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Review Article

Restrictive *vs.* liberal transfusion for cancer patients: a meta-analysis of randomized controlled trials

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Abstract: *Objective:* We attempted to find a more suitable blood transfusion strategy for cancer patients by comparing restrictive transfusion with liberal transfusion treatment results. *Methods:* In order to find all randomized controlled trials (RCT) which are relevant to comparison on restrictive transfusion with liberal transfusion treatment results, we have searched PubMed, EMBASE and Cochrane library database. *Results:* Five papers were finally included in our meta-analysis. Restrictive transfusion significantly decreased blood utilization (standard mean difference=-0.33, 95% CI=-0.5-0.17, *P*<0.0001). The incidence of 60-day mortality was significantly lower in cancer patients receiving liberal transfusion than those receiving restrictive transfusion (OR=1.58, 95% CI=1.08-2.33, *P*=0.02). There was no significant difference in length of hospitalization, ICU length of stay, bleeding events, ICU readmission and response after chemotherapy (response rate) between the two groups. *Conclusion:* According to our current study, liberal transfusion strategy was recommended for cancer patients. In the future, well-designed and larger sample sizes of RCTs are still needed.

Keywords: Oncology, transfusion, meta-analysis, randomized controlled trial

Introduction

Anemia is a common clinical symptom in cancer patients. The European Cancer Anemia Survey (ECAS) [1] has conducted a prospective epidemiological study of tumor-related anemia on 15,367 cancer patients. The results of ECAS study revealed that the incidence of anemia in primary diagnosis was 39.3% (Hb<10.0 g/dl), while its incidence was varying during the process of investigation, which was up to 67%, and the overall incidence of anemia was 53.7%. Additionally, this study also demonstrated that only 38.8% of patients received anemia correction, and the average Hb was 9.7 g/dl for the patients who began to receive anemia correction, of which 17.4% received EPO treatment, 14.9% received blood transfusion treatment and 6.5% received oral iron therapy. There are many reasons for anemia [2, 3] which can be summarized into three main aspects for cancer patients. First, factors from tumor itself lead to anemia, such as bone marrow necrosis or fibrosis caused by hemorrhage, hemolysis and tumor cell infiltration. Second, the body's nutritional absorption disorders can cause anemia. Patients with tumors often have poor appetite and anorexia. The digestive tract tumor causes the difficulty of feeding and the absorption barrier. Combined with the energy consumption of the tumor itself, there may be hematopoietic raw material deficiency result in anemia. Third, tumor related treatment, such as radiotherapy or chemotherapy, can result in the direct hematopoietic inhibition. The impact of anemia on cancer patients is multifaceted. For example, anemia in cancer patients can make patients anemia-related fatigue, with or without shortness of breath, palpitations, inattention, insomnia, menstrual disorders and other symptoms. It can also reduce the oxygen carrying ability of blood, the sensitivity of tumor radiotherapy and the patients' quality of life; shorten the survival time, thus affecting the patients' prognosis [4-6]. Systemic review conducted by Caro JJ. *et al.* found that anemia is an independent prognostic factor for survival in cancer patients, and almost all types of cancer combined with ane-

mia have shorter survival period. Overall, the relative risk of death increased by 65% in anemic patients with cancer [7]. The high incidence of anemia in cancer patients and its adverse effects on the quality of life and prognosis of patients are increasingly attracting the attentions in clinic.

Blood transfusion is a common treatment for anemia in cancer patients, and it works quickly and effectively. The main support of blood transfusions for patients with tumor may be related to the correction of anemia and increasing the blood oxygen concentration, which leads to cells (including cancer cells) more effectively oxidized and accelerates the degeneration necrosis of tumor cells. Therefore, it is essential to support the treatment of malignant cancer patients with anemia and corresponding symptoms [8]. However, it is well known that blood transfusion also has many adverse effects. Firstly, the transfusion can easily cause an allergic reaction, acute hemolytic reaction and non-cardiac pulmonary edema. Secondly, multiple blood transfusions can also produce unexpected antibodies in patients, which may lead to ineffective transfusion in which natural killer cell function is inhibited, and it is associated with tumor recurrence [9]; Thirdly, although the safety of blood transfusion has been significantly improved compared to the past, blood transfusions still have a risk of transmitting pathogens [10].

In recent years, some medical institutions have begun to recommend restricted red cell transfusion strategies [11, 12]. More and more studies have found that the restrictive transfusion strategies can reduce the use of blood without increasing morbidity or mortality [13-16]. Although in some clinical settings, restrictive transfusion is cost-effective and safe, it remains unknown whether a liberal or restrictive transfusion strategy is superior in patients with cancer.

At present, most major cancer treatment centers accept the transfusion trigger for patients with asymptomatic anemia as 7-9 g/dl, while the trigger is 8-10 g/dl for symptomatic anemia. However, these recommendations and practices are based on the clinical data of other serious diseases [17, 18]. Therefore, the grade of evidence for these recommendations is low. So, we performed a new meta-analysis to compare the outcome of cancer patients treated with restrictive and liberal transfusion.

Materials and methods

Our research was reported in strict accordance with the systematic reviews and meta-analysis of PRISMA statements.

Eligibility criteria

We included all relevant randomized controlled trials comparing the outcome of cancer patients between treated with restrictive and liberal transfusion, without language limit. And we excluded studies that (1) unrelated to our topics (cancer and transfusion); (2) comments, meeting or reviews, meta-analyses; (3) non-randomized comparative studies.

Study selection

In order to find all randomized controlled trials which are relevant to the comparison on restrictive transfusion with liberal transfusion treatment results, we searched PubMed, EMBASE and Cochrane library database. Without the language restrictions, we used the following combined text and Mesh terms: "Neoplasms" and "Erythrocyte Transfusion" and "Randomized Controlled Trial". The complete search used for PubMed was (cancer [Text word] OR cancers [Text word] OR tumor [Text word] OR tumors [Text word] OR neoplasm [Text word] OR neoplasia [Text word] OR neoplasias [Text word] OR malignancy [Text word] OR malignancies [Text word] OR "Neoplasms" [Mesh]) AND ((((blood [Text word]) OR red cell [Text word] OR red blood cell [Text word] OR Erythrocyte [Text word]) AND transfusion [Text word]) OR "Erythrocyte Transfusion" [Mesh]) AND (randomized [Text word] OR randomly [Text word] OR randomised [Text word] OR "Randomized Controlled Trial" [Publication Type]). A similar search strategy was used for other databases. We searched the databases between the inception and June 7th, 2017 and considered all potentially eligible studies for this meta-analysis. Two authors independently selected study according to the inclusive criteria. Disagreements were resolved by discussion with another author but this proved to be unnecessary.

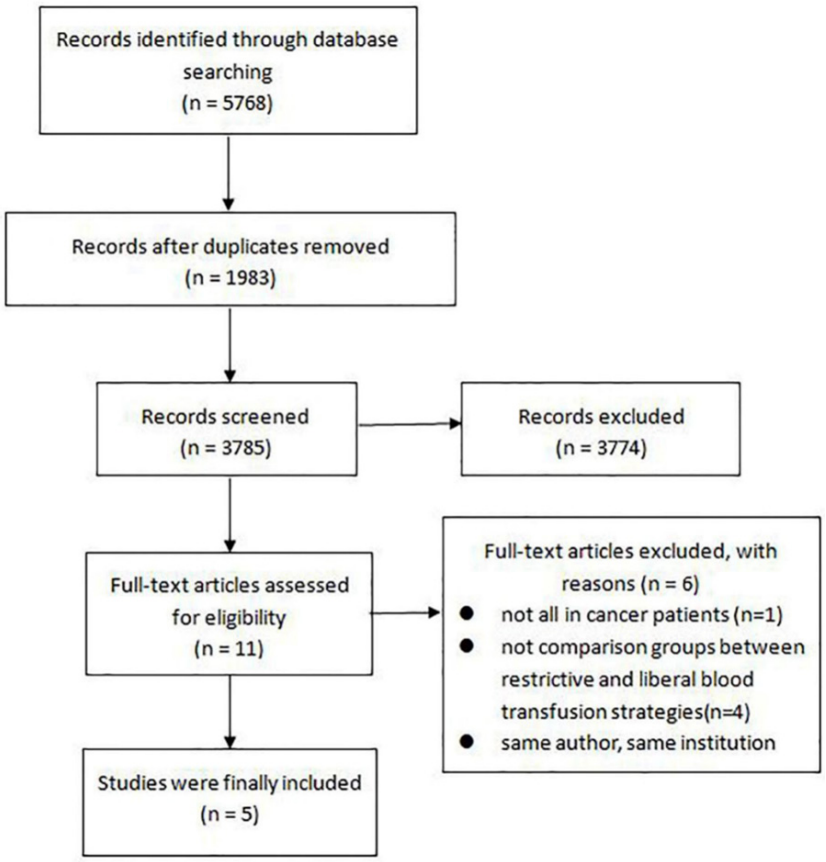

Figure 1. Study selection.

Data extraction

We recorded the following relevant data from included studies: study details (author, publication year, and country where the study was conducted, study design), description of study population (target population, sample size, age and sex, outcomes of interest). The two authors independently extracted data from the study. If they disagree with each other, the conclusion would be made by discussing with another author. Primary outcomes included amount of blood transfused and 60-day mortality, while secondary outcomes included length of hospitalization, ICU length of stay, bleeding events, ICU readmission, response after chemo therapy and other adverse events.

Assessment of study quality

We evaluated the quality of all randomized controlled trials through The Cochrane risk of bias tool [19] in which the description of 6 types of bias were assessed, including selection, peformance, detection, attrition, reporting and other bias. The tool judges the risk of each types of bias was graded as low, unclear or high.

Statistical analysis

Our meta-analysis was conducted using RevMan. For the dichotomous variables, we extracted the number of events and the total patients. For the continuous variables, we extracted the mean and standard deviation. Then, the OR or standard mean difference with 95% CI was calculated. But in some studies, the author only reported the median, and inter quartile range (IQR), not reporting the mean and standard deviation of the sample. For such a study, we estimated the sample mean and standard deviation from the median and the IQR in methods proposed by Wan X. *et al.* [20-22], so that we could summarize the results. Finally, we pooled the OR, mean and standard deviations of each study. Heterogeneity between studies was assessed by using the Cochran *Q* test and the I^2 statistic [23]. When the heterogeneity of the research was not significant ($P>0.10$, $I^2<50\%$), we adopted the fixed-effects model (Mantel-Haenszel method). When significant heterogeneity was observed ($P<0.10$, $I^2>50\%$), we adopted the random-effect model (DerSimonian and Laird method) [24]. We did not draw a funnel plots because the number of included study is small. We evaluated the reliability of meta-analysis through sensitivity analysis. Different studies may have reported different research results, and if we could not find sufficient data (<2 studies reporting on the same outcome), descriptive analysis was used.

Table 1. Characteristics of included studies

Source	Country	Design	Target population	Intervention and groups	Sample size	Sex (male gender)	Age (years)	Outcomes of interest
Park et al. 2008 [27]	Korea	Single center RCT	Patients with advanced gastric cancer (AGC). and scheduled to receive chemotherapy	Restrictive transfusion: maintain Hb≥10 g/dl	43	23	28-74	Transfusion requirements; Treatment outcomes
				Liberal transfusion: maintain Hb≥12 g/dl	43	30	32-75	
Kathryn et al. 2008 [28]	Canada	Multicenter RCT	Patients with acute leukemia receiving induction chemotherapy or those undergoing stem cell transplantation	Restrictive transfusion: Hb<80 g/L	29	18	18-77	Bleeding events; Blood product utilization
				Liberal transfusion: Hb<120 g/L	31	14	19-74	
Almeida 2015 [29]	Brazil	Single center RCT	Patients with cancer having major abdominal surgery	Restrictive transfusion: Hb<7 g/dL	101	55	64±12	Mortality; ICU readmission rate, ICU and hospital lengths of stay; Need for blood transfusion
				Liberal transfusion: Hb<9 g/dL	97	55	64±14	
Dezern 2016 [25]	America	Single center RCT	Patients with acute leukemia	Restrictive transfusion: Hb<7 g/dL	59	33	56 (45.5-67)	Number of units transfused; Bleeding events
				Liberal transfusion: Hb<8 g/dL	30	16	62.5 (55.3-67.8)	
Bergamin 2017 [30]	Brazil	Single center RCT	Patients with solid cancer and fulfilling the criteria for septic shock	Restrictive transfusion: Hb<7 g/dL	151	84	61.4±13.5	Blood Transfusion; mortality; length of ICU and hospital stay, ICU readmission
				Liberal transfusion: Hb<9 g/dL	149	70	61.6±12.9	

Age data are reported as range or as median (interquartile range), or as Mean ± SD.

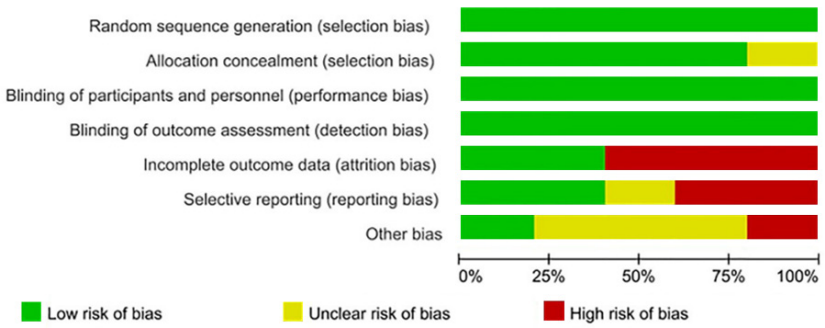

Figure 2. Risk of bias graph.

Results

Overall, 5768 papers were identified by the search strategy. After removing the duplicate records and checking the titles and abstracts, 11 articles were remained for full-text review. Five studies were further excluded for the following two reasons: the studies are not all in cancer patients, or there is no comparison between restrictive and liberal blood transfusion strategies in the excluded studies. In addition, two papers were reported by the same author [25, 26] and the same institution, so we included one study with a larger number of patients [26]. Finally, five studies [25, 27-30] that met all the criteria were included in our meta-analysis (**Figure 1**).

Study characteristics

Four of the studies we included were single-center studies, only one study [28] was a multi-center study and they were published between 2008 and 2017. Target population was in several different types of cancer including gastric cancer (AGC) [27], acuteleukemia [25, 28], solid cancer with septic shock [30] and other surgical cancer patients. Two studies were conducted in Brazil [29, 30], one in Korea [27], one in Canada [28] and one in America [25]. All patients were adult patients and all transfused blood components were leukoreduced. There was a large difference between the definition of restricted and liberal transfusion strategies in the studies. It means that the difference in the trigger value of hemoglobin is significant. The range of trigger value for the restrictive strategy hemoglobin is from 7 g/dl [25, 29-30] to 10 g/dl [27]. The study characteristics are showed in **Table 1**. A total of 733 participants were included in our study, including restrictive transfusion (n=383) and liberal transfusion (n=350).

Quality of these included studies

The risk of bias graph for randomized controlled trials is described in **Figure 2**. All five studies [25, 27-30] were judged to have low risk of random sequence generation (selection bias). In four of the five trials, there was a lower risk of allocation concealment (selection bias), while the remaining study failed to mention how it was allocated [27]. In the five studies, two studies [29, 30] reported double-blind (patients and outcome assessors), three studies [25, 27-28] reported single-blind (outcome assessor). However, the authors of these five studies supposed that the main experiment results were unaffected by blindness because the results are objective. Three of the five trials were judged to have high risk of incomplete outcome data (attrition bias) because there lack of further analysis for some missing outcomes [27, 28] and an as-treated analysis was done with disengagement from allocation [25].

Primary outcome

Amount of blood transfused: Five studies reported the amount of blood transfused in two groups, but two studies used total units of blood transfusion [27] or number of patients with RBC transfusions [28] to report blood utilization, they did not report mean, standard deviation or median, inter quartile range (IQR) and thus we were unable to combine these results. Therefore, we pooled the results of the remaining three studies [25, 29-30]. Heterogeneity between these studies was statistically low (I^2=32%; P=0.23). Therefore, we used the fixed-effect model, and restrictive transfusion appear to significant decrease blood utilization (standard mean difference: -0.33, 95% CI: -0.5-0.17, P<0.0001) (**Figure 3**).

60-day mortality: Three studies [25, 29-30] reported the incidence of 60-day mortality. Heterogeneity among the three studies was not significant (I^2=38%; P=0.2). Therefore, we used the fixed-effect model, there was a significant

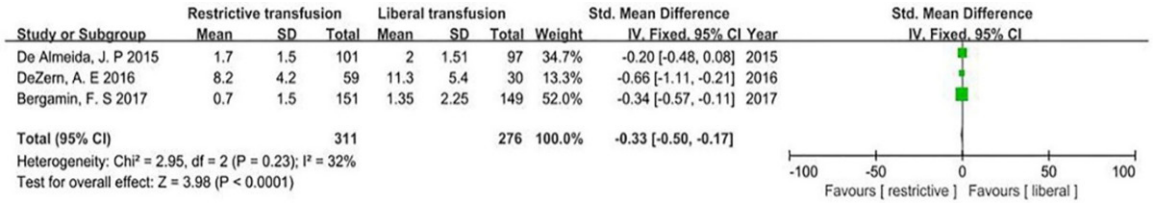

Figure 3. Amount of blood transfused.

Figure 4. 60-day mortality.

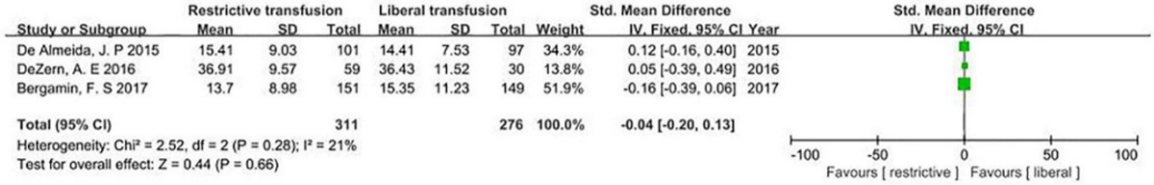

Figure 5. Length of hospitalization.

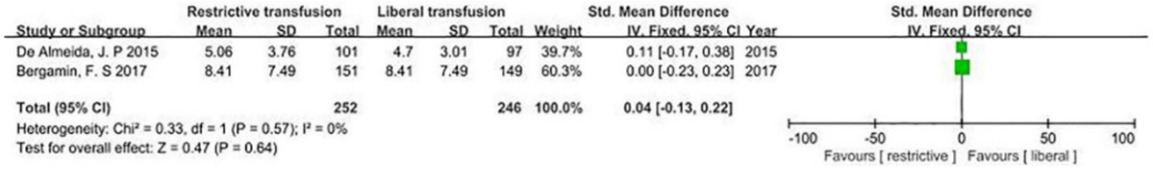

Figure 6. ICU length of stay.

beneficial trend towards the liberal blood transfusion (OR=1.58, 95% CI: 1.08-2.33, *P*=0.02) (**Figure 4**).

Secondary outcome

Length of hospitalization: Three studies [25, 29-30] reported the length of hospitalization in two groups. Heterogeneity among the two studies was not significant (I^2=21%; *P*=0.28). Using a fixed-effect model, no statistical significance was reached (standard mean difference: -0.04 95% CI: -0.2-0.13, *P*=0.66) (**Figure 5**).

ICU length of stay: Two studies [29, 30] reported the ICU length of stay in two groups. Heterogeneity between the two studies was not significant (I^2=0%; *P*=0.57). Using a fixed-effect model, no statistical significance was reached (standard mean difference=0.04 95% CI= -0.13-0.22, *P*=0.64; **Figure 6**).

Bleeding events: Two studies [25, 28] reported the incidence of bleeding events in two groups, and the target population of the two studies was acute leukemia. Heterogeneity among the two studies was not significant (I^2=0%; *P*=0.83). Using a fixed-effect model, no significant difference was found between the liberal strategy and restrictive strategy in the incidence of bleeding events (OR=0.78, 95% CI: 0.35-1.73, *P*=0.54) (**Figure 7**).

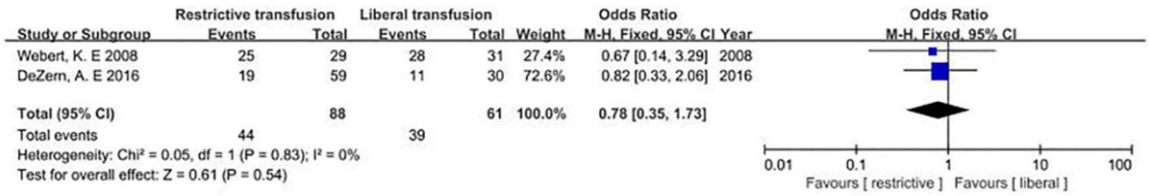

Figure 7. Bleeding events.

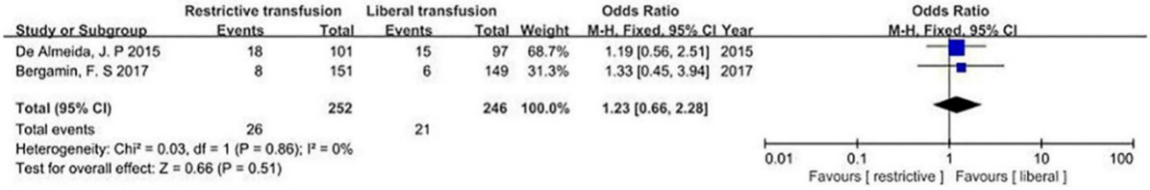

Figure 8. ICU readmission.

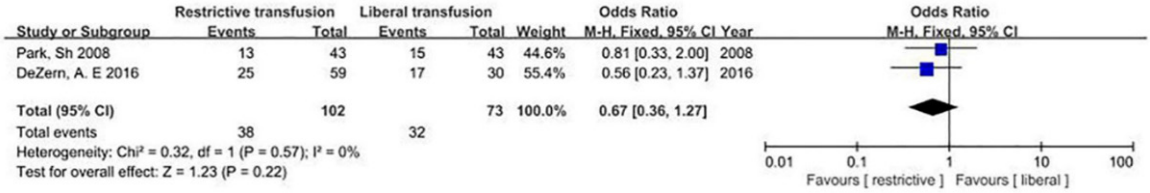

Figure 9. Response after chemotherapy.

ICU readmission: Two studies [29, 30] reported the incidence of ICU readmission in two groups. Heterogeneity among the two studies was not significant (I^2=0%; *P*=0.86). Using a fixed-effect model, no significant risk increased (OR=1.23, 95% CI=0.66-2.28, *P*=0.51; **Figure 8**).

Response after chemotherapy: Two studies [25, 27] reported the incidence of response after therapy in two groups. Heterogeneity between the two studies was not significant (I^2=0%; *P*=0.57). Using a fixed-effect model, the pooled OR was not significant (OR=0.67 95% CI: 0.36-1.27, *P*=0.22, **Figure 9**).

Other adverse events

The five studies reported different outcomes and thus we were unable to combine data for some outcomes of interest, therefore we used descriptive statistics to report these outcomes. One study [27] reported transfusion- and chemotherapy-related adverse events and there was no difference between the two strategies. one study [30] reported 28-day mortality and 90-day mortality, for 28-day mortality there was an increased mortality rate in the liberal group (45%, 67 patients) when compared with the restrictive group (56%, 84 patients; hazard ratio=0.74; 95% CI=0.53-1.04; *p*=0.08), in the contrary to mortality rate at 90 days, the liberal group presented a lower mortality rate (59.1% [88 patients] vs. 70.2% [106 patients]; hazard ratio=0.72; 95% CI=0.53-0.97; *p*=0.03). One study [29] reported 30-day mortality rate that was lower in the liberal transfusion group than in the restrictive transfusion group (8 [8.2%] vs. 23 [22.8%]; *P*=0.005), and at 30 days, the incidence of major cardiovascular events was significant lower in the liberal group (5 [5.2%] vs. 14 [13.9%]; *P*=0.038).

Sensitivity analysis

Park. *et al.* [27] compared the outcomes of cancer patients between patients receiving RBC transfusion to maintain their Hb 10 g/dl (restrictive) and 12 g/dl (liberal). But in other studies, 10 g/dl was similar to or even higher than the liberal hemoglobin trigger. Sensitivity analyses were performed after this study was excluded. This study impacted only one outcome. Since

there were only two studies that reported the incidence of response after therapy, the result of RR for the response after therapy minimally changed (from RR=0.67, 95% CI=0.36-1.27 to RR=0.56, 95% CI=0.23-1.37).

Discussion

The main results of this meta-analysis were as follows. First, restrictive transfusion appeared to decrease blood utilization. Second, the incidence of 60-day mortality was lower in patients receiving liberal blood transfusion than those receiving restrictive transfusion strategies. However, as suggested by Bergamin's study [30], the results indicated that the 28-day mortality rate in the liberal group was higher when compared with the restrictive group. On the contrary, the 90-day mortality rate in the liberal group was lower than the restrictive group. Another study [29] reported 30-day mortality rate was lower in the liberal group than the restrictive group. This inconsistent finding could be explained by the difference of tumor types and number of patients included. Third, our meta-analysis demonstrated a non-significant difference between the groups regarding requirements of length of ICU and hospital stay, ICU readmission, and bleeding events, response after chemotherapy. In summary, restrictive blood transfusion strategy appeared significantly decreased blood utilization while increased incidence of 60-day mortality in cancer patients.

In recent years, results of a number of randomized studies conducted in a variety of clinical fields [13-16], including upper gastrointestinal bleeding, children in Intensive Care Unit, orthopedic surgery, and trauma patients have supported a restrictive transfusion strategy to reduce the detrimental effects of blood transfusion. Although restrictive transfusion strategies are widely recommended in many other areas, it is still an unsolved question in oncology patients. In Prescott LS' review [31], they compared the outcomes of restrictive versus liberal transfusion strategies in patients with cancer and concluded that the restrictive blood transfusion strategy seems better. Prescott LS' review included randomized and non-randomized studies, high quality RCTs were unable to be identified and most data were unable to be pooled. Therefore, we performed our meta-analysis from documented randomized controlled trials, which led to the reliable conclusion of an increased risk of 60-day mortality with the restrictive blood transfusion strategy.

The advantages of our analysis were as follows. First, only randomized controlled trials were included. Second, we conducted a comprehensive literature search on three large databases. Third, the heterogeneity among studies was not significant.

Our meta-analysis certainly has some limitations. First, the studies that met our inclusion criteria are few. Second, the sample size of the three randomized controlled trials is relatively small, and the total number of included subjects is less than 1000. In the future, larger sample size of RCTs will be needed in further meta-analysis for cancer patients. Third, we should realize that the threshold for restrictive transfusion strategies is different in these studies. Finally, our meta-analysis contains different types of tumors, and we can't perform subtype analysis because of the small number of studies included.

Our meta-analysis summarized all randomized controlled trials which are relevant to the comparison on restrictive transfusion with liberal transfusion treatment results, although we have not yet reached a definite conclusion with the obvious limitations. Considering the limited current related reports, more randomized controlled trials are needed for more robust evaluation of the intervention's impact on clinical outcomes. In the future, well-designed and larger sample sizes of RCTs should be conducted to compare the two transfusion strategies and evaluate the better threshold value. In conclusion, the present study suggested that restrictive blood transfusion strategy is associated with a smaller amount of blood transfused and higher 60-day mortality than liberal blood transfusion in cancer patients.

Disclosure of conflict of interest

None.

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