Adherence to a restrictive red blood cell transfusion strategy in critically ill patients: An observational study

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Abstract

Background: Randomized controlled trials relatively consistently show that restrictive red blood cell (RBC) transfusion strategies are safe and associated with similar outcomes compared to liberal transfusion strategies in critically ill patients. Based on these data, the general threshold for RBC transfusion was changed to 70 g/L at a 9-bed tertiary level intensive care unit in September 2020. Implementation measures included lectures, webinars and feedback during clinical practice. The aim of this study was to investigate how implementation of a restrictive transfusion strategy influenced RBC usage, haemoglobin trigger levels and adherence to prescribed trigger levels.

Methods: In this registry-based, observational study, critically ill adult patients without massive bleeding were included and divided into a pre-cohort, with admissions prior to the change of transfusion strategy, and a post-cohort, with admissions following the change of transfusion strategy. These cohorts were compared regarding key RBC transfusion-related variables.

Results: In total 5626 admissions were included in the analyses (pre-cohort n = 4373, post-cohort n = 1253). The median volume (interquartile range, IQR) of RBC transfusions per 100 admission days, in the pre-cohort was 6120 (4110–8110) mL versus 3010 (2890–4970) mL in the post-cohort (p < .001). This corresponds to an estimated median saving of 1128 € per 100 admission days after a restrictive RBC transfusion strategy was implemented. In total, 26% of the admissions in the pre-cohort and 19% in the post-cohort (p < .001) received RBC transfusion(s) during days 0–10. Both median (IQR) prescribed trigger levels (determined by intensivist) and actual haemoglobin trigger levels (i.e., levels prior to actual administration of transfusion) were higher in the pre- versus post-cohort (90 [80–100] vs. 80 [72–90] g/L, p < .001 and 89 [82–96] g/L vs. 83 [79–94], p < .001, respectively). Percentage of
days without compliance with the prescribed transfusion trigger was higher in the pre-cohort than in the post-cohort (23% vs. 14%, p < .001). Sensitivity analyses, excluding patients with traumatic brain injury, ischemic heart disease and COVID-19 demonstrated similar results.

Conclusions: Implementation of a restrictive transfusion trigger in a critical care setting resulted in lasting decreased RBC transfusion use and costs, decreased prescribed and actual haemoglobin trigger levels and improved adherence to prescribed haemoglobin trigger levels.

KEYWORDS
adherence, critically ill, erythrocyte transfusions, guideline, healthcare economic, intensive care medicine, red blood cell transfusion, transfusion costs, transfusion strategy

Editorial Comment
Transfusion practices can be influenced by revision of practice guidelines. In this retrospective assessment of intensive care unit routine transfusion experience at one regional centre, a more restrictive red blood cell transfusion plan was shown to have good practitioner adherence and reduction in actual transfusion amounts.

1 | INTRODUCTION

When a non-bleeding critically ill patient becomes anaemic, the question whether red blood cell (RBC) transfusion will improve outcomes arises. Whereas an increase in a patient’s own RBC mass may be achieved through treatments such as iron and erythropoietin, transfusion of RBCs is often used to promptly elevate haemoglobin levels. In fact, it has been shown that 30%–50% of patients undergoing intensive care receive allogeneic RBC concentrate. Nevertheless, in the individual patient, the threshold at which risks with anaemia, due to impaired oxygen-carrying capacity of the blood, outweighs risks associated with RBC transfusion, such as haemolysis, circulatory overload, acute lung injury, alloimmunization against RBC antigens, allergic reaction and infections may be hard to determine.

Over the past two and a half decades, several randomized controlled trials have shown that restrictive transfusion strategies, with low haemoglobin transfusion triggers, are safe and associated with similar, or even better, outcomes as compared with more liberal transfusion strategies in critically ill patients. Moreover, several meta-analyses concerning different settings, for example, cardiac surgery and acute upper gastrointestinal bleeding, as well as mixed clinical conditions, provide pooled data supporting at least non-inferiority for restrictive versus liberal transfusion strategies. In contrast, some data indicate potential benefits of more liberal transfusion strategies in specific clinical settings and subgroups, for example, intra- and perioperative, ischemic heart disease, and traumatic brain injury (TBI), although results from ongoing trials are needed to guide decision-making.

Based on the growing body of evidence promoting a restrictive rather than a liberal transfusion threshold, a change in transfusion practice was implemented at the intensive care unit (ICU) at Skåne University Hospital in Lund, Sweden, in September 2020. Although the general haemoglobin transfusion trigger was changed to <70 g/L, the threshold was individualized, taking comorbidities and clinical circumstances into account. Notably, the 70 g/L threshold did not necessarily apply to patients with intracranial mass effect, active ischemic heart disease, critical hypoxia or massive bleeding.

The overarching aim of the current study was to evaluate the implementation of a restrictive transfusion strategy at a tertiary centre, general ICU. Specifically, we aimed to address whether an attempt to change the general transfusion strategy:

1. Resulted in lower total RBC transfusion use and decreased costs,
2. Resulted in a lower prescribed haemoglobin trigger level and a lower actual haemoglobin trigger level for RBC transfusion.

Importantly, we also wanted to investigate whether:

3. Adherence to transfuse RBC concentrates according to prescribed haemoglobin trigger level improved following the attempt to change transfusion strategy.

2 | METHODS

2.1 | Study design

The main objective of the current observational, registry-based cohort study was to evaluate key aspects of a changed RBC transfusion strategy towards a restrictive approach in a general 9-bed ICU (Skåne University Hospital, Lund, Sweden). The project was conducted within a study framework approved by the Swedish Ethical Review Authority (Lund, dnr 2014/916 and 2018/866; Uppsala, dnr 2020-06674).
There was no requirement for written informed consent, but participants were given the possibility to opt-out. The manuscript was written in accordance with the STROBE guidelines.

2.2 Study population and data collection

All adult patients admitted to the general ICU at Skåne University Hospital, Lund, Sweden, between 1 January 2014 and 16 September 2022, were eligible for inclusion. We included admissions from 2014 because many centres started to apply a more restrictive RBC transfusion strategy after the publication of the Transfusion Requirements in Septic Shock [TRISS] trial in 2014. At the current department, based on a local decision, a structured change in clinical practice towards a more restrictive transfusion strategy was introduced in September 2020. The timing of the change was based on accumulating data indicating that a restrictive transfusion strategy is associated with similar or even better outcomes compared to a liberal strategy in multiple clinical scenarios. Specifically, propensity score-matched observational studies from our own institution supported restrictive use of RBC transfusion in both septic and non-septic critically ill-patients, with data analysed and published 2020–2021. Prior to the change in RBC transfusion strategy, there was no explicit general haemoglobin transfusion threshold at the ICU. The implementation of the change included lectures by senior intensivists, both locally and through live webinars broadcasted by the Journal of the Swedish Medical Association (Läkartidningen) including presentation of the state of evidence, along with daily feedback related to prescribed haemoglobin trigger level during clinical practice. Hence, admissions from 2014 to September 2020 were included in a pre-cohort and admissions from October 2020 to September 2022 were included in a post-cohort. Patients with massive bleeding, defined as patients who received >2 units of RBCs, that is, >670 mL per day during any of the first 11 days (day 0–10), were excluded. Readmissions for the same patient were included. In cases where the same patient was readmitted within 12 h of discharge, the admissions were merged. Clinical data including detailed intensive care-related variables were obtained through the Swedish Intensive Care Quality Register PASIVA (Otimo Data AB, Kalmar, Sweden) and the data management system at the ICU (Intellispace Critical Care and Anaesthesia [ICCA], Philips).

According to local routines and guidelines, physicians were mandated to prescribe haemoglobin transfusion trigger levels for admitted patients on a daily basis. In the event of the haemoglobin value falling below the prescribed trigger level, RBC transfusion was generally to be carried out.

At the current institution, one unit of RBCs produced from whole blood weighs between 250 and 360 g (approximately 236–330 mL), including 20–60 mL of plasma and 100 mL of the storage medium SAGMAN (saline, adenine, glucose and mannitol). The RBC product is leukoreduced and contains less than 1 x 10⁶ leukocytes per unit in accordance with the European Directorate for the Quality of Medicines (EDQM) Blood Guide. As per June 2023, the total cost of one unit of RBCs, after reduction for overhead costs, was 103€.

2.3 Outcome variables

Outcomes for the RBC transfusion usage were the volume of RBC transfusion per 100 days for the entire study period at the group level. In addition, the number of admissions where RBC transfusion(s) were administered at any time during days 0–10, were counted. Outcomes for haemoglobin trigger level for RBC transfusion were prescribed haemoglobin trigger levels (determined by intensivist) and actual haemoglobin trigger levels (i.e., levels prior to actual administration of transfusion) along with adherence to prescribed haemoglobin trigger levels. The adherence outcome was divided into the number of events where RBC transfusions were given although the haemoglobin level was above the prescribed haemoglobin trigger level, and in the number of events where no RBC transfusion was given despite a haemoglobin level below the prescribed haemoglobin trigger level.

2.4 Statistical analysis

The total volume of RBC transfusion at the group level was calculated by summarizing RBC volumes in 100-day periods during the study period within each cohort. The outcome variables were compared between the pre-cohort and the post-cohort groups using the Mann-Whitney U-test (continuous variables) or Pearson’s Chi-square test (dichotomous variables). Furthermore, differences in dichotomous variables were also presented with relative risk including 95% confidence intervals. For consistency, continuous variables are presented as medians (interquartile range [IQR]) and dichotomous variables are presented as numbers (%). SPSS software version 28 (IBM Inc. Chicago, IL, USA) and PRISM online Chi² calculator (https://www.graphpad.com/quickcalcs/contingency1/) were used for statistical analyses. A 2-sided p-value <.05 was considered statistically significant.

2.4.1 Sensitivity analyses

To take into consideration that it is currently not known which is the lowest safe haemoglobin transfusion trigger level in certain clinical subgroups, sensitivity analyses excluding these subgroups were performed. Specifically, admissions with intracranial mass effect, cardiac arrest, cardiogenic shock and COVID-19 were excluded in the sensitivity analyses (comprehensive list reporting considerations underlying exclusion based on ICD-codes is provided in Supplemental Table 4).

3 RESULTS

3.1 Study population and characteristics

After excluding admissions with patients <18 years of age, those who were massively transfused (>670 mL/day) and duplicates due to transfer between intensive care units, 5626 admissions remained (Figure 1). Based on the September 2020 time-point (time of change in...
transfusion strategy), admissions were divided into a pre-cohort (\(n = 4373\)) and a post-cohort (\(n = 1253\)). The number of patients who met the criteria for massive bleeding were 429 (8.9%) in the pre-cohort and 82 (6.1%) in the post-cohort, \(p = .001\). Baseline characteristics relating to the main analyses are presented in Table 1. There were no significant differences in median first haemoglobin on day 0 after admission (pre-cohort 110 (96–125) g/L; post-cohort 112 (96–128) g/L; \(p = .12\)). The median Simplified Acute Physiology Score 3 (SAPS3) score was 58 (47–69) in the pre-cohort and 59 (48–70) in the post-cohort (\(p = .03\)). Overall, the most common cause of admission was respiratory, and the most common arrival route was “Other” (including delivery room, cardiac intensive care, intermediate care unit, other hospital—undefined unit, and general ward).

### 3.2 Usage of RBC transfusions

In total, 26% of the admissions in the pre-cohort and 19% in the post-cohort received RBC transfusion(s) during day 0–10, relative risk (RR) (95% CI) 0.71 (0.63–0.81), (\(p < .001\)). The median volume of RBC transfusions per 100 admission days, administered to all patients in the pre-cohort was 6120 (4110–8110) mL versus 3010 (2890–4970)
### TABLE 1  Baseline characteristics and length of stay.

<table>
<thead>
<tr>
<th></th>
<th>All admissions (n = 5626)</th>
<th>Pre-cohort (n = 4373)</th>
<th>Post-cohort (n = 1253)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) median (IQR)</td>
<td>66 (52–74)</td>
<td>66 (52–74)</td>
<td>66 (52–74)</td>
<td>.41</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2175 (39)</td>
<td>1741 (40)</td>
<td>434 (35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>3451 (61)</td>
<td>2632 (60)</td>
<td>819 (65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Median haemoglobin level on day 0, g/L, (IQR)</td>
<td>110 (96–126)</td>
<td>110 (96–125)</td>
<td>112 (96–128)</td>
<td>.12</td>
</tr>
<tr>
<td>Missing</td>
<td>311 (5.5%)</td>
<td>247 (5.6%)</td>
<td>64 (5.1%)</td>
<td>.45</td>
</tr>
<tr>
<td>Severity scoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS3 score, median (IQR)</td>
<td>59 (47–69)</td>
<td>58 (47–69)</td>
<td>59 (48–70)</td>
<td>.03</td>
</tr>
<tr>
<td>SAPS3 EMRSwe, median (IQR)</td>
<td>18 (5.2–36)</td>
<td>16 (5.2–36)</td>
<td>18 (5.8–38)</td>
<td>.03</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>150 (2.7)</td>
<td>96 (2.2)</td>
<td>54 (4.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cause of admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>570 (10)</td>
<td>427 (10)</td>
<td>143 (11)</td>
<td>.09</td>
</tr>
<tr>
<td>CNS</td>
<td>1868 (33)</td>
<td>1441 (33)</td>
<td>427 (34)</td>
<td>.46</td>
</tr>
<tr>
<td>Hematologic</td>
<td>337 (6.0)</td>
<td>250 (5.7)</td>
<td>87 (6.9)</td>
<td>.11</td>
</tr>
<tr>
<td>Gastric</td>
<td>735 (13)</td>
<td>579 (13)</td>
<td>156 (13)</td>
<td>.46</td>
</tr>
<tr>
<td>Metabolic</td>
<td>934 (17)</td>
<td>668 (15)</td>
<td>266 (21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2458 (44)</td>
<td>1847 (42)</td>
<td>611 (49)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2126 (38)</td>
<td>1658 (38)</td>
<td>468 (37)</td>
<td>.72</td>
</tr>
<tr>
<td>Hepatic</td>
<td>362 (6.4)</td>
<td>268 (6.1)</td>
<td>94 (7.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Renal</td>
<td>868 (15)</td>
<td>651 (15)</td>
<td>217 (17)</td>
<td>.04</td>
</tr>
<tr>
<td>Other</td>
<td>633 (11)</td>
<td>464 (11)</td>
<td>169 (14)</td>
<td>.004</td>
</tr>
<tr>
<td>No admission cause</td>
<td>956 (17)</td>
<td>755 (17)</td>
<td>201 (16)</td>
<td>.31</td>
</tr>
<tr>
<td>Arrival route, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>1741 (31)</td>
<td>1451 (33)</td>
<td>290 (23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Operation</td>
<td>1006 (18)</td>
<td>772 (18)</td>
<td>234 (19)</td>
<td>.41</td>
</tr>
<tr>
<td>Other ICU</td>
<td>839 (15)</td>
<td>598 (14)</td>
<td>241 (19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative care unit</td>
<td>112 (2.0)</td>
<td>90 (2.1)</td>
<td>22 (1.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Other</td>
<td>1928 (34)</td>
<td>1462 (33)</td>
<td>466 (37)</td>
<td>.01</td>
</tr>
<tr>
<td>Length of stay, days, median (IQR)</td>
<td>1.2 (0.7–3.0)</td>
<td>1.2 (0.7–2.9)</td>
<td>1.4 (0.7–4.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; ICU, intensive care unit.

*Interquartile range.

*Simplified acute physiology score.

*Estimated 30-day-mortality risk based on SAPS3 adapted to Swedish conditions.

*Patients may have more than one cause of admission.

*Delivery room, cardiac intensive care, intermediate care unit, other hospital (undefined unit), general ward.

### TABLE 2  Red blood cell (RBC) transfusions.

<table>
<thead>
<tr>
<th></th>
<th>All admissions (n = 5626)</th>
<th>Pre-cohort (n = 4373)</th>
<th>Post-cohort (n = 1253)</th>
<th>Relative risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of admissions with RBC transfusion day 0–10, n (%)</td>
<td>1373 (24)</td>
<td>1141 (26)</td>
<td>233 (19)</td>
<td>0.71 (0.63–0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total volume of RBCs transfused per cohort, mL per 100 days, median (IQR)</td>
<td>5090 (3220–7390)</td>
<td>6120 (4110–8110)</td>
<td>3010 (2090–4970)</td>
<td>N.A.</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RBC units per cohort per 100 days, median (IQR)</td>
<td>18 (11–26)</td>
<td>22 (15–29)</td>
<td>11 (7–18)</td>
<td>N.A.</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Costs for RBC transfusions per cohort per 100 days, €, median (IQR)</td>
<td>1845 (1167–2679)</td>
<td>2218 (1490–2940)</td>
<td>1091 (757–1802)</td>
<td>N.A.</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
mL in the post-cohort \((p < .001)\). This corresponds to a median saving of 1128 € per 100 admission days after a restrictive RBC transfusion strategy was implemented \((p < .001)\). For details, please see Table 2.

Figure 2 the RBC usage over time is plotted and demonstrates a lasting decrease, which starts during the year of the implementation of a restrictive RBC transfusion strategy (2020).

### 3.3 | Haemoglobin trigger level for RBC transfusion

The median prescribed haemoglobin trigger level was higher in the pre-cohort compared to the post-cohort \((90 [80–100] \text{ g/L}, p < .001)\). Congruently, the actual haemoglobin trigger level was higher in the pre-cohort compared to the post-cohort \((89 [82–96] \text{ g/L}, p < .001)\) (Figure 3).

The number of days with both available haemoglobin level and prescribed haemoglobin trigger level was 8684 in the pre-cohort and 2955 in the post-cohort. The percentage of days without compliance was higher in the pre-cohort than in the post-cohort \((23\% \text{ vs. } 14\%), \text{RR} [95\% \text{ CI}] 0.59 [0.53–0.65], p < .001\), as evidenced by a higher percentage of days with no transfusion despite haemoglobin level below prescribed trigger level \((19\% \text{ vs. } 10\%), \text{RR} [95\% \text{ CI}] 0.46 [0.40–0.52], p < .001\). The percentage of days with transfusion despite a haemoglobin level above the prescribed trigger level demonstrated the same tendency but did not differ \(4.3\% \text{ vs. } 3.5\%, \text{RR} [95\% \text{ CI}] 0.82 [0.66–1.02], p = .070\) (Table 3). Notably, data on prescribed or actual haemoglobin levels were missing in 13% and 18% of the days in the pre- and post-cohort, respectively. Median length of stay in the whole cohort with missing data was 0.6 (0.3–0.9) days.

### 3.4 | Sensitivity analyses

After excluding admissions of patients with intracranial mass effect, cardiac arrest, ischemic heart disease and COVID-19, a total of 4264 admissions, divided into a pre-cohort \((n = 3390)\) and a post-cohort \((n = 874)\), were included in the sensitivity analyses (Supplemental Figure 1). Baseline characteristics related to the sensitivity analyses cohorts are provided in Supplemental Table 1. In contrast to the full sample, there were no significant differences in SAPS 3 between the pre- and post-cohorts \((p = .30)\). The differences in RBC transfusions, prescribed/actual haemoglobin trigger levels and the compliance with those levels, were very similar compared to the main results (Supplemental Figure 1, Supplemental Tables 2 and 3).

### 4 | DISCUSSION

#### 4.1 | Summary of findings

In the current registry-based observational study, implementation of a new, restrictive transfusion strategy at a general tertiary level ICU provided substantial and lasting decreases in blood usage. The main
analyses showed that the total volume of RBC transfusions (mL per 100 days) and costs decreased, and that the portion of cases that were given RBC transfusions was reduced from 26% to 19% after the implementation. Both prescribed and actual haemoglobin transfusion trigger levels were lower and compliance to the prescribed transfusion trigger was markedly higher following the change to a more restrictive RBC transfusion strategy. These findings are important as the evidence for the application of a restrictive RBC transfusion strategy in critically ill patients is very convincing, the availability of RBC concentrates is limited and transfusions are associated with risks.

## 4.2 | Implications of improved adherence to transfusion trigger and lower RBC usage

Following the shift towards a more restrictive RBC transfusion trigger, adherence to the trigger was significantly better, as compared to the period prior to the change in strategy. These results indicate an increased awareness of the importance of compliance with a restrictive trigger, to potentially benefit patients, avoid unnecessary harm and optimize resource utilization. Our findings are encouraging given the multitude of actors and stakeholders who are involved in decisions about transfusion triggers, often with differing opinions, beliefs and emotions related to RBC transfusion.

Since the strategy to implement a change in RBC transfusion threshold at our institution was multifaceted, it is not entirely clear which method was most effective in achieving improved adherence. Increased focus on the topic of RBC transfusion through lectures, webinars and clinical discussions are likely to have contributed. Moreover, the fact that physicians were aware that their decisions related to transfusion triggers were observed and reviewed may have further strengthened and accelerated the implementation process (i.e., the Hawthorne effect)\(^{21,22}\).

Interestingly, the recent COVID-19 pandemic introduced further uncertainty regarding the optimal transfusion threshold in this specific subgroup, since the virus might exert direct negative effects related to the oxygen-carrying capacity of RBCs.\(^{23}\) The presence of anaemia has also been linked to higher COVID-19 disease severity and in-hospital mortality.\(^{24}\) Notably, our sensitivity analyses, which excluded COVID-19 admissions, showed similar results as for the full sample (Figure 3, Tables 2 and 3, Supplemental Figure 1, Supplemental Tables 2 and 3). Interestingly, despite attempts to identify physiologic triggers to guide when to transfuse, no specific measure(s) have to date been shown to be effective.\(^{25}\)

In addition to the potential clinical benefits associated with better adherence to a restrictive transfusion strategy, there are also direct resource-sparing effects, as shown by our results demonstrating a substantial decrease in RBC transfusions. Although RBCs may be stored for several weeks, increased shelf-time is associated with RBC product degradation,\(^{26}\) and periodic shortage of RBC supply can occur. Judicious, restrictive use of RBC concentrates may thus enhance adequate allocation of resources and decrease costs.

## 4.3 | Methodological considerations

Although the results of this study are encouraging, there are some limitations that should be considered: After the implementation of a restrictive transfusion strategy in September 2020, the length of stay increased (Table 1). This may be explained by the longer length of stay during the COVID-19 pandemic, which is indicated by the fact that the difference in the length of stay between the cohorts was erased in the sensitivity analysis where patients with COVID-19 were excluded (Supplemental Table 1). Moreover, although the combination of variables from the Swedish Intensive Care Quality Register and the ICU data management system enabled a relatively detailed, large cohort study, including parameters and scores reflecting several pertinent aspects of intensive care, there is still a lack of granularity in the dataset. Importantly, there was a significant proportion of missing data in the prescribed and actual haemoglobin levels. Although the median length of stay in the whole cohort with missing haemoglobin data was very short, this still limits conclusions related to the adherence to prescribed haemoglobin levels. The retrospective, observational study design carries inherent limitations. Notably, there were baseline differences in some of the variables.

### TABLE 3 Compliance with prescribed haemoglobin trigger level.

| Days with available prescribed haemoglobin level and haemoglobin level, n (%) | All admissions | Pre-cohort | Post-cohort | Relative risk (95% CI) | P-value |
| Days without transfusion despite haemoglobin level under prescribed trigger level, n (%) | 11,639 (100)\(^{a}\) | 8684 (100)\(^{b}\) | 2955 (100)\(^{c}\) | N.A. | N.A. |
| Days with transfusion despite haemoglobin level above prescribed trigger level, n (%) | 1963 (17) | 1660 (19) | 303 (10) | 0.46 (0.40–0.52) | <.001 |
| Total number of days without compliance to prescribed haemoglobin trigger level, n (%) | 476 (4.1) | 372 (4.3) | 104 (3.5) | 0.82 (0.66–1.02) | .070 |

\(^{a}\)1946 days (14%) without prescribed haemoglobin level and haemoglobin level.

\(^{b}\)1285 days (13%) without prescribed haemoglobin level and haemoglobin level.

\(^{c}\)661 days (18%) without prescribed haemoglobin level and haemoglobin level. The relative risk (95% CI) for missing values in the post-cohort was 1.42 (1.30–1.54); \(p < .001\).
including disease severity scoring (SAPS3) between the pre- and post-cohorts, with higher disease severity overall in the post-cohort. Given the before-after design, non-investigated factors may have been introduced and affected the results. One such factor may have been the emergence of the COVID-19 pandemic, with profound impact on ICUs worldwide. However, when excluding COVID-19 patients in the sensitivity analyses, the main results are consistent. Finally, we did not have access to RBC transfusion data outside the ICU; such information could have added important knowledge as to whether patients discharged from the ICU with relatively low haemoglobin values were eventually transfused on different wards, with implications for assessment of the net effect of the change in ICU-transfusion threshold.

4.4 Conclusions

To conclude, in this registry-based cohort study, we found that implementation of a new, restrictive transfusion trigger resulted in lasting decreased usage of RBCs with significantly decreased costs, decreased prescribed and actual haemoglobin trigger levels and improved adherence to prescribed transfusion triggers in a critical care setting. These effects may most importantly benefit patients directly, but also strengthen healthcare through enhanced resource utilization.

AUTHOR CONTRIBUTIONS

TK was the originator of the study. All authors contributed to the study design. YL and TK performed the compilation of the data. YL and TK performed the statistical analyses. MB wrote the first version of the manuscript. All authors revised the manuscript critically, gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

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FUNDING INFORMATION

Departmental Funding only.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors agree to make data and materials supporting the results or analyses presented in the article available upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT STATEMENT

The Swedish Ethical Review Authority waived the requirement for consent.

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REFERENCES


SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.