Original Article

Impacts of red blood cell suspension storage on pediatric outcomes: pediatric medicine and pediatric surgery

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Background: Impacts of red blood cell (RBC) suspension storage on outcomes in pediatric patients receiving RBC transfusions remains uncertain. Therefore, our objective is to examine the association between RBC storage duration and outcomes in pediatric patients.

Methods: A retrospective study was conducted on 222 patients admitted to medical and surgical departments at our center in 2021. Primary outcomes assessed were 28-day mortality and length of hospital stays, while secondary outcomes included transfusion-related complications, total volume of RBC transfusions, number of RBC transfusions, and interval between RBC transfusions. Patients were categorized into the fresh group (≤10 days) and the old group (≥21 days) based on RBC storage time.

Results: Following RBC transfusions, there was a significant improvement in post-transfusion hemoglobin, RBC counts, and hematocrit in both internal medicine and surgery departments. Among medical patients, the fresh group exhibited a shorter hospital stays compared to the old group [hazard ratio (HR) =0.677; 95% confidence interval (CI): 0.476 to 0.961; P=0.03]; however, no significant difference was observed among surgical patients. Within surgical patients, the fresh group showed longer interval between RBC transfusions (HR =2.235; 95% CI: 1.145 to 4.363; P=0.02) and required fewer number of RBC transfusions (P=0.04). No significant differences were found in hemoglobin, RBC counts, hematocrit, K^+, Ca^{2+}, lactate (Lac), and pH after RBC transfusions.

Conclusions: RBC storage was not associated with 28-day mortality in medical and surgical pediatric patients. Fresh RBC transfusions were found to reduce the length of hospital stays by 32.3% in medical patients, extend the interval between RBC transfusions by 1.235 times and decrease the number of RBC transfusions in surgical patients.

Keywords: Blood banking; blood transfusion; mortality; pediatrics

Submitted Oct 16, 2024. Accepted for publication Jan 21, 2025. Published online Feb 23, 2025.
doi: 10.21037/tp-24-433
View this article at: https://dx.doi.org/10.21037/tp-24-433

Introduction

Red blood cell (RBC) suspension, one kind of blood product, are isolated from whole blood and typically administered in cases of significant blood loos or severe anemia-related symptoms (1). In blood centers and banks, isolated RBCs are resuspended in an acidic additive solution at approximately 60% hematocrit and stored under refrigerated conditions (2–6 ℃ hypothermic storage) (2). A critical consideration in the storage of RBC products is the duration of storage, as over time they may undergo changes known as RBC storage lesions (2), encompassing alterations in cell membrane structure, metabolic waste products within the additive solution, oxygen-carrying capacity, and oxidative stress (3,4).

The association between RBC storage time and outcomes after RBC transfusion remains uncertain. Previous studies have yielded inconsistent and contradictory results, with some suggesting a potential association between longer RBC storage time and increased risk of adverse outcomes such as infection, organ failure, and mortality (5-7), while others did not confirm such associations (8,9). *In vitro* studies have reported on the pathophysiology and consequences of RBC storage; however, despite advancements in blood collection and administration safety and efficiency, it is recognized that RBCs undergo multiple metabolic and structural changes during storage that may compromise their functionality and viability post-transfusion (4). Experimental animal models have also demonstrated evidence supporting adverse consequences of RBC storage lesions, with transfusion of RBC stored for 42 days increasing mortality in dogs with experimental sepsis (10). Four randomized controlled trials (RCTs) involving patients who received RBC transfusions did not find an association between RBC storage duration and mortality or multiple organ failure (11-14), as published in the *New England Journal of Medicine*. The potential associations between RBC storage duration and infections as well as perioperative outcomes are currently being investigated (15,16), particularly among critically ill patients where the correlation appears to be more prominent (17). However, the majority of the literatures reviewed pertained to adults, with fewer studies conducted on infants and young children. Therefore, the objective of this study is to investigate the association between RBC storage and outcomes in pediatric patients. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-433/rc).

Highlight box

Key findings

- Red blood cell (RBC) storage was not associated with 28-day mortality in pediatric medical and surgical patients, but the fresh RBC transfusion was associated with shortened length of hospital stay in pediatric medical patients.

What is known and what is new?

- Association between RBC storage and mortality is still controversial. Fresh RBC transfusion is associated with shortened length of hospital stay and prolonged transfusion interval.
- RBC storage was not associated with 28-day mortality in pediatric patients. Fresh RBC (RBC stored time ≤10 days) reduced length of hospital stays by 32.3% in comparison with the old RBC transfusions (≥21 days) within medical patients, with no observed difference in surgical patients. Fresh RBC extended the transfusion interval by 1.235 times and decreased the number of RBC transfusions in comparison with the old RBC transfusions within the surgical patients, with no significant difference in medical patients.

What is the implication, and what should change now?

- Professionals from blood bank and department of blood transfusion should immediately adjust the strategy of blood issuing, to ignore RBC storage time exceeding 20 days.

Methods

Participants

This study was designed as a retrospective comparative effectiveness study (CER) and conducted at a single center. A total of 222 cases were selected from internal medical departments (including gastroenterology, neonatology, and hematology) and surgical departments (including orthopedics, general surgery, cardiothoracic surgery, neurosurgery, and oncology surgery) at Children's Hospital, Zhejiang University School of Medicine between January 1 and December 31, 2021. The eligibility criteria were as

follows.

The inclusion criteria were as follows: hospitalized pediatric patients who (I) provided informed consent for blood transfusion treatment; (II) received RBC transfusions, including leukoreduced and unleukoreduced RBC suspensions; (III) received an RBC transfusion with storage time ranging from ≤10 or ≥21 days; and (IV) had complete transfusion records.

The exclusion criteria were as follows: patients who were (I) critically ill children; (II) underwent emergency transfusions; (III) received RBC units stored between 11–20 days; or (IV) underwent multiple RBC transfusions with different storage time ranges (≤10, 11–20, and ≥21 days).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine, National Children's Regional Medical Center, National Clinical Research Center for Child Health (approval No. 2023-IRB-0197-P-01) and individual consent for this retrospective analysis was waived due to the retrospective nature.

Measurements and data collection

The exposure was designed as fresh RBC transfusion (RBC storage time ≤10 days, the additive solution: citrate, phosphate, dextrose and adenine, CPDA-1) or old RBC transfusion (≥21 days). Primary outcomes included 28-day mortality and length of hospital stays, and secondary outcomes encompassed transfusion-related complications, total volumes of RBC transfusions, number of RBC transfusions, and interval between RBC transfusions.

The 28-day mortality refers to the percentage of patients who died within 28 days after their last blood transfusion. Transfusion-related complications consist of febrile nonhemolytic reactions, chill-rigor reactions, acute hemolytic transfusion reaction (AHTR), graft-vs-host disease (GVHD), transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, altered oxygen affinity, delayed hemolytic transfusion reaction, infections, and post-transfusion purpura (18).

Two contributors were assigned to collect clinical data from the Hospital Information System (HIS) and Laboratory Information System (LIS) to minimize information bias. Propensity score matching (PSM) was employed in a 1:1 ratio to further select comparable individuals by controlling for sex, age, and department, with a match tolerance set at 0.02. The laboratory tests before and after RBC transfusion included measurements of hemoglobin, RBC counts, hematocrit, K^+, Ca^{2+}, pH, and lactate (Lac). Hemoglobin, RBC counts, and hematocrit were measured using a BC-5390 Hematology Analyzer (Mindray, Shenzhen, China), while K^+, Ca^{2+}, pH, and Lac were monitored using an ABL800 FLEX blood gas analyzer (Radiometer Medical ApS, Denmark). During this study, the laboratory analysis was processed for the same team.

Statistical analysis

Chi-squared and Fisher's exact probability tests were used to undertake bivariate tests to establish an association between the outcomes and categorical variables. Mann-Whitney *U* tests were employed for continuous variables, including before/after RBC transfusion laboratory tests and constant outcome data. Additionally, Cox regression model was used to analyze the length of hospital stays and the interval between RBC transfusions. Statistical analysis was performed using SPSS software, version 20.0 (SPSS, Chicago, IL, USA). $P<0.05$ indicated the statistical significance.

Results

Baseline characteristics

Figure 1 illustrates the cohort selection scheme, and *Table 1* presents the detailed baseline characteristics. A total of 2,100 cases were admitted to the internal medical departments (including gastroenterology, neonatology, and hematology) and surgical departments (including orthopedics, general surgery, cardiothoracic surgery, neurosurgery, and oncology surgery) at our center from January 1 to December 31, 2021. After PSM, 67 cases were recruited in the fresh and old groups within internal medicine and 44 cases each within surgery. Within internal medicine, there were 80 males (59.7%) and 54 females (40.3%), and surgery comprised 56 males (63.64%) and 32 females (36.36%). No significant differences in age or sex were observed between two groups in internal medicine and surgery (all $P>0.05$). A significant difference in distribution of ABO blood type was evident between the two groups in both internal medicine and surgery. There were no significant differences in hemoglobin levels, RBC counts, hematocrit, K^+, Ca^{2+}, Lac, or pH before or after RBC transfusion, except for Lac levels before transfusion in the internal medicine ($P=0.008$).

According to the Association for the Advancement of

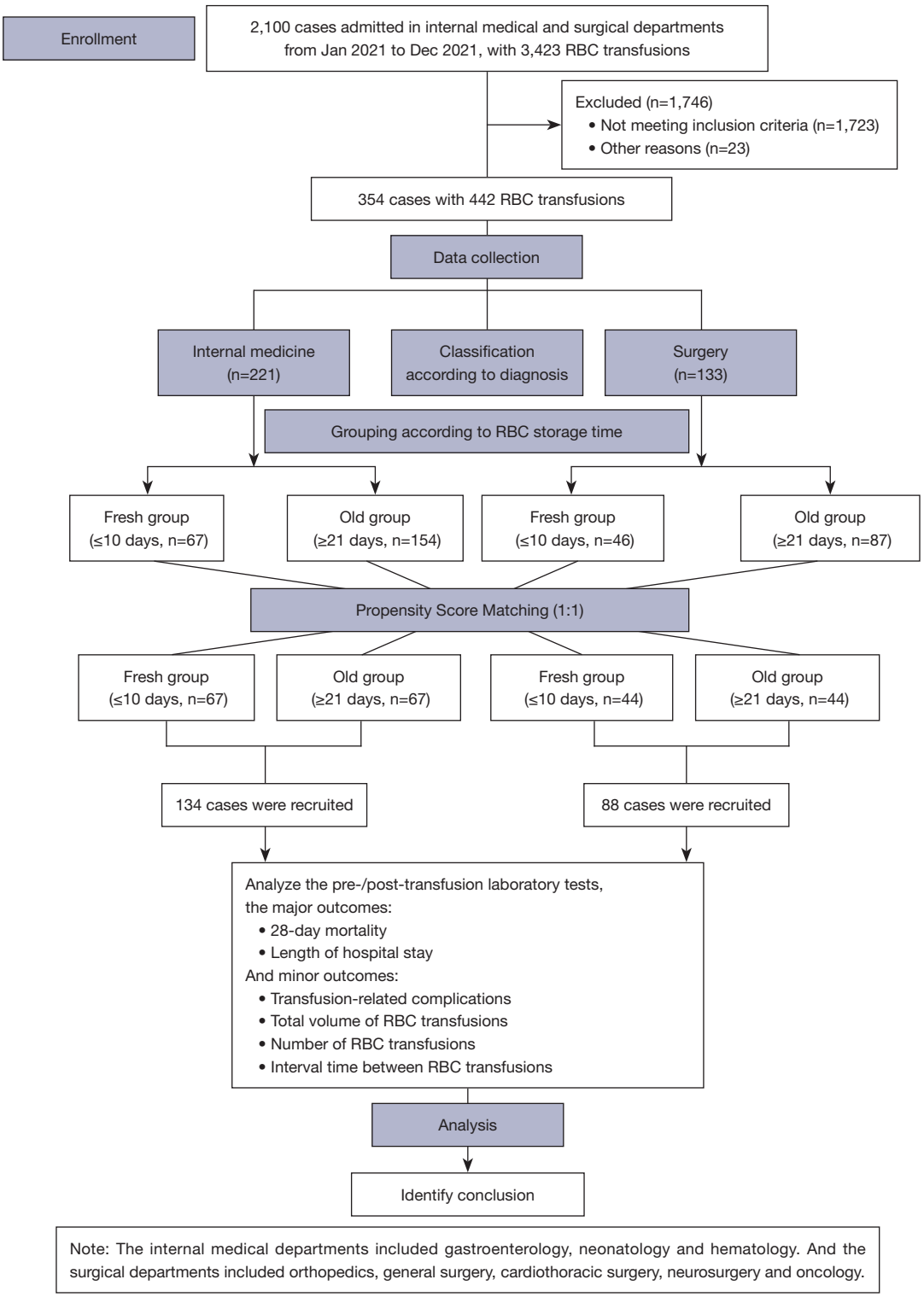

Figure 1 Flowchart of this study. According to respective departments, all patients were classified into internal medicine or surgery and further incorporated into fresh and old groups based on the storage time of transfused RBC. PSM was carried out at a 1:1 ratio, controlling for sex, age, and department. In internal medicine, 67 patients were recruited in each of the fresh and old groups, and in surgery, 44 patients were enrolled in both groups. RBC, red blood cell; PSM, propensity score matching.

Table 1 General and clinical characteristics of the study population at baseline (n=222)

Variables	Internal medicine (n=134)			Surgery (n=88)		
	Fresh group (n=67)	Old group (n=67)	P	Fresh group (n=44)	Old group (n=44)	P
Sex			>0.99			>0.99
Male	40 (59.70)	40 (59.70)		28 (63.64)	28 (63.64)	
Female	27 (40.30)	27 (40.30)		16 (36.36)	16 (36.36)	
Age (years)			0.85			>0.99
≤1	21 (31.34)	20 (29.85)		8 (18.18)	8 (18.18)	
>1	46 (68.66)	47 (70.15)		36 (81.82)	36 (81.82)	
Storage time (days)	9 [8, 10]	22 [21, 24]	<0.001	9 [9, 10]	23 [22, 24]	<0.001
Department			0.92			>0.99
Neonatology	18 (26.87)	20 (29.85)				
Gastroenterology	5 (7.46)	2 (2.99)				
Hematology	44 (65.67)	45 (67.16)				
Orthopedics				5 (11.36)	5 (11.36)	
General Surgery				3 (6.82)	3 (6.82)	
Cardiothoracic Surgery				2 (4.55)	2 (4.55)	
Neurosurgery				5 (11.36)	5 (11.36)	
Oncology Surgery				29 (65.91)	29 (65.91)	
Blood type			<0.001			<0.001
A	18 (26.87)	11 (16.41)		12 (27.27)	8 (18.18)	
B	7 (10.45)	30 (44.78)		3 (6.82)	18 (40.91)	
O	39 (58.21)	15 (22.39)		23 (52.27)	11 (25.00)	
AB	3 (4.47)	11 (16.42)		6 (13.64)	7 (15.91)	
Pre-transfusion laboratory tests						
Hemoglobin (g/L)	65 [58, 74]	67 [62.5, 78]	0.056	68 [64, 69]	66.5 [64, 69]	0.25
RBC counts ($\times10^{12}$/L)	2.11 [1.93, 2.37]	2.17 [2.02, 2.43]	0.23	2.33 [2.1, 2.59]	2.24 [2.07, 2.4]	0.20
Hematocrit (%)	19.6 [17.6, 22.35]	19.7 [18.8, 24.2]	0.25	20.6 [19.4, 21.8]	20.45 [19.1, 21.9]	0.58
K^+ (mmol/L)	4.4 [3.6, 4.65]	4.2 [3.8, 4.3]	0.37	3.85 [3.43, 4.55]	3.8 [3.45, 4.45]	>0.99
Ca^{2+} (mmol/L)	1.14 [1.01, 1.19]	1.14 [1.05, 1.25]	0.57	1.17 [1.1, 1.21]	1.25 [1.17, 1.32]	0.15
pH	7.4 [7.34, 7.48]	7.41 [7.37, 7.41]	0.94	7.44 [7.35, 7.47]	7.39 [7.33, 7.42]	0.11
Lac (mmol/L)	2.6 [2.1, 3.5]	1.8 [1.3, 2.2]	0.008	1.8 [1.13, 2.7]	1.75 [1.27, 4.93]	0.45
Post-transfusion laboratory tests						
Hemoglobin (g/L)	95 [84.75, 112]	93 [85, 111]	0.97	95 [86, 100]	92 [85, 101.75]	0.66
RBC counts ($\times10^{12}$/L)	3.07 [2.83, 3.53]	3.03 [2.72, 3.48]	0.68	3.11 [2.89, 3.6]	3.11 [2.82, 3.33]	0.25
Hematocrit (%)	28.15 [24.83, 33.23]	28 [25.65, 33.35]	0.93	28.9 [26.25, 30.6]	27.6 [24.55, 30.53]	0.33

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Internal medicine (n=134)			Surgery (n=88)		
	Fresh group (n=67)	Old group (n=67)	P	Fresh group (n=44)	Old group (n=44)	P
K^+ (mmol/L)	4.1 [3.68, 4.88]	3.95 [3.73, 4.28]	0.37	3.6 [3.5, 3.9]	3.7 [3.6, 3.9]	0.60
Ca^{2+} (mmol/L)	1.13 [1.05, 1.27]	1.15 [1.05, 1.25]	0.98	1.19 [1.14, 1.21]	1.26 [1.17, 1.28]	0.12
pH	7.41 [7.38, 7.49]	7.39 [7.36, 7.43]	0.34	7.46 [7.41, 7.47]	7.37 [7.35, 7.41]	0.08
Lac (mmol/L)	1.95 [1.05, 5.38]	1.75 [1.53, 2.2]	0.76	1.2 [1.03, 1.75]	1.4 [1.2, 1.9]	0.25

Values are presented as median [interquartile range] or n (%). Fresh group indicated that the transfused RBC storage time was equal to or less than 10 days, and old group was greater than or equal to 21 days. RBC, red blood cell; K^+, potassium; Ca^{2+}, calcium; pH, power of hydrogen; Lac, lactate.

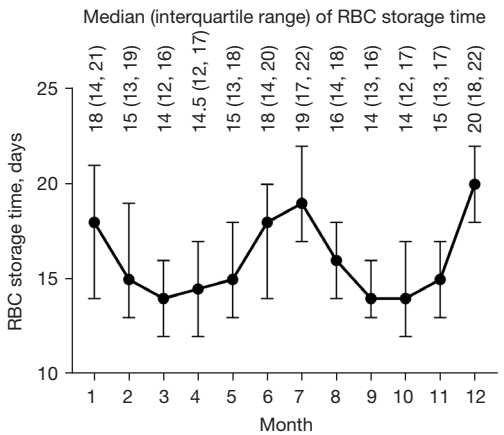

Figure 2 Distribution of transfused RBC storage time in different months of one year. The horizontal axis represents the time of transfusion, and the vertical axis denotes the duration of RBC storage in days. All the data were shown as median with interquartile range below the figure. RBC, red blood cell.

Blood & Biotherapies (AABB), RBC has a storage life of 35 days when preserved in citrate phosphate dextrose adenine (CPDA-1) solution and 42 days when preserved in saline adenine glucose mannitol (SAGM) solution (19), and the former was what we used. In this study, transfused RBC storage time ranged from 4 to 31 days, with a median storage time of 9 [8, 10] days in fresh group and 22 [21, 24] days in old group among medical patients, and 9 [9, 10] days in fresh group and 23 [22, 24] days in old group among surgical patients. The monthly distribution of transfused RBC storage time was illustrated in *Figure 2*, which showed an overall trend resembling a "W" shape, with a decrease from January to March and from July to September.

Comparisons of laboratory tests as well as major and minor outcomes in medical patients

The detailed comparisons of laboratory tests as well as primary and secondary outcomes in medical patients are presented in *Table 2*. Post-transfusion changes in hemoglobin levels, RBC counts, hematocrit, K^+, Ca^{2+}, Lac, and pH did not show statistically significant differences between the two groups. There were no occurrences of 28-day mortality or transfusion-related complications in either group. Additionally, there were no significant differences between the fresh and old groups regarding length of hospital stays, total volume of RBC transfusions, number of RBC transfusions, and interval between RBC transfusions as determined by Mann-Whitney *U* tests.

Comparisons of laboratory tests as well as major and minor outcomes in surgical patients

Table 3 presents the comparisons of laboratory tests between two groups as well as primary and secondary outcomes in surgical patients. The observed changes in all laboratory tests were not significantly different, consistent with findings in medical patients. Different to the results in the medical patients, the fresh group exhibited fewer number of RBC transfusions than the old group (P=0.04), along with a prolonged interval between RBC transfusions (P=0.03).

Associations of RBC storage with the length of hospital stays and the interval between RBC transfusions in medical and surgical patients

The Cox regression analysis presented in *Figure 3A*

Table 2 Comparisons of laboratory tests, major and minor outcomes in medical patients

Outcomes	Fresh group	Old group	H/χ^2	P
†Laboratory tests				
Hemoglobin (g/L)	30 [20, 38]	27.5 [19.25, 37]	0.301	0.76
RBC counts (×10^{12}/L)	0.97 [0.62, 1.28]	0.84 [0.58, 1.16]	0.937	0.35
Hematocrit (%)	8.9 [5.5, 10.8]	7.70 [5.7, 11.075]	0.026	0.98
K^+ (mmol/L)	−0.5 [−0.65, 0.55]	−0.1 [−0.45, 0.1]	0.068	0.95
Ca^{2+} (mmol/L)	0.02 [0, 0.145]	0.01 [−0.04, 0.055]	0.771	0.44
pH	−0.014 [−0.065, 0.013)	−0.012 [−0.046, 0.034]	0.702	0.48
Lac (mmol/L)	−1.3 [−2, 1.1]	0.2 [−0.25, 0.6]	1.111	0.27
Major outcomes				
28-day mortality			NA	NA
Yes	0 (0.0)	0 (0.0)		
No	67 (100.0)	67 (100.0)		
Length of hospital stay (days)	11 [6, 21]	13 [6, 27]	0.768	0.44
Minor outcomes				
Transfusion-related complications			NA	NA
Yes	0 (0.0)	0 (0.0)		
No	67 (100.0)	67 (100.0)		
Total volume of RBC transfusions (U)	1 [1, 2]	1.5 [1, 2]	0.138	0.90
Number of RBC transfusions (times)	1 [1, 1]	1 [1, 1]	0.779	0.44
‡Interval between RBC transfusions (days)	19 [10, 31.5]	11 [4, 31.5]	1.235	0.22

Values are presented as median [interquartile range] or n (%). Fresh group indicated that the transfused RBC storage time was equal to or less than 10 days, and old group was greater than or equal to 21 days. †, analyzed according to all RBC transfusions records; ‡, analyzed according to the patients with multiple RBC transfusions (≥2). RBC, red blood cell; K^+, potassium; Ca^{2+}, calcium; pH, power of hydrogen; Lac, lactate; NA, not applicable.

demonstrates the associations of RBC storage with the length of hospital stays and the interval between RBC transfusions in medical and surgical patients. To further investigate these relationships, we conducted Cox regression analyses with log-rank tests. In internal medicine, patients in the fresh group exhibited a shorter length of hospital stays in comparison with those in the old group [*Figure 3B*; hazard ratio (HR) =0.677; 95% confidence interval (CI): 0.476 to 0.961; P=0.03], which differed from the findings obtained using Mann-Whitney U tests as reported in result 2; while there was no significant difference in surgical patients between the two groups (*Figure 3C*; HR =1.081; 95% CI: 0.71 to 1.647; P=0.72). Within surgery, patients in the fresh group had a longer interval between RBC transfusions than those in the old group (*Figure 3D*; HR =2.235; 95% CI: 1.145 to 4.363; P=0.02); while there was no significant difference in medical patients between the two groups (*Figure 3E*; HR =1.114; 95% CI: 0.667 to 1.86; P=0.68).

Discussion

In this retrospective study of 222 pediatric patients, the length of hospital stays in the fresh group (RBC stored time ≤10 days) was found to be significantly shorter than that in the old group (≥21 days) within medical patients, with no observed difference in surgical patients. Additionally, it was found that the interval between RBC transfusions in the fresh group was longer than that in the old group within surgical patients, while no significant difference

Table 3 Comparisons of laboratory tests, major and minor outcomes in surgical patients

Outcomes	Fresh group	Old group	H/χ^2	P value
†Laboratory tests				
Hemoglobin (g/L)	23.5 [17.5, 31.25]	25 [18, 33]	0.415	0.68
RBC counts (×10^{12}/L)	0.795 [0.5425, 1.17]	0.75 [0.5825, 1.0925]	0.531	0.60
Hematocrit (%)	6.6 [5.225, 9.8]	6.9 [5, 9.85]	0.228	0.82
K^+ (mmol/L)	–0.05 [–0.45, 0.275]	–0.1 [–0.725, 0.275]	0.081	0.94
Ca^{2+} (mmol/L)	0.04 [–0.0325, 0.1125]	–0.015 [–0.0425, 0.0625]	0.803	0.42
pH	–0.023 [–0.0397, 0.068]	0.0325 [–0.0075, 0.0813]	0.961	0.34
Lac (mmol/L)	–0.65 [–1.55, 0.175]	–0.2 [–1.675, 0.25]	0.401	0.69
Major outcomes				
28-day mortality			NA	NA
Yes	0 (0.0)	0 (0.0)		
No	44 (100.0)	44 (100.0)		
Length of hospital stay (days)	12 [6.75, 20.75]	10 [5.25, 16.75]	0.635	0.53
Minor outcomes				
Transfusion-related complications			NA	NA
Yes	0 (0.0)	0 (0.0)		
No	44 (100.0)	44 (100.0)		
Total volume of RBC transfusions (U)	1 [1, 1.5]	1 [1, 1.375]	0.301	0.76
Number of RBC transfusions (times)	1 [1, 1]	1 [1, 1.5]	2.089*	0.04
‡Interval between RBC transfusions (days)	19 [7.5, 27.5]	7 [3, 13]	2.146*	0.03

Values are presented as median [interquartile range] or n (%). Fresh group indicated that the transfused RBC storage time was equal to or less than 10 days, and old group was greater than or equal to 21 days. †, analyzed according to all RBC transfusions records; ‡, analyzed according to the patients with multiple RB transfusions (≥2); *, P<0.05. RBC, red blood cell; K^+, potassium; Ca^{2+}, calcium; pH, power of hydrogen; Lac, lactate; NA, not applicable.

was observed in medical patients. Furthermore, both fresh and old RBC were found to have similar effects on short-term improvements or changes in hemoglobin levels, RBC counts, hematocrit levels, and electrolyte levels among medical and surgical pediatric patients.

We did not observe any significant associations of 28-day mortality or transfusion-related complications with RBC storage in pediatric medical and surgical patients. This finding is consistent with previous studies conducted by Lehr *et al.* (20-22). RBC storage induces progressive biochemical, biomechanical, and immunologic changes that impact cell membrane structure, viability, deformability, oxygen-carrying capacity, microcirculatory flow, and recipient response (10). Potential clinical consequences associated with transfusing RBC after the development of storage lesions include the risk of organ dysfunction, organ failure, infections, and death (10). These concerns contribute to the numerous potential adverse effects associated with RBC transfusion therapy; furthermore, the risk of harmful impacts increases as storage time extends (23). Experimental studies have characterized the evolution of human RBC and supernatant changes that occur during storage and form the basis for concern about the potential for harm from long-term storage of RBC. In a double-blind RCT, Fergusson announced that the use of fresh RBCs (stored for 7 days or less) compared with standard blood bank practice did not improve outcomes in premature, very low-birth-weight infants requiring a transfusion, including major neonatal morbidities (necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia,

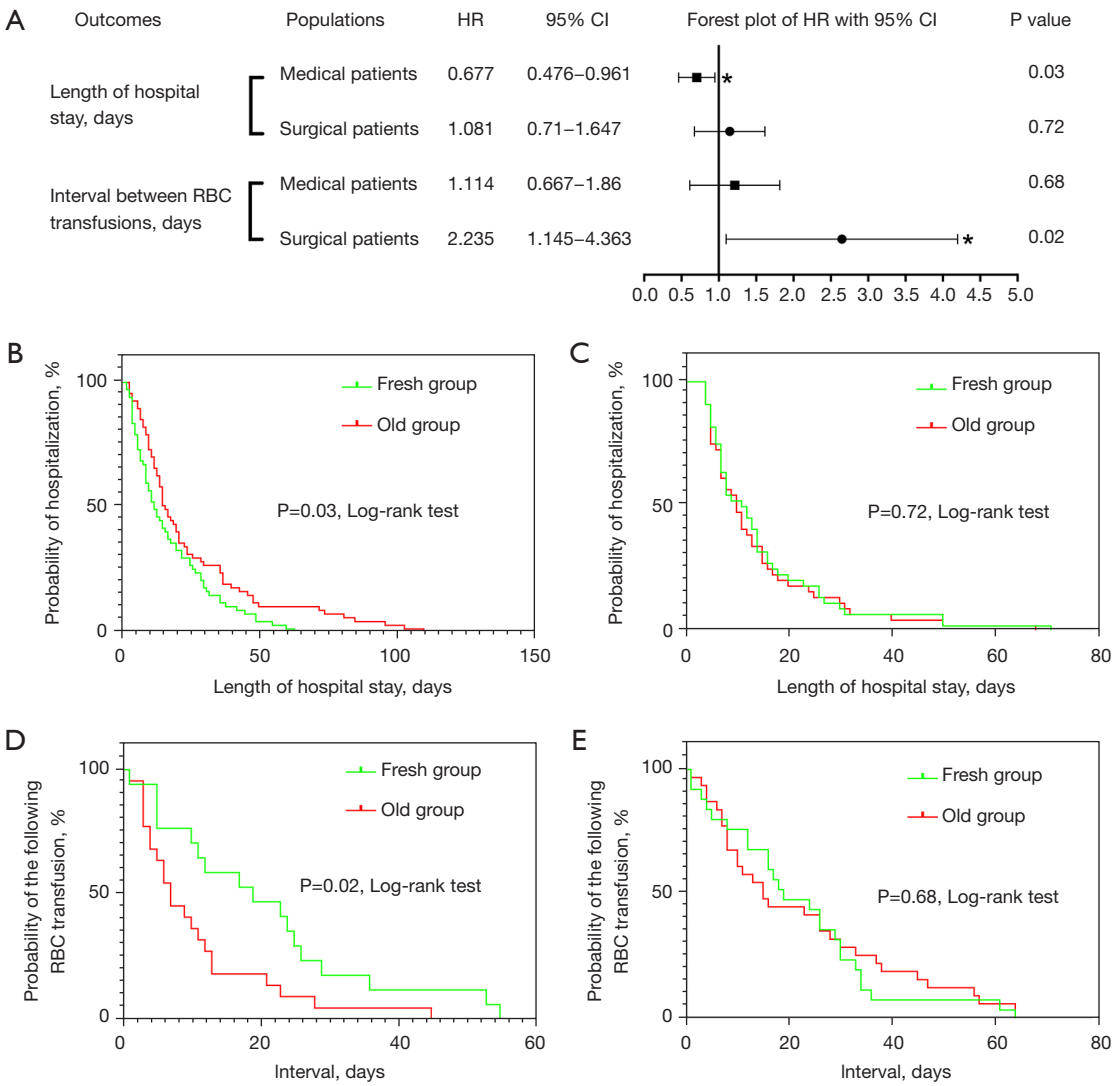

Figure 3 Association of RBC storage with length of hospital stay and interval between RBC transfusions in pediatric medical and surgical patients. (A) Cox regression analysis on length of hospital stay and interval between RBC transfusions in medical and surgical patients. The comparisons of length of hospital stay between fresh and old groups (B) in medical patients (HR =0.677, 95% CI: 0.476 to 0.961, P=0.03) and (C) in surgical patients (HR =1.081, 95% CI: 0.71 to 1.647, P=0.72). The comparisons of interval between RBC transfusions between fresh and old groups (D) in surgical patients (HR =2.235, 95% CI: 1.145 to 4.363, P=0.02) and (E) in medical patients (HR =1.114, 95% CI: 0.667 to 1.86, P=0.68). *, P<0.05. RBC, red blood cell; HR, hazard ratio; CI, confidence interval.

and intraventricular hemorrhage, as well as death) and rate of nosocomial infection as a secondary outcome (24). However, the designed group (fresh RBCs *vs.* standard-issue RBCs) was incompletely identical to that in our study (fresh RBCs *vs.* older RBCs). The INFORM study, a large RCT conducted across Australia, Canada, Israel, and the USA, aimed to compare the impact of younger versus older RBC units on in-hospital mortality among hospitalized patients. The research findings suggested that transfusion with younger RBC leads to better outcomes than standard issue RBC units (12,25). In another RCT study published in *JAMA*, Spinella *et al.* found that fresh RBC did not reduce the incidence of new or progressive multiple organ dysfunction syndrome, including mortality (26).

We observed that the length of hospital stays in the fresh group was shorter than that in the old group within medical patients (HR =0.677; 95% CI: 0.476 to 0.961; P=0.03); however, there were no significant differences

in surgical patients (HR =1.018; 95% CI: 0.71 to 1.647; P=0.72). Additionally, we discovered that longer RBC storage shortened the interval before the following RBC transfusion (HR =2.235; 95% CI: 1.145 to 4.363; P=0.02) and increased the number of RBC transfusions (P=0.04) in surgical patients, but there were no significant differences in medical patients (HR =1.114; 95% CI: 0.667 to 1.86; P=0.68, and P=0.44). The greater iatrogenic blood loss may cover the lack of significant differences in the latter two outcomes in medical patients. Approximately 20.9% of patients admitted to an internal medicine unit developed anemia during the hospital stays; the maximum drop-in hemoglobin value due to the phlebotomy was 26 g/L (27). There were no significant differences between the two groups in internal medicine or surgery regarding the total volume of RBC transfusions. In addition to the above findings, we observed in medical and surgical patients that hemoglobin, RBC counts, and hematocrit increased significantly after RBC transfusion in both the fresh and old groups but presented no significant differences in the post-transfusion laboratory tests between the two groups. Actually, except for the hemoglobin, RBC counts, and hematocrit, RBC deformability has been recognized as a sensitive indicator of RBC functionality (28). The high deformability of RBC allows them to pass through small blood vessels and significantly determines the survival of RBC. However, RBC gradually lose their deformability under cold storage conditions, and this alteration could influence their after-transfusion performance (28-30). The general implication from most of the cited publications is that cell deformability begins to decrease after 14–21 days of storage (28,31). Recently, there is an interesting study in which Huang *et al.* conducted a retrospective study in premature infants with anemia, whose increased hemoglobin levels were associated with different intervals, and an interval of 1 week had the most significant effect (32). This study may provide evidence in support of a new approach to elevate hemoglobin levels in premature infants during the blood transfusion process.

Khan *et al.* announced that transfusing RBC units stored for 28 days or longer may be associated with increased mortality in patients undergoing hip fracture or coronary artery bypass grafting (CABG) in two surgical cohorts (33). Goel *et al.* indicated that RBC transfused within the last 7 days (≥35 days) of their 42-day storage limit could be associated with adverse clinical outcomes, including morbidity and mortality, in high-risk patients (17). However, in the other particular diseases, some different statements announced that transfusion of fresher RBCs is not associated with decreased risk of death in surgical critically ill adults (20), obstetric inpatients (21), and pediatric cardiac surgery patients (22), but is associated with higher rates of transfusion reactions and potentially infections (34), particularly wound infections (35). In our study, the storage life of RBC suspension was 35 days, and the old group we defined had a storage time equal to or greater than 21 days, which was comparatively fresher than the previously mentioned reports based on a 42-day storage limit.

The need for RBC transfusions in surgical patients has traditionally been considered as temporary, as patients typically exhibit normal hematopoietic function and have no acute or chronic wasting diseases. However, patients admitted to internal medicine units often present with clinical wasting diseases, such as fever, infections, tumors, hematopoietic system abnormalities, and blood system diseases, requiring long-term blood transfusions compared to those in surgery departments (36). This study found that fresh RBC transfusions reduced the length of hospital stays by 32.3% in medical patients and extend the interval between RBC transfusions by 1.235 times in comparison with old RBC transfusions in surgical patients. Given the limited storage time of RBC suspensions, it is crucial for blood centers and blood banks to maintain an adequate supply through regular donations from eligible donors (37). However, maintaining a proper supply can sometimes be a challenging process. As a result, some blood banks may prioritize issuing old RBC products to patients who may require a higher level of oxygen-carrying capacity (7), especially during periods of decreased blood supply. But it may be important to note that professionals from blood bank and department of blood transfusion should immediately adjust the strategy of blood issuing, to ignore RBC storage time exceeding 20 days.

Strengths and limitations

Our methodology was developed to address populational bias by employing PSM to balance the ratio of patients admitted to various departments. In addition to primary outcomes (i.e., mortality and length of hospital stays), we also analyzed the secondary outcomes that may be overlooked by clinical practices, including transfusion-related complications, total volumes of RBC transfusions, number of RBC transfusions, and intervals between RBC transfusions. In this study, the distribution of ABO blood

group was unbalanced among the two groups. However, the specific association between ABO blood groups and the efficacy of transfusion has hitherto not been reported in any comprehensive or an individual study. Due to exclusion criteria resulting in most cases being excluded and only a small number of subjects being enrolled in our cohort study design, critically ill pediatrics were excluded, resulting in the association with the severity of patients cannot be fully illustrated in this paper and no mortalities or transfusion-related complications were observed within our study cohort. Therefore, we cannot provide additional support for establishing a relationship between 28-day mortality or transfusion-related complications and storage duration of RBC. Consequently, despite these results, the transfusion of older RBC suspensions has been safe. There may be insufficient compelling evidence to change current practices regarding long-term storage RBC use, even within a pediatric population.

Conclusions

In conclusion, RBC storage was not associated with 28-day mortality in pediatric medical and surgical patients. Fresh RBC transfusions were found to reduce the length of hospital stays by 32.3% in medical patients, extend the interval between RBC transfusions by 1.235 times and decrease the number of RBC transfusions in surgical patients. Both medical and surgical patients appeared to derive greater benefits from fresher RBC suspensions as opposed to older ones. However, considerable heterogeneity among different studies, including the various definitions of fresh or old/aged RBC and variations in subjects diagnosed with other diseases belonging to internal medicine or surgery, led to a poorly understood situation. Therefore, more comprehensive and precise studies or research guidelines are urgently needed.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-433/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-433/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-433/prf

Funding: This work was supported by the Key R&D Program of Zhejiang (No. 2023C03029).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-433/coif). All authors report funding from the Key R&D Program of Zhejiang (No. 2023C03029). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine, National Children's Regional Medical Center, National Clinical Research Center for Child Health (approval No. 2023-IRB-0197-P-01) and individual consent for this retrospective analysis was waived due to the retrospective nature.

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Cite this article as: Yin M, Bai G, Zhong Y, Ma J, Tian D, Guo X, Zhou C, Chen B, Chen X, Gao Z. Impacts of red blood cell suspension storage on pediatric outcomes: pediatric medicine and pediatric surgery. Transl Pediatr 2025;14(2):187-199. doi: 10.21037/tp-24-433