REVIEW

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The Red-cell Transfusion Strategy Dilemma in Critically Ill Patients in ICU: Is Restrictive or Liberal the Answer?

ABSTRACT

Background: The primary therapeutic approach for promptly increasing haemoglobin concentration is red blood cell transfusion. However, the risk associated with RBC transfusion and the overall accessibility exhibit significant variation. **Objective:** This meta-analysis evaluates the comparison and outcome of restrictive and liberal transfusion strategies in intensive care unit. **Methods:** A comprehensive search was carried out on various databases, including CENTRAL, PubMed, MEDLINE, and ScienceDirect for randomized control clinical trials evaluating the comparison of clinical outcomes of restrictive and liberal transfusion strategies in critically ill patients. The primary outcomes measure was mortality, which included ICU mortality and hospital mortality. In addition, data were pooled using random-effect models and heterogeneity was evaluated through I^2 statistics. **Results:** Out of 15 eligible RCTs obtained, involving 12,439 patients. The result demonstrated no significant difference of restrictive red-cell transfusion strategy over liberal red-cell transfusion strategy in reducing mortality outcomes with a pooled effect size (relative risk [RR] 0.92; 95% confidence interval [CI] 0.78 – 1.08; I2 = 0%, indicating minimal to no difference. Similarly, analyses of secondary outcomes identified no significant differences in several clinical results. **Conclusion:** This present meta-analysis provides evidence that restrictive red-cell transfusion strategy doesn't significantly difference in overall mortality and several secondary clinical results of critically ill patients in ICU compared to liberal red-cell transfusion strategy. Otherwise, restrictive transfusion strategy lowered RBC transfusion requirements, and was expected to be more cost-effective.

Keywords: anaemia, blood transfusion, critical illness, haemoglobin, intensive care unit.

1. BACKGROUND

Critically ill patients in intensive care unit (ICU) are often suffer from anaemia, characterized by low levels of haemoglobin (Hb) (1). Anaemia can arise from various factors, including surgical blood loss, significant bleeding, excessive blood sampling for laboratory analyses, or underlying medical conditions or diseases. Anaemia has been reported to have a dual effect in reducing the blood's oxygen delivered to the tissues, such as the myocardium, as well as increasing the demand for myocardial oxygen by necessitating a higher cardiac output to sustain sufficient systemic oxygen delivery. The presence of this condition has been linked to unfavourable outcomes in individuals who are affected before undergoing surgery or have pre-existing cardiovascular diseases (2).

Red blood cell (RBC) transfusion strategies primarily focus on increasing Hb levels to prevent or alleviate the anaemia symptoms, therefore it is crucial supportive aspect in anaemia management. However, administration of RBC transfusion relates to various potential concerns, including blood transfusion safety and appropriate use of blood products, and others which are essential to health budgeting and economics. Consequently, administering RBC transfusion should carefully evaluate its benefit against its potential risks. To prevent the blood transfusion complications, previous analysis

have indicated that adopting lower, more restrictive transfusion thresholds may be acceptable in specific patient groups to mitigate the complications associated with blood transfusions. There has been a trend shift to lowering the transfusion threshold from 10 to 8 g/dL or to administering transfusion when symptoms of anaemia arise, but it remains controversial (3).

In line with previous reports, Hb thresholds are frequently used for determining the necessity for RBC transfusion (4). Clinician decision-making about transfusion practice is often influenced by different factors, such as patients' clinical condition, age, and presence of comorbidities. However, uncertainties persist regarding thresholds at which the benefits of enhanced oxygen transportation surpass the potential risk associated with the process. The widely accepted belief that RBC transfusion must only be performed when Hb levels are <10 g/dL was opposed by several trials performed by Transfusion Requirements in Critical Care (TRICC) (5). In liberal group, RBC was administered when Hb levels were below 10 g/dL. Meanwhile, in restrictive group, transfusion was initiated when Hb levels dropped below 7.0 to 8.0 g/dL. The results showed that the primary outcome, all-cause death at 30 days, was comparable in both groups. In-hospital mortality, a secondary outcome in the study, was reported to be lower in restrictive group, but no difference in mortality at 60 days. The pivotal trial prompted a significant reassessment of transfusion strategies in patients with severe ill and had a profound impact on clinical practice (6-9).

2. OBJECTIVE

This meta-analysis aims to integrate, identify, appraise, and summarize findings from various clinical randomized controlled trials (RCTs) to assess the overall difference in clinical outcomes of varying thresholds for RBC transfusion in critically ill patients. By reviewing and synthesizing the data from the trials, this analysis provides a comprehensive understanding of whether restrictive transfusion strategy offers any tangible benefits for patients with critical condition in ICU compared to liberal transfusion strategy. The objective of this present meta-analysis is to offer evidence that could inform future clinical decision and guide further transfusion dilemma in the quest for effective treatment strategies in critically ill patients with anaemia.

3. PATEIENTS AND METHODS

Patients and study design

This review was carried out according to the Cochrane Handbook for Systematic Reviews of Intervention set forth, as well as the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) framework. The design is used to get an accurate assessment of restrictive and liberal transfusion strategies in critically ill patients in ICU and enhance the results precision and reliability. We registered the review protocol at the International Prospective register of Systematic Reviews number CRD42024546790; https://www.crd.york.ac.uk/prospero.

A comprehensive literature search was carried out across several databases and current trial registries in English, which used PRISMA protocols, including CENTRAL, MEDLINE, PubMed, and Science Direct, from 2013 to early 2023. In addition, the search was limited to specific criteria, such as date, language, publication status, and exclusively randomized controlled trials. The population included in this study was critically ill patients in ICU and the main intervention was transfusion using restrictive transfusion strategy and the control group with liberal transfusion strategy. Mortality served as the primary results in this analysis. The keywords used for the literature search were (restrictive transfusion) AND (liberal transfusion) OR (red blood cell transfusion) OR (critically ill patient) AND (randomized controlled trials) OR (mortality) OR (ICU).

To ensure a rigorous and systematic strategy, explicit selection criteria were established for the studies inclusion applying the PICOS Framework, namely a) Population: This analysis targeted articles comprising participants with critically ill status in ICU, b) Intervention: The primary outcome was interventions of restrictive transfusion strategy, c) Comparators: Articles were eligible when selected in a control group of liberal transfusion strategy, d) Outcomes: The primary outcome of interest was mortality, which included ICU mortality and hospital mortality. Secondary outcomes were 30-day and 90-day mortality, sepsis, wound infection, transfusion requirements and e) Study Design: the articles included were randomized controlled trials, which provided the highest evidence level in intervention reports.

The inclusion criteria included a) studies comparing restrictive and liberal transfusion strategies, b) critically ill patients in ICU, c) full text only, d) written in English, and e) randomized controlled trials design. Meanwhile, the exclusion criteria were a) restrictions to studies published in English appropriate to the team's linguistic abilities to ensure a comprehensive review in the set timeframe, b) non-randomized articles, reviews, and case reports were excluded, along with those that did not provide sufficient data on the certain results. Articles that did not focus on liberal and restrictive strategies of transfusion were also excluded.

Methods

To assess the transfusion thresholds impact on the RBC application and any potential alterations in clinical outcomes, this study incorporated randomized controlled trials where the comparison groups were allocated based on a predetermined 'threshold' that needed to be met before administering RBC transfusion. The liberal transfusion threshold (control) strategy was Hb of 10 g/dL and above; meanwhile, the for the restrictive transfusion (intervention) strategy was Hb of < 10 g/dL. The control group participants needed to receive transfusion of allogeneic or autologous RBC, or both, at higher levels of Hb or haematocrit (Hct) compared to the intervention group. Alternatively, patients could have been transfused based on current practices, which did not specify a clearly threshold, but instead comprised more liberal rather than restrictive strategies. Trials lacking clinical outcomes pertinent to this evaluation were omitted from consideration.

The Cochrane technique for measuring the risk of bias was employed by the Cochrane Handbook for Systematic Reviews of Interventions. The domains evaluated for each article comprised sequence generation, blinding, allocation concealment, insufficient data, selective report, and other bias causes. A risk of bias table was generated, which included an assessment of the study's performance across various domains and

No.	Author	Time	Country	Study design	Number of populations	Restrictive strategy (Transfusion threshold)	Liberal restrictive Transfusion threshold	Age, years		Male		Primary outcome
								RT	LT	RT	LT	
1	Bergamin et. al. (1)	2017	Brazil	Single center, randomized, double-blind controlled trial.	300	Hb < 7	Hb < 9	61.4±13.5	61.6±12.9	84 (56)	70 (47)	All-cause mortality by 28 days
2	de Almeida et al. (2)	2015	Brazil	Randomized, controlled, parallel-group, double-blind controlled trial	198	Hb < 7	Hb < 9	64±12	64±14	55 (54.5)	55 (56.7)	All-cause mortality by 30 days Composite endpoint of mortality and morbidity
3	Holst et.al (3)	2014	Denmark, Sweden, Finland	Multi center, randomized, controlled, parallel-group trial	998	Hb < 7	Hb < 9	67 (IQR 57 -73)	67 (IQR 58 -75)	272 (54.2)	259 (52.2)	90-days mortality
4	Jairath et al. (4)	2015	United Kingdom	Open-label, cluster, randomised controlled trial	640	Hb < 8	Hb < 10	58±20.3	60.4±20	244 (61)	322 (60)	28-days mortality, further bleeding
5	Koch et al. (5)	2017	USA, India	Randomized controlled trial	722	Hct < 24%	Hct < 28%	59±15	60±13	N/A	N/A	Composite of in-hospital postoperative morbidity and mortality
6	Murphy et al. (6)	2015	United Kingdom	Multi center, parallel-group trial	2003	Hb < 7.5	Hb < 9	69.9 (IQR 63.1 - 76)	70.8 (IQR 64.1 - 76.7)	693 (69.3)	680 (67.8)	Serious infection or an ischemic event
7	Kola et al. (7)	2021	India	Single center, prospective, open-label, parallel arm, non-inferiority, randomized controlled trial	100	Hb < 7	Hb < 8	47.86±14.75	49.76±14.87	N/A	N/A	Mortality rate
8	Mazer et al. (8)	2017	Canada	Multi center, randomized, open-label, non-inferiority trial	4860	Hb < 7.5	Hb < 9.5	72±10	72±10	1553 (639)	1586 (65.3)	Composite of endpoint of mortality from any cause
9	Moller et al. (9)	2019	New-Zealand	Single center, stratified, parallel-group, patient- and partly assessor-blinded clinical trial with central web-based randomization	58	Hb < 8	Hb <9.7	71.3 ± 9.4	73.7 ± 7.3/	19 (65.5)	18 (62.1)	All-cause mortality
10	Palmieri et al. (10)	2017	California	Multi center, open label, investigator-initiated, randomized trial	345	Hb < 7	Hb < 10	41 (IQR 27 - 55)	41 (30 - 55)	134 (79.8)	139 (78.5)	Number of blood stream infections
11	Parker et al. (11)	2013	United Kingdom	Single center, randomized controlled trial	200	Hb < 8	Hb < 9.5	84.4 (IQR 60 -104)	84.2 (60 -97)	17	15	Mortality
12	So-Osman et al. (12)	2013	Netherlands	Randomized, controlled study	603	Haemoglobin (Hb) 6.4 – 9.7 g/dL depending on patient risk and timing from surgery	Haemoglobin (Hb) 6.4 – 9.7 g/dL depending on patient risk and timing from surgery	70.7±10.2	70.3±61.2	N/A	N/A	RBC usage
13	Villnueva et al. (13)	2013	Barcelona	Randomized controlled trial	889	Hb < 7	Hb < 9	N/A	N/A	N/A	N/A	All-cause mortality by 45 days
14	Walsh et al. (14)	2013	United Kingdom	Multi center, parallel-group, randomized controlled trial	100	Hb < 7	Hb < 9	67 (7; 56–80)	68 (8; 55–83)	36 (70.6)	24 (49.0)	Mortality 30 days, adverse event
15	Zhang et al. (15)	2020	China	Multi center, randomized and double blind clinical study	423	Perioperative Transfusion Trigger Score (POTTS) Haemoglobin (Hb) < 7 g/dL	Haemoglobin (Hb) < 10 g/dL	N/A	N/A	N/A	N/A	Mortality and short term complications within 30 days after operation, overall survival rate after discharge

Table 1. Characteristics of included studies. Abbreviations: N/A = not available, RBC = red blood cell, RT = restrictive transfusion, LT = liberal transfusion, Hb = Haemoglobin

Figure 1. Risk of bias summary

an overall risk of bias determination. The bias was categorized into 3 levels which included low risk (shown by the colour green), uncertain bias (indicated by the colour yellow), and high-risk bias (indicated by the colour red). A graphical representation alongside a summary of the bias assessment is provided in Figure 1.

The main focus of this analysis was the assessment of mortality, including in-hospital mortality and ICU mortality as the primary outcome. Additionally, it also investigated mortality rates during other periods, such as in 30 days, and at 90 days. An assessment of morbidity that was seen during the period of hospitalization was conducted encompassing occurrences of infection. In this study, infection was classified into 3 distinct categories, and this included sepsis or bacteraemia, as well as wound infection. The morbidity outcomes were defined by the definitions provided in the respective individual trials.

Statistical analysis

The risk ratio (RR) in the intervention group was computed with the control group, together with the appropriate 95% CI (confidence interval) applying a random effect model. A comparable method was employed for analyzing additional transfusion-related outcomes. In instances where the event rate was low, the use of the Peto odds ratio was contemplated, provided that the requisite criteria for employing this particular method were met.

Statistical heterogeneity was assessed by employing both the I2 statistic and the Hi2 test. The I2 statistic quantifies the overall proportion variability seen in a set of articles that could be attributed to heterogeneity rather than random variation. A 0% heterogeneity signified the absence of observed heterogeneity, while higher values implied a heterogeneity growing level. When the I2 statistic surpassed 50% or 85%, it was often regarded as indicative of moderate or substantial heterogeneity, respectively. In the chi2 test, a significance level of less than 0.10 was employed to determine the existence of statistically significant heterogeneity. Due to the expected substantial clinical variability among the studies, the data was analyzed through a random-effects model. However, it is expected a significant diversity degree in transfusion rates due to variations in practices between different specializations involved in the studies, as the specialists follow distinct protocols. As elucidated subsequently, the investigators opted to furnish a concise statistical measure for transfusion outcomes, even in instances where I2 exhibited a substantial magnitude. This decision was motivated by the valuable clinical insights that such a summary statistic offered.

4. RESULTS

A total of 489 publications were recorded from several scholarly databases, including ScienceDirect, CENTRAL, EMBASE, and PubMed, for this study. After removing duplicate entries, a total of 347 article records were retained, and proceeded with the filtration of publications based on the titles and abstracts, resulting in a total of 157 articles. After conducting a comprehensive review of the entire text, 15 articles

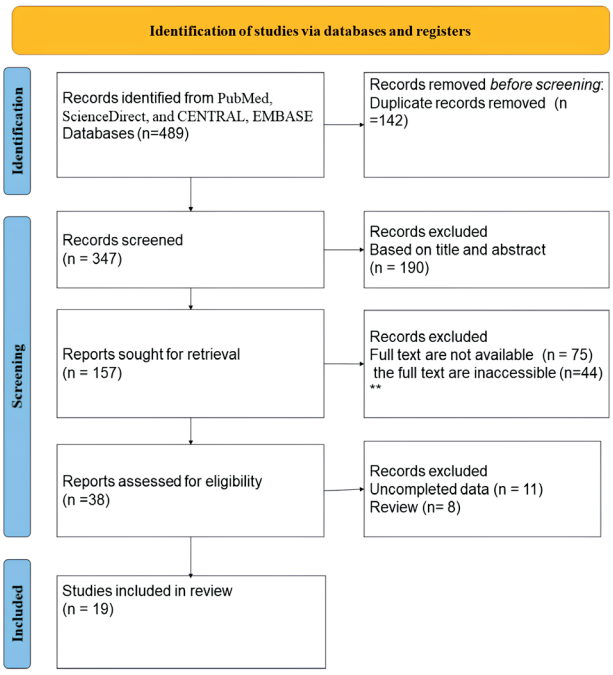

Figure 2. PRISMA flowchart of the study selection. Abbreviations: n = number

fulfilled the criteria for inclusion. Figure 2 provided a visual summary of the search and selection method, ensuring process transparency and replicability.

A comprehensive overview of the characteristics and attributes of the studies that had been incorporated into this analysis is presented in Table 1. This study comprised a total of 14,635 participants who were critically ill and admitted to ICU. Participants were divided into 2 groups, with 1 receiving liberal RBC transfusion and the other receiving restrictive RBC transfusion. All articles in this meta-analysis were randomized controlled trials. There was significant variation in the definition of restrictive transfusion strategy outlined in the guideline. These definitions ranged 7.0 - 9.7 g/dL, with 2 additional trials specifying haematocrit values of 25% or 30% (Hb levels of approximately 8 and 10 g/dL respectively).

Mortality

The mortality subgroups examined included in-hospital mortality and ICU mortality were described in 4 of the 15 articles (10-13). Restrictive threshold of 7 to 9 g/dL was used, and in-hospital mortality showed RR 0.92; 95% CI 0.75 – 1.13, p = 0.49, I2= 0%. The risk ratio of the mortality subgroup in both strategies was 0.92; 95% CI 0.78 – 1.08, overall size effect of p = 0.31, and the heterogeneity test for the subgroup was not significant with chi2 = 3.45, P = 0.49; I2 = 0% (low heterogeneity), random effect model. The result indicated that the risk of mortality in both strategies was comparable and not statistically different (Figure 3a).

A total of 4 of the 15 articles were analysed for 90-day mortality (9, 10, 14, 15). The pooled analysis showed that in both restrictive and liberal transfusion groups did not differ significantly (RR 0.97; 95% CI 0.76 – 1.22; p = 0.03; I2 = 66%), with overall size effect p = 0.77 (Figure 3b). Similarly, the analyses of the 30-day mortality (9),(10),(16),(17),(11),(18),(19),(20),(21),(22) showed that in both restrictive and liberal transfusion groups, no significant difference in 30-day mortality (RR 0.86; 95% CI 0.73 – 1.02), I2 = 27%), with overall size effect p = 0.09 and no statistically significant heterogeneity (X2 = 12.36; I2 = 27%; p = 0.19) (Figure 3c).

Adverse events

Relevant data regarding the occurrence of sepsis / bacteraemia and wound infection were extracted from three articles (23, 15, 12). The summarized estimates that the sepsis / bacteraemia did not differ significantly between both transfusion threshold groups (RR 1.55; 95% CI 0.85 – 2.80), with overall size offset p = 0.15. Additionally, the heterogeneity between these trials was not statistically significant (chi2 = 1.02, df = 2; I2 =0%; p = 0.60) (Figure 4a). Two articles provided relevant data on wound infection (12, 20). Similarly, no different in wound infection incidence in both groups (RR 0.73;

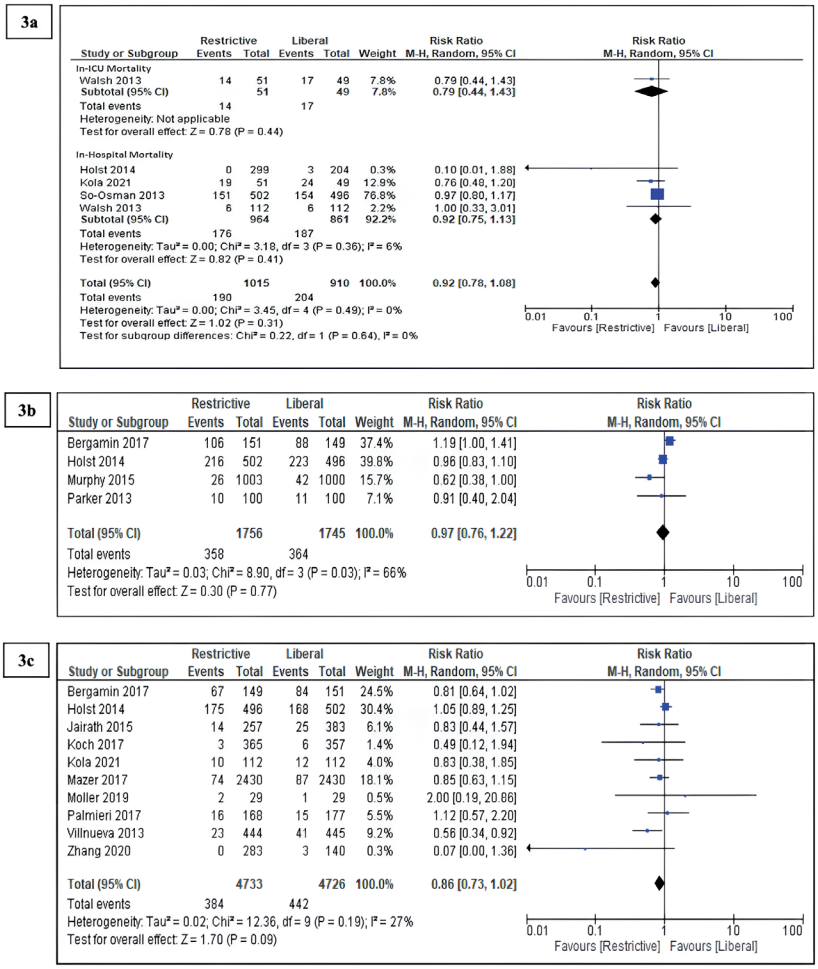

Figure 3. Forest plot of mortality. (a) Forest plot of subgroup mortality. (b) Forest plot of 90-day mortality. (c). Forest plot of 30-day mortality Abbreviations: 95% CI: 95% confidence interval; df: degrees of freedom; random: random effects model; M-H: mantel-haenszel; SD: standard deviation

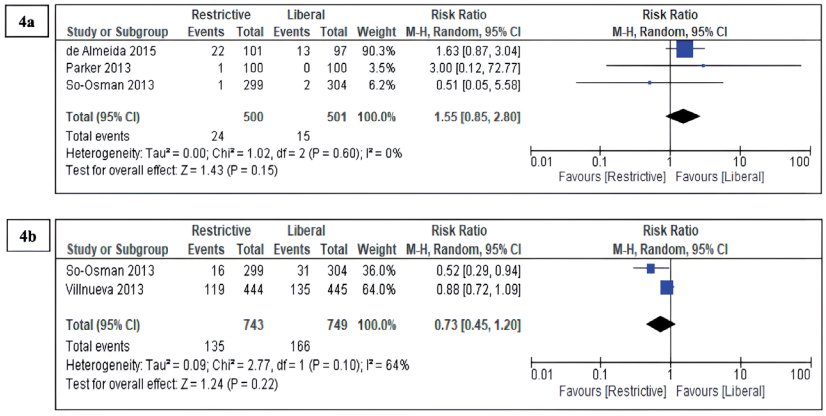

Figure 4. Adverse events related to RBC transfusion. (a) Forest plot of sepsis. (b) Forest plot of wound infection Abbreviations: 95% CI: 95% confidence interval; df: degrees of freedom; random: random effects model; M-H: mantel-haenszel; SD: standard deviation

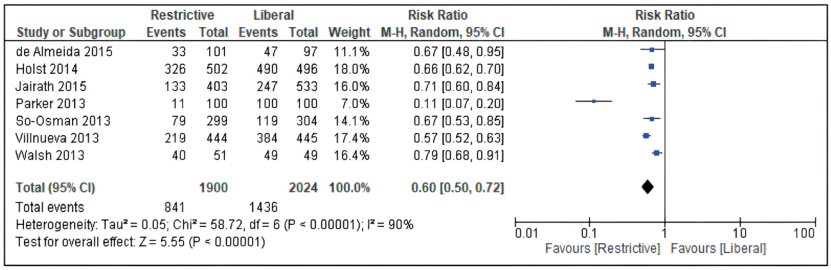

Figure 5. Forest plot of transfusion requirements. Abbreviations: 95% CI = 95% confidence interval, df = degrees of freedom, Random = random effects model, M-H = mantel-haenszel, SD = standard deviation.

95% CI 0.45 – 1.20), with overall size effect p = 0.22, with heterogeneity between included trials (X2 = 2.77; I2 = 64%; p < 0.10) (Figure 4b).

Transfusion requirements

Data regarding the transfused participants proportion were obtained from seven trials, (23, 10, 16, 15, 12, 20, 13) which collectively assessed 1900 and 2024 patients in the both transfusion threshold groups, respectively. The summarized estimates the effect size showed transfusion requirement rates in restrictive transfusion had a lower rate than the liberal transfusion (RR 0.60; 95% CI 0.50 – 0.72) with an overall size effect p < 0.00001, with a significant level of heterogeneity among the included trials (X2 = 58.72; I2 = 90%; p < 0.00001) (Figure 5).

5. DISCUSSION

This meta-analysis of RCTs analyses short-term and long-term mortality, risk of infection related to blood transfusion, and transfusion requirement following restrictive RBC than liberal RBC transfusion strategies in adult patients with critical illness hospitalized in ICU. Critically ill patients were a distinct patient population characterized by an unstable hemodynamic state, multiple organ dysfunction syndrome, or comorbidities resulting from compromised organ compensatory function. Patients with low Hb levels who were critically ill due to any causes in ICU required careful management, and blood transfusion strategy was a crucial component of the treatment. Nowadays, many clinicians believed that maintaining a higher Hb level could enhance oxygen transport in these individuals, but it remains controversial (24). This was the primary rationale behind the extensive commitment of numerous clinicians to conducting significant studies in the field over an extended period. The results provided insights into the ongoing dilemma regarding the optimal RBC transfusion threshold strategies for critically ill patients in ICU.

A total of 15 randomized controlled studies were identified, which investigated the outcomes of patients who were allocated to receive transfusions of RBC based on threshold of Hb threshold. The trials were carried out for 10 years, from 2013 to 2023, and encompassed a diverse cohort of 12,439 participants from various disease categories. The results from our meta-analysis revealed that the adoption of restrictive transfusion threshold strategy was linked to a decrease in the number of individuals necessitating blood transfusions, a diminished requirement for RBC transfusion, and a lower mean Hb concentration of approximately 1.32 g/dL in comparison to individuals belonging to liberal transfusion groups. This meta-analysis did not find any evidence suggesting mortality and adverse effects on the participants or any benefits related to the adoption of liberal transfusion threshold strategy, based on the specific criteria described in the studies. The results suggested that the wider adoption of restrictive transfusion protocols could potentially aid in the preservation of the blood supply.

The analysis of mortality subgroup (in-hospital mortality and ICU mortality) outcomes did not reveal a statistically significant difference between restrictive and liberal transfusion strategies. However, the majority of the articles indicated lower mortality in restrictive group than liberal group with no significant heterogeneity observed in these outcomes (I2 = 0%). The results on 30-day mortality were consistent with those of 90-day mortality, which was noteworthy, the analysis of 30-day mortality did not reveal a statistically significant difference between both transfusion strategies. There was moderate heterogeneity in these outcomes (I2 = 27%), suggesting some variability in the reported 30-day mortality outcomes across studies. However, the p-value for this parameter was close to statistical significance (p = 0.09), and the analysis of 90-day mortality from 4 articles in both transfusion strategies also showed comparable. However, most articles showed lower mortality in restrictive group than liberal group.

Moller et al. (22) observed a significant increase in a combined measure of perioperative mortality and significant vascular complications. In addition, meta-analysis revealed that there was no statistically significant evidence of an elevated risk of cardiac morbidity among patients in restrictive strategy group (RR 1.24; 95% CI 0.88 – 1.75) . Additional studies were necessary to evaluate the safety of restrictive transfusion strategy, specifically in patients with pre-existing cardiovascular conditions who could face a risk of cardiac complica-

tions during the perioperative period (25). According to Wu et al. (26), which explored 310,311 patients aged 65 or older who had major noncardiac surgery, there was a 1.6% increase in 30-day postoperative mortality for every 1% fall in preoperative haematocrit (27). The study demonstrated that patients who underwent significant non-cardiac surgery experienced a decrease in mortality when receiving a blood transfusion during the operation. This was particularly true for patients with preoperative haematocrit levels below 24% or those who experienced blood loss over 500 ml (28). Transfusion triggers primarily fell between 7 g/dL to 10 g/dL, and transfusion triggers labelled as 'restrictive' in certain trials were comparable to 'liberal' triggers employed in other trials.

Another crucial aspect of RBC transfusion was the incidence of adverse events, and the results showed the risk of adverse events, such as sepsis and wound infection risk were comparable between restrictive and liberal blood transfusion strategies. An additional outcome measured the outcome was influenced by multiple factors beyond RBC transfusion, such as the severity of critically ill patients and comorbidities. The observed effects were comparable to those reported in meta-analysis of trials investigating blood-conserving strategies, including cell salvage and antifibrinolytic medicines. Implementing a restrictive transfusion threshold seemed to be equally effective as these technologies in preventing the need for transfusion and was expected to be more cost-effective (29, 30). Several guidelines suggested that RBC transfusion must be considered for symptoms/hemodynamic instability, rather than being solely based on a specified trigger Hb level.

Meta-analysis revealed a significant difference in blood transfusion between restrictive and liberal strategies, and there was substantial heterogeneity in this outcome (I2 = 90%). The variability in reported blood transfusion across studies could reflect differences in patient populations. This result was consistent with the observation of several trials that recorded substantial decreases in the likelihood of RBC transfusion and valuable preservation of blood (31).

Meta-analysis had several limitations, including the potential for variability even when the target sample was limited to critically ill patients due to the different disease categories. In addition, the blinding strategy was challenging to apply in this study because of the uniqueness of red-cell transfusion administration.

6. CONCLUSION

This meta-analysis assessed 15 articles comprising more than 12,000 critically ill patients in ICU. The results showed that restrictive and liberal blood transfusion strategies yielded comparable outcomes in terms of mortality (in-hospital, ICU, 30-day, and 90-day mortality), sepsis, and wound infection. However, the more restrictive blood transfusion strategy was related to a reduction of transfusion requirement in critically ill patients, making it a more cost-effective option. Clinicians must carefully consider patients' clinical status, comorbidities, and specific clinical context of each patient when determining decisions regarding RBC transfusion in critically ill patients in ICU.

- **Author's contribution:** (I) Conception and design: ADF Wisnawa*, IW Aryabiantara*; (II) Acquisition of data: ADF Wisnawa*, TGA Senapathi, IW Aryabiantara*; (III) Data analysis and interpretation: ADF Wisnawa*, IW Aryabiantara*, TGA Senapathi; (IV) ADF Wisnawa*, IW Aryabiantara*; (V) Revising and Approval Final Version: All authors. *These authors contributed equally to this work.
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