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Original Article

Blood transfusions may adversely affect survival outcomes of patients with lung cancer: a systematic review and meta-analysis

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Background: Despite common use in clinical practice, the impact of blood transfusions on prognosis among patients with lung cancer remains unclear. The purpose of the current study is to perform an updated systematic review and meta-analysis to evaluate the influence of blood transfusions on survival outcomes of lung cancer patients.

Methods: We searched PubMed, Embase, Cochrane Library, and Ovid MEDLINE for publications illustrating the association between blood transfusions and prognosis among people with lung cancer from inception to November 2019. Overall survival (OS) and disease-free survival (DFS) were the outcomes of interest. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using the random-effects model. Study heterogeneity was evaluated with the I^2 test. Publication bias was explored via funnel plot and trim-and-fill analyses.

Results: We included 23 cohort studies with 12,175 patients (3,027 cases and 9,148 controls) for meta-analysis. Among these records, 22 studies investigated the effect of perioperative transfusions, while one examined that of transfusions during chemotherapy. Two studies suggested the possible dose-dependent effect in accordance with the number of transfused units. In pooled analyses, blood transfusions deleteriously influenced both OS (HR=1.35, 95% CI: 1.14–1.61, P<0.001, I^2=0%) and DFS (HR=1.46, 95% CI: 1.15–1.86, P=0.001, I^2=0%) of people with lung cancer. No evidence of significant publication bias was detected in funnel plot and trim-and-fill analyses (OS: HR=1.26, 95% CI: 1.07–1.49, P=0.006; DFS: HR=1.35, 95% CI: 1.08–1.69, P=0.008).

Conclusions: Blood transfusions were associated with decreased survival of patients with lung cancer.

Keywords: Transfusion; cancer; lung cancer; survival; meta-analysis

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Introduction

Lung cancer has the highest mortality rate among tumor entities in the United States, accounting for a quarter of all cancer deaths annually (1). Patients with lung cancer may require blood transfusions due to cancer-induced anemia, blood loss during surgery, or bone marrow suppression caused by chemoradiation (2). Despite common use in clinical practice, the impact of blood transfusions on prognosis among patients with lung cancer remains unclear. Over the past 35 years, efforts have been made to discern the relationship between blood transfusions and survival outcomes [e.g., overall survival (OS) and disease-free survival (DFS)] of lung cancer patients. Of note, there have been long-standing concerns on the associated risk, including possible contamination by undetected malignant cells in the blood products (3,4). In addition, the potential immunomodulatory effect of blood transfusions has been explored (5). It has been hypothesized that blood transfusions may suppress the anti-tumor immunosurveillance and promote growth of tumor cells (6). Previous efforts to elucidate the relationship between transfusions and cancer recurrence have focused primarily on other types of cancer such as colorectal cancer (7). We thus performed an updated systematic review and meta-analysis to evaluate the influence of blood transfusions on survival outcomes of lung cancer patients. The following article is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (8) (available at http://dx.doi.org/10.21037/tlcr-20-933).

Methods

Data sources and search strategy

We searched PubMed, Embase, Cochrane Library, and Ovid MEDLINE for relevant published or unpublished studies from inception to November 2019. Detailed search strategy is shown in Table S1. The electronic search strategy was supplemented by manually reviewing references of identified articles including recent reviews. We imposed no restrictions on the language, the study period, and the sample size.

Study selection and outcome definition

Studies which met the following criteria were eligible for meta-analysis: (I) conducted before November 2019; (II) enrolling patients diagnosed with lung cancer; (III) comparing prognosis between transfused and non-transfused patients. All types of lung cancer and all TNM stages were included. All types of blood products were considered. The outcomes of interest were OS and DFS. We only selected the studies reporting the hazard ratio (HR) for OS or DFS or providing sufficient data to calculate them (9). We screened search results by assessing titles and abstracts, eliminated duplicates, reviewed full-text articles if available, and determined their inclusion independently. Disagreements were settled by consensus among all contributors.

Data extraction and quality assessment

OS, DFS, and their HR with the 95% CI from included studies were extracted using a standardized form. Other compiled study characteristics were as follows: the first author, the publication year, the location of study, the enrollment period, the sample size, the type and stage of cancer, and the type of transfused blood components. Given lack of randomized-controlled trials on the current topic, we utilized the Newcastle-Ottawa Scale (NOS) to evaluate the quality of collected cohort studies. The elements of the NOS are described fully in Table S2.

Data synthesis and statistical analysis

We applied the random-effects model to analyze primary endpoints and presented combined HRs for OS and DFS with their 95% CIs as summary statistics. Pooled HRs were calculated with the restricted maximum-likelihood estimator. The results were illustrated in forest plots. Statistical heterogeneity was quantified using the I^2 statistics (10). Publication bias was examined through funnel plots, along with the trim-and-fill method. Two-sided $P<0.05$ was considered to achieve statistical significance. Subgroup analyses of OS and DFS in patients with lung cancer who received transfusions during surgical resection to detect possible difference between surgical and non-surgical blood transfusions. All statistical computations were performed on R 3.5.1 using the package 'metafor' 2.1-0.

Results

Search results

We identified 843 citations by searching electronic

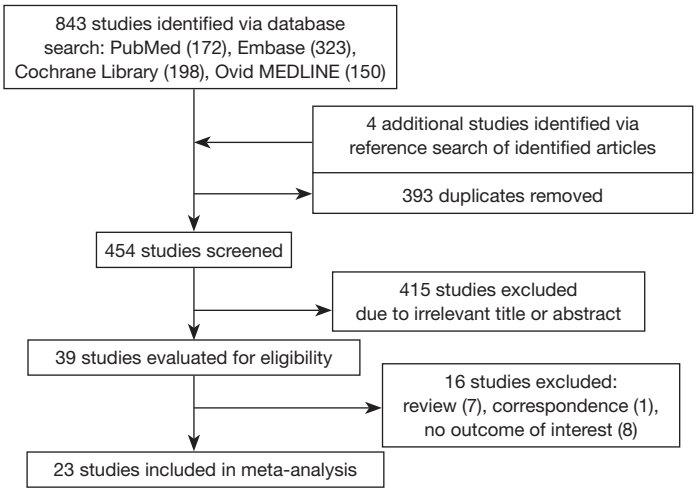

Figure 1 Flow diagram of study selection.

databases including PubMed (n=172), Embase (n=323), Cochrane Library (n=198), and Ovid MEDLINE (n=150) (*Figure 1*). Four studies were added by investigating reference lists of the initially identified articles. After evaluating titles and abstracts, we excluded 393 duplicates and 415 irrelevant articles. Among the remaining 39 studies, 16 studies were removed given that they were review (n=7) or correspondence (n=1) articles or lacked the outcome of interest (n=8). The detailed characteristics of 16 excluded studies are summarized in Table S3. Consequently, 23 studies qualified for subsequent meta-analysis.

Study characteristics

The summaries of individual studies are listed in *Table 1*. All the included records were cohort studies published from 1984 to 2019, including 12,175 patients (3,027 cases and 9,148 controls) in total. Among these trials, ten were conducted in the United States, three in Italy, two in Spain, one in Germany, one in Finland, one in Poland, one in the United Kingdom, one in France, one in China, one Greece, and one in Turkey. The sample size for each of the studies ranged from 105 to 4,847. The pathology and the disease stage of lung cancer varied. Diverse blood products such as whole blood, packed red blood cells, and fresh frozen plasma were transfused. One study compared the effects of allogeneic and autologous transfusions on survival outcomes of patients with non-small cell lung cancer (NSCLC) (23).

Perioperative transfusions were addressed in all included studies except for a recent one dealing with transfusions during chemotherapy (33). Nineteen studies imposed no restriction on the extent of resection, while three studies only investigated patients with early-stage lung cancer who underwent lobectomy (11,22,30). A large U.S. cohort study included records of surgical approaches such as minimally invasive thoracic surgery, although no further analysis was performed with the data (32).

Of note, there exist two recent publications suggesting the possible dose-dependent effect of packed red blood cells on long-term cancer outcomes (31,32). Both articles demonstrated a dose-response relationship between blood transfusions and survival outcomes, particularly in patients who received at least two units of red cells.

Survival analysis

As shown in the forest plot of *Figure 2*, we extracted HRs for OS from 20 records (11-13,15,17-27,29-33). The pooled HR from the random-effects model favored non-transfused patients over transfused patients for OS (HR=1.35, 95% CI: 1.14–1.61, P<0.001). The corresponding I^2 test found no significant heterogeneity among the studies (I^2=0%).

HRs for DFS were compiled from 13 articles (11,13-17,19,22,28,30-33). The forest plot of *Figure 3* illustrates HRs from each of the studies as well as the net HR. The combined results from the random effects model showed that transfused patients had worse DFS than non-transfused patients (HR=1.46, 95% CI: 1.15–1.86, P=0.001). There was no evidence of study heterogeneity (I^2=0%).

To discern any difference between surgical and non-surgical blood transfusions, in addition, we performed subgroup analyses of OS and DFS in patients who

Table 1 Characteristics of included studies

First author	Year	Location	Enrollment period	Size	Cancer pathology	Stage	Blood components
Tartter (11)	1984	USA	1966–1980	165	NSCLC	I (N0)	NA
Hyman (12)	1985	USA	1971–1979	105	Any lung cancer	I–II	WB, PRBC
Pastorino (13)	1986	Italy	1974–1979	283	NSCLC	IA	WB, PRBC
Keller (14)	1988	USA	1974–1981	352	NSCLC	I–II	WB, PRBC
Moores (15)	1989	USA	NA	330	NSCLC	NA	WB, PRBC, FFP
Little (16)	1990	USA	1977–1986	117	NSCLC	I	WB, PRBC
Pena (17)	1992	USA	1980–1984	127	NSCLC	I–II	Any component
Zimmermann (18)	1993	Germany	1976–1985	224	Any lung cancer	I–III	NA
Piantadosi (19)	1994	USA	1988–1989	330	Any lung cancer	I–III	NA
Rainio (20)	1996	Finland	1978–1980	208	Any lung cancer	I–IIIA	Any component
Casanova Viúdez (21)	1999	Spain	1991–1995	281	NSCLC	I–IIIA	NA
Nosotti (22)	2003	Italy	1995–2000	281	NSCLC	I	Any component
Rzyman (23)	2003	Poland	1993–1997	493	NSCLC	I–IV	WB, PRBC
Ghosh (24)	2004	UK	1996–2003	329	AC, SCC	I–IIIB	NA
Peñalver (25)	2005	Spain	1969–2000	856	NSCLC	I	WB, PRBC
Berardi (26)	2005	Italy	1996–2001	439	NSCLC	I–IIIB	NA
Thomas (27)	2007	France	1993–2002	367	Any lung cancer	I–IV	PRBC, PLT, FFP, coagulation factor VIII
Chen (28)	2007	China	1993–2002	280	NSCLC	I–III	NA
Panagopoulos (29)	2008	Greece	1999–2005	331	NSCLC	I–IV	PRBC
Ng (30)	2012	USA	2001–2009	361	NSCLC	I	Leukocyte-depleted PRBC
Cata (31)	2013	USA	2004–2006	636	NSCLC	I–IIIA	PRBC
Latif (32)	2019	USA	2000–2016	4,847	NSCLC	I–IIIA	PRBC
Sakin (33)	2019	Turkey	2012–2018	433	NSCLC	IV	NA

NSCLC, non-small cell lung cancer; NA, not available; WB, whole blood; PRBC, packed red blood cells; AC, adenocarcinoma; SCC, squamous cell carcinoma; FFP, fresh frozen plasma; PLT, platelets.

underwent resection of lung cancer. The analyses showed unchanged results: perioperative blood transfusions were associated with shortened OS (HR=1.35, 95% CI: 1.13–1.62, P=0.001, I^2=0%) and DFS (HR=1.46, 95% CI: 1.13–1.88, P=0.004, I^2=0%).

In short, blood transfusions deleteriously influenced both OS and DFS of people with lung cancer. Such results did not change after exclusively including surgical blood transfusions.

Publication bias

The risk of publication bias was examined by inspecting funnel plots for OS and DFS, respectively. Evident asymmetry was observed in both plots (*Figure 3A*,*B*). Correspondingly, we performed the trim-and-fill analyses for both outcomes, which computed potential four missing studies for OS and four for DFS (*Figure 3C*,*D*). However, the adjustments indicated only slight alterations for both estimates (OS: HR=1.26, 95% CI: 1.07–1.49, P=0.006; DFS: HR=1.35, 95% CI: 1.08–1.69, P=0.008).

Discussion

We conducted a systematic review and meta-analysis of

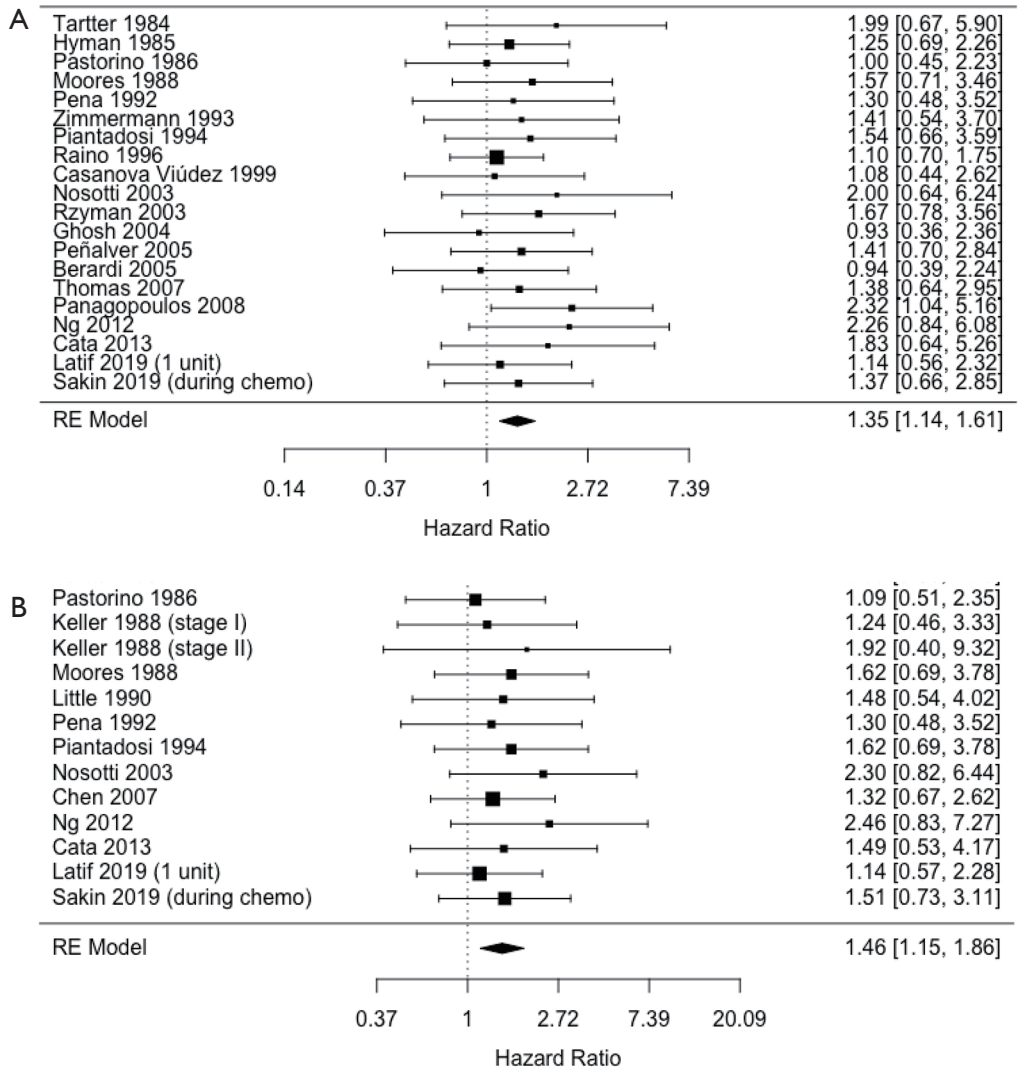

Figure 2 Forest plots showing the effect of blood transfusions on (A) overall survival (OS) and (B) disease-free survival (DFS).

23 cohort studies that examined the influence of blood transfusions on survival outcomes of people with lung cancer. The results showed that the receipt of blood components shortened both OS and DFS of patients with lung cancer. Our study is the most up-to-date and comprehensive systematic review and meta-analysis on the present topic. In comparison to prior meta-analyses (34-36), our study encompassed four recent trials (31-33) with resultant increase in the sample size (n=12,175).

Of note, two of these added studies demonstrated potential dose-dependent association between the amount of blood transfusions and survival outcomes of patients with lung cancer (31,32), which was not attested in preceding studies (13,14,16,22). A U.S. cohort study including 636 patients who underwent surgery for NSCLC showed that the 5-year recurrence-free survival decreased proportionately with the number of units transfused (31). More recently, another U.S. cohort study involving 5,709 patients undergoing NSCLC resection described that the increasing volume of blood transfusions was associated with worse OS, DFS, and recurrence (32). Given that features of both studies coincided in cancer type and stage (i.e., stage I–IIIA NSCLC) as well as blood components (i.e., packed red blood cells), efforts to conduct a subgroup analysis for the potential dose-response relationship between the quantity of blood transfusions and survival outcomes of lung cancer

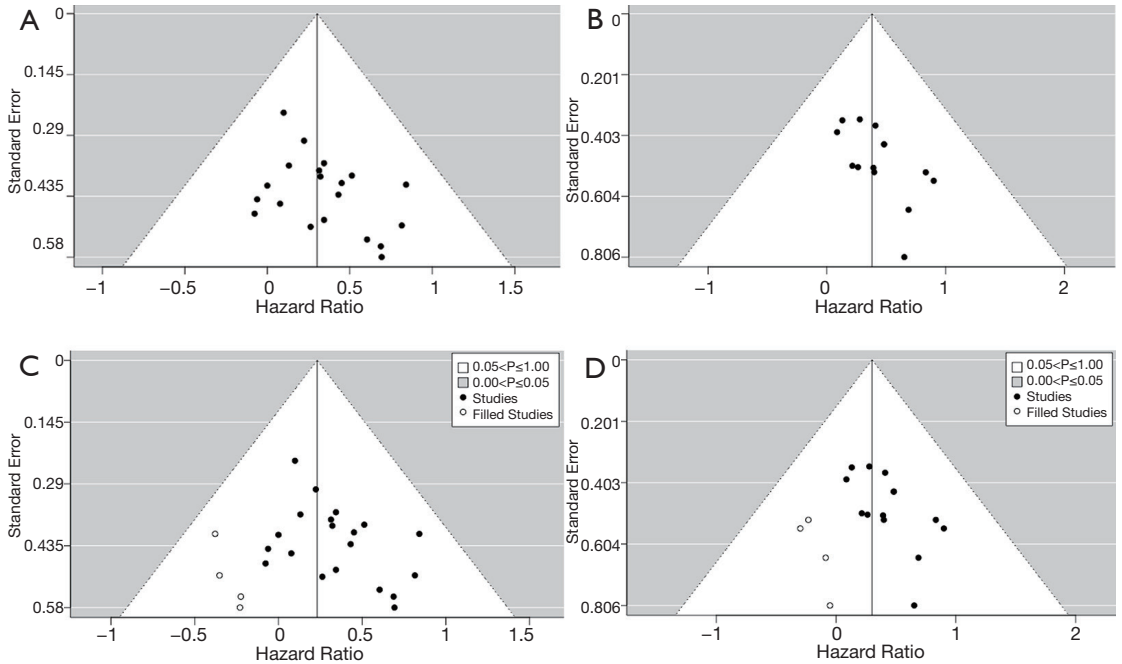

Figure 3 Assessment of publication bias: funnel plots for (A) overall survival (OS) and (B) disease-free survival (DFS); trim-and-fill analyses for (C) OS and (D) DFS.

patients. However, we were unable to combine the results of two studies due to discrepant cut-off values for the transfused units among individual studies.

Nonetheless, these recent findings that larger volumes of blood transfusions were associated with worse prognosis of lung cancer are worthy of being noted given stronger evidence in another type of cancer. In a landmark meta-analysis evaluating the effect of perioperative blood transfusions on recurrence of colorectal cancer (7), recurrence risks increased by 40, 69, and 102% were observed with 1 to 2, 3 to 4, and 5 or more units of blood transfusions, respectively. Furthermore, a more recent study utilizing propensity score matching to minimize possible imbalances in patient characteristics showed a significant dose-response relationship between transfused units and overall mortality following colorectal cancer resection (37). Likewise, more evidence can be gathered in lung cancer if more studies using proper statistical techniques are performed.

Of note, our study also included a recent study investigating the impact of blood transfusions on non-surgical patients with lung cancer for the first time (33). Unlike prior studies mostly focusing on early-stage lung cancer requiring surgical resection, this study addressed advanced stage lung cancer requiring chemotherapy. In the analysis, blood transfusions were associated with significantly shorter DFS and OS, particularly in patients with adenocarcinoma. Such results suggest that blood transfusions per se might be more related to cancer outcomes, rather than operational complexity and aggressiveness of tumors.

One proposed mechanism for this association is direct transmission of the concealed tumor cell in the blood products. The idea of cancer seeding has been explored as a probable rationale for decades, classically in the context of autotransfusion in cancer surgery (3). The theoretical fear of re-infusing malignant cells directly into the bloodstream was fueled by a case report in which unfiltered tumor cells were detected in the intraoperatively salvaged blood (38). These concerns were significantly resolved by multiple trials investigating the safety of cell salvage in cancer surgery where leukoreduction filters were used (39-44). However, the plausibility of such idea was further supported by the reports of long-term leukocyte microchimerism after blood transfusions (45-47) and transferred malignancies through various organ transplantations (4,48-52). Of note, two individuals who had received renal transplants from the same cadaver donor developed fatal melanoma in their donated kidneys (48). These melanomas were considered secondary as the donor had been diagnosed with the same condition at an early, localized stage and treated successfully with curative resection 16 years before

her death. One interpretation of this report is that the donated kidneys had contained dormant melanoma cells, which later grew out into clinically apparent malignancies in the immunosuppressed recipients (53). Such speculation strongly supports the theory of contamination by unfound cancer cells. Moreover, there have been scattered reports of transmitted malignancies via needles (54) or surgical instruments (55), which suggest the capability of tumor cells to survive even in the healthy recipients (56).

Another putative rationale is the immunosuppressive effect of allogeneic blood transfusions, also known as transfusion-related immunomodulation (TRIM). This phenomenon was first described in the reports illustrating the influence of pretransplant transfusions on allograft survival among patients who underwent renal transplantation (57-59). Of note, infusing blood products into these patients improved kidney-graft survival. In addition, there was a dose-response relationship between the amount of transfusions and long-term transplant survival. The same phenomenon has been observed in transplantations of heart (60) and lung (61), although controversies persist (62). The recognition of this transfusion-induced immunosuppression prompted concerns that blood transfusions may increase the risk of cancer recurrence after curative surgery (63). Over the past four decades, it has been speculated that blood transfusions may attribute to cancer progression by dampening recipients' immunity (64).

Such speculation has been further corroborated by the emerging cancer immunoediting theory (53). This theory insists that tumors continuously proliferate and mutate against the immune system. In case of immunosuppression, therefore, tumors escape the anti-cancer surveillance more readily. This plausibility was substantiated in studies regarding various immunocompromising conditions. For example, it was shown that lifelong use of immunosuppressants in transplant patients led to significant increases in more than 30 different malignancies (65-70). Escalated risks for various cancers were also detected among people with human immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS) (71-73). Added to these acquired immunodeficient conditions, moreover, a recent study discovered elevated cancer incidence in innate primary immunodeficiencies as well (74).

However, the exact mechanism of TRIM remains still unclear. Suggested mediators for TRIM include conveyed mononuclear cells, leukocyte-derived cytokines and/or soluble human leukocyte antigen (HLA) peptides (5,6). In particular, transferred leukocytes has been contemplated to disturb the host's immune system (63), as in graft-versus-host disease (GVHD) (75). In other words, the equilibrium between tumors and the anti-tumor immunosurveillance might be disturbed by donated white cells, thereby causing clinically apparent cancer (53). However, there has been emerging evidence that leukoreduction filters had no effect on TRIM. For instance, the use of leukocyte-depleted red cells did not prevent either GVHD (76,77) or long-term transfusion-associated microchimerism (45). According to some randomized trials, moreover, leukoreduction was not associated with improved survival outcomes of patients with colon cancer (78-81). These findings were also concordant with one of the included studies in our meta-analysis. A retrospective study addressing 361 U.S. patients with stage I NSCLC found that transfusion of leukoreduced blood was associated with worse DFS and OS when compared with no transfusion (30).

To understand the effect of blood transfusions on cancer outcomes, attention was given to perioperative transfusions during curative surgery in general, measuring relapse of cancer. Unlike these strategies, scattered investigations estimated cancer incidence in people who received transfusions to address this issue. For example, a Scandinavian cohort study showed marked increase in overall cancer incidence among transfusion recipients, specifically within six months after transfusions (82). A U.S. population-based case-control study also detected increased risk of all cancer, particularly within a year after transfusions (83). Although both studies explained such results by incipient cancer that caused anemia requiring transfusions, they did not fully exclude the possible effect of blood transfusions on new cancer diagnoses.

We also found a report that analyzed data on peripartum transfusions, where the likelihood of predisposing comorbidities and undetected cancer supposedly diminishes (84). In this retrospective cohort study with the 30-year follow-up, cancer incidence in 621 women who received transfusions during childbirth was compared with that in 1,216 women who did not. The results showed no significant difference between the two groups. However, our recent study utilizing a national cohort of 270,529 pregnant women in South Korea showed that receipt of 3 or more units of blood transfusions during delivery was associated with significantly elevated risk of developing cancer (85). Such elevated risk was observed in brain, lung, ovarian, and gallbladder malignancies. Furthermore, the difference between transfused and non-transfused groups was seen

both at the first and second years after delivery. Despite retrospective and observational nature, our study strongly suggests the plausibility that blood transfusions might cause cancer development given a complete and representative dataset from a national registry.

Several limitations to this analysis need to be acknowledged. Firstly, in terms of addressing the relationship between transfusions and survival among patients with lung cancer, it is impossible to perform randomized trials for obvious ethical reasons. All available publications were conducted retrospectively. Such retrospective nature is subject to the effects of various confounding factors which are unavailable in our collected data. For example, our data did not include information on postoperative complications, which could have influenced both transfusion rates and mortality rates of patients who underwent major thoracic surgery (86). Secondly, although the I^2 statistics failed to detect quantitative heterogeneity among the included studies, we could still observe qualitative disparities, including types and stages of cancer. Details of transfusions such as the type of blood products and the number of transfused units also varied. Such differences could have affected the results of our analysis.

Conclusions

In conclusion, our findings suggest that blood transfusions may adversely influence survival of patients with lung cancer. Although the exact mechanism remains unclear, there exist concerns for direct transmission of tumor cells as well as the immunomodulatory effect of transfusions. If these hypotheses could be scientifically validated, it would have significant implications for public health and future policies. Therefore, prospective studies and *in vivo* experiments attesting such speculations are warranted. Moreover, restrictive transfusion strategies should be instituted while caring for patients with cancer.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-20-933

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-933). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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