Research Paper

Preoperative anemia as a prognostic factor in patients with lung cancer: a systematic review and meta-analysis of epidemiological studies

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Abstract

The evidence of current epidemiological studies investigating the relationship between preoperative anemia and progression of lung cancer (LC) patients remains controversial. The PubMed, EMBASE, and Web of Science databases were comprehensively searched by two independent authors to identify related epidemiological studies from inception through January 31, 2019. Similarly, two researchers separately extracted data and any differences were resolved by discussion. Summarized hazard ratios (HRs) and 95% confidence intervals (CIs) were summarized with inverse variance weighted random effects meta-analysis. Heterogeneity among studies was assessed with the I^2 statistic. Twenty-two studies were included in this meta-analysis. As compared with LC patients without anemia, those with pre-operative anemia were at a 1.6-fold greater risk of death (summarized HR = 1.58; 95% CI = 1.44–1.75), with moderate heterogeneity (I^2 = 53.1%). Funnel plot and statistical analyses showed no evidence of publication bias. Associations between pre-operative anemia and OS were broadly consistent across numerous subgroups analyses stratified by the study design, geographic location, number of cases, tumor, node, and metastasis (TNM) stage, histology, quality, and adjustment for potential confounders (age, sex, body mass index, TNM stage, histology, performance status, surgery, blood transfusion, and systemic inflammatory response markers). Similar patterns were observed in the sensitivity analyses. The results of meta-regression analysis suggested no evidence of significant heterogeneity between subgroups. In conclusion, pre-operative anemia was associated with poorer overall survival among LC patients.

Key words: pre-operative anemia, overall survival, lung cancer (LC) patients, meta-analysis

Introduction

Lung cancer (LC) is the leading cause of cancer-related death worldwide, accounting for approximately 1.59 million deaths in 2012 [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all LCs and almost 70% of patients present with locally advanced or metastatic disease at the time of diagnosis [2, 3]. Despite advances in treatment, the 5-year overall survival (OS) rate remains at less than 20% [4]. Established predictors of OS among LC patients include age at diagnosis, sex, tumor stage, histologic type, and certain genetic mutations [4]. However, monitoring of these factors is either invasive or costly and provides insufficient evidence for validation [5-7]. Therefore, economical and convenient clinical biomarkers for individualized prognosis and prediction of treatment outcomes are still urgently required for LC patients.

Hemoglobin (Hb) is a biochemical biomarker commonly assessed during clinical examinations [8]. Notably, anemia and low Hb levels are quite common in patients with malignant tumors, including LC, and might be multifactorial. Indeed, low Hb levels,

particularly in patients with more aggressive tumors, may also be related to complex interactions among the immune system, tumor microenvironment, and cancer cells [9, 10]. Although the number of studies exploring the prognostic role of preoperative anemia and Hb levels has been increasing, the results are inconsistent and often based on small samples. Of note, Caro et al. [11] summarized the evidence of this topic in 2001 and several later reports have indicated that preoperative anemia or low Hb levels are associated with poor survival among LC patients [8, 12-33]; however, contradictory or null reports also exist [34-37].

Importantly, to the best of our knowledge, the prognostic value of preoperative anemia in LC patients has not been investigated in any systematic review or meta-analysis since 2001. Therefore, the purpose of this study was to summarize and update the currently available evidence from epidemiological studies regarding the association between pre-operative anemia and OS of LC patients.

Material and Methods

Search strategy

Two authors (YL and X-XF) independently and systematically searched the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.elsevier.com/solutions/embase-biom edical-research), and Web of Science (https://www.webofknowledge.com) databases from inception to the end of January 2019 for relevant epidemiological studies investigating the association between pre-operative anemia and progression of LC using the following search algorithm: "(anemia OR hemoglobin OR hematocrit OR transfusion OR blood cell OR hematology) AND (lung OR pulmonary) AND (cancer OR neoplasm OR carcinoma OR tumor)". A manual review of references from eligible systematic and narrative reviews was also performed. A meta-analysis was planned, conducted, and reported according to the guidelines of the Meta-Analysis of Observational Studies in Epidemiology group [38].

Study selection and exclusion

The following inclusion criteria were used: (i) observational or experimental study design; (ii) studies that evaluated the association between preoperative anemia status or Hb level and prognostic outcomes of LC patients; (iii) reported at least one of the outcomes of interest (i.e., OS, cancer-specific mortality, disease-free survival, event-free survival, progression-free survival, and recurrence-free survival); and (iv) studies that included the hazard ratio (HR) or relative risk (RR)

with a 95% confidence intervals (CI), or reported sufficient data to calculate those risk estimates. The following exclusion criteria were used: (i) reviews without original data, ecological studies, editorials, and case reports; and (ii) studies that reported risk estimates without a 95% CI (e.g., could not be included in the statistical summary). If multiple studies had a duplicate patient cohort, only that with the largest sample size was included for the same outcome. If multiple studies had a duplicate patient cohort as well as the same sample size, only that with the longest follow-up duration was included for the same outcome. However, multiple studies with duplicate patient cohorts but with different outcomes of interest were included for analysis separately for each outcome.

The titles and abstracts of the retrieved articles were checked for relevancy before the full-text article was examined. The relevant data were extracted from the complete articles. Also, the bibliographies of the selected articles were manually reviewed. The titles, abstracts, and full texts of the resulting articles were examined in detail by two independent authors (YL and X-XF) and discrepancies were resolved by consensus.

Data abstraction and quality assessment

The following information was extracted from each included study by a single investigator (YL): first author, publication year, country, study design, number of patients, outcomes characteristics, and study-specific adjusted risk estimates with 95% CIs. For risk estimates, if both univariate and multivariate analyses were provided, data from multivariate analysis were extracted; otherwise, data from univariate analysis were used. The predefined primary outcome was progression-free survival and the secondary outcome was OS. Extracted data were entered into a standardized Excel (Microsoft Corporation, Redmond, WA, USA) file. Subsequently, an independent author (Y-PB) checked the data and all differences were resolved by a third investigator (X-XF). Although five included studies were randomized controlled trials [22, 23, 33, 34, 37], each retrospectively analyzed the prognostic role of pre-operative anemia in the include patients. Therefore, two independent authors (YL and X-XF) assessed the methodological quality of the included studies according to the Newcastle–Ottawa Scale [39].

Statistical analysis

The HR and 95% CI are presented as summaries of the risk estimates of each study as calculated with a random effects model to investigate the association between preoperative anemia status and Hb levels

with the progression of LC. For studies [12-14, 18, 22, 25-27] that set patients with anemia as the reference group, the counting method proposed by Hamling et al. [40] was used to recalculate the HR and 95% CI. Heterogeneity across the studies was quantified using the I^2 statistic, which indicates significant heterogeneity when $I^2 > 50\%$ [41]. Also, *post hoc* subgroup analyses was conducted according to the study design (retrospective *vs.* prospective), geographic location (Asia, Europe, and North America), tumor, node, and metastasis (TNM) stage (all, advanced stage, and early stage), histology (non-small cell *vs.* small cell), study quality (low *vs.* high risk), the median number of LC cases (≥ 300 *vs.* < 300), and adjustments made for potential confounders (including age at surgery/diagnosis, sex, body mass index, TNM stage, histology, performance status, surgery, blood transfusion, and systemic inflammatory response markers). Heterogeneity between subgroups was evaluated by meta-regression analysis. Small study biases (e.g., publication bias) were assessed by visually inspecting a funnel plot and conducting tests according to Begg et al. [42] and Egger et al. [43] Sensitivity analyses were conducted by removing one study at a time to examine the effect of data from each study on the overall estimate. The sequential exclusion strategy proposed by Patsopoulos et al. [44] was used to determine whether the overall estimates were influenced by the substantial heterogeneity observed. Studies that accounted for the largest share of heterogeneity were sequentially and cumulatively excluded until I^2 was < 50%. Then, further examinations were conducted to determine whether the risk estimates were consistent [45, 46]. All statistical analyses were performed using the Stata statistical software package (ver. 12.0; StataCorp LP, College Station, TX, USA).
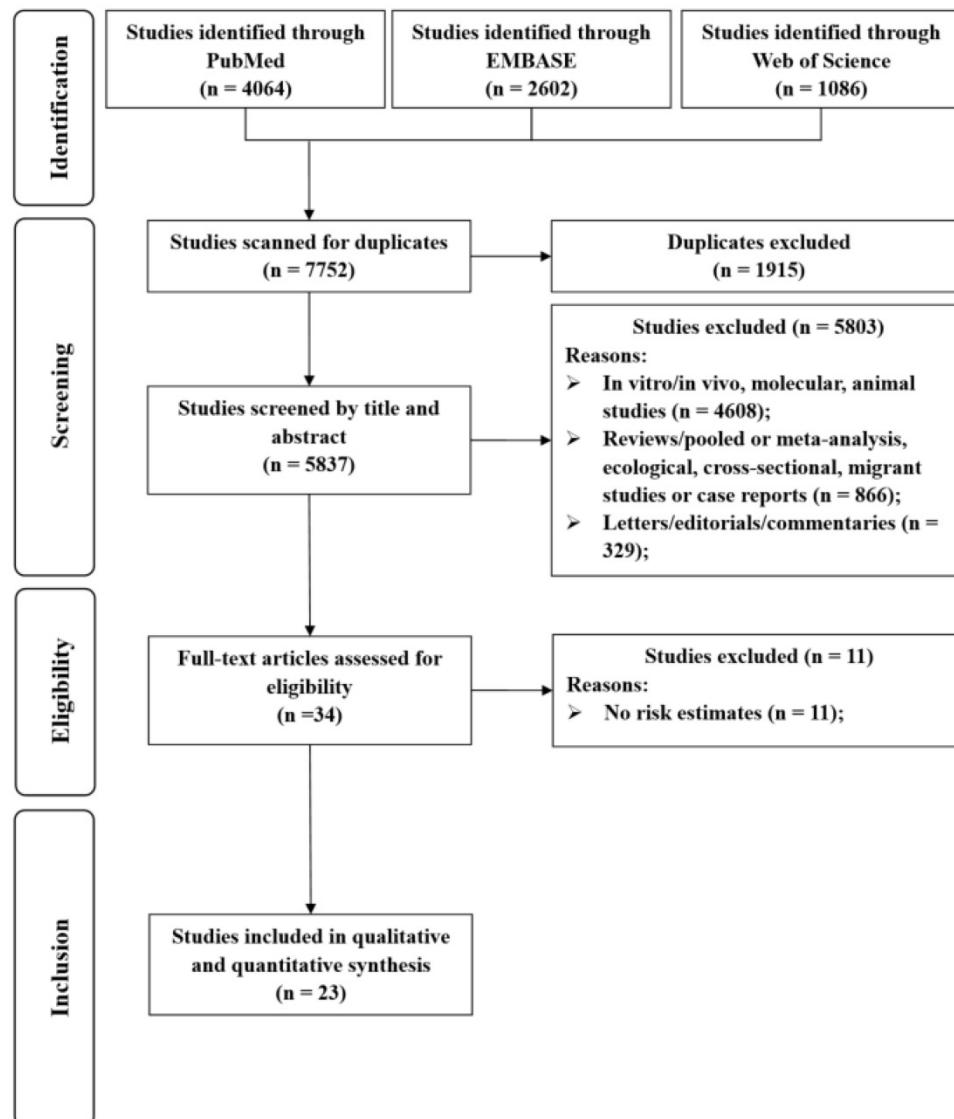

Figure 1. Selection of studies for inclusion in this meta-analysis.

Results

Search results, study characteristics, and quality assessment

The detailed processes of literature screening, study selection, and study exclusion are summarized in Figure 1. The initial search retrieved 7752 unique reports. After removing duplicates and screening the titles and abstracts, the reviewers judged that 34 articles were potentially eligible for inclusion and thus consequently subjected to full-text review. After exclusion, 23 studies were included in the meta-analysis.

Table 1 presents the main characteristics of the 23 included studies. These studies were published from 1991 to 2018 and included a total of 10,612 LC patients with a range of 99–2351 cases among the individual studies. These 23 reports were designed as retrospective (n = 16) and prospective studies (n = 7). The majority of the included studies were conducted in North America (n = 9), seven in Asia, and six in Europe. More than half of the included studies adjusted for age at diagnosis/surgery (n = 16) and TNM stage (n = 14), while less than half adjusted for performance status (n = 11), sex (n = 10), histology (n = 10), and surgery (n = 8). Fewer studies adjusted for systemic inflammatory response markers (n = 6), blood transfusion (n = 5), body mass index (n = 2), and chemotherapy (n = 3).

Table 1. Characteristics of 23 studies included in the meta-analysis

First author, [ref], year, country	Study design	No. of cases	TNM stage	Histology	Anemia cut-off (unit)	Outcome	Adjustment
Zhang et al. [8], 2018, China	Retrospective cohort	416	I-IV	NSCLC	<120 (M) ≤110 (F) (g/L)	OS	Age, sex, TNM stage, PS, Lung lobectomy, chemotherapy, and radiotherapy
Holgersson et al. [34], 2017, Multi-centers	RCT	99	IIIB-IV	NSCLC	<110 (g/L)	OS	Age at diagnosis, sex, histology, PS, white blood cell and platelet at baseline and treatment arm
Holgersson et al. [35], 2017, Sweden	RCT	222	IIIA-IIIB	NSCLC	<110 (g/L)	OS	Age at diagnosis, sex, histology, PS, white blood cell and platelet, weight loss, and TNM stage
Lee et al. [12], 2017, Koera	Retrospective cohort	135	IIIB-IV	NSCLC	<13 (M) <12 (F) (g/dL)	OS	N/A
Liu et al. [13], 2017, China	Retrospective cohort	139	ED/LD	SCLC	N/A	OS	N/A
Cata et al. [14], 2016, USA	Retrospective cohort	861	I	NSCLC	<13 (M) <12 (F) (g/dL)	RFS/OS	Age, body mass index, sex, PS, histology, preoperative neutrophil-to-lymphocyte ratio, blood transfusion, and surgery type
Ng et al. [36], 2012, USA	Prospective cohort	361	IA-IB	NSCLC	<13 (M) <12 (F) (g/dL)	DFS/OS	Age, sex, blood transfusion, and TNM stage
Wu et al. [16], 2012, China	Retrospective cohort	200	ED	SCLC	N/A	OS	N/A
Park et al. [17], 2009, Koera	Retrospective cohort	316	IIIB-IV	NSCLC	<11 (g/dL)	OS	N/A
Chamogeorgakis et al. [18], 2008, USA	Retrospective cohort	214	IA-IIB	NSCLC	≤12 (g/dL)	CSM/OS	N/A
Panagopoulos et al. [20], 2008, Greece	Retrospective cohort	331	I-IV	NSCLC	<12 (g/dL)	OS	Age, sex, operation severity, operation type, histology, TNM stage postoperative hospital stay, blood transfusion and number of red blood cell units transfused
Tomita et al. [21], 2008, Japan	Retrospective cohort	240	I-IV	NSCLC	N/A	OS	Age, sex, histology, TNM stage, and preoperative serum carcinoma embryonic antigen level
Ademuyiwa et al. [22], 2007, USA	RCT	203	IIIA-IIIB	NSCLC	<12 (g/dL)	OS	Age ,sex, ethnicity, body mass index, PS, FEV 1, smoking, use of positron emission tomography scan in staging and stage
Gauthier et al. [37], 2007, Canada	RCT	482	IB- II	NSCLC	<120 (g/L)	OS	Age, sex, PS, TNM stage, histology, type of surgery, and baseline lactic dehydrogenase
Mandrekar et al. [23], 2006, USA and Canada	RCT	1053	IIIB-IV	NSCLC	<13.2 (M) <11.5 (F) (g/dL)	OS	Age, sex, PS, TNM stage, BMI, white blood cell, and platelet count
Aoe et al. [24], 2005, Japan	Retrospective cohort	611	I-IV	LC	<13 (M) <12 (F) (g/dL)	OS	Age, sex, PS, histology, TNM stage, and lactic dehydrogenase
Berardi et al. [25], 2005, Italy	Retrospective cohort	439	IA-IIIB	NSCLC	≤10 (g/dL)	OS	Age, sex, smoking, PS, histology, TNM stage, type of surgery, and transfusions
Yovino et al. [26], 2005, USA	Retrospective cohort	125	I-II	NSCLC	<12 (g/dL)	OS	Age, sex, histology, TNM stage, p53 status, and type of surgery
Rzyman et al. [27], 2003, Poland	Retrospective cohort	493	I-IV	NSCLC	≤12 (g/dL)	OS	Age, sex, amount and type of transfused blood, sedimentation rate, histology, tumor location, type of resection, and TNM stage
Jazieh et al. [28], 2000, USA	Retrospective cohort	454	I-II	NSCLC	≤10 (g/dL)	EFS/OS	Age, sex, race, TNM stage, histology, and type of surgery
Wigren et al. [31], 1997, Finland	Retrospective cohort	502	I-IV	NSCLC	≤125 (g/L)	OS	TNM stage, symptoms, PS, and tumor size
Takigawa et al. [32], 1996, Japan	Retrospective cohort	185	III-IV	NSCLC	≤11 (g/dL)	OS	PS, TNM stage, calcium
Albain et al. [33], 1991, USA	RCT	2351	I-IV	NSCLC	≤11 (g/dL)	OS	Lactic dehydrogenase, calcium metastasis, therapy, year of registration, other therapy groupings, sex, age, smoking, weight loss, and alkaline phosphatase

CSM, cancer-specific mortality; DFS, disease-free survival; ED, extensive stage; EFS, event-free survival; F, female; LC, lung cancer; LD, limited stage; M, male; NSCLC, non-small cell lung cancer; N/A, not available; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; RFS, recurrence-free survival; SCLC, small cell lung cancer.

Table 2. Methodological quality of all included cohort studies

First author (reference), year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor †	Assessment of outcome	Follow-up long enough for outcomes to occur‡	Adequacy of cohort follow-up§
Zhang et al. [8], 2018	*	*	*	*	**	*	*	*
Holgersson et al.[34], 2017	*	*	*	*	**	*	-	*
Holgersson et al. [35], 2017	*	*	*	*	**	*	*	*
Lee et al. [12], 2017	*	*	*	*	-	*	-	*
Liu et al. [13], 2017	*	*	*	*	-	*	*	*
Cata et al. [14], 2016	*	*	*	*	**	*	*	*
Ng et al. [36], 2012	*	*	*	*	**	*	*	*
Wu et al. [16], 2012	*	*	*	*	-	*	*	*
Park et al. [17], 2009	*	*	*	*	-	*	*	*
Chamogeorgakis et al. [18], 2008	*	*	*	*	-	*	*	*
Panagopoulos et al. [20], 2008	*	*	*	*	**	*	*	*
Tomita et al. [21], 2008	*	*	*	*	*	*	*	*
Ademuyiwa et al. [22], 2007	*	*	*	*	*	*	*	*
Gauthier et al. [37], 2007	*	*	*	*	*	*	-	*
Mandrekar et al. [23], 2006	*	*	*	*	-	*	*	*
Aoe et al. [24], 2005	*	*	*	*	**	*	-	*
Berardi et al. [25], 2005	*	*	*	*	**	*	*	*
Yovino et al. [26], 2005	*	*	*	*	**	*	*	*
Rzyman et al. [27], 2003	*	*	*	*	**	*	*	*
Jazieh et al. [28], 2000	*	*	*	*	**	*	*	*
Wigren et al. [31], 1997	*	*	*	*	**	*	-	*
Takigawa et al. [32], 1996	*	*	*	*	**	*	*	*
Albain et al. [33], 1991	*	*	*	*	*	*	-	*

A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor."

† A maximum of two stars could be awarded for this item. Studies that controlled for age at diagnosis/TNM stage received one star, whereas those that controlled for other important confounders (i.e., performance status, blood transfusion, and surgery/chemotherapy) received an additional star.

‡ A cohort study with a median follow-up time >1 year was assigned one star.

§ A cohort study with a follow-up rate >75% was assigned one star.

The quality assessment characteristics of the included studies are shown in Table 2. The major difference among the included studies was the control for an important factor or an additional factor category; 13 of the included studies were assigned two full scores. Six studies [12, 24, 31, 33, 34, 37] had follow-up periods of less than one year or were not mentioned; therefore, these studies were not assigned a score when testing for whether the follow-up duration was sufficiently long for outcomes to occur.

Pre-operative anemia and OS of LC patients

As compared with LC patients without anemia, those with pre-operative anemia were at approximately a 1.58-fold greater risk of death (summarized HR = 1.58; 95% CI = 1.44–1.75) (Figure 2), with moderate heterogeneity (I^2 = 53.1%). Funnel plot and statistical analyses showed no evidence of publication bias (Figure 3).

Subgroup and sensitivity analyses

To determine whether the study characteristics and adjustment for potential confounders had any impact on risk estimates, numerous subgroup analyses stratified by these issues were performed. Significant positive findings were observed throughout these subgroup analyses (Table 3). Sensitivity analyses using an alternative statistical model (fixed-effects HR = 1.50, 95% CI = 1.42–1.60) and by excluding five studies [12, 13, 16-18] without adjustment for any potential confounders (summarized HR = 1.54, 95% CI = 1.38–1.72; I^2 = 56.4%) showed robust findings. Additionally, the sensitivity analysis showed that the summarized HR

ranged from 1.55 (95% CI = 1.41–1.69; I^2 = 44.3%; exclusion of Takigawa et al. [32]) to 1.62 (95% CI = 1.48–1.77; I^2 = 37.0%; exclusion of Ademuyiwa et al. [22]) (Figure 4). When the studies that contributed the largest amount to heterogeneity until I^2 was less than 50% were sequentially excluded, the summarized HR was 1.62 (95% CI = 1.48–1.77; I^2 = 37.0%), which was similar to the original estimate.

Discussion

This systematic review and meta-analysis with a large sample size (comprising 10,612 LC patients) provides support for the hypothesis that pre-operative anemia is associated with increased mortality among LC patients. This finding should improve the attention of both patents and clinicians to better management of pre-operative anemia before further treatment of LC.

Table 3. Risk estimate summary of the relationship between pre-operative anemia and OS of LC patients

	No. of studies	HR	95% CI	I^2 (%)	P_h†	P_h‡
Overall	23	1.58	1.44–1.75	53.1	0.001	
Subgroup analyses						
Study design						0.104
Retrospective	16	1.67	1.49–1.86	45.2	0.026	
Prospective	7	1.40	1.19–1.64	46.2	0.084	
Geographic location						0.116
Asia	8	1.73	1.48–2.02	54.8	0.030	
North America	9	1.61	1.34–1.94	65.3	0.003	
Europe	6	1.41	1.22–1.62	0	0.815	
Number of cases (median)						0.818
≥ 300	13	1.59	1.44–1.76	34.3	0.108	
< 300	10	1.61	1.31–1.97	64.3	0.003	
TNM stage						0.415
All	8	1.50	1.37–1.65	0	0.546	
Advanced stage	9	1.63	1.34–1.99	73.3	<0.001	
Early stage	6	1.74	1.33–2.28	47.8	0.088	
Histology						0.823
Non-small cell	20	1.59	1.42–1.77	57.3	0.001	
Small cell	2	1.91	1.37–2.66	0	0.941	
Quality of study						0.847
Low risk	20	1.59	1.42–1.76	56.9	0.001	
High risk	3	1.63	1.28–2.08	13.3	0.316	
Adjustment for potential confounders or risk factors						
Age at diagnosis/surgery						0.125
Yes	16	1.51	1.35–1.67	47.7	0.018	
No	7	1.80	1.49–2.17	48.6	0.069	
Sex						0.303
Yes	14	1.65	1.48–1.85	30.0	0.144	
No	9	1.51	1.30–1.76	61.6	0.005	
Body mass index						0.119
Yes	2	1.33	1.06–1.69	78.8	0.030	
No	21	1.64	1.48–1.81	39.3	0.034	
TNM stage						0.892
Yes	14	1.58	1.40–1.77	49.1	0.020	
No	9	1.62	1.35–1.94	61.3	0.008	
Histology						0.375
Yes	14	1.49	1.30–1.70	28.9	0.179	
No	9	1.66	1.45–1.91	64.6	0.001	
Performance status						0.102
Yes	11	1.47	1.29–1.67	58.9	0.007	
No	12	1.73	1.53–1.96	22.8	0.219	
Surgery						0.232
Yes	8	1.74	1.46–2.07	40.3	0.110	
No	15	1.52	1.36–1.70	53.4	0.008	
Blood transfusion						0.374
Yes	5	1.45	1.24–1.70	0	0.978	
No	18	1.64	1.46–1.85	63.3	<0.001	
SIR markers						0.208
Yes	6	1.46	1.29–1.65	0	0.817	
No	17	1.67	1.47–1.89	64.0	<0.001	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; LC, lung cancer; N/A, not available; OS, overall survival; SIR, systemic inflammatory response.

† *p*-value for heterogeneity within each subgroup.

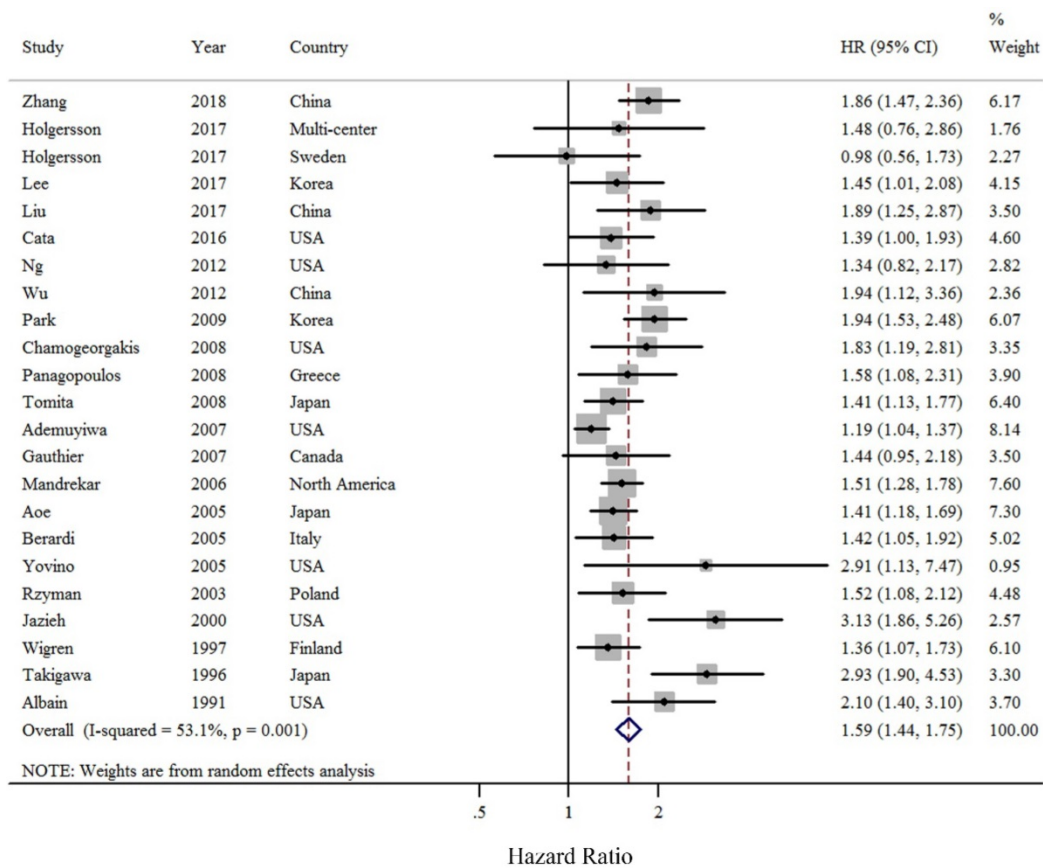‡ *p*-value for heterogeneity between subgroups with meta-regression analysis.

Study	Year	Country		HR (95% CI)	% Weight
Zhang	2018	China		1.86 (1.47, 2.36)	6.17
Holgersson	2017	Multi-center		1.48 (0.76, 2.86)	1.76
Holgersson	2017	Sweden		0.98 (0.56, 1.73)	2.27
Lee	2017	Korea		1.45 (1.01, 2.08)	4.15
Liu	2017	China		1.89 (1.25, 2.87)	3.50
Cata	2016	USA		1.39 (1.00, 1.93)	4.60
Ng	2012	USA		1.34 (0.82, 2.17)	2.82
Wu	2012	China		1.94 (1.12, 3.36)	2.36
Park	2009	Korea		1.94 (1.53, 2.48)	6.07
Chamogeorgakis	2008	USA		1.83 (1.19, 2.81)	3.35
Panagopoulos	2008	Greece		1.58 (1.08, 2.31)	3.90
Tomita	2008	Japan		1.41 (1.13, 1.77)	6.40
Ademuyiwa	2007	USA		1.19 (1.04, 1.37)	8.14
Gauthier	2007	Canada		1.44 (0.95, 2.18)	3.50
Mandrekar	2006	North America		1.51 (1.28, 1.78)	7.60
Aoe	2005	Japan		1.41 (1.18, 1.69)	7.30
Berardi	2005	Italy		1.42 (1.05, 1.92)	5.02
Yovino	2005	USA		2.91 (1.13, 7.47)	0.95
Rzyman	2003	Poland		1.52 (1.08, 2.12)	4.48
Jazieh	2000	USA		3.13 (1.86, 5.26)	2.57
Wigren	1997	Finland		1.36 (1.07, 1.73)	6.10
Takigawa	1996	Japan		2.93 (1.90, 4.53)	3.30
Albain	1991	USA		2.10 (1.40, 3.10)	3.70
Overall (I-squared = 53.1%, p = 0.001)				1.59 (1.44, 1.75)	100.00

NOTE: Weights are from random effects analysis

Figure 2. Forest plot (random effects model) of pre-operative anemia and OS of LC patients. The squares indicate study-specific hazard ratios (size of the square reflects the study-specific statistical weight); the horizontal lines indicate 95% CIs; and the diamond indicates the summary hazard ratio estimate with its 95% CI.
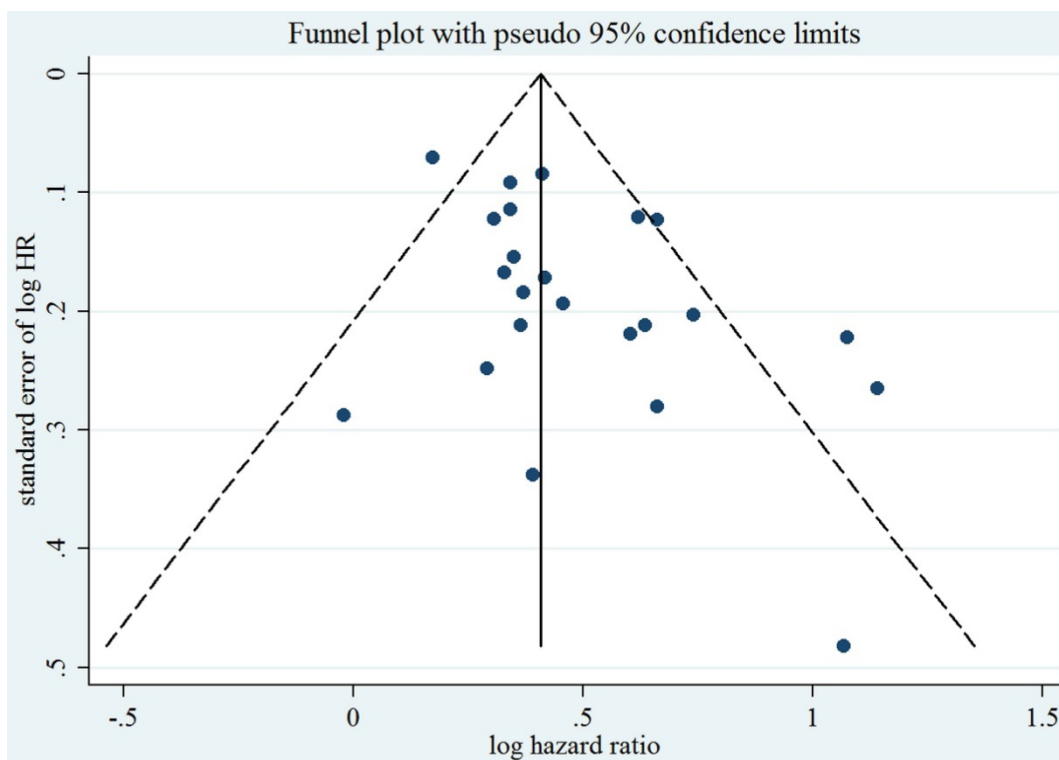
Figure 3. Test for publication bias for OS through Begg's funnel plot. HR, hazard ratio; SE, standard error. The circles alone are real studies. The vertical lines represent the summary effect estimates and the dashed lines represent pseudo-95% CI limits.
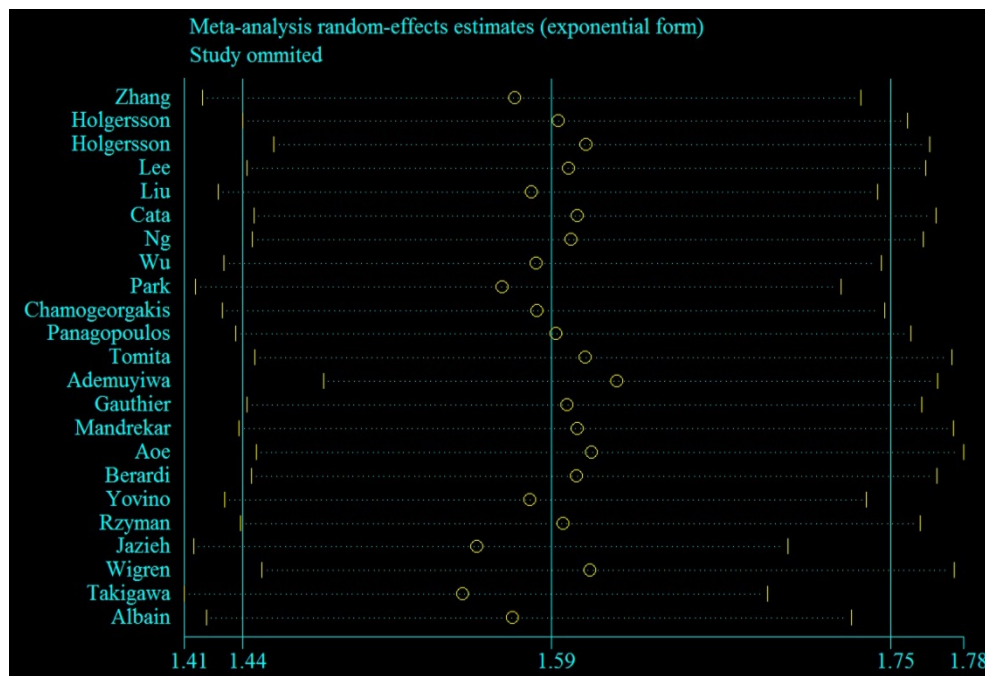
Figure 4. Sensitivity plot corresponding to the relationship between pre-operative anemia and OS of LC patients. The circle indicates the study-specific hazard ratio after excluding the present study; the horizontal dotted lines indicate 95% CIs.

One previous systematic review reported an overall estimate of the effect of anemia on survival in patients with malignant disease [11]. In 2001, Caro et al. [11] found that the relative risk of death was increased by 19% among anemic patients with lung carcinoma. However, this report did not provide details of the extracted information. Furthermore, several included studies [47-51] failed to a risk estimate in the primary analysis. In comparison, the results of the present study, which were primarily based on the most comprehensive published studies, suggested a relatively stronger relationship between pre-operative anemia and survival of LC patients. Of note, these findings were robust in subgroup analyses, which were not performed by Caro et al. [11] in 2001.

The precise mechanisms underlying the association between pre-operative anemia and survival in LC patients have not been fully elucidated. In general, cancer-related anemia is due to multiple etiologies, including blood loss, functional iron deficiency, erythropoietin deficiency from renal disease, and bone marrow involvement with cancer, as well as other factors [52]. One hypothesis is that tumor hypoxia may stimulate angiogenesis, which is a marker of increased tumor aggressiveness [53]. Tumor cells are known to secrete various soluble molecules, including interleukin-6 and tumor necrosis factor-α [8]. These molecules can decrease Hb concentrations by changing the hematopoietic environment [54, 55], suppressing erythropoiesis and

erythropoietin [56], and impairing the erythropoietin response of erythroid progenitor cells [57]. Additionally, in patients with bone metastasis, bone marrow involvement may lead to bone morrow failure, which may then cause low Hb levels [58] and subsequently lead to hypoxia, which could induce genomic changes and enhance the development of malignancy [59]. Hypoxia may also boost tumor angiogenesis and accelerate metastasis [60]. Furthermore, hypoxia may enhance tumor cell resistance to chemotherapy and radiotherapy through the development of multi-drug resistance [61].

The strengths of this study include the systematic and rigorous approach to the identification of epidemiological studies investigating the impact of pre-operative anemia on survival of LC patients. Furthermore, to the best of our knowledge, the present study included the most published studies and had the largest sample size, which allowed for numerous preplanned subgroup analyses to explore differences in the risks for mortality.

This study also had some limitations that should be addressed. First, the majority of the included studies were retrospective, which might have had potential selection and recall biases, thereby diminishing the general credibility of these findings. However, no significant difference was found in the subgroup analysis stratified by study design. Furthermore, most of included studies were scored as low risk after quality assessment. The only three studies with high risk might be attributed to the

adjustment for limited confounders as well as short follow-up periods. Second, the cut-off value and unit of pre-operative anemia varied. For example, six of the included studies defined pre-operative anemia according to patient sex. However, three studies only reported pre-operative anemia as low or normal. Furthermore, five studies used g/L as the unit of anemia. In contrast, 15 studies used g/dL as the unit of anemia. Third, since the majority of the included studies were observational, the association between pre-operative anemia and prognosis of LC may have resulted from unmeasured or residual confounding by other factors. Pre-operative anemia in LC patients may be associated with age at diagnosis, body mass index, TNM stage, histology, performance status, and blood transfusion, which possibly could confound the aforementioned associations. For example, several previous studies have mentioned that blood transfusion might affect adversely the survival of LC patients, especially for stage I non-small cell LC patients [20]. Although the findings were robust in studies that adjusted for these potential confounders, not all were fully adjusted. Notably, five studies provided the risk estimates on the basis of a univariate model, but without adjustment for any confounders. Interestingly, the results of the sensitivity analysis were robust when excluding these five studies. Furthermore, the results of meta-regression analyses found no evidence that these findings differed significantly between studies adjusted for these confounders or not. Fourth, since a limited number of studies reported secondary outcomes (i.e., progression-free survival, recurrence-free survival, or event-free survival), the main focus of the present study was the association between pre-operative anemia and OS of LC patients. Further studies are warranted to provide more information on this issue.

The findings of the present study not only indicate a significant association between pre-operative anemia and an increased risk of LC mortality, but also emphasize the role of systematic reviews to examine focused clinical questions. Pre-operative anemia might be a useful indicator of the prognosis of LC patients. Clinicians should fully consider the status and severity of pre-operative anemia when deciding on an appropriate individualized LC management regime.

Author Contributions

Study concepts: X-XF. Study design: YL, Y-PB, and X-XF. Data acquisition: YL, Y-PB, and X-XF. Quality control of data and algorithms: Z-FZ and C-RJ. Data analysis and interpretation: YL and X-XF. Statistical analysis: YL and X-XF. Manuscript preparation: YL, Y-PB, Z-FZ, C-RJ, ZX, and X-XF. Manuscript editing: X-XF. Manuscript review: YL, Y-PB, Z-FZ, C-RJ, ZX, and X-XF.

Competing Interests

The authors have declared that no competing interest exists.

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