TRANSFUSION MEDICINE

Review

From liberal to restrictive and beyond: a narrative review of red blood cell transfusion strategies in the modern era

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Background - Red blood cell (RBC) transfusion remains a cornerstone of modern medicine, yet optimal transfusion thresholds continue to be debated. Historically, liberal strategies –maintaining hemoglobin (Hb) concentration above 10 g/dL– predominated, but evidence from the 1990s onward has favored restrictive approaches (Hb threshold 7-8 g/dL). This narrative review synthesizes contemporary evidence on restrictive versus liberal transfusion strategies published between 2021 and 2026, evaluates population-specific considerations, and explores emerging ultra-restrictive thresholds.

Materials and methods - A structured narrative literature search was conducted in PubMed and Google Scholar with particular emphasis on evidence published between 2021 and 2026. Evidence from randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines is critically discussed.

Results - The 2025 Cochrane update (48 trials, >20,000 participants) provided high-certainty evidence that restrictive strategies induce a reduction in the risk or proportion of patients receiving at least one RBC transfusion by 41% without increasing 30-day mortality or major morbidity. Restrictive thresholds are safe in stable critically ill patients, in those undergoing non-cardiac surgery, and in patients with acute gastrointestinal bleeding. However, important exceptions include: acute myocardial infarction (in which liberal strategies may reduce cardiac events), neurocritical care (conflicting evidence on neurological outcomes), chronic transfusion-dependent conditions such as thalassemia (liberal strategies are disease-modifying), and hematologic malignancies (individualized approach required). Ultra-restrictive thresholds (Hb <6-7 g/dL) have emerged as a potential blood conservation tool during shortages but require further safety validation.

Discussion - Restrictive transfusion strategies are safe and effective for many stable adult hospitalized patients, reducing blood product utilization without compromising outcomes. However, individualized approaches remain essential for specific high-risk populations. Ultra-restrictive strategies are promising, but these approaches should currently be considered only in selected contexts pending further safety validation.

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INTRODUCTION

Red blood cell (RBC) transfusion has been a cornerstone of modern medicine for over a century, yet the optimal approach to transfusion decision-making remains one of the most debated topics in clinical practice. The decision to transfuse should be based not only on hemoglobin (Hb) concentration but also on the balance between oxygen delivery and consumption, clinical symptoms, hemodynamic status, and the overall clinical context[1]. The fundamental purpose of a RBC transfusion is to restore or maintain adequate tissue oxygenation. From a physiological standpoint, a transfusion is warranted when the body's compensatory mechanisms, such as increased cardiac output, increased extraction of oxygen, and redistribution of blood flow, are overwhelmed. Physiologically, the decision to transfuse should never be about a number (Hb concentration) alone, it should be about the balance between oxygen supply and oxygen demand. A Hb of 7 g/dL might be perfectly safe for a healthy, resting young adult, but physiologically catastrophic for an elderly patient with unstable angina (high demand, low reserve). That is why incorporating clinical status and comorbidities is the only physiologically sound way to practice transfusion medicine.

Historically, transfusion practices were guided by a liberal strategy of maintaining Hb level above 10 g/dL. Although this practice was intuitively appealing, it lacked robust scientific support and potentially exposed patients to unnecessary risks while consuming limited blood resources. As is widely known, blood is both a costly and scarce asset mainly collected from volunteer donors, accounting for a noteworthy percentage of the total health care costs in developed countries, and should therefore be used wisely[2]. In addition, blood transfusion is an invasive therapy and as such is associated with possible adverse events such as thromboembolism, cerebrovascular accidents, myocardial infarction, transfusion-associated circulatory overload, transfusion-related acute lung injury, alloimmunization, transfusion reactions, infections, and immunomodulatory effects that increase the risk of morbidity and mortality[3,4].

The liberal strategy began changing in the 1990s with landmark studies questioning the efficacy of liberal transfusion thresholds. The Canadian Critical Care Trials Group's TRICC trial, published in 1999, demonstrated that a restrictive strategy (Hb threshold of 7 g/dL) was at least as safe as a liberal strategy (10 g/dL) in critically ill patients[5]. This finding fundamentally challenged liberal practice and provided the foundation for subsequent trials evaluating restrictive *versus* liberal transfusion thresholds across different clinical settings.

The period from 2021 to 2026 has witnessed remarkable growth in the evidence base and transfusion guidelines suggesting a restrictive transfusion strategy (transfusing when Hb level is <7 g/dL) instead of a liberal transfusion strategy (transfusing when Hb level is <8-10 g/dL) in several well-studied clinical settings[6]. Thus, our attention focuses on recent evidence in order to provide an updated and clinically meaningful review while contextualizing it within the broader historical development of transfusion practice.

This narrative review aims to provide a comprehensive, critical synthesis of contemporary evidence on current transfusion strategies. We examine the evolution of transfusion practices, critically evaluate evidence across diverse populations, explore ongoing controversies, and identify implementation challenges in an effort to highlight and update, in relation to existing systematic reviews, the rationale for optimizing the balance between the benefits and risks of blood transfusion. This optimization, along with strict adherence to current clinical guidelines, is essential for improving patients' outcomes.

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MATERIALS AND METHODS

Narrative review approach

This narrative review integrates evidence from randomized controlled trials, observational research, systematic and narrative reviews, meta-analyses, as well as international guidelines concerning restrictive transfusion practices. Only articles in English language were considered. The methodological approach was in accordance with the general framework of narrative reviews[7]. Given the nature of this narrative review, we included both primary studies and published systematic reviews/meta-analyses. When dealing with overlapping evidence, we prioritized primary clinical trials for individual outcomes. Meta-analyses that included these same trials were not treated as separate data, instead they were used conceptually to discuss broader statistical trends, guidelines and consensus in literature.

Employing a comprehensive yet interpretative framework, this review critically appraises and synthesizes contemporary evidence of the last 6 years. In contrast to systematic reviews, which are characterized by predefined protocols and quantitative meta-analytic techniques, the narrative approach facilitates broader thematic exploration, expert evaluation, and contextual integration of findings. Such a methodology is particularly appropriate for multifaceted and rapidly advancing domains in which variability in evidence quality exists, and clinical applicability necessitates nuanced interpretation.

Literature search strategy

A comprehensive literature search was performed in two major databases, PubMed and Google Scholar. The search focused on publications from January 2021 through March 2026. This timeframe was selected to provide the most contemporary evidence in the field of liberal and restrictive transfusion strategies, while acknowledging that fundamental studies conducted before 2021 still play a crucial role in clinical practice. Furthermore, it was intended to capture the changes concerning the management of blood resources and transfusions in general due to the coronavirus disease 2019 (COVID-19) outbreak and the constantly variable economic environment throughout the world that directly affects money allocated to healthcare[8]. The search was conducted from February 2026 to April 2026 and the following filters were applied: English language, age >18 years old, and publication date from January 2021 to March 2026.

Selection and eligibility criteria

The search strategy employed combinations of the following key words: restrictive transfusion strategy OR liberal transfusion strategy OR transfusion threshold OR hemoglobin trigger OR red blood cell transfusion OR transfusion strategy OR blood conservation. The following inclusion criteria were applied (and were also used as filters during the literature search): controlled randomized trials, observation studies, systematic reviews, meta-analyses, narrative reviews. Guidelines and consensus statements were also included. The exclusion criteria used were studies lacking clear distinction between the two strategies (restrictive or liberal), studies involving patients with massive bleeding (hemorrhagic shock) in whom fixed thresholds cannot be applied, studies including transfusion of blood products other than RBC (plasma, platelets), studies addressing autologous transfusion, and neonatal and pediatric populations.

Studies were selected based on relevance to transfusion thresholds, methodological quality, and contribution to understanding optimal transfusion strategies across adult populations in diverse clinical environments. Heterogeneity across studies, exploring potential sources including differences in patient populations, clinical contexts, transfusion protocols, and outcome definitions, was of utmost importance.

Data synthesis and critical appraisal

The initial literature search revealed 1,263 articles (after applying filters and combining keywords). After screening titles and abstracts, 200 articles remained. After full text screening and removal of duplicates, 92 articles remained. Sixty-one articles were rejected as not relevant or because they met the exclusion criteria. Finally, 31 articles were included in the analysis that forms the evidence base for this review. Evidence quality was assessed considering study design, sample size, risk of bias, consistency of findings, directness and precision of evidence in the context of an informal appraisal. Analysis of the included studies revealed several key areas: evolution of transfusion practices, comparative effectiveness of restrictive *versus* liberal strategies, population-specific considerations, controversies and conflicting evidence, emerging challenges and future directions.

RESULTS

Historical evolution of transfusion practices

The history of transfusion medicine reflects a gradual transition from empiricism and tradition to evidence-based practice. During the 20th century a convention suggesting transfusion when Hb fell below 10 g/dL or hematocrit below 30% perpetuated liberal transfusion practices[9]. Awareness of transfusion-associated risks emerged and grew throughout the 1980s and 1990s. The HIV/AIDS epidemic, hepatitis C transmission, and recognition of immunomodulatory effects of transfusion raised concerns about the safety profile of blood products. While improved screening led to a dramatic decrease in viral transmission risks[10], other non-infectious transfusion complications including

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transfusion-related acute lung injury, transfusion-associated circulatory overload, and alloimmunization remained[11]. Contemporaneously, observational studies of this period that documented associations between RBC transfusion and adverse outcomes, including increased infection rates, longer hospital stay, and higher mortality, raised important concerns about optimal transfusion thresholds[12,13].

The TRICC trial

In 1999, Hebert and colleagues published the findings of the multicenter randomized controlled trial known as the Transfusion Requirements in Critical Care (TRICC) trial. This trial compared restrictive *versus* liberal transfusion strategies in 838 critically ill patients. The restrictive arm aimed to maintain Hb between 7 and 9 g/dL, whereas the liberal arm aimed to maintain Hb between 10 and 12 g/dL. The restrictive strategy did not increase 30-day mortality compared with the liberal strategy. A notable subgroup finding was that the restrictive strategy was associated with lower mortality and was associated with lower mortality in less severely ill patients and those under 55 years of age. Moreover, the restrictive group received significantly fewer transfusions without adverse consequences. The TRICC trial demonstrated the feasibility and safety of randomized trials comparing transfusion strategies, established a methodological template for subsequent studies, and provided high-quality evidence challenging decades of conventional practice[5].

Expansion of the evidence base (2000-2020)

After the TRICC trial, many randomized trials examined transfusion thresholds in diverse clinical settings: cardiac surgery, orthopedic surgery, gastrointestinal bleeding, acute coronary syndromes, and others. The 2011 FOCUS trial in hip fracture surgery[14] and the 2014 TRISS trial in septic shock[15] further supported restrictive strategies. By 2020 clinical practice guidelines from major organizations including the AABB (formerly American Association of Blood Banks), and European societies endorsed restrictive approaches (typically thresholds of 7-8 g/dL) and supported restrictive transfusion strategies as safe and effective in most hospitalized patients[16,17]. However, important questions regarding specific populations, such as those with acute cardiac disease and neurological injury, remain in doubt[13].

Contemporary era (2021-2026)

Recent evidence has refined the role of restrictive transfusion strategies while identifying clinical contexts in which higher thresholds may still be appropriate. More specifically, large trials have been conducted in understudied populations such as the TOP trial that examined patients at high cardiac risk undergoing major vascular or general surgery with postoperative anemia and multiple trials that focused on populations with acute brain injury[18,19]. Emerging evidence from systematic reviews and meta-analyses, including a Cochrane review in 2025, had greater statistical power and questioned the universality of restrictive strategies in certain settings, such as gastrointestinal bleeding and neurocritical care. Despite strong evidence and guidelines in favor of restrictive strategies, practice variation persists and many patients continue to receive transfusions at higher thresholds than recommended[20]. On the other hand, several researchers have begun exploring "ultra-restrictive" strategies with even lower thresholds –often around 6-6.5 g/dL– questioning whether current restrictive thresholds represent the optimal balance of safety and resource conservation[6].

This narrative review is based upon this contemporary evidence examining specific populations, outcomes, controversies, and implications for clinical practice.

Evidence for restrictive *versus* liberal transfusion strategies

The Cochrane review

The Cochrane systematic review "Transfusion Thresholds for guiding red blood cell transfusion" represents the most comprehensive and rigorous synthesis of evidence on this topic. This study was first published in 2012 but since then it has been updated several times. According to the 2025 update, the review included 79 studies overall, while the adult threshold comparison included 61 trials and 27,639 participants; restrictive strategies reduced the risk of receiving at least one RBC transfusion by 42% with a relative risk (RR) of 0.58 representing a substantial reduction in blood product utilization compared to liberal strategies (Hb 9-10 g/dL)[6]. As far as mortality is concerned, most of the studies supported the concept that restrictive strategies do not increase 30-day mortality compared to liberal strategies (no clear difference in 30-day mortality with RR=1.01, 95% confidence interval [CI]: 0.90-1.14

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in the comparison of thresholds in adults). Only a few analyses suggested potential mortality due to restrictive strategies, in situations such as gastrointestinal bleeding and neurocritical care, but did not reach statistical significance in the overall analysis. Major morbidity outcomes such as cardiac events, myocardial infarction, stroke, thromboembolism and infection were also found not to differ significantly between patients managed with restrictive or liberal strategies. This is particularly important given the historical concerns that lower Hb levels might increase cardiac complications or that reduced transfusion rates might decrease infection risk through immunomodulatory processes[13]. The findings of the Cochrane study were consistent in most of the subgroups included and this benefits confidence and generalizability. Nevertheless, it must be referred that certain subgroups, such as patients with hematologic malignancies, chronic anemia or receiving chemotherapy, were underrepresented in this study and that longer term outcomes (late mortality, quality of life, functional recovery) were less frequently reported.

Intraoperative and perioperative transfusions (non-cardiac surgery)

Intraoperative transfusion is a complex and dynamic process that relies on shared decision-making and communication among surgeons and anesthesiologists[21]. It differs from other clinical settings because of there being less time for assessment and greater hemodynamic instability[22]. In the United States alone, one million units of RBC administered annually are given to surgical patients although the risk of over transfusion during surgery is of great concern to surgeons when considering reports of transfusion- associated immunomodulation, post-operative complications and possibly worse cancer outcomes[21]. A systematic review and meta-analysis by Lenet *et al.* examined intraoperative RBC transfusion strategies, analyzing 14 randomized trials involving 8,641 patients. All but two small trials found that 30-day mortality and post-operative morbidity were not significantly different when comparing restrictive and liberal transfusion protocols (RR=0.96, 95% CI: 0.71-1.29) for the 30-day mortality outcome[22]. Intraoperative restrictive transfusion strategies decreased intraoperative and perioperative RBC transfusions, reducing the number of patients exposed to blood products. Moreover, the Ottawa Intraoperative Transfusion Consensus validated the use of a 7 g/dL restrictive trigger in clinical trials for patients without major cardiac comorbidity. The Consensus emphasized the supply challenges arising from the COVID-19 pandemic and the fact that 20%-50% of RBC transfusions in the intraoperative context could be avoided if the decision for transfusion relied on patient-related and surgical factors rather than on clinicians' preferences or institutional practice patterns. Therefore, it suggested that the implementation of a restrictive transfusion protocol would be feasible in the operating room[23].

On the other hand, a systematic review of clinical practice guidelines regarding intraoperative RBC transfusions recommended Hb thresholds prompting transfusion ranging from 6 g/dL to 10 g/dL. This wide range in Hb thresholds points out the role of intraoperative blood loss and end-organ perfusion when deciding to transfuse. Although, the guidelines suggest single unit transfusion and reassessment before additional units are given, there are no specific indications for the frequency of Hb testing/monitoring during surgery or a directive for the estimation of surgical bleeding that should trigger transfusion. This reflects that transfusion in the intraoperative setting requires a careful risk benefit approach and highlights the need for constant evaluation of the patients as they transition through the pre-, intra- and post-operative periods[21].

As for perioperative transfusion, a substudy from the Vascular Events in Non-Cardiac Surgery Patients Cohort Evaluation (VISION) prospective cohort study observed adult patients who underwent non-cardiac surgery for 30 days. There was a substantial decrease in transfused patients from 20% to 13% over a 6-year period. This variation in transfusion practice and the subsequent reduction in transfusions seem to have resulted from local factors (reliability of blood supply, limited evidence concerning appropriate blood transfusion, decreased bleeding episodes) rather than the application of a restrictive strategy. Lower Hb values and anemia were associated with increased 30-day mortality and complications in surgical patients[24]. However, given that these data are derived from an observational study, they should not be interpreted as direct evidence for the safety or efficacy of a restrictive transfusion strategy.

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Available information suggests that interpretation of observational studies needs considerable attention. Clinical trials are strongly recommended to demonstrate whether a restrictive transfusion strategy can be used with safety in selected perioperative settings.

High-risk cardiac patients

The Transfusion in Patients at High Cardiac Risk (TOP) randomized clinical trial evaluated postoperative transfusion strategies in patients at high cardiac risk undergoing major vascular or general surgery who developed postoperative anemia[18]. It was designed to compare a restrictive strategy with a trigger of <7 g/dL against a liberal strategy with a trigger of <10 g/dL in this clinical setting. The primary composite outcome (all-cause death, myocardial infarction, coronary revascularization, acute kidney failure, or ischemic stroke at 90 days) was not significantly different between the two groups (RR=0.90, 95% CI: 0.65-1.24). The Cochrane review, which included multiple trials with cardiac surgery patients, found no evidence that restrictive strategies increased cardiac complications[6,13].

Critically ill patients

Approximately 5 million patients in the United States are admitted to the Intensive Care Unit (ICU) each year and one quarter of them receive RBC transfusions[25]. Multiple meta-analyses have specifically examined transfusion strategies in critically ill adults, consistently supporting restrictive approaches. Zhang *et al.* analyzed seven randomized trials involving 7,363 ICU patients and found that a restrictive transfusion threshold (<7 g/dL) did not significantly differ from liberal strategies for ICU mortality, 28/30-day mortality or longer-term mortality. Interestingly, restrictive strategies potentially reduced in-hospital mortality (RR=0.79, 95% CI: 0.64-0.97, p=0.03)[26]. Similarly, the guideline synthesized evidence from 23 studies (22 randomized controlled trials and 1 cohort study) involving approximately 16,000 critically ill patients, and recommended a restrictive threshold of 7-8 g/dL over a liberal one of 8.5-10 g/dL by demonstrating no significant difference in ICU mortality, 30-day mortality, 1-year mortality, ICU length of stay and organ/system specific adverse events, while the restrictive strategy decreased the number of RBC units transfused by 50%[25]. All these findings are notable given the fact that critically ill patients often have several comorbidities, hemodynamic instability and increased oxygen demands which might favor higher transfusion thresholds. However, they should be interpreted cautiously, since most mortality outcomes were not significantly different.

Neurocritical care constitutes a special subgroup of critically ill patients. Acute brain injury represents perhaps the most important exception to universal restrictive transfusion strategies. The physiological changes of the injured brain, including impaired autoregulation, increased metabolic demands and vulnerability to secondary injury from hypoxia, have led to ongoing debate about optimal transfusion thresholds. A systematic review and meta-analysis by Quan *et al.* of critically ill adults found that patients with closed head injuries and comorbidities appeared at higher risk of mortality when transfused based on restrictive thresholds compared to those transfused based on liberal thresholds[27]. In contrast to these findings, the systematic review conducted by Shaukat *et al.* evaluating restrictive *versus* liberal transfusion strategies in neurocritical adult patients demonstrated that the restrictive transfusion strategy was as effective as the liberal one in terms of 6-month and long-term mortality, length of ICU and in-hospital stay, neurological complications and secondary outcomes (stroke, hypoxia, intracranial hypertension)[28].

Yuan *et al.* analyzed five randomized trials involving 1,528 patients with traumatic brain injury. They found that restrictive strategies (≤7 g/dL) had no impact on mortality (RR=1.00, 95% CI: 0.80-1.24) or unfavorable neurological outcome at 6 months (RR=1.06, 95% CI: 0.94-1.20) compared to liberal strategies (≤9-10 g/dL)[29].

On the contrary, a meta-analysis by Sud *et al.* that examined the effects of a liberal transfusion strategy (≤9-10 g/dL) compared to a restrictive strategy (≤7-8 g/dL) on long-term neurological function outcomes, involving 2,364 anemic adult patients with acute acquired brain injury, found that the liberal transfusion threshold reduced unfavorable neurological outcomes (RR=0.89, 95% CI: 0.84-0.95) and severe disability (RR=0.82, 95% CI: 0.66-1.02) while it increased good recovery (RR=1.29, 95% CI: 0.95-1.76)[30].

While the evidence is heterogeneous, the potential for improved neurological outcomes with higher transfusion thresholds (9-10 g/dL) deserves serious consideration. However, individualized decision-making based on overall clinical context remains essential in order to retain

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balance against possible transfusion risks. Larger trials in the field might identify which category of neurocritical ill patients would benefit from liberal strategies and examine longer-term functional outcomes.

Acute gastrointestinal bleeding

A systematic review and meta-analysis by Teutsch *et al.* examined the efficacy and safety of restrictive transfusion strategies compared to liberal strategies in patients with acute upper gastrointestinal bleeding. The results from the randomized controlled trials proved that patients in the restrictive arm of the studies received fewer RBC units and experienced less unfavorable outcomes (in-hospital mortality, in-hospital rebleeding, 30-day mortality, acute kidney injury, etc.). No difference in length of hospital stay was found between the two strategies. However, higher mortality rate and risk of rebleeding was associated with the number of RBC units transfused. Some individual studies revealed lower ischemic, thromboembolic and adverse event rates with the restrictive strategy[31].

Regarding lower gastrointestinal bleeding, in 2021, the European Society of Gastrointestinal Endoscopy published a guideline for acute lower gastrointestinal bleeding recommending a restrictive transfusion threshold (Hb 7-8 g/dL) for hemodynamically stable patients with acute lower gastrointestinal bleeding, based on evidence of improved survival, reduced transfusion requirements, and shorter hospital stay[21]. While this strategy is broadly supported in this specific population, caution is warranted when extrapolating these findings to all settings of gastrointestinal bleeding, and clinicians should individualize transfusion decisions according to their patients' hemodynamic status, comorbidities, and bleeding severity. The findings for critically ill patients with upper or lower acute gastrointestinal bleeding are similar, as described in the clinical practice guideline of the American College of Chest Physicians[25].

Findings only differ in older patients (with a median age of 74 years) and patients with cardiovascular disease in whom the risks of acute coronary syndrome, as well as 30-day and 90-day mortality were significantly increased in those who received transfusion according to a restrictive threshold[32]. Therefore, a more liberal threshold may be appropriate in patients with acute or chronic cardiovascular disease, but this should be considered as a specific exception rather than as a general contradiction to restrictive transfusion strategies.

Special population considerations

Acute myocardial infarction

The Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY) trial was the first large, randomized trial to directly compare restrictive *versus* liberal blood transfusion strategies specifically in patients with acute myocardial infarction and anemia[33]. It demonstrated that a restrictive transfusion strategy (triggered at Hb ≤8 g/dL) was non-inferior to a liberal strategy (triggered at ≤10 g/dL) for 30-day major adverse cardiovascular events in patients with acute myocardial infarction and anemia, while reducing blood product use and infection rates. However, a later 1-year analysis noted that the restrictive strategy did not achieve non-inferiority at 1 year, suggesting potential late harm from persistent anemia

In an interventional trial by Carson *et al*., 3,504 patients were randomly assigned to a liberal (Hb cutoff <10 g/dL) or a restrictive (Hb cutoff 7-8 g/dL) transfusion strategy and primary outcome events were studied (composite of myocardial infarction or death at 30 days). The liberal transfusion strategy may not significantly reduce the risk of recurrent myocardial infarction or death at 30 days but since potential harm of a restrictive transfusion cannot be excluded, a liberal approach is recommended over a restrictive one for these patients[34].

An analysis of the Myocardial Ischemia and Transfusion (MINT) trial, in which patients were randomly assigned to either a liberal or a restrictive transfusion strategy, pointed out that patients who were transfused based on a liberal Hb threshold received more than three times the number of RBC units compared to patients who were transfused based on a restrictive transfusion threshold. Adverse events in the liberal transfusion arm increased proportionally to the number of RBC units transfused. Although a higher rate of major adverse events was observed in the liberal arm, myocardial infarction and 30-day mortality were found to be higher in the restrictive transfusion arm[35].

In another meta-analysis of four randomized trials which evaluated restrictive *versus* liberal transfusion in patients with myocardial infarction, the restrictive transfusion strategy was associated with increased risk of 30-day

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cardiac mortality and 6-month all-cause mortality[36]. The individual patient-level meta-analysis warrants particular emphasis, as it offers the most comprehensive and robust synthesis of randomized evidence currently available in this setting.

Zhang *et al.* in their systematic review and meta-analysis that included 6,630 patients (2,008 received RBC transfusion according to a restrictive threshold, 4,622 received liberal RBC transfusion) demonstrated no difference in overall mortality, follow-up mortality and secondary outcomes (reinfarction, stroke, acute heart failure) but in-hospital mortality tended to be higher in the restrictive transfusion group[37].

The most recent AABB guideline specifically addressing red cell transfusion in patients with acute myocardial infarction suggests a liberal RBC transfusion strategy for hospitalized patients with acute myocardial infarction when the Hb is below 10 g/dL, although this is a conditional recommendation based on low-certainty evidence[38].

Although liberal strategies seem to have potential benefits for patients with acute myocardial infarction, they cannot be recommended as a routine and therefore optimal transfusion thresholds remain controversial for this challenging clinical population.

Thalassemia

Thalassemia results from defective globin chain synthesis leading to chronic hemolytic anemia. Although thalassemia was once confined to certain geographic areas (Mediterranean Basin, Middle East and Southeast Asia), massive migratory movements from the Middle East and Asia to Europe have led to the global spread of thalassemias. Based on their clinical severity and transfusion requirement, thalassemia syndromes can be classified phenotypically into transfusion-dependent thalassemias and non-transfusion-dependent thalassemias. The most clinically relevant types are α and β thalassemia[39].

In patients with thalassemia, the classic distinction between restrictive and liberal transfusion strategies is less applicable, as transfusion entails a central, disease-modifying role rather than simply correcting anemia. In transfusion-dependent thalassemia, current international guidelines support a liberal transfusion strategy with pre-transfusion Hb levels above 9.0-10.5 g/dL through regular transfusions every 2-4 weeks, with higher targets in patients with cardiac complications.

This strategy prevents disease-related complications, further bone marrow expansion, and extramedullary hematopoiesis and suppresses ineffective erythropoiesis. Emerging evidence also shows that higher Hb levels improve patients' quality of life as well as survival through better growth and organ function[26]. In their retrospective cohort study, Musallam *et al.* established an association between higher pretransfusion Hb levels and lower thalassemia-related mortality in adults with transfusion-dependent thalassemia, as indicated by the 2021 guidelines[40,41]. In non-transfusion-dependent thalassemia, including HbH disease in α-thalassemia, transfusion practices are more individualized and the decision to transfuse derives from specific clinical indications (such as symptomatic anemia, pregnancy, infection, or complications). Notably, α-thalassemia syndromes have a wide clinical spectrum, from asymptomatic individuals requiring no transfusion to severe forms necessitating lifelong support[42,43]. Nevertheless, risks of chronic transfusion, such as iron overload, alloimmunization and transfusion reactions, must always be weighed against potential benefits when deciding to transfuse.

As evidence clearly demonstrates, transfusion strategies in thalassemia are guided less by universal Hb thresholds and more by disease phenotype and long-term pathophysiological targets, distinguishing this population from the standard restrictive-*versus*-liberal transfusion pattern[13].

Hematologic malignancies

Patients with hematologic malignancies, including leukemia, lymphoma and myelodysplastic syndrome frequently experience anemia due to bone marrow involvement, chemotherapy effects and bleeding complications. Despite the frequency of transfusion in this population, high-quality evidence regarding the optimal transfusion threshold is limited.

Interventional trials conducted in a diverse global setting by Radford *et al.* involving patients with hematologic disorders undergoing myelosuppressive chemotherapy, radiotherapy (or both), or stem cell transplantation demonstrated little to no difference between liberal and restrictive transfusion strategies with respect to primary outcomes studied (all-cause mortality at day 31 to 100,

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quality of life, infections, bleeding, length of hospital stay, hospital readmission). Regarding secondary outcomes, results demonstrated a significant reduction of over two RBC units per participant when a restrictive strategy was used. This gives the potential for conservation of a valuable and limited resource with significant cost savings[44]. These findings should be interpreted cautiously, since the available evidence remains limited and heterogeneous. Especially for patients with myelodysplastic syndrome, who require chronic transfusion therapy, an individual patient-centered and symptom-based approach is necessary rather than Hb level. It is strongly recommended that patients with severe anemia (Hb <8 g/dL) or symptomatic anemia (Hb ≥8 g/dL) receive transfusion[45].

Restrictive transfusion strategies that are commonly used in patients with non-hematologic disorders should be cautiously considered for patients with hematologic disorders. Although many of these patients tolerate chronic anemia well, those receiving intensive chemotherapy or who have active bleeding may benefit from higher transfusion thresholds. Therefore, as such patients receive a substantial proportion of blood products, an important research priority is to examine transfusion thresholds, practice impact and resource utilization in this population.

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Extracorporeal membrane oxygenation

Patients receiving extracorporeal membrane oxygenation (ECMO) support, for either cardiac or respiratory failure, present unique transfusion challenges due to circuit-related hemolysis, anticoagulation requirements and their critical condition. In their review, Boscolo *et al.* compared the efficacy of restrictive transfusion thresholds *versus* liberal ones for patients during ECMO. While findings are not definitive (especially for patients with severe thrombocytopenia, bleeding disorders, or underlying cardiac conditions), since the evidence is based on a small number of observational studies, the authors highlighted that restrictive thresholds led to a reduction in blood products administered, in ECMO duration and in mortality at 28 days[46]. It is of note that the review by Boscolo *et al.* included patient populations receiving both venovenous (VV) and venoarterial (VA) ECMO, but it did not present separate subgroup analyses.

Abbasciano *et al.* also aimed to evaluate the effects of liberal *versus* restrictive red cell transfusion thresholds in ECMO patients, but they identified significant variability in transfusion practices and outcomes among the patients. Mortality rate, transfusion thresholds and transfusion rate depended on whether a VV or VA procedure was concerned[47]. Despite the differences, excessive transfusion may worsen outcomes through inflammatory effects and volume overload in all ECMO patients.

Recent observational evidence, including PROTECMO in VV-ECMO[48] and the OBLEX target trial emulation in VA-ECMO[49], suggests that transfusion needs may differ according to ECMO modality and phase of support. More specifically, the PROTECMO study evaluated transfusion practices in adult patients receiving VV-ECMO for severe respiratory failure. The study demonstrated that transfusion significantly reduced mortality only when Hb was below 7 g/dL (HR=0.15; 95% CI: 0.03-0.74).

The OBLEX study, using a target trial emulation approach, enrolled 534 VA-ECMO patients and the investigators compared a liberal strategy (transfusion at Hb ≥9 g/dL) *versus* a restrictive strategy (transfusion at Hb ≤70 g/dL). The liberal strategy provided a modest survival benefit during the early phase of VA-ECMO. However, no significant survival difference was found after day 3.

In conclusion, restrictive transfusion strategies may be feasible in selected ECMO patients, but the optimal threshold remains uncertain and should be individualized according to ECMO type, bleeding risk, tissue oxygenation, cardiac function, and clinical phase. Therefore, detailed research is needed to fill this knowledge gap.

The Hb thresholds and recommendations for restrictive or liberal transfusion strategies for different categories of patients are summarized in **Table I**.

Emerging trend: ultra-restrictive transfusion strategies (hemoglobin <6-7 g/dL)

The concept of an ultra-restrictive transfusion strategy –typically defined by Hb thresholds below 6-6.5 g/dL– has gained increasing attention over the past 5 years. Recent studies suggest that ultra-restrictive approaches may be safe and can further reduce exposure to transfusion-related complications[50,51].

Schaap *et al.* examined several groups of patients in whom a Hb level below 7 g/dL was applied and well tolerated –such as patients with aplastic anemia– while in other groups, including extensively burned patients, ultra-restrictive thresholds were found to negatively

Table I - *Restrictive versus liberal transfusion strategy*

Patient category	Hb threshold	Recommendation	Comments
Intraoperative	=7 g/dL	✓Restrictive	
Perioperative	Unclear	Unclear	
Postoperative (cardiac surgery)	<7-8 g/dL	✓Restrictive	
Sepsis/septic patients	<7 g/dL	✓Restrictive (unless ischemia/shock)	
Cardiovascular disease	<8 g/dL (or individualized)	Ongoing debate (may favor slightly liberal)	
ICU (stable)	<7 g/dL	✓Restrictive	
Acute brain injury	= 9-10 g/dL (or individualized)	✓Liberal	Evidence heterogeneity
Acute gastrointestinal bleeding (stable patients <74 years, without cardiovascular disease)	=7-8 g/dL	✓Restrictive	
Acute myocardial infarction	<10 g/dL	✓Liberal	Conditional recommendation based on low-certainty evidence
Thalassemia	=9.0-10.5 g/dL	✓Liberal/Individualized approach	
Hematologic malignancies	No strict threshold	Clinical status >Hb level	
ECMO	Not defined	Ongoing debate	Individualized according to ECMO type and other risk factors

ECMO: extracorporeal membrane oxygenation; Hb: hemoglobin; ICU: Intensive Care Unit.

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affect in-hospital mortality[50]. Their central question was whether the current standard restrictive threshold of 7 g/dL can be safely lowered further in critically ill patients. Overall, the findings imply that the current transfusion threshold for critically ill patients may be safely revised downward, as Hb levels below 7 g/dL do not appear to be independently associated with increased mortality or morbidity. Rather than adhering to a fixed numerical trigger, a more individualized, physiology-based approach to transfusion decisions might be preferable. Such a paradigm shift could not only reduce unnecessary blood product utilization and associated healthcare costs but also mitigate the well-documented risks of allogeneic blood transfusion.

The risk of severe blood shortages during crises, whether caused by natural events or human actions, has long been acknowledged and documented. Indisputably, the COVID-19 pandemic posed innumerable challenges to healthcare systems with increased consumption of blood products being one of them. During the pandemic, a prolonged and notable decline in blood supply was observed. Studies on ultra-restrictive strategies encompass mostly ICU patients because of existing evidence supporting restrictive transfusion (Hb=7 g/dL) and constant monitoring that allows implementation of ultra-restrictive transfusion protocols. A study by Kheirbek *et al.* examined the implementation of an ultra-restrictive transfusion protocol during a blood shortage crisis[51]. They established a threshold of 6 g/dL for patients <65 years old and 6.5 g/dL for those ≥65 years old admitted in general surgical or trauma ICU and compared patients retrospectively before and after the implementation. Although the protocol appeared feasible and effective as a blood conservation strategy given the shortage caused by the pandemic, the small sample size and the short implementation period did not lead to safe results concerning in-hospital mortality or ischemic complications[51]. In this context, these findings should not be regarded as definitive evidence of safety, but as a retrospective feasibility study conducted during a blood shortage crisis. As far as extensively burned patients are concerned, a study by Wang *et al.* showed that a RBC transfusion threshold less than 7 g/dL did not have a significant effect on hospital mortality, hospital length of stay, wound healing time or risk of infection. However, a RBC transfusion threshold less than 6 g/dL could possibly

increase mortality risk. Therefore, it was suggested that when the blood supply is tight, it is acceptable to adopt a RBC transfusion threshold of less than 7 g/dL but not less than 6 g/dL[52]. Thus, based on these findings, thresholds below 7 g/dL may be feasible in selected circumstances, whereas thresholds below 6 g/dL may be associated with an increased mortality risk.

Overall, ultra-restrictive transfusion should be considered as a possible blood-conservation strategy for selected patients or crisis settings, rather than as a broadly applicable evolution of restrictive transfusion practice

Limitations

Several limitations of this narrative review should be acknowledged. The appraisal framework was informal and only PubMed and Google Scholar were searched. Thus, a more comprehensive search (including multiple databases and a documented search strategy) would be beneficial for future systematic updates. Additionally, certain groups of patients, including brain-dead organ donors, were not analyzed, representing an understudied population that merits dedicated investigation. However, considering the evidence in a broader context, the decision to transfuse should not be about the number (Hb level) alone, but about the balance between oxygen supply and oxygen demand. By accounting for comorbidities that compromise oxygen-carrying capacity –including coronary artery disease with unstable angina, hemodynamic instability, pulmonary disease, malignancy, and hemorrhage– clinicians can adopt a patient-based transfusion model, moving beyond the simplistic use of a single laboratory value as the sole indication for transfusion. The ongoing reliance on large, costly randomized trials to define a single transfusion trigger has produced equivocal results, often confounded by design and potentially obscuring subset-specific harm. The methodological artifacts, particularly pre-randomization transfusion confounding, are insufficiently addressed, while the physiological variability of Hb is systematically ignored. Although epidemiological data consistently associate lower Hb levels with survival, this does not validate a numerical threshold as a clinical target. A more productive path forward would involve developing a physiology-guided, patient-centered strategy that treats anemia in its clinical context and measures meaningful, individualized outcomes, an approach that would better equip clinicians for real-world decision-making.

CONCLUSIONS

The evolution of transfusion medicine from liberal practices to restrictive, evidence-based strategies represents significant progress in patient care. The evidence synthesized in this narrative review demonstrates that for more patients less is more when it comes to blood transfusion. Restrictive strategies seem to reduce unnecessary exposure to blood products and their associated risks, such as thromboembolic events and myocardial infarction without compromising patients' safety. Of course, the risk of adverse events may vary considerably across clinical settings and patient populations.

As research continues to refine optimal transfusion strategies, ultra-restrictive transfusion represents a promising but still intriguing evolution in transfusion medicine that requires cautious application. The challenge for clinicians, healthcare systems and researchers is to continue advancing the evidence base, not as a fixed numeric threshold but as part of a broader, individualized approach, integrating patient-specific factors, clinical context and physiological assessment with the ultimate goal being the patients' welfare.

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Authors' contribution

AK and ST conceived the review thesis. All Authors contributed to the design of the review. AK, ST, EK, SK, AT, EL and EAT conducted the work and collected the data. SB and GKN. verified the statistical data. All the Authors contributed to the interpretation of data for the work. AK, EP, AT and AET drafted the manuscript. All Authors critically revised the paper for important intellectual content and approved the final version to be published.

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