Effects of Red Blood Cell Transfusions on Morbidity and Mortality in Non-Septic Critically Ill Patients; A Propensity Score Matched Study

Thomas Kander (thomas.kander@med.lu.se)
Lunds universitet Medicinska fakulteten https://orcid.org/0000-0002-5404-2981
Caroline Ulfsdotter Nilsson
Lunds universitet Medicinska fakulteten
Daniel Larsson
Lunds universitet Medicinska fakulteten
Peter Bentzer
Lunds universitet Medicinska fakulteten

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Abstract

Background

RBC-transfusions can be lifesaving, but are also associated with harm. To further examine any effect of red blood cell (RBC)-transfusions given to critically ill patients that were not exposed to the risks of anemia or sepsis, we designed this retrospective propensity score matched study. The aim was to compare mortality and morbidity in non-septic critically ill patients that were given low-grade RBC-transfusions at hemoglobin level > 70 g/L with patients without RBC-transfusions any of the first 5 days in intensive care.

Methods

Adult patients admitted to a general 9-bed intensive care unit between 2007-2018 at a tertiary university hospital, were eligible for inclusion. Patients that received > 2 units RBC-transfusion during the first five days after admission, with pre-transfusion hemoglobin level <70 g/L or with severe sepsis or septic shock were excluded. Outcomes were 28-, 90- and 180-day mortality, highest acute kidney injury network (AKIN) score, days alive and free of organ support the first 28 days and highest sequential organ failure assessment score (SOFA-max).

Results

In total 9491 admissions were recorded during the study period. Propensity score matching at 1:1 ratio resulted in two well matched group with 682 unique patients in each. Median pre-transfusion hemoglobin was 98 g/L (interquartile range 91-106 g/L). Mortality at the measured time points were higher in the RBC-group with an absolute risk increase for death at 180 days of 4.8% [95% confidence interval 2.5 to 7.2%], ($p<0.001$). Low grade RBC-transfusion was also associated with renal, circulatory and respiratory failure as well as higher SOFA-max score.

Conclusion

Low-grade leukoreduced RBC-transfusions given to non-septic critically ill patients without significant anemia, was strongly associated with increased mortality, increased kidney-, circulatory- and respiratory- failure as well as with higher SOFA-max score. These findings further strengthen the evidence supporting a restrictive use of RBC-transfusions in critically ill patients.

Introduction

Anemia is common in critically ill patients and more than one fourth are transfused with allogenic red blood cell transfusions (RBC) [1,2]. RBC-transfusions can be lifesaving for many patients, but are also associated with harm such as transfusion-associated circulatory overload (TACO), transfusion-related immune modulation (TRIM), transfusion-related acute lung injury (TRALI) hemolytic reactions and infections [3]. However, also anemia is dangerous which makes risk-benefit assessment of RBC- transfusions important and necessary [4]. Many large randomized controlled trials (RCT) with high level of evidence demonstrate that a restrictive transfusion strategy (hemoglobin level > 70 g/L) is as safe as a liberal transfusion strategy (hemoglobin level > 90-100 g/L) [5-10]. In those RCTs, patients in both groups received RBC-transfusions and many patients may also have been exposed to the risk of anemia. Consequently, potentially 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]. In an attempt to evaluate if the harmful effect of RBC transfusions in non-septic critically ill patients that were not exposed to the risks of anemia, 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 that were given low-grade RBC-transfusions at hemoglobin level > 70 g/L with

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

Methods

Data collection and study population

The study was approved by 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 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 exclude patients with massive bleeding, patients who received high grade RBC-transfusion (defined as > 670 ml or two units) any of the first five days in the ICU were excluded. 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 exclude patients exposed to the risks of anemia, all patients with a pre-transfusion hemoglobin level <70 g/L were excluded.

Mortality data was collected from the Swedish intensive care quality register PASIVA (Otimo Data AB, Kalmar, Sweden). Physiological and laboratory data and pre-existing conditions (age, gender, chronic obstructive pulmonary disease (COPD), renal failure, diabetes), 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 [15]. 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.

Statistics

Patients receiving low grade RBC-transfusion (< 670 mL/day) during the first 5 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 [16], with the covariates specified in Table 1. Physiological and laboratory variables used in the propensity score matching were collected within 90 min of admission to the ICU.

Sample size was based on the number of available patients during the study period. Variables were summarized using mean (standard deviation), median (interquartile range) or numbers (percentage). The propensity score matching was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) prior to any comparison between the groups. Kaplan-Meier survival analysis was performed and is presented in graphs with corresponding stratified log-rank test. In accordance with previous recommendations comparisons between the groups after propensity score matching was performed with paired hypothesis testing [17]. The propensity score matching was performed by an independent statistician using SAS version 9.4 (SAS

Institute Inc., Cary, NC, USA). Other analyses were performed with SPSS Statistics version 26 (SPSS Inc., Chicago, Ill., USA). A two-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 9 491 patients 5 240 patients remained after removing patients < 18 years of age, multiple admissions, high-grade RBC-transfusion (>670 ml/day), patients with pre-transfusion hemoglobin < 70 g/L and patients with severe sepsis or septic shock. After propensity score match 682 patients were included in the RBC-group and 682 patients in the control group. The annual inclusion rate in both groups was similar (Additional file 1). Baseline demographics, comorbidity, and clinical, physiologic, and laboratory data in both groups are summarized in Table 1 and 2. After the propensity score match the standardized difference 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 leucoreduced. The median hemoglobin level before transfusion in the RBC-group was 98 g/L (91-106 g/L). The median hemoglobin level on day 0 was 108 (104-111 g/L) for the RBC group and 109 (106-111 g/L) for the control group (P=0.95). Daily median hemoglobin levels for the five first days for both groups are illustrated in Figure 2. The median volumes of RBC-transfusion in the RBC- group the first five days after admission are shown in Figure 3.

Outcomes

Detailed results are presented in Table 3. Mortality at 28, 90 and 180 days were 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 4.8% [95% CI: 2.5 to 7.2%]; (P<0.001). RRT and AKINmax 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.

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.

Discussion

In this propensity score matched study, low-grade leukoreduced RBC-transfusions given to non-septic critically ill patients without significant anemia, was associated with increased mortality, increased kidney-, circulatory- and respiratory- failure as well as with higher SOFA-max score. This confirms the hypothesis that RBC-transfusions given to non-septic critically ill patients without significant anemia are harmful.

We collected data from 2007, prior to many high quality RCTs recommending a transfusion thresh-hold of 70 g/L. As recommended in the beginning of the study period, RBC-transfusions were often given in an ambition to increase oxygen delivery [18]. Hence, the vast majority of patients in the RBC group were transfused at a “safe” hemoglobin level without being exposed to the risks of anemia, indicated by a median pre-transfusion hemoglobin level of 98 g/L (91-106). These data can therefore be used to evaluate the effect of RBC-transfusion itself on critically ill non-anemic, 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 the 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 underline the validity of the propensity score-matching.

Given that propensity score matching corrected for differences between the groups and that median hemoglobin level the first day 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 itself are responsible for the worse outcomes in the RBC group. This has previously been suggested in several reports, studies and guidelines [1,3,4,11,18-21]. In a retrospective registry study, similar to the present, Leal-Noval et al. included moderately anemic non-bleeding critically ill patients and matched patients that received RBC-transfusion with non-transfused patients [4]. Hospital mortality, ICU re-admissions, nosocomial infections and acute renal failure favored the non-transfused group. In contrast to the present study, pre-transfusion hemoglobin level was not reported and patients with nadir hemoglobin level > 95 g/L were excluded from that study. As the patients in the present study were transfused at a higher hemoglobin level, thus not exposed for the risk of anemia and as the results showed an even stronger correlation between RBC-transfusion and bad outcome, this further strengthens the evidence that RBC-transfusions should not be given to non-anemic critically ill patients.

The reasons RBC-transfusions are harmful for non-anemic 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 one case in 6 000 to 600 000 transfusions [22]. 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 moment of the transfusion [23]. 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[23].

The most obvious measure to avoid RBC-transfusions in critically ill would be to avoid anemia. As blood loss through diagnostic testing has been shown to be substantial and associated with RBC-transfusions it should be standard to minimize blood sampling and to use low-volume blood sampling tubes and in-line closed blood conservation devices on arterial lines for reinfusion of waste blood [24]. It would also be desirable to treat anemia without giving RBC-transfusion. A common type of anemia in critically ill patients is similar to the anemia described in chronic disease and the state of inflammation [1]. The pathophysiology of this anemia includes high levels of hepcidin leading to a state of functional iron deficiency [25] and a blunted response to erythropoietin [26]. Erythropoietin and iron supplementation have been studied in several RCTs but unfortunately without reduction in RBC-transfusions [27,28]. However, results of several ongoing trials on iron administration to critically ill patients are pending [21].

Finally, it is worth noting that our study has limitations and strengths. Limitations include that the study was retrospective and single center. Secondly baseline characteristics affecting outcomes were cautiously adjusted for, but it cannot be ruled out that undetected variables also were present. Strengths include that patients in neither group were exposed for the risk of anemia as patients with pre-transfusion hemoglobin level < 70g/L were excluded. This suggests that outcomes were less biased by any negative effect of anemia. Further, all physiological and laboratory variables and many pre-existing conditions were registered prospectively in electronic charts and collected as raw data directly from the electronic charts.

Conclusion

Low-grade leukoreduced RBC-transfusions given to non-septic critically ill patients without significant anemia correlated strongly with increased mortality, increased kidney-, circulatory- and respiratory- failure as well as with higher SOFA-max score. These findings further strengthen the evidence supporting a restrictive use of RBC-transfusions in critically ill patients.

Abbreviations

AKIN: Acute kidney injury network

DAF: Days alive and free

ICU: Intensive care unit

RBC: Red blood cell

RCT: Randomized controlled trials

RRT: Renal replacement therapy

TACO: Transfusion-associated cardiac overload

TRALI: Transfusion related acute lung injury

TRIM: Transfusion-related immunomodulation

Declarations

Ethics approval and consent to participate

This study was approved by Swedish Ethical Review Authority in Lund, Sweden (registration numbers 2014/916 and 2018/866). All participants were offered an opt-out via advertisement in the local newspaper and the board waived the requirement for written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

TK designed the study, built the database, wrote the first version of the manuscript and performed the statistical analyses after the propensity score match that was performed by a statistician. PB contributed to study design and did the first revision of the manuscript. All authors contributed to the interpretation of the data, revised the manuscript critically, and gave final approval of the version to be published.

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Tables

Table 1. Patient demographics before and after propensity matching

	Unmatched groups				Propensity-matched groups			
	Control N= 3949	RBC[i] N= 1291	Standardized difference	P-value	Control N= 682	RBC N= 682	Standardized difference	P-value
Pre-existing conditions								
Age, mean (SD[ii])	58 (19)	64 (16)	0.315	<0.001	63 (17)	63 (16)	0.022	0.686
Male gender, no (%)	2342 (59)	745 (58)	0.032	0.311	405 (59)	393(58)	0.039	0.475
Blood malignancy[iii], no (%)	40 (1.0)	37 (2.9)	0.140	<0.001	13 (1.8)	14 (2.1)	0.021	0.692
COPD[iv], no (%)	340 (8.6)	96 (7.4)	0.043	0.185	69 (10)	68(9.8)	0.010	0.857
Cirrhosis, no (%)	40 (1.0)	25 (1.9)	0.076	0.010	13 (1.8)	13 (1.8)	0.000	1.000
Immunosuppression[v], no (%)	727 (18)	74 (5.7)	0.107	<0.001	39 (5.7)	35 (5.1)	0.026	0.633
Malignancy[vi], no (%)	525 (13)	296 (23)	0.250	<0.001	127 (19)	135 (20)	0.037	0.492
Nosocomial infection[vii], no (%)	138 (3.5)	48 (3.7)	0.013	0.674	28 (4.1)	30 (4.4)	0.014	0.789
Airway infection, no (%)	494 (12)	159 (12)	0.005	0.874	82 (12)	84 (12)	0.004	0.934
Surgery[viii], no (%)	908 (23)	513(40)	0.367	<0.001	230 (34)	238(35)	0.028	0.608
GI[ix]-bleeding, no (%)	71(1.8)	25 (1.9)	0.012	0.702	15 (2.1)	13 (1.8)	0.021	0.692
DIC[x], no (%)	103(2.6)	25(1.9)	0.467	0.161	12 (1.8)	13 (1.9)	0.011	0.840
I.C.[xi] volume effect, no (%)	123 (3.1)	38 (2.9)	0.011	0.723	12 (1.8)	16 (2.3)	0.041	0.445
Physiological and laboratory variables at admission[xii], mean (SD)								
Heart rate, mean (SD)	92 (23)	94 (24)	0.113	<0.001	93 (24)	94 (24)	0.025	0.645
SBP[xiii], (mmHg)	126 (30)	119 (29)	0.234	<0.001	120 (29)	122 (30)	0.054	0.316
Lactate (mmol/L)	2.3 (2.5)	2.4 (2.3)	0.031	0.346	2.5 (2.6)	2.5 (2.4)	0.014	0.801
Norepinephrine (µg/min)	0.91 (3.2)	1.8 (5.0)	0.205	<0.001	1.6 (4.3)	1.8 (5.4)	0.038	0.479
Temperature (°Celcius)	36.6 (1.2)	36.7 (1.4)	0.058	0.061	36.6 (1.4)	36.7 (1.5)	0.038	0.489
PaO_2/FiO_2 (kPa)	33 (18)	32 (20)	0.014	0.672	33 (18)	33 (22)	0.038	0.488
Leucocytes (x 10^9/L)	14 (10)	13 (8.1)	0.036	0.291	14 (15)	14 (7.9)	0.009	0.867
Platelets (x 10^9/L)	225 (97)	210 (110)	0.140	<0.001	217 (104)	218 (118)	0.010	0.850

pH	7.34 (0.12)	7.35 (0.11)	0.139	<0.001	7.34 (0.12)	7.34 (0.11)	0.024	0.651
Bilirubin (µmol/L)	12 (19)	17 (30)	0.179	<0.001	14 (28)	14 (16)	0.003	0.961
Creatinine (µmol/L)	104 (110)	125 (150)	0.152	<0.001	117 (129)	118 (148)	0.003	0.949
PT/INR[xiv]	1.3 (0.65)	1.4 (0.72)	0.141	<0.001	1.4 (0.73)	1.4 (0.68)	0.006	0.909
APTT[xv] (sec)	35 (17)	39 (19)	0.227	<0.001	38 (12)	39 (20)	0.021	0.694
Hb[xvi]	122 (18)	105 (15)	1.037	<0.001	109 (14)	109 (14)	0.016	0.766

[a] Low grade red blood cell transfusion defined as <670 ml any of the first 5 days

[b] Standard deviation

[c] Lymphoma, acute leukaemia or myeloma

[d] Chronic obstructive pulmonary disease

[e] Chronic steroid treatment correlative to ≥ 0.3 mg/kg prednisolone/day, radiation, or chemo therapy

[f] Cancer spread beyond the regional lymph nodes

[g] Infection that developed after ≥ 48 hours in hospital or secondary to surgical or medical procedure

[h] Before admission to intensive care

[i] Gastro-intestinal

[j] Disseminated intravascular coagulopathy

[k] Intra-cranial

[l] First value within 90 min after admission except for “Norepinephrine” which is the mean dose the first 12 hours

[m] Systolic blood pressure

[n] Prothrombin time

[o] Activated partial thromboplastin time

[p] Median hemoglobin level day 0

Table 2. Unmatched baseline characteristics						
	Unmatched groups			Propensity-matched groups		
	Controls, n=3949	RBC[i], n=1291	P-value[ii]	Controls, n=682	RBC, n=682	P-value[iii]
SAPS 3[iv], median (IQR[v])	54 (43-66)	62 (51-73)	<0.001	60 (47-69)	60 (50-71)	N.S.
Reasons for admission[vi], n (%)						
Trauma	272 (6.9)	122 (9.5)	0.003	35 (5.1)	43 (6.3)	N.S.
CNS[vii]	1334 (31)	431 (25)	<0.001	192 (28)	227 (33)	0.02
Hematologic	109 (2.5)	128 (7.5)	<0.001	19 (2.8)	23 (3.4)	N.S.
Gastric	333 (7.7)	323 (19)	<0.001	68 (10)	72 (11)	N.S.
Metabolic	505 (12)	211 (12)	N.S.	66 (10)	64 (9.4)	N.S.
Respiratory	1531 (35)	692 (40)	<0.001	292 (43)	272 (40)	N.S.
Cardiovascular	952 (22)	660 (39)	<0.001	188 (26)	199 (29)	N.S.
Hepatic	151 (3.5)	113 (6.6)	0.02	34 (5.0)	31 (4.6)	N.S.
Renal	393 (9.1)	316 (18)	<0.001	62 (9.1)	78 (11)	N.S.
Other	347 (8.0)	136 (7.9)	N.S.	46 (6.7)	53 (7.8)	N.S.
Arrival route n (%)						
Emergency department	1885 (44)	371 (22)	<0.001	187 (27)	186 (27)	N.S.
General ward	1106 (26)	603 (35)	<0.001	196 (29)	186 (27)	N.S.
Intermediate care	56 (1.3)	38 (2.2)	0.02	15 (2.2)	12 (1.8)	N.S.
Operation	564 (13)	341 (20)	<0.001	124 (18)	135 (20)	N.S.
Other ICU	440 (10.2)	231 (13)	0.02	115 (17)	102 (15)	N.S.
Postoperative care unit	576 (13)	349 (8.1)	0.01	125 (18)	158 (23)	0.03
Other	237 (6.0)	90 (7.0)	N.S.	44 (6.5)	38 (5.6)	N.S.

[a] Red blood cell transfusion

[b] Mann-Whitney-U or Chi-2-test

[c] Wilcoxon rang sum or McNemars´ test

[d] Simplified acute physiology score 3

[e] Interquartile range

[f] Patients may have more than one reason for admission

[g] Central nervous system

Table 3. Main outcome variables

	Propensity-matched groups		Relative risk (95% CI[i])	Absolute risk increase (95% CI)	P[ii]
Outcome	**Control**	**RBC[iii]**			
	n= 682	**n= 682**			
28-day mortality	146 (21)	188 (28)	1.29 (1.07 to 1.55)	6.2% (1.6 to 11%)	0.01
90-day mortality	188 (28)	231 (34)	1.23 (1.05 to 1.44)	6.3% (1.4 to 11%)	0.01
180-day mortality	211 (31	269 (39)	1.27 (1.10 to 1.47)	8.5% (3.5 to 14%)	0.001
RRT[iv]	19 (2.8	52(7.6)	2.74 (1.64 to 4.58)	4.8% (2.5 to 7.2%)	<0.001
AKIN[v]	0 (0-0)	0 (0-1)			<0.001
DAF of vasopressors	28 (25-28)	26 (14-28)			<0.001
DAF of mechanical ventilation	27 (23-28)	25 (9-27)			<0.001
SOFA max[vi]	6 (4-9)	8 (5-10))			<0.001

Data are presented as number (%) or median (interquartile range)

[a] Confidence interval

[b] Wilcoxon rang sum or McNemar´s test

[c] Low grade red blood cell transfusion defined as <670 ml any of the first 5 days

[d] Renal Replacement Therapy

[e] AKIN max the first 10 days after admission

[f] Maxiumum Sequential Organ Failure Assesment score the first 10 days after admission

Table 4. Fluid therapy, first 5 day

Propensity score matched groups					
Fluids per day[i]	**Control, n=737**		**RBC[ii], n=737**		**P[iii]**
	Median	IQR[iv]	**Median**	IQR	
Colloids[v] (ml)	170	0 to 530	291	130 to 655	n.s.
Crystalloids[vi] (ml)	1100	270 to 2500	1100	890 to 3600	n.s.
Fluids in, total[vii] (ml)	3000	1700 to 4500	3400	2800 to 5000	<0.001
Urine output (ml)	1800	790 to 2700	2100	920 to 2900	0.04
Total fluid balance[viii] (ml)	340	-30 to 1900	710	-90 to 1700	n.s.
RBC-transfusion (ml)	0	0 to 0	300	120 to 410	<0.001

Table 4. 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) any of the first 5 days

[c] Wilcoxon rang sum test

[d] Interquartile range

[e] Defined as albumin (200 mg/ml), albumin (5 mg/ml), dextran 70 (60 mg/ml) and hydroxyethyl starch (200/0.5 and 130/0.4)

[f] Crystalloids represents the sum of NaCl 9 mg/ml and Ringer´s Acetate

[g] Fluids in, total represents the sum of all enteral and parenteral administered fluids but not RBC-transfusions

[h] Insensible perspiration and RBC-transfusions not included

Figures

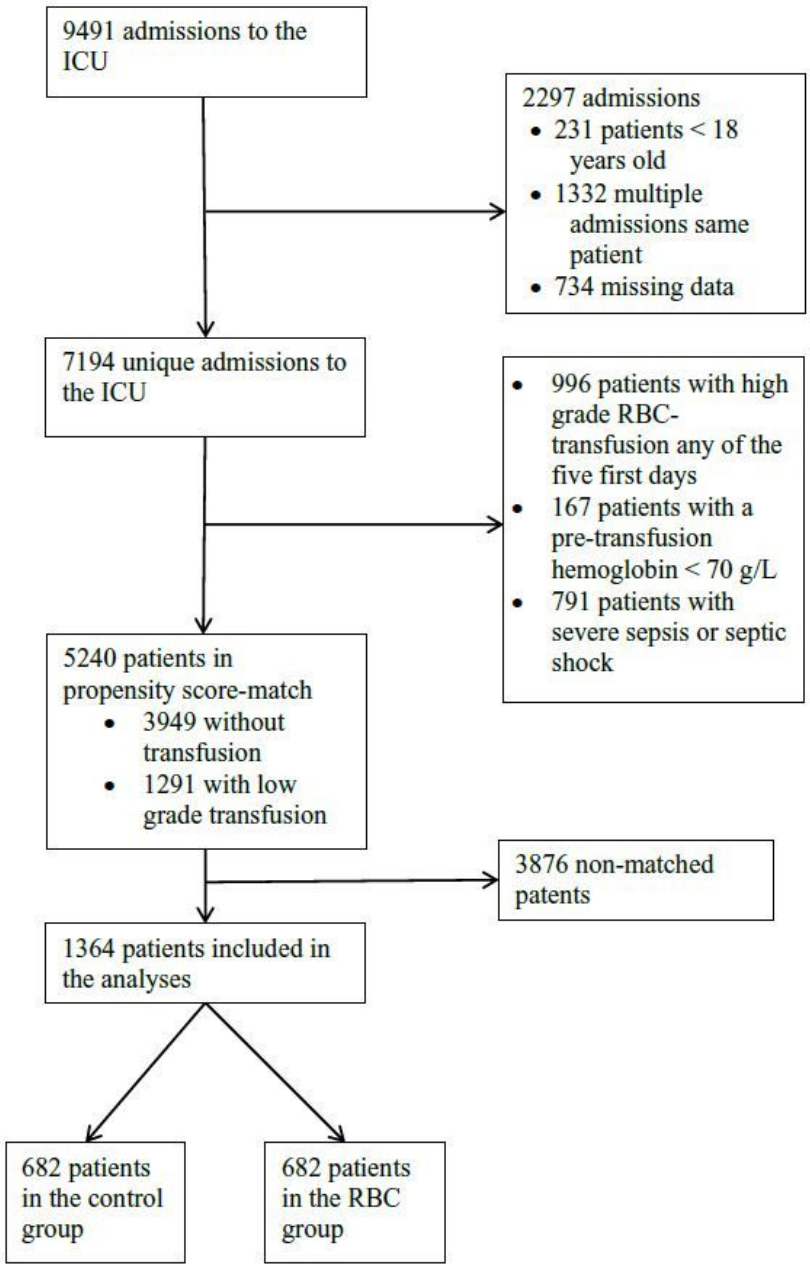

Figure 1

Consort diagram

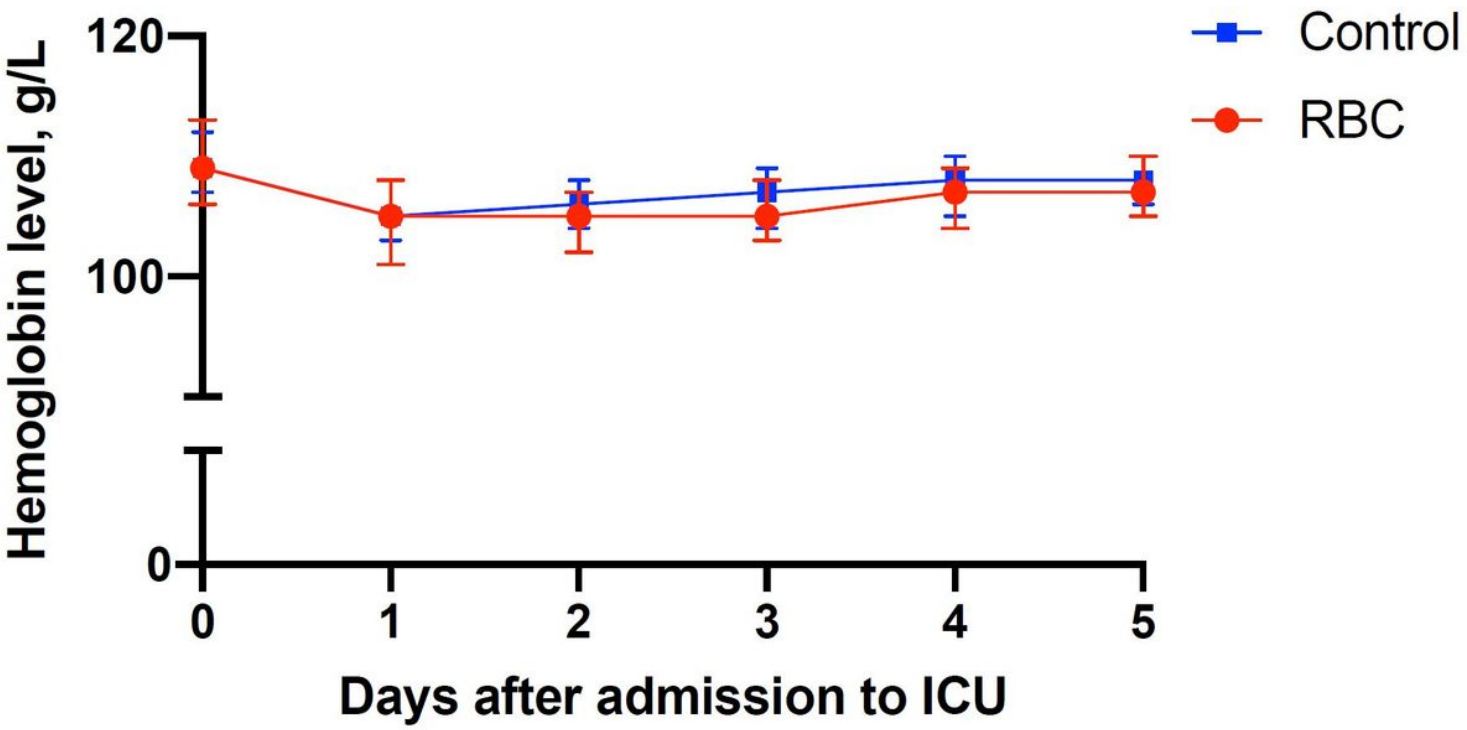

Figure 2

Median hemoglobin level with interquartile range. RBC= group with patients who received red blood cell transfusion any of the first five days.

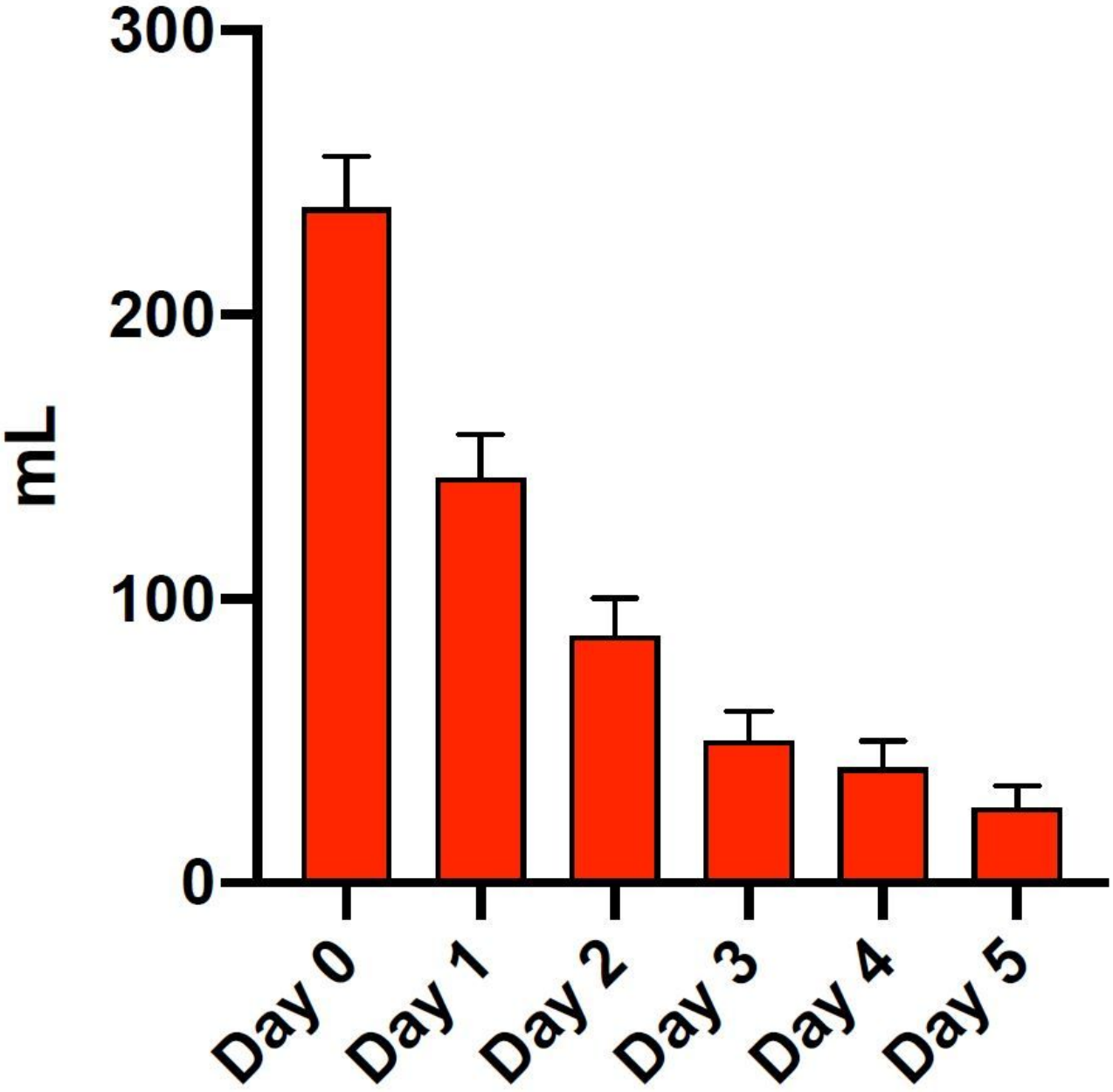

Figure 3

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

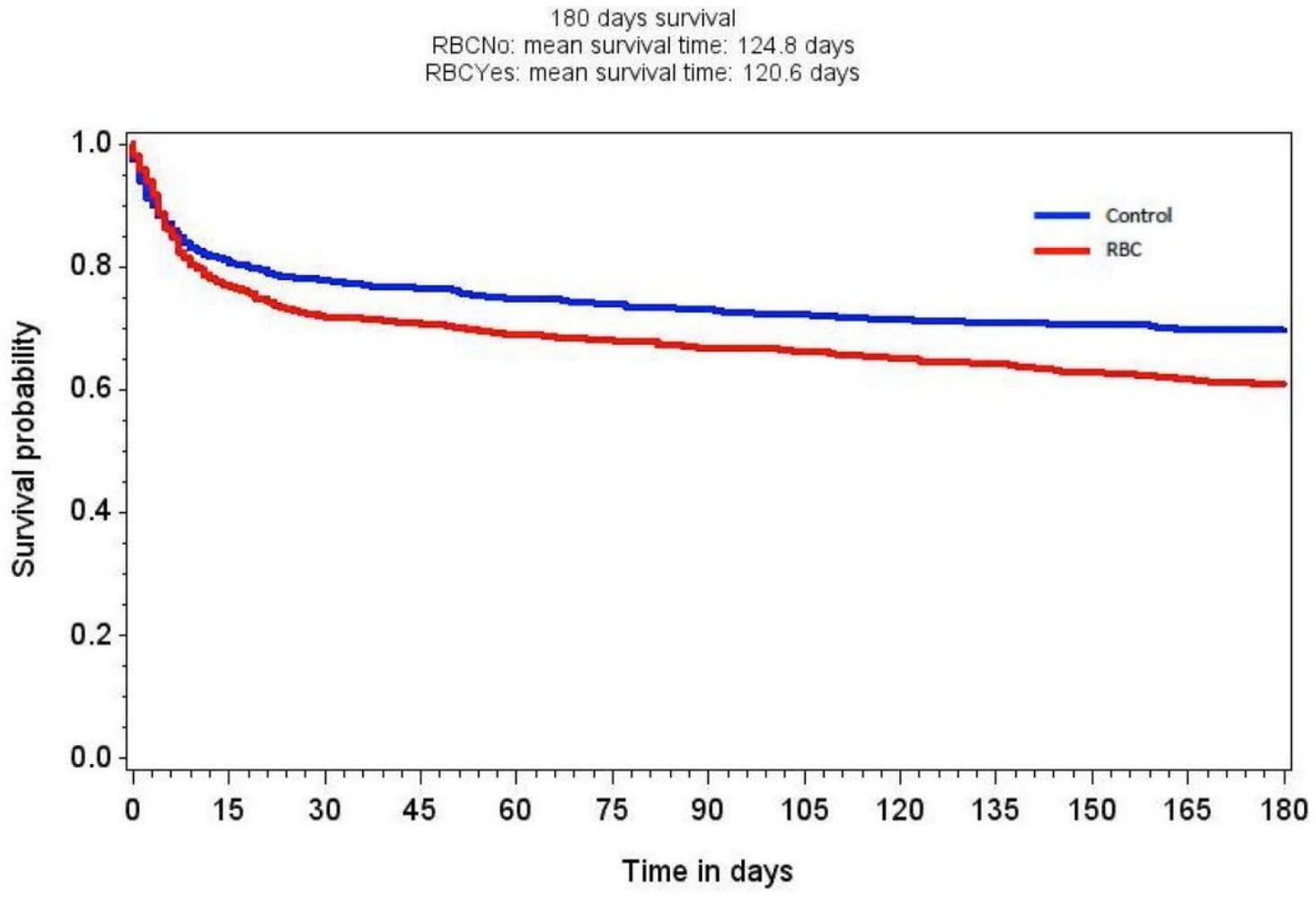

Figure 4

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 five days.