Perioperative Blood Transfusion Is Associated With Worse Clinical Outcomes in Resected Lung Cancer

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The deleterious effect of perioperative allogeneic blood transfusion in patients with resected lung cancer has been controversial. We conducted this meta-analysis to answer the question of whether perioperative allogeneic blood transfusion adversely affects recurrence and survival in patients with resected lung cancer. Included were 23 studies with 6,474 patients. The result showed allogeneic blood transfusion was significantly associated with earlier recurrence and worse survival in patients with surgically resected lung cancer. We suggest transfusion policy should be stricter in lung cancer patients undergoing resection, especially with early-stage disease. Prospective large-scale studies are still warranted.

Lung cancer has been estimated as the most common cancer in the world for several decades [1]. During the past decades, surgical resection has remained the most important means of curative treatment for lung cancer. A considerable percentage of patients undergoing lung cancer operations require blood transfusions, especially allogeneic packed red blood cells (pRBCs) [2]. Although blood transfusion can improve the patient’s symptoms of anemia, there are also some hazards that accompany transfusion. Since World War II, the hazards of blood transfusions, including infectious complications, hemolytic-related reactions, transfusion-related lung injuries, and transfusion-related immunomodulation have been documented and reported gradually [3]. During the 1970s, Opelz and colleagues [4] first reported that better allograft survival was observed in recipients who had a history of blood transfusion than in those who had never received a transfusion. This finding implied that transfusion led to a downregulation of the host immune response to the transplanted organ.

In lung cancer, Tartter and colleagues [5] first reported the perioperative allogeneic blood transfusion (ABT) accelerated the appearance of recurrent or metastatic cancer. Evidence from many studies in the following 3 decades also indicated that perioperative ABT had an adverse effect on tumor recurrence or survival, or both, in patients with lung cancer undergoing resection [6–17]. However, other studies during the same period failed to validate this correlation [18–27].

The evidence on this topic is controversial. Although several published reviews have been published, objective and quantitative conclusions were difficult to derive in those reviews. We therefore conducted this meta-analysis to answer the question whether perioperative ABT will increase the risk of recurrence and decrease survival in lung cancer patients undergoing resection.

Material and Methods

Eligibility Criteria

We included cohort studies that were published from inception to August 24, 2013, and included a comparison of recurrence and survival outcomes between patients with or without blood transfusion. The study participants were patients aged 18 years or older who had histologically or cytologically confirmed lung cancer suitable for pulmonary resection. The main intervention was blood transfusion. All types of blood transfusions were eligible. We also considered studies comparing different types of blood products, for example, RBCs vs whole blood. The outcomes of interest were overall survival (OS), disease-free survival (DFS), recurrence rate (5 years or longer), and 5-year survival rate.

Search Strategy

An electronic search was conducted in August 2013. PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure were searched from inception to August 24, 2013. We used the following key words in combination as medical subject heading terms and text words: “blood transfusion,” and “surgical resection,” “thoracic surgery,” “thoracic Surgery,” “pneumonectomy,” “lobectomy,” “limited resection,” “segmentectomy sleeve resection,” and “lung neoplasms,” “NSCLC,” and “SCLC.” Two investigators (T.W, L.L.) independently identified the potentially relevant articles from the electronic search by reading titles and abstracts. The full texts

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of the potentially relevant articles were read to determine whether they met the inclusion criteria. Disagreements were resolved by consensus. We also searched the references to identify relevant studies.

Data Extraction
Two investigators (T.W., H.H.) extracted the data using a unified form. Both investigators approved the data, and any dispute was solved by discussion. Study information recorded included author name, publication date, study country, study design, sample size, age, disease stage, blood components, number of units, type of operation, cancer classification, follow-up time, adjuvant therapy, and recurrence rate, DFS, OS, and 5-year survival rate. When data overlapped between studies, we included the study with largest number of patients and excluded the others.

Quality Assessment
Two independent investigators (J.Y. C.P.) assessed the risk of bias of included studies. For cohort studies, the 9-star Newcastle-Ottawa Quality Assessment Scale was used to assess the risk of bias [28]. This scale is an 8-item instrument that allows for assessment of patient population and selection, study comparability, follow-up, and outcome of interest. Interpretation of the scale is performed by awarding points or stars for high-quality elements. Stars are then added and used to compare study quality in a quantitative manner. Studies with 5 or more stars were defined as high-quality studies and were included. Any disagreement was presented to all authors for discussion.

Statistical Analysis
Statistical analysis was performed with STATA 12.0 software (StataCorp LP, College Station, TX). For dichotomous variables, transfusion effect on recurrence rate was measured with relative risk (RR) and effect on 5-year survival with the odds ratio (OR). For time-to-event variables, the hazard ratio (HR) was used to measure the transfusion effect on DFS and OS. Statistical heterogeneity between studies was examined using the Cochrane $Q$ test (significant at $p < 0.1$) and by calculating the $I^2$ value [29]. An $I^2$ value exceeding 50% was considered to represent significant heterogeneity [29]. A fixed-effect model was used when heterogeneity was not detected ($p > 0.10$); otherwise, a random-effect model was used.

For survival data, if the original HR was not reported, the curves for OS and DFS were extracted to calculate the HR according to the methods described by Tierney and colleagues [30] in 2007. The pooled RR, OR, and HR and the 95% confidence interval (CI) were calculated using the Mantel-Haenszel formula (fixed-effect model) or the DerSimonian-Laird formula (random-effect model) [31]. When studies reported the outcomes according to the pathologic subtypes, disease stages, or other subtypes, respectively, the data for each subgroup was pooled as from individual study. A significant two-way $p$ value for comparison was defined as $p$ of less than 0.05. The results were described by forest plots.

Publication bias was evaluated using the funnel plot and the Begg test [32]. Subgroup analysis was performed according to the disease stage to reduce heterogeneity among studies. An influence analysis was conducted to describe how robust the pooled estimator was by removing individual studies [33]. An individual study was suspected of excessive influence if the point estimate of its omitted analysis was outside the 95% CI of the combined analysis.

Results

Literature Search
We identified 208 potentially relevant references through electronic search of PubMed ($n = 46$), EMBASE ($n = 103$), China National Knowledge Infrastructure ($n = 51$), and Cochrane Library ($n = 8$). One reference was identified by checking the reference list [22]. Nine duplicates and 173 clearly irrelevant references were excluded through reading the abstracts. Twenty-seven references were read in full, and 26 studies were identified. Of those studies, 3 were excluded for lack of data on outcomes [34–36]. Finally, 23 references fulfilled the inclusion criteria and could provide data for the meta-analysis [5–27]. Figure 1 shows the flowchart of the search results.

Characteristics and Quality Assessment of Included Studies
All included articles were cohort studies published from 1984 to 2012, comprising two perspective, two partially retrospective, and 19 retrospective cohort studies. This study, including 6,474 patients (2,460 cases and 4,014 controls), contained five studies from Asia (China), eight studies from North America (United States, Canada) and 10 studies from Europe (United Kingdom, Italy, Greece, etc.).
Germany, Poland, Spain, and France). Most studies were retrospective, and only two were prospective cohort studies.

The disease stage of patients varied from stage I to stage I to IV. Potential confounders, such as disease stage, anemia, and type of operation, were reported and adjusted in part of the included studies. The quality score of the 23 included studies ranged from 5 to 8 stars. Characteristics of the included studies are listed in Table 1, and the quality scores are listed in Table 2.

**Overall Survival**
The HRs of OS were available from 14 studies [5–7, 10, 12, 16–18, 20, 23–27]; of which, seven were directly reported [5–7, 10, 20, 23, 25], and seven were calculated from Kaplan-Meier curves [12, 16–18, 24, 26, 27]. Significant heterogeneity was found among the studies ($\chi^2 = 54.62$, $p < 0.001$, $I^2 = 72.53\%$). A random-effect model was used. The overall effect estimate was an HR of 1.42 (95% CI, 1.20 to 1.69; $p < 0.001$; Fig 2A), which means the OS was significantly shorter in ABT patients than in patients without transfusion.

**Disease-Free Survival**
The HRs of DFS were available from 11 studies [5, 7, 9, 10, 12, 13, 15, 17–20]; of these, six HRs from five studies were reported directly [7, 10, 12, 19, 20], and seven HRs from six studies were calculated from Kaplan-Meier curves [5, 9, 13, 15, 17, 18]. No significant heterogeneity was found among studies ($\chi^2 = 15.91$, $p = 0.196$, $I^2 = 24.6\%$). A fixed-effect model was used. Pooled data analysis showed the DFS was also shorter in patients who received an ABT than in patients without transfusion (HR, 1.49; 95% CI, 1.29 to 1.65; $p = 0.000$; Fig 2B).

**Recurrence Rate**
The recurrence data were available in 13 studies [5, 7–13, 15, 17–20]. Significant heterogeneity was found among studies ($\chi^2 = 81.53$, $p = 0.000$, $I^2 = 85.3\%$); thus, a random-effect model was used. The recurrence rate was significantly higher in the ABT group than in the no-transfusion group (RR, 1.33; 95% CI, 1.11 to 1.61; $p = 0.003$; Fig 2C). This result suggests that ABT is significantly associated with early recurrence in patients.
### Table 1. Characteristics of Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study (First author)</th>
<th>Year</th>
<th>Location</th>
<th>Patients (No.)</th>
<th>Pathologic Type</th>
<th>Disease Stage</th>
<th>Blood Components</th>
<th>Transfused (units)</th>
<th>Surgical Approach</th>
<th>Hemoglobin or Hematocrit (transfusion/none) (g/dL or %)</th>
<th>Adjuvant Therapy</th>
<th>Follow-Up (mon or y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartter 1984 USA</td>
<td>1984</td>
<td>USA</td>
<td>165 NA</td>
<td>NSCLC</td>
<td>I</td>
<td>NA</td>
<td>2.56 (1-12)</td>
<td>Lobectomy</td>
<td>NA</td>
<td>NA</td>
<td>≥24 mon</td>
</tr>
<tr>
<td>Hyman 1985 USA</td>
<td>1985</td>
<td>USA</td>
<td>105 59.5/62.3</td>
<td>Lung cancer</td>
<td>I-II (UICC 1976)</td>
<td>pRBCs, whole blood</td>
<td>2.2</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>NA</td>
<td>97 (alive)/61 (dead) mon</td>
</tr>
<tr>
<td>Pastorino 1986 Italy</td>
<td>1986</td>
<td>Italy</td>
<td>283 NA</td>
<td>NSCLC</td>
<td>I (UICC 1978)</td>
<td>pRBCs, whole blood</td>
<td>1 (n = 106), ≥2 (n = 51)</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Keller 1988 USA</td>
<td>1988</td>
<td>USA</td>
<td>352 NA</td>
<td>NSCLC</td>
<td>I-II</td>
<td>pRBCs, whole blood</td>
<td>NA</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>NA</td>
<td>≥36 mon</td>
</tr>
<tr>
<td>Moores 1989 USA</td>
<td>1989</td>
<td>USA</td>
<td>330 NA</td>
<td>NSCLC</td>
<td>I-III (UICC 1976)</td>
<td>pRBCs, whole blood, fresh frozen plasma</td>
<td>2.8</td>
<td>Lobectomy, pneumonectomy</td>
<td>NA</td>
<td>NA</td>
<td>3.6 y</td>
</tr>
<tr>
<td>Wu 1989 China</td>
<td>1989</td>
<td>China</td>
<td>53 61.5</td>
<td>NSCLC</td>
<td>I</td>
<td>pRBCs, whole blood, fresh frozen plasma</td>
<td>5.6</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>36 mon</td>
</tr>
<tr>
<td>Little 1990 USA</td>
<td>1990</td>
<td>USA</td>
<td>117 61.3/60.1</td>
<td>NSCLC</td>
<td>I</td>
<td>pRBCs, whole blood</td>
<td>NA</td>
<td>Lobectomy, sublobar resection</td>
<td>37.7/39.8</td>
<td>No</td>
<td>47 mon</td>
</tr>
<tr>
<td>Zimmermann 1993 Germany</td>
<td>1993</td>
<td>Germany</td>
<td>224 57</td>
<td>Lung cancer</td>
<td>I-III</td>
<td>NA</td>
<td>NA</td>
<td>Lobectomy, pneumonectomy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Piantadosi 1994 Canada</td>
<td>1994</td>
<td>Canada</td>
<td>330 NA</td>
<td>NSCLC</td>
<td>I-III</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.6 y</td>
</tr>
<tr>
<td>Wang 1999 China</td>
<td>1999</td>
<td>China</td>
<td>48 62.5</td>
<td>NSCLC</td>
<td>I-II</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.6 y</td>
</tr>
<tr>
<td>Casanova 1999 Spain</td>
<td>1999</td>
<td>Spain</td>
<td>281 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nosotti 2003 Italy</td>
<td>2003</td>
<td>Italy</td>
<td>281 64.5</td>
<td>NSCLC</td>
<td>I</td>
<td>pRBCs, fresh frozen plasma</td>
<td>NA</td>
<td>Lobectomy</td>
<td>12.5/13.3</td>
<td>No</td>
<td>34 mon</td>
</tr>
<tr>
<td>Rayman 2003 Poland</td>
<td>2003</td>
<td>Poland</td>
<td>493 59.7</td>
<td>NSCLC</td>
<td>I-IV (UICC 1997)</td>
<td>pRBCs, whole blood</td>
<td>1 (n = 121), 2 (n = 87), ≥3 (n = 121)</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>Chemotherapy/ radiotherapy</td>
<td>46 mon</td>
</tr>
<tr>
<td>Ghosh 2004 UK</td>
<td>2004</td>
<td>UK</td>
<td>329 67</td>
<td>NSCLC</td>
<td>I-III (AJCC 3rd ed.)</td>
<td>NA</td>
<td>NA</td>
<td>Lobectomy, pneumonectomy</td>
<td>NA</td>
<td>Chemotherapy/ radiotherapy</td>
<td>23.2 mon</td>
</tr>
<tr>
<td>Jiao 2004 China</td>
<td>2004</td>
<td>China</td>
<td>70 45–78</td>
<td>NSCLC</td>
<td>I-III (UICC 1997)</td>
<td>pRBCs, whole blood</td>
<td>1 (n = 2), 2 (n = 17), ≥3 (n = 34)</td>
<td>lobectomy</td>
<td>NA</td>
<td>Chemotherapy/ radiotherapy</td>
<td>20 mon</td>
</tr>
<tr>
<td>Penalver 2005 Spain</td>
<td>2005</td>
<td>Spain</td>
<td>856 62.07</td>
<td>NSCLC</td>
<td>I (SEPAP 1998)</td>
<td>pRBCs, whole blood</td>
<td>3.48 (1-35)</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>No</td>
<td>17.4 y</td>
</tr>
<tr>
<td>Berardi 2005 Italy</td>
<td>2005</td>
<td>Italy</td>
<td>439 68</td>
<td>NSCLC</td>
<td>I-III</td>
<td>NA</td>
<td>NA</td>
<td>Lobectomy, pneumonectomy, sublobar resection</td>
<td>NA</td>
<td>NA</td>
<td>27 mon</td>
</tr>
<tr>
<td>Thomas 2007 France</td>
<td>2007</td>
<td>France</td>
<td>367 60</td>
<td>NSCLC</td>
<td>I-IV</td>
<td>pRBCs, platelets, fresh frozen plasma, other</td>
<td>5 (1-30)</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>9 y</td>
</tr>
</tbody>
</table>

(Continued)
Five-Year Survival

The 5-year survival data were available in 14 studies [7, 11, 12, 14, 16-18, 20-24, 26, 27]. Significant heterogeneity was found among studies ($\chi^2 = 33.79, p = 0.002, I^2 = 58.6\%$). A random-effect model was used and showed that the 5-year survival rate of patients who received ABT was significantly lower than in patients without ABT (OR, 0.61; 95% CI, 0.49 to 0.76; $p = 0.000$; Fig 2D).

Subgroup Analysis

Different stages of included patients would be a potential confounding factor and bring up heterogeneity among studies. We tried to conduct the subgroup analysis on different stages; however, subgroup analysis was performed only in stage I patients because most studies did not report the detailed data of stages II, III, or IV. Ten studies reported information about the number of transfused units, but only two studies reported the outcome of groups with different amounts of transfused units. One study [18] reported no difference in survival rate between patients who received 1 unit or 2 units. Another study [16] reported that hazard of death was increased (HR, 1.119; 95% CI, 1.035 to 1.210) accompanied by each unit increase of blood transfused. Subgroup analysis according to the number of transfused units was also not available currently.

OVERALL SURVIVAL. Six HRs from five included studies contribute to the subgroup analysis. The estimate effect is a HR of 1.8 (95% CI, 1.24 to 2.61; $p = 0.002$). The result shows that ABT is associated with a 70% relative hazard of increasing the incidence of death in stage I patients (Fig 3A).

DISEASE-FREE SURVIVAL. Seven HRs from six included studies contributed to the subgroup analysis. The estimate effect is a HR of 1.7 (95% CI, 1.20 to 2.42; $p = 0.003$), indicating that ABT is associated with a 70% relative hazard of increasing the incidence of death or recurrence (Fig 3B).

RECURRENCE RATE. Nine studies were included in the meta-analysis. The estimate effect is a RR of 1.55 (95% CI, 1.20 to 1.99), which means patients who received ABT have a 55% higher RR of recurrence than patients without ABT (Fig 3C).

FIVE-YEAR SURVIVAL. Five studies contributed to the meta-analysis. The estimate effect is an OR of 0.51 (95% CI, 0.30 to 0.87). The result demonstrates that ABT is associated with a 49% relative odds reduction in the incidence of death within 5 years after the operation (Fig 3D).

Publication Bias

Publication bias was detected by the Begg test and funnel plot. Visual inspection of the Begg funnel plot for OS, recurrent rate, and 5-year survival did not show the asymmetry typically associated with publication bias (Figs 4A, 4C, and 4D). Evidence of publication bias was also not seen with the Begg tests of OS ($p = 0.224$), recurrent rate ($p = 0.067$), and 5-year survival ($p = 0.692$). For the outcome DFS, visual inspection of the
Table 2. Quality Assessments of Included Studies

<table>
<thead>
<tr>
<th>Study ID (First author)</th>
<th>Selection (4 stars)</th>
<th>Comparability (2 stars)</th>
<th>Outcome (3 stars)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the Exposed Cohort</td>
<td>Selection of the Nonexposed Cohort</td>
<td>Ascertainment of Exposure</td>
</tr>
<tr>
<td>Tartter, 1984</td>
<td>*</td>
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<td>Hyman, 1985</td>
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<td>Pastorino, 1986</td>
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<td>Keller, 1988</td>
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<td>Moores, 1989</td>
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<td>Wu, 1989</td>
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<td>Little, 1990</td>
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<td>*</td>
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<tr>
<td>Pena, 1992</td>
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<td>Zimmermann, 1993</td>
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<td>Piantadosi, 1994</td>
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<td>Wang, 1999</td>
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<td>Casanova, 1999</td>
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<td>Ryzman, 2003</td>
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<td>Ghosh, 2004</td>
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<td>Guo, 2004</td>
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<td>Jiao, 2004</td>
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<td></td>
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<tr>
<td>Penalver, 2005</td>
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<tr>
<td>Berardi, 2005</td>
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<tr>
<td>Thomas, 2007</td>
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<td>Chen, 2007</td>
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</tr>
<tr>
<td>Panagopoulos, 2008</td>
<td>*</td>
<td>*</td>
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</tr>
<tr>
<td>Ngô, 2012</td>
<td>*</td>
<td>*</td>
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</tbody>
</table>
Begg funnel plot shows a disproportionate number of studies with positive results (Fig 4B), demonstrating that the bias is significant ($p = 0.01$). These studies included a smaller number of participants, and the results favored the no-transfusion group, which suggests that smaller studies show more positive effects than larger studies.

**Sensitivity Analysis**

To explore heterogeneity among studies, we performed a sensitivity analysis that excluded one study at a time and calculated the pooled ORs, RRs, and HRs for the remaining studies. The result demonstrated that no individual study had excessive influence on the stability of the pooled effect and that the result of this analysis is robust (Fig 5).

**Comment**

Although perioperative ABT is very common in lung cancer patients, its potential deleterious effect on recurrence and survival remains indefinite. Previous studies have repeatedly reported postoperative complications, such as the initiation of pneumonia, wound infections, sepsis, systemic inflammatory response syndrome, renal dysfunction, and operative death, became more frequent in patients who received a transfusion than in patients without transfusion [37-39]. The mechanisms of inducing transfusion-related immunomodulation are still unknown. Most experimental studies have suggested that the transfused leukocytes mediate injuries to the immune system [37]. But a meta-analysis conducted by Vamvakas [40] reported that no significant mortality difference was found between patients receiving leukocyte-reduced and nonreduced pRBCs. The 2012 study by Ng and colleagues [17] also reported that transfusion of leukocyte-depleted blood was associated with a worse DFS and OS in patients with resected lung cancer [17], which also supports the hypothesis that some other mechanism might be involved. The most commonly reported mechanisms of transfusion-related immunomodulation include decreased function of killer cells, decreased ratio of helper-to-suppressor T lymphocytes, decreased efficacy of antigen presentation, induced tolerance for specific antigens, and suppression of hematopoiesis [41, 42]. Different from others, Procter and colleagues [43] reported that depletion of extracellular arginine in serum, an amino acid essential for normal immunity, might be the mechanism of the immunosuppressive effect of pRBCs.

This study confirms that ABT is significantly associated with increased recurrence and decreased survival of operated-on lung cancer patients. Patients who received a perioperative blood transfusion had 33% and 42% higher risk of long-term recurrence and death, respectively, than patients without transfusion. Especially in early-stage (stage I) patients, the deleterious effect is more significant and consistent than in patients without transfusion.
with later-stage disease. This finding supports the hypothesis that ABT has an adverse effect in surgical lung cancer patients.

The included studies collected patients with widely varied stages of disease, including stage I, I to II, I to III, and I to IV. Stage of the disease is the most important prognostic factor of recurrence and survival in lung cancer patients. Besides, the disease stage is a significant confounding factor that was hard to control for in retrospective cohort studies. Many of the included studies reported higher proportions of more advanced disease in patients who received transfusions compared with patients without transfusion. Therefore, it is reasonable to doubt whether blood transfusion was an independent

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**Fig 3.** Subgroup analyses by stage I patients of the effect of allogenic blood transfusion on (A) the hazard ratio for overall survival, (B) the hazard ratio for progression-free survival, (C) the relative risk for recurrence rate, and (D) the odds ratio for 5-year survival. The solid squares denote the mean difference and are proportional to weights used in meta-analysis. The solid vertical line indicates no effect. The dashed line indicates the summary measure, with the associated diamond denoting the weighted mean difference and the lateral tips of the diamond indicating the associated confidence intervals (CIs). The horizontal lines represent the 95% CIs. (ID = identifier.)

**Fig 4.** Funnel plots are presented for (A) overall survival, (B) progression-free survival, (C) recurrence rate, and (D) 5-year survival in patients with surgically resected lung cancer. (HR = hazard ratio; RR = relative risk.)
prognostic factor or just an indirect reflection of advanced disease, which was the real causal factor of recurrence and poor survival.

The subgroup analysis in this study consistently confirms the negative effect of ABT on OS, DFS, recurrent rate, and 5-year survival rate in stage I lung cancer patients (Fig 3). In our opinion, this result provides reliable evidence for the correlation between blood transfusion and the recurrence and long-term mortality of lung cancer. However, in other subgroups that include patients with advanced disease, we still could not draw a definite conclusion because of insufficient data. Our study confirms the concept that lung cancer is controlled by immune mechanisms that are significant in the early stage (stage I), where the immune mechanisms were overridden. Moreover, the patients with advanced disease were more likely to receive adjuvant therapy, which might be another confounder.

It is important to note that some included patients with transfusion had lower hemoglobin levels or hematocrit values before the operation compared with patients without transfusion. Some of the included studies, along with other published studies, have demonstrated that anemia, a condition directly associated with the need of a perioperative transfusion, is an independent adverse prognostic factor in lung cancer and that low hemoglobin may reflect not only tumor extension but also the inflammatory profile that adversely affects surgical patients [16, 44]. Conducting a subgroup analysis based on preoperative hemoglobin level was difficult because only six studies reported the hemoglobin level and few studies included the preoperative hemoglobin level in the analysis.

Moreover, some studies included the patients throughout a long follow-up of 20 or 30 years. Many important changes have occurred during this time in staging systems, surgical techniques, adjuvant therapies, transfusion criteria, and supportive care, among others. Besides, the surgical approach of included studies varied a lot: four studies included only lobectomy, but most others included many surgical approaches, including lobectomy, sublobar resection, bilobectomy, and pneumonectomy. Patients who underwent pneumonectomy for stage I non-small cell lung cancer were reported to have significantly poorer survival than patients who underwent a smaller lung resection [45]. Recent meta-analysis reported that for stage I patients, sublobectomy results in lower survival than lobectomy [46]. Patients in transfusion group were more likely to have received a pneumonectomy. Therefore, the adverse effect of blood transfusion may be covered and hard to detect in retrospective studies.
Most included studies were retrospective cohort studies, and many confounding factors cannot be eliminated, which may contribute significantly to the heterogeneity; thus, the results should be explained with caution. Theoretically, a large-scale randomized clinical trial could avoid many of these limitations but would be very difficult to implement. In this situation, a randomized clinical trial would be unethical because it would be unacceptable to administer a transfusion without a clinical indication or to withhold transfusion from a patient who needed blood.

In conclusion, our findings suggest that the perioperative ABT was significantly associated with the earlier recurrence and shorter survival of lung cancer patients. Evidence for a direct causal relationship between perioperative ABT and worse outcomes of lung cancer patients is insufficient. We suggest transfusion policy should be stricter, especially in patients with early-stage lung cancer. A prospective large-scale study, in which the confounding factors are strictly balanced, is warranted.

References


36. Dougenis D, Patrinou V, Filios K, Theodori E, Vagianos K, Maniati A. Blood use in lung resection for carcinoma:


