The association between thrombocytosis and subtype of lung cancer: a systematic review and meta-analysis

Melissa Barlow (0000-0002-0746-1868), Willie Hamilton (0000-0003-1611-1373), Obioha Chukwunyere Ukoumunne (0000-0002-0551-9157), Sarah Elizabeth Rose Bailey (0000-0003-0020-4778)

Melissa Barlow, PhD Student
University of Exeter Medical School, St Luke’s Campus. Heavitree Road, Exeter, EX1 2LU

Willie Hamilton, Professor of Primary Care Diagnostics
University of Exeter Medical School, St Luke’s Campus. Heavitree Road, Exeter, EX1 2LU

Obioha Chukwunyere Ukoumunne, Associate Professor in Medical Statistics
NIHR ARC, SW Peninsula, University of Exeter Medical School, St Luke’s Campus. Heavitree Road, Exeter, EX1 2LU

Sarah Elizabeth Rose Bailey, Research Fellow
University of Exeter Medical School, St Luke’s Campus. Heavitree Road, Exeter, EX1 2LU

Correspondence to: Melissa Barlow ms748@exeter.ac.uk

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
ABSTRACT

Background

Thrombocytosis is associated with poor lung cancer prognosis and has recently been identified as having a high predictive value in lung cancer detection. Lung cancer has multiple histological and genetic subtypes and it is not known whether platelet levels differ across subtypes.

Methods

Pub Med and Embase were systematically searched for studies that reported pre-treatment platelet count, as either averages or proportion of patients with thrombocytosis, by histological subtype of lung cancer. Suitable studies were synthesised in meta-analyses; subgroup analyses examined for differences across subtypes.

Results

The prevalence of pre-treatment thrombocytosis across all lung cancer patients was 27% (95% CI: 17 to 37%). By subtype, this was 22% (95% CI: 7 to 41%) for adenocarcinoma (ADC), 28% (95% CI: 15 to 43%) for squamous cell carcinoma (SCC), 36% (95% CI: 13 to 62%) for large cell carcinoma, and 30% (95% CI: 8 to 58%) for small cell lung cancer (SCLC). The pooled mean platelet count for lung cancer patients was 289x10^9/L (95% CI: 268 to 311). By subtype, this was 282x10^9/L (95% CI: 259 to 306) for ADC, 297x10^9/L (95% CI: 238 to 356) for SCC, 290x10^9/L (95% CI: 176 to 404) for LCC, and 293x10^9/L (95% CI: 244 to 342) for SCLC. There was no difference in thrombocytosis prevalence (p=0.76) or mean platelet count (p=0.96) across the subtypes.

Conclusion

We report no evidence of differences in platelet levels across the major subtypes of lung cancer. A high platelet level is likely to be generic across all lung cancer subtypes.
KEY MESSAGES

What is the key question?

Which (if any) subtype(s) of lung cancer are more associated with thrombocytosis?

What is the bottom line?

This can facilitate lung cancer diagnostics and provide insights into the biological mechanism between lung cancer and thrombocytosis.

Why read on?

This is the first systematic review to compare platelet count across different subtypes of lung cancer, combining data from 9,891 patients across 38 studies.
**INTRODUCTION**

Lung cancer is the leading cause of cancer death worldwide. Patients often present at an advanced stage and as a result, the five-year survival rate for lung cancer in the UK is only 16.2%. As such, research has focused on identifying biomarkers that can help identify lung cancer at earlier stages and therefore improve survival rates. Thrombocytosis (a peripheral platelet level of $>400 \times 10^9$/L of blood) has been long recognised as a marker of poor prognosis in lung cancer patients. Recently, thrombocytosis has been identified as having a particularly high predictive value for the identification of undiagnosed lung cancer, thus making it a promising biomarker in lung cancer diagnostics. However, lung cancer is heterogeneous, with multiple histological and genetic subtypes, and these subtypes each have distinct pathologies, treatment options, and prognoses. Histological lung cancer subtypes are broadly divided into non-small cell lung cancer (NSCLC), which represents 80-85% of all lung cancers, and small cell lung cancer (SCLC) which represents 15-20%. NSCLC is further divided into adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC). There are several less common histological subtypes, including adenosquamous carcinoma, though distinguishing between these subtypes can be difficult. In addition to the diversity of the histological subtypes, lung cancers can also be distinguished by their genetic subtype. Most lung cancer genetic mutations are somatic, acquired through environmental factors such as tobacco smoking, and include driver mutations in genes such as EGFR, KRAS and TP53 and rearrangements in the ALK gene. Currently, it is not known whether the platelet level differs across subtypes of lung cancer, and therefore whether thrombocytosis is a generic feature of lung cancer, or specific to some subtypes. The answer may facilitate improved lung cancer detection while also providing insights into the biological mechanism between lung cancer and thrombocytosis.

The aim of this systematic review and meta-analysis is to compare lung cancer patients’ pre-treatment platelet counts across lung cancer subtypes to identify which (if any) subtype(s) are more associated with thrombocytosis.
METHODS

Search Strategy

This systematic review and meta-analysis followed MOOSE and PRISMA-P guidelines. We identified relevant studies that reported the platelet count, either as an average or as the proportion of patients with thrombocytosis, by histological subtype of lung cancer. We searched PubMed and Embase on the 14th January 2020 using search terms related to lung cancer and thrombocytosis or platelet count without a date limit (full search terms in Appendix 1). Inclusion criteria for the meta-analysis were: participants were diagnosed with a specific histological or genetic subtype of lung cancer; participants were aged 18 years or over; reported mean platelet count or diagnosis of thrombocytosis before treatments such as surgery, chemotherapy or radiotherapy (as these can affect platelet counts); studies must have reported the mean platelet count or prevalence of thrombocytosis by subtype of lung cancer. Studies were independently screened by two reviewers; conflicts were resolved by discussion. For studies that reported the same cohorts of participants, the study with the largest sample size was selected for the meta-analysis. Studies that reported median platelet count or did not use a thrombocytosis threshold of 400 x 10^9/L were excluded from the meta-analysis and were discussed narratively.

Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale independently by three reviewers. Scoring was based on three domains: selection, comparability and exposure/outcome for a maximum of 9 points, based on the aims reported in the study rather than the aims of this review. The mean was taken of the three reviewers' scores and studies were judged as 'good', 'fair', or 'poor' quality based on the Newcastle-Ottawa Scale thresholds. As the main extracted data for this analysis were the histological diagnoses and average platelet count (or thrombocytosis proportions), rather than the outcome of the studies, studies rated as 'poor' were not excluded from the analyses; however, a sensitivity analysis was conducted to investigate the potential influence of study quality on the findings.

Data extraction

The following data were extracted independently by two reviewers and cross-referenced for discrepancies: country of study, age of participants, sex ratio, smoking status, number of patients
with each histological subtype, and average platelet count and/or proportion of patients with thrombocytosis. Study authors were contacted where data were missing or to confirm whether the inclusion criteria was met. Reminder emails were sent at two monthly intervals if no reply was received.

**Analysis**

Analyses were carried out using STATA version 16. Random effects meta-analysis was used to pool the mean platelet count and the proportion of patients with thrombocytosis, using the *meta set* and *metaprop* commands, respectively. The restricted maximum likelihood estimation method was used to pool the mean platelet counts, and when pooling proportions the Freeman-Tukey double arcsine transformation was used to stabilise the variances. Findings were graphically displayed using forest plots. A subgroup analysis compared pooled mean platelet counts and the pooled proportions of patients with thrombocytosis across histological subtypes of lung cancer. The $I^2$ statistic quantified heterogeneity. Sensitivity analyses explored potential sources of heterogeneity: first examining only advanced stage cancers, second removing the papers scoring ‘poor’ on the Newcastle-Ottawa Scale, and third removing studies that had a small sample size (less than 50 participants) for each histological subtype.

**RESULTS**

**Data retrieval and study quality**

6,118 studies were returned from the search, including 1,352 duplicates. Abstracts of the remaining 4,766 studies were screened, resulting in 82 studies eligible for full-text screening. Thirty-eight studies met the criteria for the narrative synthesis with a total of twenty studies that fulfilled the inclusion criteria for meta-analysis (Figure 1). Eighteen studies were assessed as ‘good’ quality, five as ‘fair’, and fifteen as ‘poor’ according to the Newcastle-Ottawa Scale thresholds.

**Study characteristics**

There was a total of 2,974 patients across 20 different studies included in the meta-analyses (Table 1). This consisted of 1,894 patients with ADC, 777 patients with SCC, 55 patients with LCC, and 248 patients with SCLC. Study countries included Bulgaria, Canada, China, Denmark, Greece, India, Japan, Korea, Poland, and Turkey. The ages ranged from 20 to 92 with a mean age of 58 years and median
age of 63 years. Three-quarters (73.5%) of participants were male. Sample size ranged from 17 to 347 with a median sample size of 61. Twelve studies reported mean platelet counts and ten studies reported the proportion of patients with thrombocytosis (defined as a platelet level of over 400 x $10^9$/L); two studies reported both. Seven studies were assessed as ‘good’ quality, four as ‘fair’, and nine as ‘poor’.

Table 1: Characteristics of studies included in meta-analyses. Thrombocytosis proportions and mean platelet count.

| Study                  | Study Design | Country   | Males (%) | Mean age, years (SD) | Smoking history (%) | Clinical stage | Histological subtype, n | Thrombocytosis (%) |
|------------------------|--------------|-----------|-----------|----------------------|---------------------|----------------|-------------------------|---------------------|
| Alexandraki (2002)     | Case-Control | Greece    | 72%       | 66 (NR)              | NR                  | NR            | ADC, 20                | 50%                 |
|                        |              |           |           |                      |                     |               | SCC, 8                 | 100%                |
|                        |              |           |           |                      |                     |               | LCC, 2                | 64%                 |
|                        |              |           |           |                      |                     |               | SCLC, 11              |                     |
| Davidov (2014)         | Cohort       | Bulgaria  | 84%       | Median 56            | NR                  | IIIB-IV       | ADC, 56                | 20%                 |
|                        |              |           |           | Range 39-76          |                     |               | SCC, 277              | 21%                 |
|                        |              |           |           |                      |                     |               | LCC, 14               | 21%                 |
| Du (2013)              | Cohort       | China     | 76%       | Median 53            | NR                  | IIIA-IV       | ADC, 163              | 61%                 |
|                        |              |           |           | Range 31-75          |                     |               | SCC, 95               | 55%                 |
| Kim (2014)             | Cohort       | Korea     | 75%       | Median 65            | 68%                 | I-III         | ADC, 107              | 3%                  |
|                        |              |           |           | Range 20-84          |                     |               | SCC, 75               | 16%                 |
| Michael (1999)         | Cohort       | Canada    | 65%       | Median 63            | NR                  | LD-ED         | SCLC, 46              | 33%                 |
|                        |              |           |           |                      |                     |               |                         |                     |
| Nankano, T (1986)      | Cohort       | Japan     | NR        | NR                   | NR                  | I-IV          | ADC, 53               | 8%                  |
|                        |              |           |           |                      |                     |               | SCC, 56               | 22%                 |
|                        |              |           |           |                      |                     |               | LCC, 12               | 42%                 |
|                        |              |           |           |                      |                     |               | SCLC, 39              | 5%                  |
| Olsen (1988)           | Cohort       | Denmark   | NR        | NR                   | NR                  | NR            | ADC, 18               | 28%                 |
|                        |              |           |           |                      |                     |               |                         |                     |
| Pederson (2003)        | Cohort       | Denmark   | 80%       | Median 63            | NR                  | I-IV          | ADC, 13               | 54%                 |
|                        |              |           |           |                      |                     |               | SCC, 20               | 60%                 |
|                        |              |           |           |                      |                     |               | LCC, 7                | 57%                 |
|                        |              |           |           |                      |                     |               | SCLC, 11              | 36%                 |
| Skorek (2018)          | Cohort       | Poland    | 64%       | 67 (9)               | 63%                 | I-IV          | ADC, 128              | 9%                  |
|                        |              |           |           |                      |                     |               | SCC, 130              | 11%                 |
|                        |              |           |           |                      |                     |               | LCC, 16               | 13%                 |
| Tomita (2010)          | Cohort       | Japan     | 63%       | 67                   | NR                  | I-III         | ADC, 210              | 3%                  |
|                        |              |           |           | Range 26-86          |                     |               |                         |                     |
|                        |              |           |           |                      |                     |               |                         |                     |

| Study                  | Study Design | Country   | Males (%) | Mean age, years (SD) | Smoking history (%) | Clinical stage | Histological subtype, n | Mean platelet count (SD) |
|------------------------|--------------|-----------|-----------|----------------------|---------------------|----------------|-------------------------|------------------------|
| Biswas (2010)          | Cohort       | India     | 93%       | 56                   | NR                  | I-III         | ADC, 20                | 247 (25)              |
|                        |              |           |           | Range 30-76          |                     |               | SCC, 28                | 257 (20)              |
|                        |              |           |           |                      |                     |               | LCC, 4                 | 237 (28)              |
|                        |              |           |           |                      |                     |               | SCLC, 9                | 235 (19)              |
| Demirkazik             | Cohort       | Turkey    | 95%       | 59 (SE: 2)           | NR                  | IIIB-IV       | ADC, 17               | 326 (SE: 28)          |
The search also returned an additional 18 studies with a further 6,917 lung cancer patients that did not fulfil the criteria for a meta-analysis, and are therefore discussed narratively. There was an inadequate number of studies per subtype for six of studies, seven studies defined thrombocytosis as a value other than $400 \times 10^9/L$, and eleven reported median platelet count (some studies included more than one of these criteria). Eleven of these were assessed as ‘good’, one as ‘fair’, and six as ‘poor’ based on the Newcastle-Ottawa Scale.\(^6\)

**Meta-analysis of thrombocytosis proportions**

We pooled the proportions of patients with thrombocytosis (defined as $400 \times 10^9/L$).\(^7-16\) The overall pooled percentage of lung cancer patients with thrombocytosis was 27% (95% CI: 17 to 37%). By subtype, this proportion was 22% (95% CI: 7 to 41%) for ADC patients; 28% (95% CI: 15 to 43%) for SCC patients; 36% (95% CI: 13 to 62%) for LCC patients; and 30% (95% CI: 8 to 58%) for SCLC patients (Figure 2). There was little evidence of differences in thrombocytosis prevalence between these subtypes (p=0.76). The heterogeneity ($I^2$ statistic) across subtypes was 97% for ADC, 92% for SCC,
61% for LCC, 86% for SCLC, and 93% across all studies. This was not affected by any of the sensitivity analyses.

**Meta-analysis of mean platelet count**

Of the 12 studies that reported a mean platelet count, the pooled mean across all histological subtypes of lung cancer was $289 \times 10^9/L$ (95% CI: 268 to 311) (Figure 3). By subtype, the pooled mean platelet counts were $282 \times 10^9/L$ (95% CI: 259 to 306) for ADC; $297 \times 10^9/L$ (95% CI: 238 to 356) for SCC; $290 \times 10^9/L$ (95% CI: 176 to 404) for LCC; and $293 \times 10^9/L$ (95% CI: 244 to 342) for SCLC. The $I^2$ statistic for heterogeneity across studies was: 95% for ADC, 96% for SCC, 89% for LCC, 93% for SCLC, and 97% overall. There was little evidence of differences in mean platelet count across the histological subtypes of lung cancer ($p=0.96$). None of the sensitivity analyses changed the main results; however, the analysis restricted to advanced stage cancers reduced heterogeneity for the ADC and SCC subgroups to 46% and 0%, respectively. There were too few studies for LCC and SCLC to conduct a sensitivity analysis exclusively for advanced staged cancers.

**Median platelet counts and thrombocytosis proportions using different thresholds**

There was also little evidence of differences across lung cancer subtypes in 11 studies, inclusive of 4,887 lung cancer patients that reported median platelet count values, and seven studies of 2,795 lung cancer patients that used a different threshold to define thrombocytosis.

**Other subtypes of lung cancer**

Six studies, totalling 841 patients, were returned that examined platelet levels across other subtypes of lung cancer.

**Adenosquamous carcinoma**

Two studies had available platelet counts or thrombocytosis proportions for patients with ADSq: Skorek and colleagues (2018) reported 1/11 (9%) patients with ADSq had thrombocytosis ($400 \times 10^9/L$ threshold), and Wang and colleagues (2017) reported a mean (SD) platelet count of 143 (65) across 134 patients.
**ALK rearrangements**

He and colleagues (2019)\textsuperscript{42} studied 344 patients with ALK-positive lung cancer and stratified patients’ platelet counts by percentage of ALK-positive tumour cells (15-49% and ≥50%), as detected by fluorescence \textit{in situ} hybridisation. They reported 57% of patients with 15-49% of ALK-positive tumour cells and only 33% of patients with ≥50% ALK-positive tumour cells as having a platelet count of over \(300 \times 10^9\)/L blood. Yang and colleagues (2019)\textsuperscript{43} reported a median platelet count of 246 for 113 ALK-positive advanced NSCLC patients.

**EGFR mutations**

Two papers studied 112\textsuperscript{44} and 127\textsuperscript{45} advanced NSCLC patients, with either an \textit{EGFR} exon 19 deletion or an \textit{EGFR} exon 21 substitution mutation (L858R). They reported median platelet counts of 290\textsuperscript{44} and 232 \(\times 10^9\)/L,\textsuperscript{45} respectively.

**DISCUSSION**

This is the first systematic review to compare platelet count across different subtypes of lung cancer. Data from 2,974 patients across 20 independent studies\textsuperscript{7-26} were synthesised and meta-analyses examined differences in mean platelet count and proportion of patients with thrombocytosis across ADC, SCC, LCC, and SCLC, finding no difference in mean platelet count or the percentage with thrombocytosis across the four subtypes. Similar results were observed in a further 18 studies of 6,917 additional participants that reported median platelet counts\textsuperscript{27-37} or proportion of patients with thrombocytosis using a lower threshold platelet count.\textsuperscript{29-31,37-40} There were too few papers on adenosquamous,\textsuperscript{15,41} ALK-positive,\textsuperscript{42,43} and \textit{EGFR}-positive\textsuperscript{44,45} lung cancers to perform a meta-analysis, although the available evidence suggested thrombocytosis was not a prominent feature of any of these subtypes. Our results indicate that the relationship between pre-treatment thrombocytosis and lung cancer is a generic one, rather than being restricted to one or more cancer subtypes.

**Strengths and Limitations**
This systematic review collated data from a very large number of lung cancer patients to analyse platelet count and proportion of thrombocytosis. We were meticulous in studying only pre-treatment platelet values: lung cancer therapies such as surgery, chemotherapy, and radiotherapy can affect platelet count. While most studies were assessed as ‘poor’ based on the Newcastle-Ottawa Scale, all studies scored highly in the ‘selection’ domain. As the key data points extracted from each study were subtype diagnosis and platelet count, found in the patient characteristics rather than the results of the study, the ‘selection’ domain was the most important for the purpose of this review. Importantly, subtype diagnosis and platelet count were both obtained by robust, internationally recognised methods. The sensitivity analysis by study quality supported this. Furthermore, as this systematic review was concerned with patient characteristics (lung cancer subtype, platelet count) rather than the specific outcome of the included studies, any effect of publication bias should be small or absent.

There was a high level of heterogeneity throughout. To explore this, sensitivity analyses were conducted to analyse the effect of lung cancer stage, study quality and sample size. The sensitivity analysis that only included advanced lung stage cancers was the only one to reduce heterogeneity, perhaps because advanced stage cancers are more strongly associated with raised platelet count. Another source of heterogeneity may be attributed to smoking status, as smoking is not only a risk factor for lung cancer but also elevates the platelet count. Only a small number of studies reported smoking status but none differentiated smoking status in terms of platelet count and subtype: therefore, we were unable to analyse the effects of this.

**Comparison with the existing literature**

We identified 27% (95% CI: 17 to 37%) of lung cancer patients to have pre-treatment thrombocytosis; this is much higher than the 1.5-2.2% found in the general (healthy) population. This is in keeping with previous studies: Hamilton and Peters (2005) reported that 26% of lung cancer patients had thrombocytosis and Bailey et al (2017) found 23% of males with undiagnosed lung cancer present in primary care with thrombocytosis 12 months before their diagnosis. We also reported an overall mean platelet count of $289 \times 10^9/L$ (95% CI: 268 to 311) for lung cancer patients, again above the estimated mean platelet count of $258 \times 10^9/L$ (SD: 62) for healthy individuals. As these figures did not vary between lung cancer subtypes, we propose there is a generic relationship between lung cancer and a raised platelet count across the major lung cancer subtypes. This may reflect the lungs being the site of 50% of platelet biogenesis, which could be stimulated by over-expression of cytokines and growth factors in the tumour microenvironment, irrespective of the
tissue subtype. He et al., (2019)\textsuperscript{42} reported a reduced proportion of thrombocytosis in patients with \( \geq 50\% \) ALK-positive tumour cells, compared to patients with 15-49\% ALK-positive tumour cells, which may be suggestive of a negative association between ALK translocations and thrombocytosis. As the only known study to report such a finding, it requires confirmation.

Platelets assist tumour metastasis in a number of ways. Tumour cells activate platelets upon dissemination, causing them to surround and protect the disseminated tumour cells from immune destruction and shear stress to facilitate their haematological metastasis.\textsuperscript{50} Furthermore, platelet-derived growth factors promote endothelial permeability to expedite transendothelial migration for tumour extravasation in distant tissues and organs.\textsuperscript{51} Platelet-derived growth factors also stimulate tumour cell proliferation in order to establish and sustain secondary tumour growth at these distant sites. Of note, the platelet-derived growth factor pathway is regulated by the tumour suppressor p53, encoded by the \textit{TP53} gene, which is commonly mutated in lung cancer patients.\textsuperscript{52}

Unfortunately, there is no existing literature regarding platelet count in lung cancer patients with \textit{TP53} mutations.

Whether thrombocytosis is due to the development of lung cancer or whether lung cancer development is enhanced by thrombocytosis is as yet unknown, and it may be truly bidirectional. Thrombocytosis can be a reactive condition that develops secondary to other disease, including lung cancer.\textsuperscript{53} However, a recent Mendelian randomisation analysis suggested a causal relationship between raised platelet count and increased lung cancer risk.\textsuperscript{54}

\textbf{Clinical implications}

These findings will be of interest to clinicians involved in diagnosing and estimating prognosis in lung cancer. Platelet count has long been used as a marker of prognosis in several cancer types; these results show that an elevated platelet count is no more strongly indicative of one lung cancer subtype over any other, and that lung cancer should be considered in a patient with an otherwise unexplained raised platelet count.

\textbf{CONCLUSION}

This systematic review and meta-analysis is the first to assess the relationship between platelet count and the subtypes of lung cancer. We report a 27\% prevalence (95\% CI: 17\% to 37\%) of thrombocytosis across lung cancer patients and a mean platelet count of 289 \( \times 10^9 \)/L (95\% CI: 268 to
We report no evidence of differences in platelet levels across the major subtypes of lung cancer and therefore suggest that a thrombocytosis is likely to be a generic feature across all lung cancer subtypes.

**FUNDING**

This work was supported by grant MR/N0137941/1 for the GW4 BIOMED DTP, awarded to the Universities of Bath, Bristol, Cardiff and Exeter from the Medical Research Council (MRC)/UKRI held by MB. This work was also supported by the CanTest Collaborative (funded by Cancer Research UK C8640/A23385) of which WH is a co-director, and from which SERB receives salary support. OU was supported by the National Institute for Health Research (NIHR) Applied Research Collaboration SouthWest Peninsula (PenARC). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health and Social Care. The funding sources had no role in the study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit for publication.
REFERENCES

1. Office of National Statistics. Cancer survival in England - adults diagnosed. 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. [accessed 28 April 2020]

2. 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;8(4):5379-87.

3. Bailey SE, Ukoumunne OC, Shephard EA, et al. Clinical relevance of thrombocytosis in primary care: a prospective cohort study of cancer incidence using English electronic medical records and cancer registry data. *Br J Gen Pract* 2017;67(659):e405-e13. doi: 10.3399/bjgp17X691109

4. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000;283(15):2008-12. doi: 10.1001/jama.283.15.2008

5. Shamsan L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ: British Medical Journal* 2015;349:g7647. doi: 10.1136/bmj.g7647

6. Baevsky SE, O'Connell D, et al. Thrombocytosis as prognostic factor for survival in patients with advanced non small cell lung cancer treated with first-line chemotherapy. *Journal of IMAB - Annual Proceeding (Scientific Papers)* 2014;20(6):560-64.

7. Davidov D. Thrombocytosis and immunohistochemical expression of connexin 43 at diagnosis predict survival in advanced non-small-cell lung cancer treated with cisplatin-based chemotherapy. *Cancer Chemother Pharmacol* 2013;71(4):893-904. doi: 10.1007/s00280-013-2080-6

8. 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;12:67. doi: 10.1186/1477-7819-12-67

9. Nakano T, Fuji J, Tamura S, et al. Thrombocytosis in patients with malignant pleural mesothelioma. *Cancer* 1986;58(8):1699-701. doi: 10.1002/1097-0142(19861015)58:8<1699::aid-cncr2820580820>3.0.co;2-b

10. Pedersen LM, Milman N. Diagnostic significance of platelet count and other blood analyses in patients with lung cancer. *Oncl Rep* 2003;10(1):213-6.

11. Skorek P, Stepien K, Fila M, et al. Prognostic significance of the combined use of preoperative platelet count and serum carcinoembryonic antigen level in non-small-cell lung cancer. *Gen Thorac Cardiovasc Surg* 2010;58(11):573-6. doi: 10.1007/s11748-010-0647-2
17. Biswas S, Sarkar S, Chakraborty J, et al. Occult micrometastasis to bone marrow in early lung cancer: a clinicopathologic study from West Bengal, India. *Asian Pac J Cancer Prev* 2010;11(3):747-51.

18. Demirkazik A, Asik M, Yalcin B, et al. The prognostic importance of leucocytosis, thrombocytosis and serum vascular endothelial growth factor (VEGF) level in inoperable non-small cell lung cancer (NSCLC): A match-pair analysis. *UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi* 2010;20(1):14-19.

19. Karagoz B, Alacacioglu A, Bilgi O, et al. Platelet count and platelet distribution width increase in lung cancer patients. *Anatolian Journal of Clinical Investigation* 2009;3(1):32-34.

20. Li MM, Wang X, Yun ZY, et al. Platelet indices in non-small cell lung cancer patients with brain metastases. *Cancer Biomark* 2019;24(4):515-19. doi: 10.3233/CBM-192393

21. Nakano K, Sugiyama K, Satoh H, et al. Risk factors for disseminated intravascular coagulation in patients with lung cancer. *Thorac Cancer* 2018;9(8):931-38. doi: 10.1111/1759-7714.12766

22. Sakin A, Yasar N, Arici S, et al. Effect of Pretreatment Platelet Parameters on Survival in Limited Disease Small Cell Lung Cancer. *Asian Pac J Cancer Prev* 2019;20(6):1879-85. doi: 10.31557/APJCP.2019.20.6.1879

23. Unsal E, Atalay F, Atikcan S, et al. Prognostic significance of hemostatic parameters in patients with lung cancer. *Respir Med* 2004;98(2):93-8. doi: 10.1016/j.rmed.2003.07.001

24. Xu C, Fu X. The changes of blood coagulation in surgical patients with lung cancer. *Zhongguo Fei Ai Za Zhi* 2010;13(2):136-9. doi: 10.3779/j.issn.1009-3419.2010.02.11

25. Zhang W, Yu C, Huang B, et al. Correlation between bone metastasis and thrombocytosis in pulmonary adenocarcinoma patients. *Oncol Lett* 2015;9(2):762-68. doi: 10.3892/ol.2014.2770

26. Zhu JF, Cai L, Zhang XW, 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(2):96-104. doi: 10.5732/cjc.012.10307

27. Bernhardt D, Aufderstrasse S, König L, et al. Impact of inflammatory markers on survival in patients with limited disease small-cell lung cancer undergoing chemoradiotherapy. *Cancer Management and Research* 2018;10:6563-69.

28. de Campos E, Radford J, Steward W, et al. Clinical and in vitro effects of recombinant human erythropoietin in patients receiving intensive chemotherapy for small-cell lung cancer. *J Clin Oncol* 1995;13(7):1623-31. doi: 10.1200/JCO.1995.13.7.1623

29. Fang L, Sheng H, Wan D, et al. Prognostic role of multidrug resistance-associated protein 1 expression and platelet count in operable non-small cell lung cancer. *Oncol Lett* 2018;16(1):1123-32. doi: 10.3892/ol.2018.8763

30. 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. *Clin Respir J* 2018;12(2):433-47. doi: 10.1111/crj.12534

31. Ji Y, Sheng L, Du X, et al. Elevated platelet count is a strong predictor of poor prognosis in stage I non-small cell lung cancer patients. *Platelets* 2015;26(2):138-42. doi: 10.3109/09537104.2014.888547

32. Li SQ, Jiang YH, Lin J, et al. Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. *Cancer Med* 2018;7(4):1221-31. doi: 10.1002/cam4.1428

33. Li Y, Wei S, Wang J, et al. Analysis of the factors associated with abnormal coagulation and prognosis in patients with non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2014;17(11):789-96. doi: 10.3779/j.issn.1009-3419.2014.11.04

34. Phan TT, Nguyen ATT, Van Nguyen AN, et al. Neutrophil to lymphocyte with monocyte to lymphocyte ratio and white blood cell count in prediction of lung cancer. *Australasian Medical Journal* 2018;11(4):231-36.
35. Shi L, Li Y, Yu T, et al. Predictable Resistance and Overall Survival of Gemcitabine/Cisplatin by Platelet Activation Index in Non-Small Cell Lung Cancer. *Med Sci Monit* 2018;24:8655-68. doi: 10.12659/MSM.911125
36. Suzuki R, Wei X, Allen PK, et al. Hematologic variables associated with brain failure in patients with small-cell lung cancer. *Radiother Oncol* 2018;128(3):505-12. doi: 10.1016/j.radonc.2018.05.026
37. Yu D, Liu B, Zhang L, et al. Platelet count predicts prognosis in operable non-small cell lung cancer. *Exp Ther Med* 2013;5(5):1351-54. doi: 10.3892/etm.2013.1003
38. Abrahim VT, Radhakrishna BS, Abdulwahab MO. A study of paraneoplastic syndrome patterns in patients with bronchogenic carcinoma. *Bahrain Medical Bulletin* 2005;27(4):172-74.
39. Demirci NY, Turay UY, Yılmaz A, et al. Vascular events in lung cancer. *Asian Pac J Cancer Prev* 2011;12(10):2685-7.
40. Gonzalez Barcala FJ, Garcia Prim JM, Maldes Rodriguez M, et al. Platelet count: association with prognosis in lung cancer. *Med Oncol* 2010;27(2):357-62. doi: 10.1007/s12032-009-9217-9
41. Wang YQ, Zhi QJ, Wang XY, et al. Prognostic value of combined platelet, fibrinogen, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with lung adenocarcinoma. *Oncol Lett* 2017;14(4):4331-38. doi: 10.3892/ol.2017.6660
42. He Y, Gong R, Sun LY, et al. The Percentage of Anaplastic Lymphoma Kinase-Positive Tumor Cells Has Clinical Implications for Patients with Non-Small Cell Lung Cancer. *Genet Test Mol Biomarkers* 2019;23(8):589-97. doi: 10.1089/gtmb.2019.0038
43. Yang Y, Xu H, Yang G, et al. The value of blood biomarkers of progression and prognosis in ALK-positive patients with non-small cell lung cancer treated with crizotinib. *Asia Pac J Clin Oncol* 2019;12:12. doi: 10.1111/ajco.13284
44. Phan TT, Ho TT, Nguyen HT, et al. The prognostic impact of neutrophil to lymphocyte ratio in advanced non-small cell lung cancer patients treated with EGFR TKI. *Int J Gen Med* 2018;11:423-30. doi: 10.2147/IJG.M.S174605
45. Zhang Y, Feng YC, Zhu HG, et al. The peripheral blood neutrophil-to-lymphocyte ratio is a prognostic predictor for survival of EGFR-mutant nonsmall cell lung cancer patients treated with EGFR-TKIs. *Medicine (United States)* 2018;97(30)
46. Erikssen J, Hellem A, Stormorken H. Chronic effect of smoking on platelet count and “platelet adhesiveness” in presumably healthy middle-aged men. *Thromb Haemost* 1977;38(3):606-11.
47. Hamilton W, Peters TJ, Round A, et al. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. *Thorax* 2005;60(12):1059-65. doi: 10.1136/thx.2005.043880
48. Demirin H, Ozhan H, Ugun T, et al. Normal range of mean platelet volume in healthy subjects: Insight from a large epidemiologic study. *Thrombosis Research* 2011;128(4):358-60. doi: https://doi.org/10.1016/j.thromres.2011.05.007
49. Lefrançais E, Ortiz-Muñoz G, Caudriller A, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. *Nature* 2017;544(7648):105-09. doi: 10.1038/nature21706
50. Gay L, Felding-Hebermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer* 2011;11:123-34. doi: https://doi.org/10.1038/nrc3004
51. Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. *J Hematol Oncol* 2018;11(1):125-25. doi: 10.1186/s13045-018-0669-2
52. Farooqi AA, Siddik ZH. Platelet-derived growth factor (PDGF) signalling in cancer: rapidly emerging signalling landscape. *Cell Biochem Funct* 2015;33(5):257-65. doi: 10.1002/cbf.3120
53. Weryńska B, Ramlau R, Podolak-Dawidziak M, et al. Serum thrombopoietin levels in patients with reactive thrombocytosis due to lung cancer and in patients with essential thrombocytethemia. *Neoplasma* 2003;50(6):447-51.
54. Zhu Y, Wei Y, Zhang R, et al. Elevated Platelet Count Appears to Be Causally Associated with Increased Risk of Lung Cancer: A Mendelian Randomization Analysis. *Cancer Epidemiology Biomarkers & Prevention* 2019;28(5):935-42. doi: 10.1158/1055-9965.Epi-18-0356

**FIGURE LEGENDS**

Figure 1: A flow diagram of the study selection process in accordance to PRISMA-P^5 guidelines.

Figure 2: Random effects meta-analysis of studies that reported the proportion of patients with thrombocytosis. ^7-16 Bars, 95% CI.

Figure 3: Random effects meta-analysis of studies that reported mean platelet count. ^12,13,17-26 Bars, 95% CI.
6,118 records identified through database searching

1,352 duplicates removed

4,766 records screened

1,681 records excluded

82 full text records assessed for eligibility

44 full text records excluded because:
- Platelet count not stratified by lung cancer subtype
- Platelet count not obtained pre-treatment

38 studies included in qualitative synthesis

18 full text records excluded because:
- Platelet count reported as median
- Thrombocytosis proportion > 400 x 10^9/l
- Inadequate number of studies per subtype for meta-analysis (<2)

20 studies included in quantitative synthesis
| Study                      | ES (95% CI)     | Weight |
|----------------------------|-----------------|--------|
| **ADC**                    |                 |        |
| Alexandrakis (2002)        | 0.50 (0.30, 0.70)| 3.94   |
| Davidov (2014)             | 0.20 (0.11, 0.32)| 4.42   |
| Du (2013)                  | 0.61 (0.53, 0.68)| 4.63   |
| Kim (2014)                 | 0.03 (0.01, 0.08)| 4.57   |
| Nankano, T (1986)          | 0.08 (0.03, 0.18)| 4.40   |
| Olesen (1988)              | 0.28 (0.12, 0.51)| 3.87   |
| Pederson (2003)            | 0.54 (0.29, 0.77)| 3.62   |
| Skorek (2018)              | 0.09 (0.05, 0.16)| 4.60   |
| Tomita (2010)              | 0.03 (0.02, 0.07)| 4.66   |
| **Subtotal (I^2 = 96.75%, p = 0.00)** | 0.22 (0.07, 0.41)| 38.72  |
| **SCC**                    |                 |        |
| Alexandrakis (2002)        | 0.50 (0.22, 0.78)| 3.17   |
| Davidov (2014)             | 0.21 (0.17, 0.26)| 4.68   |
| Du (2013)                  | 0.55 (0.45, 0.64)| 4.55   |
| Kim (2014)                 | 0.16 (0.09, 0.26)| 4.50   |
| Nankano, T (1986)          | 0.13 (0.06, 0.24)| 4.42   |
| Pederson (2003)            | 0.60 (0.39, 0.78)| 3.94   |
| Skorek (2018)              | 0.11 (0.07, 0.17)| 4.60   |
| **Subtotal (I^2 = 92.17%, p = 0.00)** | 0.28 (0.15, 0.43)| 29.87  |
| **LCC**                    |                 |        |
| Alexandrakis (2002)        | 1.00 (0.34, 1.00)| 1.76   |
| Davidov (2014)             | 0.21 (0.08, 0.48)| 3.68   |
| Nankano, T (1986)          | 0.42 (0.19, 0.68)| 3.55   |
| Pederson (2003)            | 0.57 (0.25, 0.84)| 3.04   |
| Skorek (2018)              | 0.13 (0.03, 0.36)| 3.78   |
| **Subtotal (I^2 = 60.93%, p = 0.04)** | 0.36 (0.13, 0.62)| 15.82  |
| **SCLC**                   |                 |        |
| Alexandrakis (2002)        | 0.64 (0.35, 0.85)| 3.47   |
| Michael (1999)             | 0.33 (0.21, 0.47)| 4.36   |
| Nankano, T (1986)          | 0.05 (0.01, 0.17)| 4.29   |
| Pederson (2003)            | 0.36 (0.15, 0.65)| 3.47   |
| **Subtotal (I^2 = 85.66%, p = 0.00)** | 0.30 (0.08, 0.58)| 15.60  |

Heterogeneity between groups: p = 0.761
Overall (I^2 = 93.49%, p = 0.00): 0.27 (0.17, 0.37) 100.00
