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Impact of red blood cell transfusion in massive burn: a multicenter cohort study

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Blood transfusions were frequently in massive burn patients, current studies focus on the trigger threshold of red blood cell transfusion, and few studies focus on the impact of red blood cell transfusion volume on patient outcomes. We initiated a multicenter cohort study to explore the impact of red blood cell transfusions volume on patient mortality. 379 patients in three centers were enrolled to the cohort. The extroperative and overall RBC transfusion in the death group were significantly higher than those in the survival group ($p < 0.001$), and this difference became insignificant within the operation ($p = 0.312$). RBC transfusion volume and mortality risk of patients was obviously not linear ($p < 0.0001$) and would be L-shaped, and the threshold would be 6U. 1:1propensity matching was used to adjust the burn area, full thickness burned area and inhalation injury. There was no significant difference in the outcome and bloodstream infection between the two groups, but the length of stay, length of stay in burn ICU and mechanical ventilation time of the low red blood cell group were significantly lower than those of the high red blood cell group. Our findings therefore support the approach of a restrictive transfusion strategy in severely burned patients. This also confirms the scientificity of restrictive transfusion strategy and suggests that unnecessary red blood cell transfusion should be avoided in clinic.

Keywords Burn, Massive burn, Transfusion, Red blood cell, Cohort study

Abbreviations

RBC	Red blood cell
FNHTR	Febrile nonhemolytic transfusion reactions
TACO	Transfusion-associated circulatory overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-transmitted infections
BSI	Bloodstream infection
PBM	Patient Blood Management
FDA	Food and Drug Administration
TBSA	total body surface area
PA	Pseudomonas aeruginosa
MRSA	Methicillin-resistant Staphylococcus aureus
EC	Enterobacter cloacae
LOS	Length of stay

Blood transfusion is common in patients admitted to the intensive care unit (ICU), especially in burn ICU. During 2021,10.7 million red blood cell(RBC) units were transfused in United States, and more than 1.7 million were transfused in a critical care setting[1]. Unfortunately, there was a lack of nationwide blood transfusion volume data for burn ICU, but the transfusion rate in different burn centers was reported to be 57.7-97.7%[2,3]. Blood transfusions were frequently used to treat frequent anemia and coagulopathy which results from multiple operations, massive loss of skin tissue, systemic and local effects of inhalation injury in massive burn patients[4].

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Although blood products may be lifesaving, transfusion is also associated with potentially life-threatening adverse effects including: febrile nonhemolytic transfusion reactions (FNHTR), transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-transmitted infections (TTI). Studies have shown that burn patients who receive massive blood transfusions have an increased risk of bloodstream infections(BSI), a longer ICU and hospital stay and a higher mortality[3,5,6].In addition, the World Health Organization (WHO) introduced the Patient Blood Management (PBM) project in 2019 to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products. Food and Drug Administration (FDA) also emphasizes the importance of blood transfusion should base on evidence, focusing on the patient's needs, and be used cautiously[7].Therefore, blood transfusion must be used judiciously[8].

Many studies have confirmed the advantages of restrictive transfusion strategy in different subject, including general surgery[9], cardiac surgery[10], burns[11], and gastrointestinal bleeding[12]. Different guidelines also recommend restrictive transfusion strategies[13,14]. The study published in the New England Journal of Medicine in 2011 first proposed restrictive transfusion after hip surgery. It found that liberal transfusion strategy, as compared with a restrictive strategy, did not reduce rates of death, or reduce in-hospital morbidity in elderly patients at high cardiovascular risk[9]. The TRIBE trial illustrate that restrictive strategy did not decrease bloodstream infection, mortality, or organ dysfunction in massive burn injury, these outcomes were no worse than the liberal strategy[11].

However, current studies focus on the trigger threshold of RBC transfusion, and few studies focus on the impact of RBC transfusion volume on patient outcomes .As a result, we initiated a multicenter cohort study to explore the impact of RBC transfusions volume on patient mortality. We hypothesized that the relationship would not simply linear.

Methods

Study design, population, and outcomes

This is a retrospective study that include greater than 50% burn total body surface area (TBSA) massive burn patients who were admitted to three participating burn centers in China–the Second Affiliated Hospital of Zhejiang University College of Medicine, the First Affiliated Hospital of Nanchang University, and the First Affiliated Hospital of Anhui Medical University. The three hospitals are the burn centers of their provinces. Admissions in centers were analyzed between the 1 January 2016 to 30 June 2022, Only the first burn ICU admission of every patient within the defined period of the study was analyzed. These patients were sub-grouped into high RBC transfusion and low RBC transfusion groups based on the threshold for RBC transfusion volume. Thresholds were derived from restricted cube analysis of transfused RBC transfusion volumes and patient outcomes.

Exclusion criteria included: hospitalization for less than 24 h or death within 24 h of admission; Pediatric burn patients; incomplete medical records; The primary outcomes were in-hospital mortality and Secondary outcomes were burn ICU and hospital length of stay (LOS), mechanical ventilation time, and the incidence of BSI.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for conducting this retrospective cohort study.

The research was approved by the Institutional Ethical Committee of the Second Affiliated Hospital of Zhejiang University College of Medicine (I20221060), the Institutional Ethical Committee of the First Affiliated Hospital of Nanchang University ((2023)CDYFYYLK(01–043)), and the Institutional Ethical Committee of the First Affiliated Hospital of Anhui Medical University (PJ 2023-10-12). All of the Institutional Ethical Committees waived the requirement for informed consent due to the observational, retrospective nature of this study.

Red blood cell transfusion strategy

Each center follows a restrictive transfusions strategy, but trigger threshold may vary depending on the blood resources of blood bank. Specifically, when the blood bank was sufficient, hemoglobin < 7 g/dL will trigger the blood transfusion threshold, and it was 6 g/dL when the resources are tight.

Data collection

we use the same checklist to collect all information from the electronic medical record systems of different centers. Demographics and clinical characteristics were collected: age, sex, TBSA, full thickness burned area, inhalation injury, mechanical ventilation time, burn ICU and hospital length of stay, bloodstream infection. Laboratory indicators were collected: lactate, creatinine, bilirubin, platelet, hemoglobin on admission. RBC transfusion volume was collected : extraoperative, intraoperative and overall. All medical records are exported to researchers by the institutional information center, and patient names are hidden.

Statistical analysis

Demographics and baseline clinical characteristics are presented as mean (SD) or median (IQR) as appropriate. When appropriate, we made univariate comparisons using $\chi 2$-test for categorical variables and using the independent samples t-test or Mann-Whitney test for quantitative variables.

We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals. We also used restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th centiles to flexibly model the association of extraoperative RBC transfusion volume and overall RBC transfusion volume with mortality.1:1 Propensity score matching was performed to adjust for differences in baseline characteristics include TBSA, full thickness burned area and inhalation injury between groups.

A p value of 0.05 or less (two-sided) was considered statistically significant. Statistical analyses were performed with SPSS Version 22.0 (IBM Corporation, Armonk, NY) or R-4.3.0. (R Project for Statistical Computing, Austria, Vienna)

Results

We recruited a total of 474 eligible patients in three centers, with 75,209 and 190 patients in each center. Excluding 56 cases with admission time beyond 48 h, 7 cases with age less than 18 years, 4 cases with death or automatic discharge within 24 h of admission, 8 cases with unpredictable prognosis and 28 cases with incomplete records, finally, 379 patients were enrolled to the cohort (Fig. 1).

The general demographic data and clinical characteristics of the 379 remaining eligible patients are shown in Table 1. Among them, 272 (71.77%) were men,, the mean of age was 46.20 ± 14.22 years. The median TBSA burned area and full thickness burned area ware 70.0% (60.0%, 86.5%) and 33.0%(18.0%,55.0%), respectively. Hemoglobin and platelets were significantly elevated, which was result in massive exudation of tissue fluid and highly concentrated blood in the early stage of burn. There were significant differences in age, burn area, full thickness burned area, inhalation injury, lactate, creatinine, bilirubin, hemoglobin and platelet between groups.

The median of overall RBC transfusion volume in death and survive group were 14(6,24.38)U and 8(4,17) U respectively. Box plot of RBC transfusion volume was shown in Fig. 2. The extroperative and overall RBC transfusion in the death group were significantly higher than those in the survival group($p < 0.001$),and this difference became insignificant within the operation($p = 0.312$). Therefore, we focused on the impact of extraoperative RBC transfusion on patient prognosis.

Impact of extraoperative RBC transfusion volume on prognosis

Restricted cubic spline analysis indicated that the relationship between overall and extraoperative RBC transfusion volume and mortality risk of patients was obviously not linear($p < 0.0001$) and would be L-shaped (Fig. 3). A marked increase in risk was observed at low RBC transfusion volume, but minimal diminution in risk at higher RBC transfusion volume, and the threshold would be 6U and 10U respectively.

Since our study focused on extraoperative RBC transfusion, we chose 6U as the threshold for our grouping. We divided the patients into "low RBC transfusion" group and "high RBC transfusion" group. There were significant differences in sex, burn area, full thickness burned area, inhalation injury, lactate, creatinine, bilirubin, albumin and platelet between the two groups. Therefore, 1:1propensity matching was used to adjust the above factors

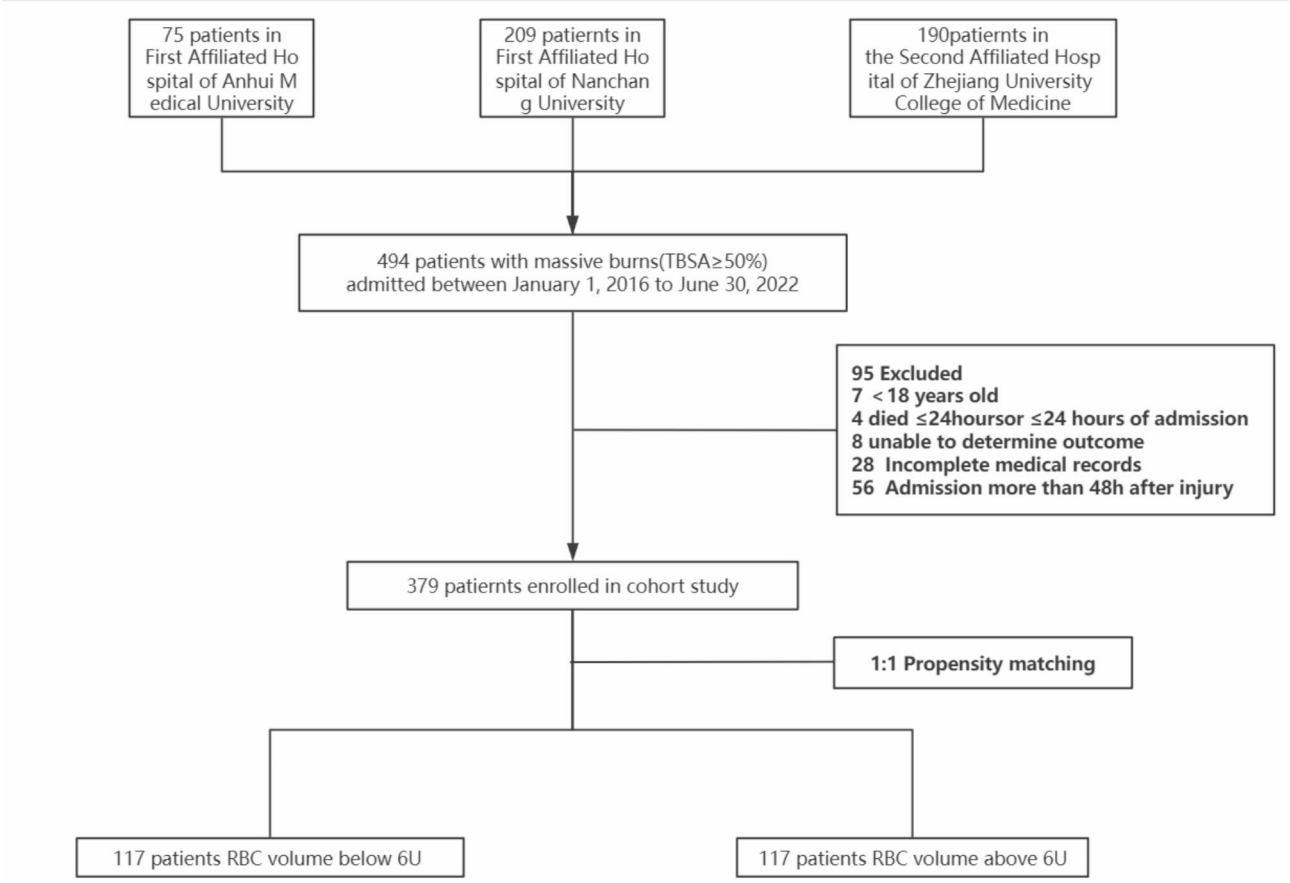

Fig. 1. Flowchart of participants selected and data analysis. TBSA total body surface area, RBC red blood cell.

		Overall($n=379$)	death($n=116$)	survive($n=263$)	p
Age(years)		46.20 ± 14.22	50.60 ± 15.18	44.26 ± 13.34	0.0001①
Sex (%)	Male	272 (71.77)	80 (68.97)	192 (73.00)	0.4958③
	Female	107 (28.23)	36 (31.03)	71 (27.00)	
TBSA burned%		70.00 (60.00, 86.50)	87.50(75.00, 95.00)	65.00(55.00, 80.00)	< 0.0001②
Full thickness burned area		33.00 (18.00, 55.00)	60.50 (39.00, 80.00)	25.00 (14.00, 41.75)	< 0.0001②
Inhalation injury (%)	N	148 (39.05)	71 (61.21)	7 (29.28)	< 0.0001②
	Y	231 (60.95)	45 (38.79)	186 (70.72)	
smoking (%)	N	122 (32.19)	41 (35.34)	81 (30.80)	0.451③
	Y	257 (67.81)	75 (64.66)	182 (69.20)	
Alcohol (%)	N	118 (31.13)	33 (28.45)	85 (32.32)	0.5289③
	Y	261 (68.87)	83 (71.55)	178 (67.68)	
hypertension (%)	N	335 (88.39)	100 (86.21)	235 (89.35)	0.4793③
	Y	44 (11.61)	16 (13.79)	28 (10.65)	
diabetes (%)	N	361 (95.25)	110 (94.83)	251 (95.44)	1③
	Y	18 (4.75)	6 (5.17)	12 (4.56)	
Lactate (mmol/L)		4.20 ± 2.99	5.66 ± 4.41	3.55 ± 1.74	< 0.0001①
Creatinine (μmol/L)		76.70 (61.00, 97.55)	93.25 (71.35, 128.10)	69.00 (58.80, 89.20)	< 0.0001②
Bilirubin (μmol/L)		17.40 (12.60, 25.70)	22.65 (16.80, 31.90)	15.70 (11.75, 21.58)	< 0.0001②
albumin1		29.72 ± 8.68	28.95 ± 9.07	30.06 ± 8.50	0.2522①
RBC (U)		10.00 (4.00, 19.00)	14.00 (6.00, 24.38)	8.00 (4.00, 17.00)	0.0004②
Hemoglobin (g/dL)		16.70 ± 3.17	17.11 ± 3.66	16.52 ± 29.24	0.0942①
Hbmin (g/dL)		73.88 + 17.26	70.43 ± 20.30	75.40 ± 15.54	0.0097①
Platelet		242.00 (173.00, 335.50)	274.50 (193.25, 443.50)	231.00 (168.00, 305.00)	< 0.0001②

Table 1. General demographic data and clinical characteristics. RBC red blood cell ①independent samples t-test ②Mann-Whitney test;③χ2-test.The lactate, creatinine, bilirubin, albumin, Hemoglobin was tested on admission ; Data are shown as the median (25th percentile, 75th percentile), mean ± standard deviation or the number of patients (%), as appropriate.

affecting patient outcomes, making the baseline data of the two more comparable (Table 2). We did not match albumin because albumin levels had less impact on patient outcomes(Table 1).

After propensity matching, there was no significant difference in the outcome and bloodstream infection between groups($P=0.887$ and 0.1165) (Table 3). However, the Nadir hemoglobin in high RBC transfusion group was significantly lower than that in the low RBC transfusion group($P<0.0001$). Additionally, the burn ICU and hospital stay and mechanical ventilation time of the high RBC transfusion group were significantly higher than those of the low low RBC transfusion group($P<0.001$). Surprisingly, the AB infection rate of the high threshold group was significantly lower($P=0.0413$).

Discussion

RBC transfusion is common in the treatment of massive burn patients as massive tissue loss and frequent surgery. However, transfusions may additionally lead to complications and worse clinical outcomes[15]. Our multicenter cohort study enrolled 379 patients from 3 centers and found that the impact of RBC transfusion on the outcome of massive burn patients is not linear. The threshold for extraoperative RBC transfusion would be 6U. When the transfusion volume is lower than 6U, the risk of death for patients decreases with the increase of transfusion volume (HR = 2.92 95%CI = 2.04,4.21), this means that for each additional unit of RBC transfusion, the risk of death is reduced by 2.96 times. Once the transfusion volume is greater than 6unit, this improvement effect becomes extremely limited. This may be attributed to the significantly higher burn area and full thickness burned area of patients in the high RBC transfusion group, and the larger proportion of inhalation injury. These factors have been proven to have a huge impact on the outcome of burn patients[16]. Therefore, the improvement effect of RBC transfusion on patient outcomes appears to be limited in this context. After PSM analysis, the differences in age, TBSA, and inhalation injury that affect outcomes between the two groups of patients became insignificant. However, the difference in outcomes between the two groups of patients also became insignificant. This indicates that the effect of RBC transfusion on the outcome of massive burn patients is not a simple linear relationship. In other words, with the increase of RBC transfusion, the patient outcome cannot always be improved, and sometimes there is no effect.

Additionally, the difference in blood stream infection rates between the two groups of patients is not significant. Our overall blood stream infection rate was 49.6% (188/379). Tang et al. in their multicenter retrospective study indicated high blood stream infection rate in patients with massive burn, reaching upward of

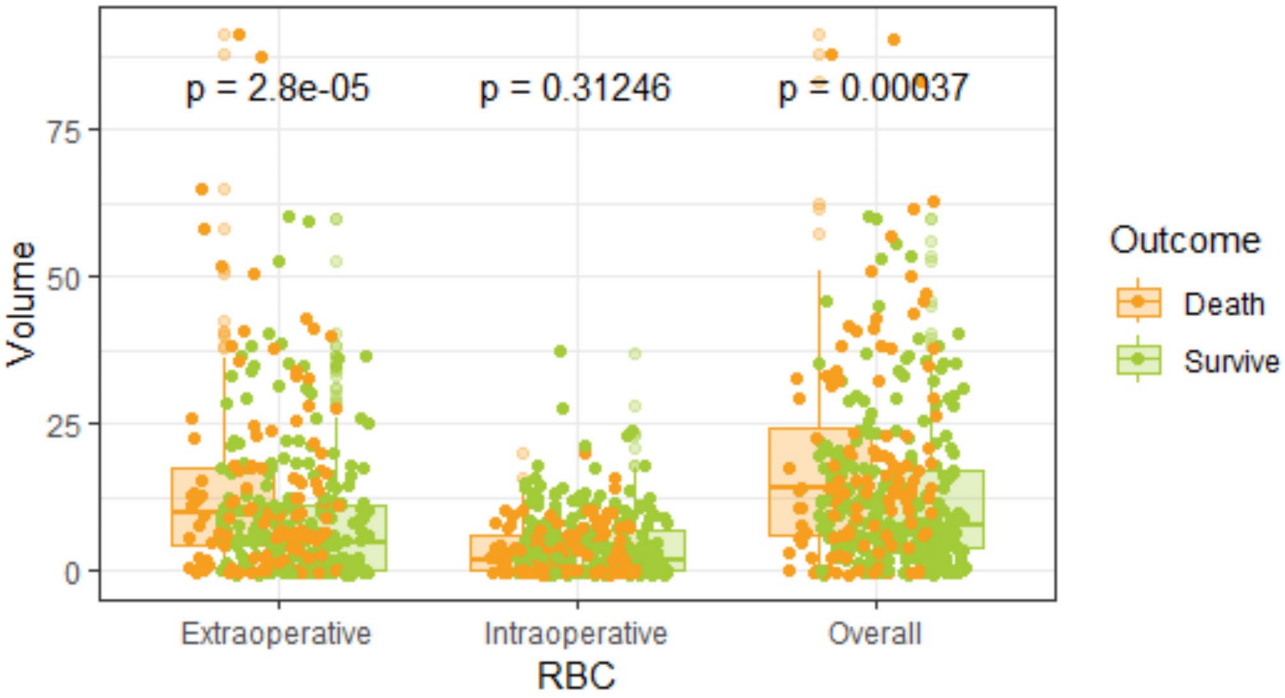

Fig. 2. The distributions of RBC transfusion volumes are represented by Box plots. The thicker line in the middle of the box is the median, the upper and lower boundaries of the box represent the third and the first quartile, and each dot represents the RBC transfusion volume of a single patient. The overall RBC transfusion volume and extraoperative RBC transfusion volume in Survive group were significantly lower than death group. RBC red blood cell.

67.8%(120/177)[17], but Hu et al. in their study reported low blood stream infection rate of 27.5%(136/495)[18].The differences in blood stream infection rates may be attributed to differences in burn area, as the larger the burn area, the higher the bloodstream infection rate[18]. The median burn area of the Tang et al. and our study were 95%TBSA and 70%TBSA, respectively. 69.1% patients had a burn area less than 60%TBSA in Hu et al. study. The larger the burn area, the longer the time for patients to completely repair the wound, and during the period when the skin barrier is not fully established, patients are always at risk of infection. High bloodstream infection rate in burn patients should be attributed to the wounds of the patients. Although bloodstream infections may occur due to transfusion of red blood cells[19], at such high levels of bloodstream infection, this effect appears to have a relatively minor impact. Surprisingly, we found a significant difference in the infection rates of Acinetobacter baumannii between the two groups of patients. This may be related to the different types of colonizing bacteria in different ICU environments and methods of infection prevention[20]. In PSM cohort, over half of (68%) the Acinetobacter baumannii-infected patients came from a single center.

We found that high RBC transfusions patients had significantly longer hospital stay, burn ICU stay and mechanical ventilation time. This is similar to previous study[6], red blood cell transfusion was an independent risk factor for length of stay and ICU stay in their study. Red blood cell transfusion can cause transfusion related lung injury[21], on the other hand, it will increase the incidence of pneumonia[22], both of which will lead to the prolongation of mechanical ventilation time of burn patients. Therefore, prolonged mechanical ventilation will lead to prolonged hospitalization and ICU time[23].

Our study has some limitations. First, three centers followed the same red blood cell transfusion strategy, but due to their locations in different regions with varying populations and economic conditions, there are differences in blood resources[24]. China has the highest volume of annual blood collection and number of volunteer donors in the world. Nonetheless, because of demographic, the blood resources in China remain in a state where demand exceeds supply, which could affect clinical blood supply, thereby impacting the RBC transfusion volume. Then, we failed to collect data on the occurrence of sepsis and septic shock in cohort patients, which, compared to blood stream infection, better reflects the severity of infection in massive burn patients. Furthermore, despite adjusting for some indicators that affect patient outcomes, we still couldn't eliminate the dynamic differences during the clinical treatment process. Thirdly, red blood cell transfusion may be influenced by clinical decisions of physicians, as in situations of tight blood resources, they may tend to allocate red blood cells to patients with more critical conditions, which may introduce bias in the transfusion volume for patients who have already reached the red blood cell threshold. Finally, burn patients often experience sepsis and elevated body temperature[25], and will experience blood transfusion at high body temperature, so we cannot collect data on transfusion related febrile reactions. In addition, because it is a retrospective study of transfusion related lung injury and allergic reactions, we also did not trace back, so our study lacks indicators of transfusion safety.

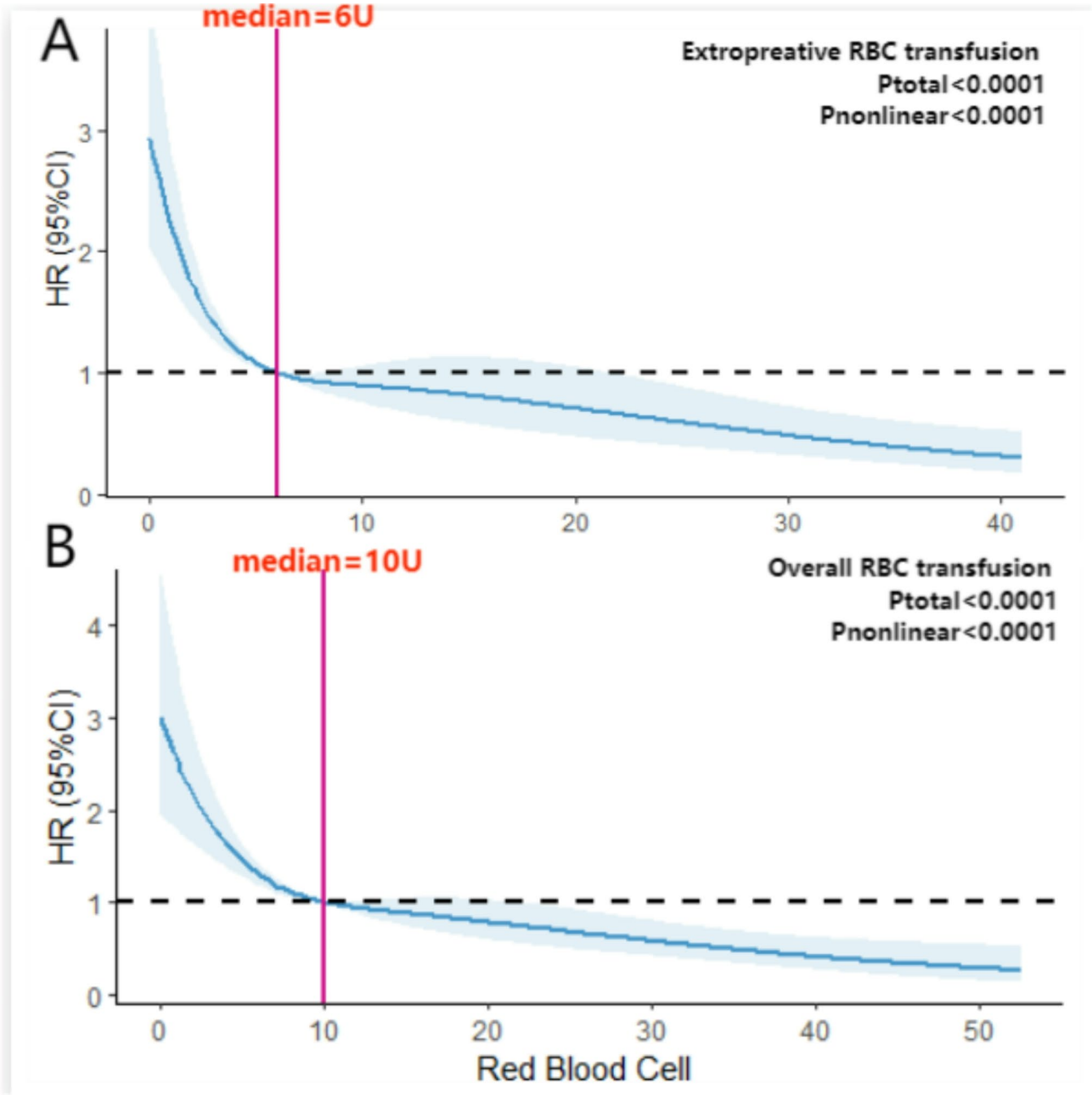

Fig. 3. association of RBC transfusion volumes with all cause mortality in massive burn patients. A: Extraoperative RBC transfusion volume and all cause mortality. B: Overall RBC transfusion volume and all cause mortality. Hazard ratios are indicated by solid lines and 95% cis by shaded areas. reference point is median of extraoperative RBC transfusion volume and overall RBC transfusion, with knots placed at 5th, 35th, 65th, and 95th centiles of each extraoperative RBC transfusion volume and overall RBC transfusion distribution.HR Hazard Risk.

Conclutions

Our findings therefore support the approach of a restrictive transfusion strategy in severely burned patients. There was no significant difference in the outcome and bloodstream infection between the two groups, but the length of stay, length of stay in burn ICU and mechanical ventilation time of the low RBC group were significantly lower than those of the high RBC group.This also confirms the scientificity of restrictive transfusion strategy and suggests that unnecessary red blood cell transfusion should be avoided in clinic.

		Overall cohort($n=379$)			PSM cohort($n=334$)		
		Low RBC transfusion($n=199$)	High RBC transfusion ($n=180$)	p	Low RBC transfusion ($n=117$)	High RBC transfusion ($n=117$)	p
Age(years)		46.92 ± 14.92	45.40 ± 13.39	0.299	46.91 ± 15.05	45.94 ± 14.10	0.613
Sex(%)	Male	152 (76.38)	120(66.67)	0.047	87 (74.36)	74 (63.25)	0.119
	Female	47 (23.62)	60 (33.33)		30 (25.64)	43 (36.75)	
TBSA burned%		66.0(55.0, 82.5)	79.50(65.0, 90.0)	< 0.0001	72.0(60.0,88.0)	71.5(60.0,84.0)	0.832
Full thickness burned area		24.0(12.5, 40.0)	46.0(29.0, 63.0)	< 0.0001	35.0(22.0,55.0)	38.0(21.0,52.0)	0.861
Inhalation injury (%)	Y	145 (72.86)	86 (47.78)	< 0.0001	71 (60.68)	68 (58.12)	0.790
	N	54 (27.14)	94 (52.22)		46 (39.32)	49 (41.88)	
smoking (%)	N	63 (31.66)	59 (32.78)	0.902	35 (29.91)	37 (31.62)	0.887
	Y	136 (68.34)	121(67.22)		82 (70.09)	80 (68.38)	
Alcohol(%)	N	58 (29.15)	60 (33.33)	0.442	31 (26.50)	41 (35.04)	0.202
	Y	141 (70.85)	120(66.67)		86 (73.50)	76 (64.96)	
Hypertension (%)	N	177 (88.94)	158(87.78)	0.847	105(89.74)	98 (83.76)	0.247
	Y	22 (11.06)	22 (12.22)		12 (10.26)	19 (16.24)	
Diabetes (%)	N	187 (93.97)	174(96.67)	0.322	114(97.44)	113(96.58)	1
	Y	12 (6.03)	6 (3.33)		3 (2.56)	4 (3.42)	
Lactate (mmol/L)		3.79 ± 2.32	4.63 ± 3.55	0.006	4.01 ± 2.41	4.66 ± 3.86	0.123
Creatinine (μmol/L)		79.17 ± 32.31	92.45 ± 46.20	0.001	80.37 ± 31.66	85.71 ± 38.73	0.249
Bilirubin(μmol/L)		19.15 ± 12.52	24.20 ± 20.93	0.004	20.81 ± 14.79	23.85 ± 21.39	0.207
Albumin(g/L)		30.78 ± 8.86	28.55 ± 8.34	0.012	31.28 ± 9.25	28.65 ± 8.32	0.023
Hemoglobin (g/dl)		16.59 ± 3.06	16.83 ± 3.30	0.461	16.74 ± 3.13	16.47 ± 3.24	0.516
Platelet		251.45 ± 132.83	284.28 ± 168.71	0.035	273.50 ± 153.01	282.40162.29	0.667

Table 2. Baseline and after PSM characteristics of patients. ① independent samples t-test ②Mann-Whitney test;③χ2-test. Data are shown as the median (25th percentile, 75th percentile), mean ± standard deviation or the number of patients (%), as appropriate. TBSA total body surface area, RBC red blood cell.

		Low RBC transfusion ($n=117$)	High RBC transfusion ($n=117$)	p
Nadir hemoglobin (g/dl)		8.0(7.03, 8.90)	6.5(5.60, 7.58)	< 0.0001①
Length of stay in burn ICU		12.00 (0.00, 24.00)	28.00 (15.00, 44.00)	< 0.0001①
Length of stay		39.00 (14.00, 60.00)	54.00 (29.00, 82.00)	0.0001①
Mechanical ventilation time		5.00 (0.00, 14.00)	14.00 (0.00, 30.00)	< 0.0001①
Outcome (%)	Death	40 (34.19)	38 (32.48)	0.8897②
	Survive	77 (65.81)	79 (67.52)	
Bloodstream infection	N	54 (46.15)	67 (57.26)	0.1165②
	Y	63 (53.85)	50 (42.74)	
Acinetobacter baumannii, (%)	N	94 (80.34)	106 (90.60)	0.0413②
	Y	23 (19.66)	11 (9.40)	
Klebsiella pneumoniae, (%)	N	87 (74.36)	98 (83.76)	0.1081②
	Y	30 (25.64)	19 (16.24)	
Pseudomonas aeruginosa (%)	N	103 (88.03)	109 (93.16)	0.2627②
	Y	14 (11.97)	8 (6.84)	
Methicillin-resistant Staphylococcus aureus (%)	N	102 (87.18)	105 (89.74)	0.6824②
	Y	15 (12.82)	12 (10.26)	
Enterobacter cloacae (%)	N	110 (94.02)	113 (96.58)	0.5368②
	Y	7 (5.98)	4 (3.42)	

Table 3. Outcome measures of high RBC transfusion group and low RBC transfusion. ①Mann-Whitney test; ②χ2-test Data are shown as the median (25th percentile, 75th percentile), mean ± standard deviation or the number of patients (%), as appropriate.

Data availability

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

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Author contributions

Y.D.: Study conception and design; acquisition, analysis, and interpretation of data; drafting the article. Y.X.: Co-supervision and critical revisions for important intellectual content. C.Y.: Critical revisions for important intellectual content. Y.W. : Provide data support and statistic analysis, D.D. Provide data support, W.X.: Provide data support, Q.X.: Provide data support, H.Z.: Provide data support, C.H.: Critical revisions for important intellectual content.

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Declarations

Competing interests
The authors declare no competing interests.

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