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.

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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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Abbreviations and Acronyms

ABT = allogeneic blood transfusion
AJCC = American Joint Committee on Cancer
CI = confidence interval
CNKI = China National Knowledge Infrastructure
DFS = disease-free survival
HR = hazard ratio
NA = not available
NOS = Newcastle-Ottawa Quality Assessment Scale
NSCLC = non-small cell lung cancer
OR = odds ratio
OS = overall survival
pRBCs = packed red blood cells
RR = relative risk
SEPAR = Spanish Society of Pulmonology and Thoracic Surgery
UICC = Union for International Cancer Control

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,