Effects of red blood cell transfusions given to non-septic critically ill patients: a propensity score matched study

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Abstract

Background: Previous studies have demonstrated that low-grade red blood cell transfusions (RBC) given to septic patients are harmful. The objectives of the present study were to compare mortality and morbidity in non-septic critically ill patients who were given low-grade RBC transfusions at haemoglobin level > 70 g L^{-1} with patients without RBC-transfusions any of the first 5 days in intensive care.

Methods: Adult patients admitted to a general intensive care unit between 2007 and 2018 at a university hospital were eligible for inclusion. Patients who received > 2 units RBC transfusion per day during the first 5 days after admission, with pre-transfusion haemoglobin level < 70 g L^{-1} or with severe sepsis or septic shock, were excluded.

Results: In total, 9491 admissions were recorded during the study period. Propensity score matching resulted in 2 well matched groups with 674 unique patients in each. Median pre-transfusion haemoglobin was 98 g L^{-1} (interquartile range 91–107 g L^{-1}). Mortality was higher in the RBC group with an absolute risk increase for death at 180 days of 5.9% (95% CI: 3.6–8.3; $P < 0.001$). Low-grade RBC-transfusion was also associated with renal, circulatory, and respiratory failure as well as a higher SOFA-max score. Sensitivity analyses suggested that disease trajectories during the exposure time did not significantly differ between the groups.

Conclusions: Low-grade RBC-transfusions given to non-septic critically ill patients without significant anaemia were associated with increased mortality, increased kidney, circulatory, and respiratory failure, as well as higher SOFA-max score.

Key words: blood transfusion, renal failure, respiratory failure, mortality, circulatory failure, days alive and free, erythrocyte transfusion.

Anestezjologia Intensywna Terapia 2021; 53, 5: 391–398

Otrzymano: 06.04.2021,
zaakceptowano: 13.07.2021

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Anaemia is common in critically ill patients, and more than one-fourth are transfused with allogenic red blood cell (RBC) transfusions [1, 2]. RBC transfusions can be lifesaving for many patients, but they are also associated with harm such as transfusion-associated circulatory overload (TACO), transfusion-related immune modulation (TRIM), transfusion-related acute lung injury (TRALI), haemolytic reactions, and infections [3]. However, anaemia is also harmful, which makes risk-benefit assessment of RBC-transfusions important and necessary [4]. Many large randomized controlled trials (RCT) with high levels of evidence have demonstrated that a restrictive transfusion strategy (haemoglobin level > 70 g L^{-1}) is as safe as a liberal transfusion strategy (haemoglobin level > 90–100 g L^{-1}) [5–10]. In those RCTs, patients in both groups received RBC transfusions, and many patients may also have been exposed to the risk of anaemia. Consequently, adverse effects related to the low-grade RBC transfusion itself could be difficult to ascertain.

We have recently demonstrated that low-grade RBC transfusions given to septic patients were associated with increased mortality and morbidity in a liberal transfusion setting [11]. Given that RBC transfusions may trigger TRIM, it is possible that harmful effects are more pronounced in septic patients than in other patient groups [11, 12]. To evaluate the harmful effect of RBC transfusions in non-septic critically ill patients who were not exposed to the risks of anaemia, we designed this retrospective propensity score matched study. The aim was to compare mortality and morbidity in critically ill patients without severe sepsis or septic shock, who were given low-grade RBC transfusions at haemoglobin level > 70 g L^{-1} to those of controls without

Należy cytować anglojęzyczną wersję: Kander T, Nilsson CU, Larsson D, Bentzer P. Effects of red blood cell transfusions given to non-septic critically ill patients: a propensity score matched study. Anaesthesiol Intensive Ther 2021; 53, 5: 390–397. DOI: https://doi.org/10.5114/ait.2021.111739

RBC transfusions in the first 5 days in intensive care. The hypothesis was that RBC transfusions are harmful in non-septic critically ill patients without significant anaemia.

METHODS

Data collection and study population

The study was approved by the Swedish Ethical Review Authority in Lund, Sweden (registration numbers 2014/916 and 2018/866), and the board waived the requirement for written informed consent. The manuscript was prepared according to the STROBE guidelines for observational studies [13].

All patients ≥ 18 years of age, admitted to the 9-bed general intensive care unit (ICU) at Skåne University Hospital, Lund, Sweden between 2007 and March 2018 were eligible for inclusion. For patients with multiple admissions to the ICU during the time of the study, only the first admission was included. To allow significant RBC-transfusions but exclude patients with massive bleeding, patients who received high-grade RBC transfusion (defined as a total of > 670 mL or 2 units per day) during the first 5 days in the ICU were excluded. Day 0 was the day of the admission. All patients with severe sepsis or septic shock according to the Sepsis-2 definition [14] were excluded. RBC transfusions were given at the discretion of the treating physician to maintain a haemoglobin level of 80–100 g L^{-1} according to local guidelines. To exclude patients exposed to the risks of anaemia, all patients with a pre-transfusion haemoglobin level < 70 g L^{-1} were excluded.

Mortality data were collected from the Swedish intensive care quality register PASIVA (Otimo Data AB, Kalmar, Sweden). Simplified Acute Physiology Score 3 was registered according to the original publication [15]. Physiological and laboratory data and pre-existing conditions (age, gender, chronic obstructive pulmonary disease [COPD], renal failure), outcome variables (except mortality), and fluid administration data were collected from raw data, i.e. from the electronic master chart system of the hospital (Melior, Cerner, N. Kansas City, MO, USA) or from the patient data management system at the ICU (Intellispace critical care and anaesthesia [ICCA], Philips, Amsterdam, the Netherlands).

Outcome variables

Mortality was assessed at 28, 90, and 180 days after ICU admission, and organ support was assessed by calculating days alive and free (DAF) of organ support for the first 28 days after admission to the ICU. For patients who died in the ICU, we counted the days without the specified organ support before death as previously described [16]. Organ support measures were vasopressors for circulatory failure, invasive mechanical ventilation for respiratory failure, and renal replacement therapy (RRT) for renal failure. Renal failure was also evaluated according to the acute kidney injury network (AKIN) scoring system. The maximal AKIN score the first 10 days after ICU admission was used for analysis. To obtain an overall measure of organ failure we also used the maximum sequential organ failure assessment (SOFA) score during the first 28 days after admission.

Statistical analysis

Patients receiving low-grade RBC transfusion (< 670 mL day^{-1}) during the first five days of ICU admission were propensity score matched with non-transfused patients to adjust for differences in baseline variables associated with outcome. The propensity score was calculated with linear logistic regression using a one-to-many macro for SAS as previously described, with the covariates specified in Table 1 [17]. Physiological and laboratory variables used in the propensity score matching were collected within 90 min of admission to the ICU.

The sample size was based on the number of available patients during the study period. Variables were summarized using mean (standard deviation), median (interquartile range, i.e. 25^{th} to 75^{th} percentiles), or numbers (percentage). The propensity score matching was performed by an independent statistician using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) prior to any comparison between the groups. Kaplan-Meier survival analyses were performed, and the results are presented in graphs with corresponding stratified log-rank test. In accordance with previous recommendations, comparisons between the groups after propensity score matching were performed with paired hypothesis testing [18]. Differences between groups over time were compared using the Kruskal-Wallis test, and circulatory SOFA at each of the 5 days were compared using Mann-Whitney *U*-test. Other analyses were performed with SPSS Statistics version 26 (SPSS Inc., Chicago, Ill., USA). A 2-sided *P*-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A consort diagram of all patients is presented in Figure 1. Out of 9491 patients 5240 remained after removing patients < 18 years of age, multiple admissions, high-grade RBC transfusion (> 670 mL day^{-1}), patients with pre-transfusion haemoglobin < 70 g L^{-1}, and patients with severe sepsis or septic shock. After propensity score matching, 674 patients were included in the RBC group and 674 patients in the

TABLE 1. Patient demographics before and after propensity matching

Factor	Unmatched groups				Propensity-matched groups			
	Control $n = 3949$	RBC[a] $n = 1291$	Standardized difference	*P*-value	Control $n = 674$	RBC $n = 674$	Standardized difference	*P*-value
Pre-existing conditions								
Age, mean (SD)	58 (19)	64 (16)	0.315	< 0.001	62 (17)	63 (16)	0.041	0.375
Male gender, no (%)	2342 (59)	745 (58)	0.032	0.311	408 (60)	392 (58)	0.048	0.375
Blood malignancy[b], no (%)	40 (1.0)	37 (2.9)	0.140	< 0.001	13 (1.9)	12 (1.8)	0.011	0.840
Chronic obstructive pulmonary disease, no (%)	340 (8.6)	96 (7.4)	0.043	0.185	62 (9.2)	64 (9.5)	0.010	0.852
Cirrhosis, no (%)	40 (1.0)	25 (1.9)	0.076	0.010	10 (1.5)	12 (1.8)	0.023	0.667
Immunosuppression[c], no (%)	727 (18)	74 (5.7)	0.107	< 0.001	31 (4.6)	33 (4.7)	0.007	0.897
Malignancy[d], no (%)	525 (13)	296 (23)	0.250	< 0.001	130 (19)	131 (19)	0.007	0.890
Nosocomial infection[e], no (%)	138 (3.5)	48 (3.7)	0.013	0.674	26 (3.9)	26 (3.9)	0.000	1.000
Airway infection, no (%)	494 (12)	159 (12)	0.005	0.874	93 (14)	85 (13)	0.035	0.520
Surgery[f], no (%)	908 (23)	513 (40)	0.367	< 0.001	231 (34)	222 (33)	0.025	0.608
Gastro-intestinal-bleeding, no (%)	71 (1.8)	25 (1.9)	0.012	0.702	13 (1.9)	13 (1.9)	0.000	1.000
Disseminated intravascular coagulopathy, no (%)	103 (2.6)	25 (1.9)	0.467	0.161	15 (2.2)	13 (1.9)	0.021	0.703
Intra-cranial volume effect, no (%)	123 (3.1)	38 (2.9)	0.011	0.723	16 (2.4)	17 (2.5)	0.009	0.860
Physiological and laboratory variables at admission[g], mean (SD)								
Heart rate, mean (SD)	92 (23)	94 (24)	0.113	< 0.001	93 (24)	94 (25)	0.012	0.827
Systolic blood pressure (mmHg)	126 (30)	119 (29)	0.234	< 0.001	120 (29)	121 (30)	0.005	0.933
Lactate (mmol L^{-1})	2.3 (2.5)	2.4 (2.3)	0.031	0.346	2.5 (2.6)	2.6 (2.5)	0.004	0.945
Norepinephrine (µg min^{-1})	0.91 (3.2)	1.8 (5.0)	0.205	< 0.001	1.6 (4.3)	2.0 (5.9)	0.076	0.163
Temperature (°C)	36.6 (1.2)	36.7 (1.4)	0.058	0.061	36.6 (1.3)	36.6 (1.4)	0.019	0.724
PaO_2/FiO_2 (kPa)	33 (18)	32 (20)	0.014	0.672	33 (18)	32 (21)	0.049	0.368
Leucocytes ($\times 10^9$ L^{-1})	14 (10)	13 (8.1)	0.036	0.291	14 (15)	14 (8.0)	0.024	0.657
Platelets ($\times 10^9$ L^{-1})	225 (97)	210 (110)	0.140	< 0.001	220 (110)	222 (118)	0.017	0.753
pH	7.34 (0.12)	7.35 (0.11)	0.139	< 0.001	7.35 (0.12)	7.34 (0.11)	0.064	0.240
Bilirubin (µmol L^{-1})	12 (19)	17 (30)	0.179	< 0.001	14 (27)	16 (29)	0.043	0.424
Creatinine (µmol L^{-1})	104 (110)	125 (150)	0.152	< 0.001	120 (126)	122 (153)	0.013	0.806
Prothrombin time (PT)/INRn	1.3 (0.65)	1.4 (0.72)	0.141	< 0.001	1.4 (0.76)	1.4 (0.74)	0.015	0.780
Activated partial thromboplastin time (APTT) (s)	35 (17)	39 (19)	0.227	< 0.001	39 (21)	39 (21)	0.009	0.871
Hb[h]	122 (18)	105 (15)	1.037	< 0.001	109 (14)	109 (14)	0.008	0.882
Circulatory Sequential Organ Failure Assessment (SOFA)	1.4 (1.1)	1.8 (1.2)	0.316	< 0.001	1.7 (1.3)	1.8 (1.3)	0.029	0.592

[a]Low-grade red blood cell transfusion defined as < 670 mL any of the first 5 days, [b]Lymphoma, acute leukaemia, or myeloma, [c]Chronic steroid treatment correlative to ≥ 0.3 mg kg^{-1} prednisolone/day, radiation, or chemotherapy, [d]Cancer spread beyond the regional lymph nodes, [e]Infection that developed after ≥ 48 hours in hospital or secondary to surgical or medical procedure, [f]Before admission to intensive care, [g]First value within 90 min after admission except for "Norepinephrine" which is the mean dose the first 12 hours, [h]Median haemoglobin level day 0.

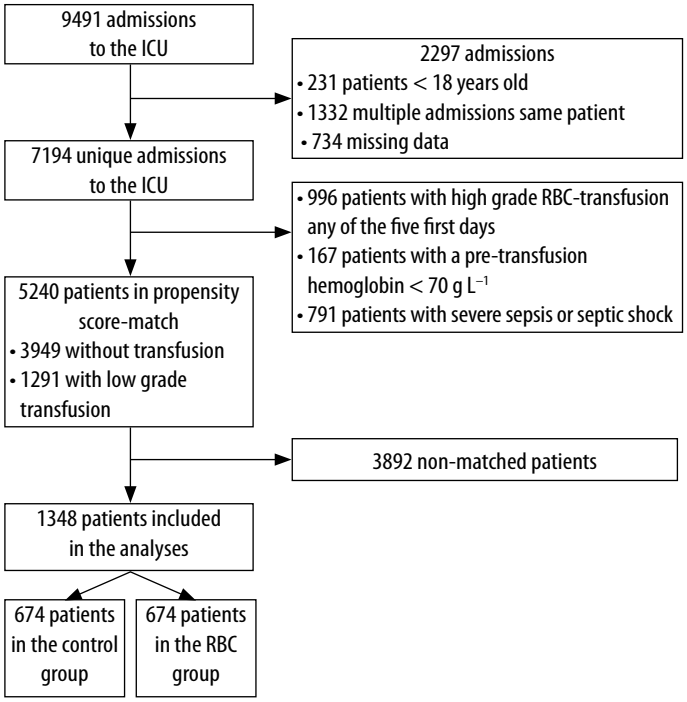

FIGURE 1. Consort diagram

control group. The annual inclusion rate in both groups was similar (Supplemental File 1). Baseline demographics, comorbidity, clinical, physiologic, and laboratory data in both groups are summarized in Tables 1 and 2. Detailed diagnosis at admission for the propensity score matched groups are presented in Supplemental File 2. After the propensity score matching the standardized differences between groups for included baseline variables were reduced to < 10%. For the baseline variables that were not included in the matching, differences between the groups were eliminated after the matching for all variables except for "Reason for admission, central nervous system" (Table 2).

All RBC transfusions were leukoreduced. The median haemoglobin level before transfusion in the RBC group was 98 g L^{-1} (91–107 g L^{-1}). The median haemoglobin levels before transfusion per year are illustrated in Supplemental File 3. The median haemoglobin level on day 0 was 109 g L^{-1} (107–112 g L^{-1}) for the RBC group and 109 g L^{-1} (106–113 g L^{-1}) for the control group (P = 0.96). Daily median haemoglobin levels for the first 5 days for both groups are illustrated in Figure 2. The median volumes of RBC transfusion in the RBC group the first 5 days after admission are shown in Figure 3. The total RBC volume given during the ICU-stay were 0 mL (0–0 mL) for the control group and 595 mL (315–899 mL) for the RBC group.

TABLE 2. Unmatched baseline characteristics

Factor	Unmatched groups			Propensity-matched groups		
	Controls, n = 3949	RBC[a], n = 1291	P-value[b]	Controls, n = 674	RBC, n = 674	P-value[c]
SAPS 3[d], median (IQR)	54 (43–66)	62 (51–73)	< 0.001	60 (48–70)	60 (50–71)	0.426.
Reasons for admission[e], n (%)						
Trauma	272 (6.9)	122 (9.5)	0.003	40 (5.9)	50 (7.4)	0.326
Central nervous system	1334 (31)	431 (25)	< 0.001	116 (17)	170 (25)	< 0.001
Haematological	109 (2.5)	128 (7.5)	< 0.001	20 (3.0)	24 (3.6)	0.646
Gastric	333 (7.7)	323 (19)	< 0.001	67 (10)	70 (10)	0.857
Metabolic	505 (12)	211 (12)	0.733	63 (9.3)	66 (10)	0.853
Respiratory	1531 (35)	692 (40)	< 0.001	290 (43)	273 (41)	0.377
Cardiovascular	952 (22)	660 (39)	< 0.001	189 (28)	204 (30)	0.402
Hepatic	151 (3.5)	113 (6.6)	0.02	31 (4.6)	30 (4.4)	0.402
Renal	393 (9.1)	316 (18)	< 0.001	63 (9.3)	73 (11)	0.416
Other	347 (8.0)	136 (7.9)	0.853	45 (6.7)	50 (7.4)	0.670
Arrival route, n (%)						
Emergency department	1885 (44)	371 (22)	< 0.001	192 (28)	184 (27)	0.564
General ward	1106 (26)	603 (35)	< 0.001	205 (30)	195 (29)	0.416
Intermediate care	56 (1.3)	38 (2.2)	0.02	13 (1.9)	12 (1.8)	0.413
Surgery	564 (13)	341 (20)	< 0.001	123 (18)	135 (20)	0.245
Other ICU	440 (10.2)	231 (13)	0.02	101 (15)	102 (15)	0.844
Other	237 (6.0)	90 (7.0)	0.480	40 (5.9)	41 (6.1)	0.533

[a]Red blood cell transfusion, [b]Mann-Whitney-U or χ^2 test, [c]Wilcoxon rang sum or McNemars' test, [d]Simplified acute physiology score 3, [e]Each diagnostic group as defined in the SAPS 3 original publication [15]. Patients may have more than one reason for admission.

Outcomes

Detailed results are presented in Table 3. Mortality at 28, 90, and 180 days was higher in the RBC group (Table 3 and Figure 4). The absolute risk increase for death at 180 days for patients in the RBC group was 5.9% [95% CI: 3.6–8.3%] ($P < 0.001$). RRT and $AKIN_{max}$ demonstrated an increased risk for acute renal failure in the RBC group. Low-grade RBC transfusion was also associated with circulatory and respiratory failure as well as higher SOFA-max score.

To investigate if different trajectories in illness in the days after the matching may explain the results, 2 different sensitivity analyses were performed. Firstly, a shorter exposure time was applied, where patients receiving low-grade RBC transfusion (< 670 mL day^{-1}) during the first day after admission were propensity score matched at a ratio of 1 : 1 to controls without RBC transfusion during the first day after admission. The matching was good with a standardized difference < 10% for all variables. After propensity score matching, 477 patients were included in the RBC group and 477 patients in the control group. The differences between the groups were essentially unchanged compared to the main analysis. For details, please see Supplemental File 4. Secondly, circulatory SOFA day 1 to 5 was compared between the groups. The median score was 1 (1–3) for both groups all of the days and there were no differences between the groups on any of the days.

Fluids

There was no difference either in the median daily administration of colloids, crystalloids, or total fluid balance between the groups. The daily median total fluid administration and urinary output was larger in the RBC group compared to the controls (Table 4). The total fluid balance during the length of stay was +2300 mL (360–3900 mL) for the control group and +2700 mL (210–4100 mL) for the RBC-group, $P = 0.094$.

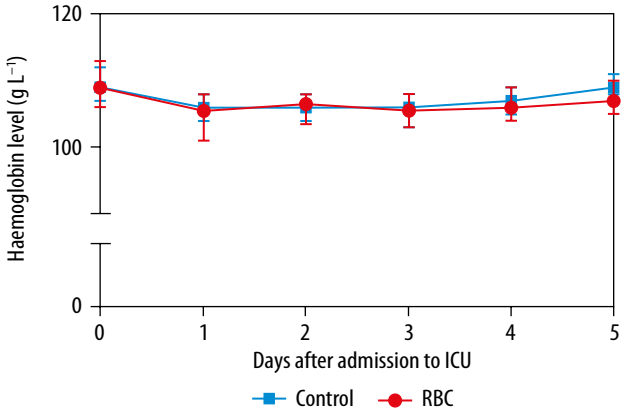

FIGURE 2. Median haemoglobin level in the 2 groups with interquartile range. There were no differences between the groups over time (Kruskal-Wallis test, $P = 0.15$). RBC = group with patients who received red blood cell transfusion on any of the first 5 days

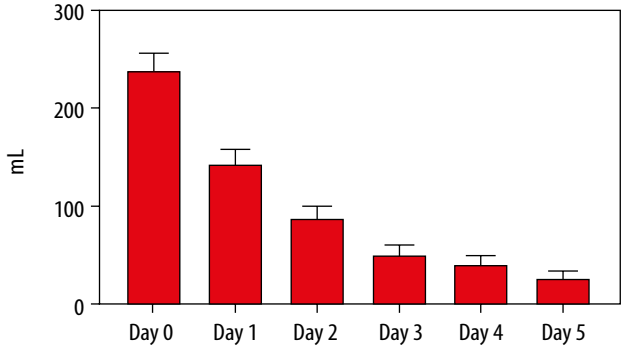

FIGURE 3. Mean red blood cell transfusion per day with 95% confidence interval in the RBC group. RBC = group

DISCUSSION

In this propensity score matched study, low-grade leukoreduced RBC transfusions given to non-septic critically ill patients without significant anaemia were associated with increased mortality, increased kidney, circulatory, and respiratory failure, as well as higher SOFA-max score.

TABLE 3. Main outcome variables

Outcome	Propensity-matched groups		Relative risk (95% CI)	Absolute risk increase (95% CI)	*P*-value[a]
	Control, $n = 674$	RBC[b], $n = 674$			
28-day mortality	151 (22)	206 (31)	1.36 (1.14 to 1.63)	8.1% (3.5 to 13%)	0.001
90-day mortality	188 (28)	244 (36)	1.37 (1.17 to 1.60)	9.8% (4.9 to 15%)	0.001
180-day mortality	212 (31)	281 (42)	1.33 (1.15 to 1.53)	10% (5.1 to 15%)	< 0.001
Renal replacement therapy	16 (2.4)	56 (8.3)	3.50 (2.03 to 6.04)	5.9% (3.6 to 8.3%)	< 0.001
AKIN[c]	0 (0–0)	0 (0–1)			< 0.001
DAF of vasopressors	28 (24–28)	26 (9–28)			< 0.001
DAF of mechanical ventilation	27 (22–28)	25 (6–27)			< 0.001
SOFA max[d]	6 (4–9)	8 (5–10)			< 0.001

Data are presented as number (%) or median (interquartile range). [a] Wilcoxon rang sum or McNemar's test, [b]Low grade red blood cell transfusion defined as < 670 mL any of the first 5 days, [c]AKIN max the first 10 days after admission, [d]Maximum Sequential Organ Failure Assessment score the first 10 days after admission.

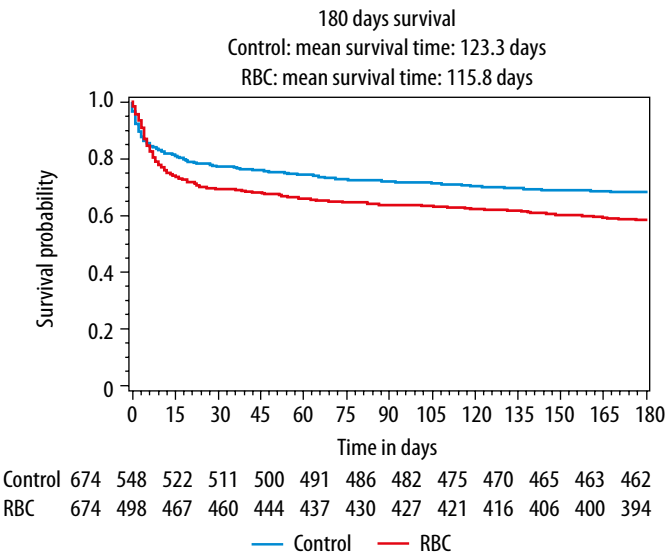

FIGURE 4. Kaplan–Meier curves of 180-day survival in the control group (blue line) and the RBC group (red line) ($P < 0.001$, stratified log-rank test). RBC = group with patients who received red blood cell transfusion any of the first 5 days

We collected data from 2007, prior to many high-quality RCTs recommending a transfusion threshold of 70 g L^{-1}. Altogether, most patients in the RBC group were transfused at a "safe" haemoglobin level without being exposed to the risks of anaemia, indicated by a median pre-transfusion haemoglobin level of 98 g L^{-1} (91–107 g L^{-1}). Although the haemoglobin level before transfusion demonstrated some variation over time, as illustrated in Supplemental File 3, it was still within a safe non-anaemic limit throughout the study period. These data can therefore be used to evaluate the effect of RBC transfusion itself on critically ill non-anaemic, non-septic patients.

Previous large RCTs have demonstrated the safety of a restrictive transfusion strategy [5–10]. However, it should be noted that most patients in both the low- and high-threshold arms in those RCTs received RBC transfusions. Furthermore, any positive effects of fewer RBC transfusions in the low-threshold group may be offset by a longer exposure of anaemia as compared to the high-threshold group. In the present study the haemoglobin level did not differ between the groups and patients in the control group were neither given any RBC transfusions during the first 5 days after admission nor significantly exposed to anaemia. The current study is more likely to be biased given its retrospective nature, but the methodological differences described above imply that the current study adds further knowledge to the risk-benefit assessment of RBC-transfusions in the critically ill non-septic patients.

The propensity score-matching was performed to minimize the differences in baseline variables between the groups and to create the RBC and control groups as similar as possible at ICU admission. Differences between the groups in variables not included in the matching, such as SAPS 3, disappeared after the matching, with the exception of "Reason for admission, central nervous system" (Table 2). This further underlines the validity of the propensity score matching.

In the present study the exposure time was set to 5 days. The decision to transfuse could reflect differences in the trajectory of the disease some days after admission, which was not matched for. This can be exemplified in the present study with the risk that patients who deteriorate some days after admission may be more likely to receive RBC transfusions than patients who improve. To assess this potential confounder, 2 different sensitivity analyses were performed. Firstly, a shorter exposure time of 1 day was applied prior to a propensity score matching. Secondly, differences in circulatory SOFA score between the groups on day 1 to 5 was investigated. The results after the first sensitivity analysis with shorter exposure time were largely the same as in the main analyses (Supplemental File 4), and there were no differences between the groups in circulatory SOFA the first 5 days. Moreover, there were no

TABLE 4. Fluid therapy, first 5 days

Fluids per day[a]	Propensity score matched groups				*P*-value[c]
	Control, $n = 674$		RBC[b], $n = 674$		
	Median	IQR	Median	IQR	
Colloids[d] (mL)	180	0 to 610	290	140 to 680	0.078
Crystalloids[e] (mL)	1200	260 to 2600	1200	890 to 3600	0.133
Fluids in, total[f] (mL)	2900	1600 to 4600	3100	2500 to 5200	< 0.001
Urine output (mL)	1900	880 to 2600	2100	910 to 2900	0.040
Total fluid balance[g] (mL)	340	50 to 2100	710	−10 to 1800	0.111
RBC-transfusion (mL)	0	0 to 0	290	110 to 400	< 0.001

Volumes are presented with 2 value figures. [a]For patients with ICU-stay < 5 days the mean per day was calculated for the length of stay. [b]Low grade red blood cell transfusion defined as < 670 mL (< 2 units) on any of the first 5 days, [c]Wilcoxon rang sum test, [d]Defined as albumin (200 mg mL^{-1}), albumin (5 mg mL^{-1}), dextran 70 (60 mg mL^{-1}) and hydroxyethyl starch (200/0.5 and 130/0.4), [e]Crystalloids represents the sum of NaCl 9 mg mL^{-1} and Ringer's acetate, [f]Fluids in total represents the sum of all enteral and parenteral administered fluids but not RBC transfusions, [g]Insensible perspiration and RBC transfusions not included

differences in the total fluid balance between the groups the first 5 days (Table 4). This all suggests that neither differences in the trajectory of the disease between the groups nor shortening the exposure time explain our findings.

Given that propensity score matching corrected for differences between the groups and that median haemoglobin level in the first 5 days of ICU admission did not differ between groups (Figure 2), the results in the present study imply that any adverse effects of the RBC transfusion are responsible for the worse outcomes in the RBC group. This has previously been suggested in several reports, studies, and guidelines [1, 3, 4, 11, 19–22]. In a retrospective registry study, similarly to the present one, Leal-Noval *et al.* [4] included moderately anaemic non-bleeding critically ill patients and matched patients who received an RBC transfusion with non-transfused patients. Hospital mortality, number of ICU re-admissions, number of nosocomial infections, and incidence of acute renal failure were lower in the non-transfused group. In contrast to the present study, the pre-transfusion haemoglobin level was not reported and patients with nadir haemoglobin level > 95 g L^{-1} were excluded from that study. Because the patients in the present study were transfused at a higher haemoglobin level and thus not exposed to the risk of anaemia, and because the results showed an even stronger correlation between RBC-transfusion and worse outcome, this further strengthens the evidence that RBC transfusions should not be given to non-anaemic critically ill patients.

The reasons RBC transfusions are harmful for non-anaemic non-septic critically ill patients remain elusive, but as mentioned above, known adverse effects of RBC transfusion include TACO, TRALI, and TRIM. Given that the total fluid balance between the groups did not differ (Table 4), TACO is a less likely explanation. Even if TRALI is the leading cause of direct transfusion-related death, it is a rare event reported to occur in 1 case in 6000 to 600,000 transfusions [23]. Also, TRALI is most common after plasma transfusion, which makes this an unlikely cause of worse outcome after RBC transfusion in the present study. RBC transfusions contain many different immunomodulatory mediators that interact with and alter immune cell function in-vivo. The effect of these interactions may be both proinflammatory and immunosuppressive but are seldom obvious at the time of transfusion [24]. Nevertheless, these immunomodulatory properties of RBC transfusions may be detrimental over time for critically ill septic and non-septic patients and may be responsible for the results in the present study.

Finally, it is worth noting that our study has some limitations. These include its retrospective nature, which by default makes conclusions regarding causality uncertain. While baseline characteristics affecting outcomes were cautiously adjusted for and differences in disease trajectory were evaluated in a sensitivity analysis, we cannot rule out residual confounding. For example, cardiac output data and plasma lactate at the time of the transfusion could have differed between the groups. Moreover, the single-centre design may limit the external validity of our results. Strengths include the fact that no patients in either group were exposed to the risk of anaemia because patients with pre-transfusion haemoglobin level < 70 g L^{-1} were excluded. This suggests that outcomes were less biased by any negative effect of anaemia. Furthermore, all physiological and laboratory variables and many pre-existing conditions were registered prospectively in electronic charts and collected as raw data directly from these electronic charts.

CONCLUSIONS

Low-grade leukoreduced RBC transfusions given to non-septic critically ill patients without significant anaemia correlated with increased mortality, increased kidney, circulatory, and respiratory failure, as well as higher SOFA-max score.

ACKNOWLEDGEMENTS

1. We thank intensive care nurse Ann Svensson Gustafsson and computer technician Jan Karlsson for their invaluable help with data extraction from the patient data management system.
2. Financial support and sponsorship: none.
3. Conflict of interest: none.
4. The study was published as a "Pre-print" at Research Square with the URL https://www.researchsquare.com/article/rs-81334/v1.

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