China    | 258  | NSCLC   | IIIA-IV | 400 | OS,PFS | U |
| Zhang T | 2014 | China    | 400  | NSCLC   | I-II  | 190    | OS,DFT | U |
| Wu G    | 2015 | China    | 366  | NSCLC   | III-IV | 117.5 | OS,PFS | U |
| Study          | Selection | Comparability | Outcome | Total score |
|---------------|-----------|---------------|---------|-------------|
| Pedersen LM   | 4         | 1             | 3       | 8           |
| Cox G         | 4         | 2             | 2       | 8           |
| Suzuki M      | 4         | 0             | 2       | 6           |
| Swinson DE    | 4         | 0             | 2       | 6           |
| Bremnes RM    | 4         | 0             | 2       | 6           |
| Unsal E       | 4         | 1             | 2       | 7           |
| Aoe K         | 4         | 0             | 2       | 6           |
| Mandrekar SJ  | 4         | 1             | 2       | 7           |
| Prévost S     | 4         | 0             | 2       | 6           |
| Altiay G      | 4         | 0             | 2       | 6           |
| Tomita M      | 4         | 2             | 2       | 8           |
| Qiu MZ        | 4         | 2             | 2       | 6           |
| Gonzalez Barcala FJ | 4 | 2 | 2 | 8 |
| Gonzalez Barcala FJ | 4 | 2 | 2 | 8 |
| Luo J         | 4         | 1             | 2       | 7           |
| Holgersson G  | 4         | 1             | 2       | 7           |
| Yu D          | 4         | 2             | 2       | 8           |
| Liu HB        | 4         | 0             | 2       | 6           |
| Maráz A       | 4         | 0             | 2       | 6           |
| Du G          | 4         | 1             | 2       | 7           |

**NSCLC**: non-small cell lung cancer; **SCLC**: small cell lung cancer; **OS**: overall survival; **DFS**: disease-free survival; **PFS**: progression-free survival; **TTP**: time to progression; **HR**: hazard ratio; **CI**: confidence interval; **M**: multivariate analysis; **U**: univariate analysis
Table 3. The results of subgroup analysis in meta-analysis of OS and DFS/PFS/TTP

| variable             | No. of studies | HR (95% CI)    | P    | Heterogeneity |
|----------------------|----------------|----------------|------|---------------|
|                      |                |                |      | I² (%)        | P₁       |
| OS                   |                |                |      |               |          |
| Analysis of variable |                |                |      |               |          |
| Multivariate         | 28             | 1.47(1.31-1.66)| <0.001| 80.60%        | <0.001   |
| Univariate           | 11             | 1.62(1.33-1.99)| <0.001| 81.70%        | <0.001   |
| Ethnicity            |                |                |      |               |          |
| Asian                | 22             | 1.54(1.32-1.80)| <0.001| 89.80%        | <0.001   |
| non-Asian            | 17             | 1.42(1.32-1.53)| <0.001| 37.00%        | 0.0      |
| Tumor stage          |                |                |      |               |          |
| I-III                | 9              | 1.52(1.22-1.89)| <0.001| 89.00%        | <0.001   |
| III-IV               | 8              | 1.70(1.26-2.29)| 0.001| 85.80%        | <0.001   |
| I-IV                 | 15             | 1.37(1.26-1.49)| <0.001| 38.20%        | 0.0      |
|                | Cases | Hazard Ratio (95% CI) | p-value | DFS/PFS (%) | p-value |
|----------------|-------|-----------------------|---------|-------------|---------|
| **Histology**  |       |                       |         |             |         |
| NSCLC          | 29    | 1.58 (1.38-1.82)      | <0.001  | 89.80%      | <0.001  |
| SCLC           | 2     | 1.64 (0.55-4.87)      | 0.371   | 85.60%      | 0.0     |
| NSCLC+SCLC     | 8     | 1.39 (1.14-1.70)      | 0.001   | 53.40%      | 0.0     |
| **cut-off value** |      |                       |         |             |         |
| 300×10^9/L     | 7     | 1.64 (1.25-2.15)      | <0.001  | 58.80%      | 0.0     |
| 300×10^9/L ≤ cut-off value | 18 | 1.40 (1.27-1.55) | <0.001 | 55.40% | 0.0 |
| ≥ 400×10^9/L   | 13    | 1.73 (1.35-2.21)      | <0.001  | 77.90%      | <0.001  |
| **Quality score** |      |                       |         |             |         |
| > 6            | 23    | 1.59 (1.36-1.85)      | <0.001  | 91.20%      | <0.001  |
| ≤ 6            | 16    | 1.30 (1.19-1.41)      | <0.001  | 48.60%      | 0.0     |
| **DFS/PFS/TTP** |      |                       |         |             |         |
| Multivariate   | 28    | 1.47 (1.31-1.66)      | <0.001  | 80.60%      | <0.001  |
| Univariate     | 11    | 1.62 (1.33-1.99)      | <0.001  | 81.70%      | <0.001  |
| **Ethnicity**  |       |                       |         |             |         |
| Asian          | 22    | 1.54 (1.32-1.80)      | <0.001  | 89.80%      | <0.001  |
| non-Asian      | 17    | 1.42 (1.32-1.53)      | <0.001  | 37.00%      | 0.0     |
| **Tumor stage**|       |                       |         |             |         |
| I-III          | 9     | 1.52 (1.22-1.89)      | <0.001  | 89.00%      | <0.001  |
| III-IV         | 8     | 1.70 (1.26-2.29)      | 0.001   | 85.80%      | <0.001  |
| I-IV           | 15    | 1.37 (1.26-1.49)      | <0.001  | 38.20%      | 0.0     |
| **Histology**  |       |                       |         |             |         |
| NSCLC          | 29    | 1.58 (1.38-1.82)      | <0.001  | 89.80%      | <0.001  |
| SCLC           | 2     | 1.64 (0.55-4.87)      | 0.371   | 85.60%      | 0.0     |
| NSCLC+SCLC     | 8     | 1.39 (1.14-1.70)      | 0.001   | 53.40%      | 0.0     |
| **cut-off value** |      |                       |         |             |         |
| 300×10^9/L     | 7     | 1.64 (1.25-2.15)      | <0.001  | 58.80%      | 0.0     |
| 300×10^9/L ≤ cut-off value | 18 | 1.40 (1.27-1.55) | <0.001 | 55.40% | 0.0 |
| Quality score | n  | HR (CI)         | p-value     | OS (%) | p-value |
|---------------|----|----------------|-------------|--------|---------|
| ≥400×10<sup>9</sup>/L | 13 | 1.73 (1.35-2.21) | <0.001      | 77.90% | <0.01   |
| >6            | 23 | 1.59 (1.36-1.85) | <0.001      | 91.20% | <0.01   |
| ≤6            | 16 | 1.30 (1.19-1.41) | <0.001      | 48.60% | 0.015   |

OS: overall survival; DFS: disease-free survival; PFS: progress-free survival; TTP: time to progress; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; HR: hazard ratio; CI: confidence interval

Figures
Figure 1

Flow chart representing search steps and study selection.
Figure 2

Forest plot showing the HR with 95% CI for association between elevated PLT and OS (A) or DFS/PFS/TTP (B).
Figure 3

Begg’s funnel plots and Egger’s test evaluating possible publication bias for (A) OS; (B) DFS/PFS/TTP.
Figure 4

Sensitivity on the relationship between elevated platelet and OS (A) or DFS/PFS/TTP (B).