



Evaluation of the Incidence and Predictor Factors for Red Blood Cell Transfusion in the Mechanically Ventilated Children

Mekanik Ventilasyon Uygulanan Çocuklarda Eritrosit Transfüzyonu Sıklığı ve Belirleyici Etmenlerin Değerlendirilmesi

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¹Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Child Intensive Care Unit, İstanbul, Turkey

²University of Health Science, Okmeydanı Training and Research Hospital, Clinic of Child Hematology - Oncology, İstanbul, Turkey

³University of Health Science, Okmeydanı Training and Research Hospital, Clinic of Child Intensive Care, İstanbul, Turkey

⁴University of Health Science, Okmeydanı Training and Research Hospital, Clinic of Pediatric Emergency Medicine, İstanbul, Turkey

Abstract

Introduction: Transfusion of blood components, including red blood cells (RBC), platelets and plasma, is the fastest way to improve the haematological state of critically ill patients and can be a lifesaving intervention. Although transfusion is a common practice in paediatric intensive care units (PICUs), its adverse effects are not clearly defined. Therefore, we aimed to evaluate the incidence and predictors of RBC transfusion in mechanically ventilated children.

Methods: Data of patients admitted to PICUs from January 2014 to April 2019 were extracted. The mechanically ventilated patients were categorised into two groups, and the relationship between transfusion and prognostic factors was examined.

Results: This study investigated 373 children with a mean age of 3.86±4.86 years. Among these children, 239 received RBC transfusion (64.1%). Inotropic drug usage, acute kidney injury, continuous renal replacement therapy (CRRT), mortality, length of mechanical ventilation, and duration of PICU stay were associated with RBC transfusion. Logistic regression analysis revealed that inotropic drug usage increased the RBC transfusion requirement by 5.168 fold, and CRRT increased it by 2.804 fold.

Conclusion: Blood transfusion is an associated adversity in critically ill children. Therefore, patients who need transfusion should be followed up more carefully and closely.

Keywords: Pediatric intensive care unit, red blood cell, transfusion, mechanical ventilation

Öz

Giriş: Eritrosit, trombosit ve plazma dahil olmak üzere kan bileşenlerinin transfüzyonu, kritik hastaların hematolojik durumunu iyileştirmenin en hızlı yoludur ve yaşam kurtarıcı bir girişim olabilir. Transfüzyon, çocuk yoğun bakım ünitelerinde (ÇYBÜ) yaygın bir uygulama olmasına rağmen, yan etkileri açıkça tanımlanmamıştır. Bu nedenle mekanik ventilasyon uygulanan çocuklarda eritrosit süspansiyonu transfüzyonu sıklığını ve belirleyici etmenlerini değerlendirmeyi amaçladık.

Yöntemler: ÇYBÜ'ye Ocak 2014-Nisan 2019 tarihleri arasında başvuran hasta verileri toplandı. Mekanik ventilasyon uygulanan hastalar iki gruba ayrıldı ve transfüzyon ile prognostik faktörler arasındaki ilişki incelendi.

Bulgular: Yaş ortalaması 3,86±4,86 yıl olan toplam 373 çocuk incelendi. Bu çocukların 239'u eritrosit süspansiyonu transfüzyonu aldı (%64,1). İnotropik ilaç kullanımı, akut böbrek hasarı, sürekli böbrek replasman tedavisi (SRRT), mortalite, mekanik ventilasyon süresi ve PYB'da kalma süresi, eritrosit süspansiyonu transfüzyonu ile ilişkilendirildi. Lojistik regresyon analizi, inotropik ilaç kullanımının eritrosit süspansiyonu transfüzyon gereksinimini 5.168 kat, SRRT kullanımını 2.804 kat artırdığını göstermiştir.

Sonuç: Kan transfüzyonu, kritik hasta çocuklarda daha kötü prognoz ile ilişkilidir. Bu nedenle transfüzyona ihtiyaç duyan hastaların daha dikkatli ve yakından takip edilmeleri gerektiği unutulmamalıdır.

Anahtar Kelimeler: Çocuk yoğun bakım ünitesi, eritrosit, transfüzyon, mekanik ventilasyon

Yazışma Adresi/Address for Correspondence: Fatih Aygün, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Child Intensive Care Unit, İstanbul, Turkey

E-posta: faygun9@hotmail.com **ORCID ID:** orcid.org/0000-0001-6519-6583

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Introduction

Pediatric intensive care units (PICUs) are units where life-threatening organ insufficiencies and diseases can be closely monitored and interventions can be performed rapidly. Patients in the PICU are at high risk of developing life-threatening alterations in hemostasis. Red blood cell (RBC) transfusion is the fastest way to improve the hematological state in critical patients and can be a lifesaving intervention. It has been reported that almost half of the patients who need intensive care for more 48 hours require transfusion.¹ Anemia secondary to poor nutrition, underlying disease, iatrogenic blood loss, hemodilution and diminished bone marrow response is a common hematological finding in critically ill patients.^{2,3} The incidence of anemia can be as high as 74% in PICU patients and transfusion of these patients is reported to have worse outcomes.⁴ However, there have been insufficient studies investigating RBC transfusion in pediatric patients. Therefore, in the present study, we aimed to evaluate incidence and predictor factors for RBC transfusion in the mechanically ventilated children.

Materials and Methods

Study Design

Healthcare was provided to children aged <18 years in two PICUs. The first center was equipped with 7 beds, 7 ventilators, 2 isolation rooms, and 2 high flow machines. The second center was a tertiary, multidisciplinary PICU located in a training and research hospital in İstanbul, Turkey, having 12 beds, 2 isolation rooms, 10 ventilators, and 5 high flow machines. The patient data admitted to the PICUs from January 2014 to April 2019 were extracted from both electronic and written medical records (conforming to the ethical principles for medical research), and we included patients who received NIV in this study (Figure 1).

We excluded the patients with a history of PICU stay lasting less than 24 hours, who died on the first day of admission and with incomplete data. Ethical approval with waiver of consent was obtained from each institution that approved the study (Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee, ethical committee no. 29430533903.99-113999, August 2019). All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki of 1975, revised in 2013.⁵

We recorded all materials, data, computer codes, and protocols associated with the publication for readers.

Patient Population and Data Collection

The patients' gender, diagnosis at admission, age, acute kidney injury (AKI) during PICU stay, inotropic drug usage, continuous

renal replacement treatment (CRRT), length of mechanical ventilator usage and intensive care unit stay, pediatric risk of mortality (PRISM) score, number of patients administered RBC transfusion, transfusion sessions, and mortality were investigated (Table 1).

We divided the patients two groups according to RBC transfusion during MV usage. We compared these two groups in terms of prognostic and laboratory results (Table 2).

The PRISM score was calculated using the lowest and highest systolic blood pressure values during the first 24 hours for each patient and the diastolic blood pressure, heart rate and respiratory rate per minute, PaO₂/FiO₂, PaCO₂, calcium, potassium, glucose, bicarbonate level, pupillary response, Glasgow Coma score, prothrombin time-partial thromboplastin time, and serum total bilirubin.⁶

Acute kidney injury was defined as oliguria (urine output <0.5 mL/kg/h) and increased serum creatinine level based on the patient's age or 1.5-fold increase in basal creatinine level within 24 hours. The estimated glomerular filtration rate was calculated according to the original Schwartz formula. Additionally, when measuring serum urea and creatinine levels, the glomerular filtration rate was measured routinely by our laboratory using a scale.

Mechanic Ventilator Devices and Equipment

We used Maquet Servo-i® and Servo-u® (Maquet Critical Care, Solna, Sweden) as ventilators. All ventilators of the first center were Servo-i®. There were six Servo-i® and four Servo-u® in the second center. The MR850 (Fisher Paykel Healthcare, Auckland, New Zealand) was used as a humidifier in our study. All patients were continuously monitored during MV usage.

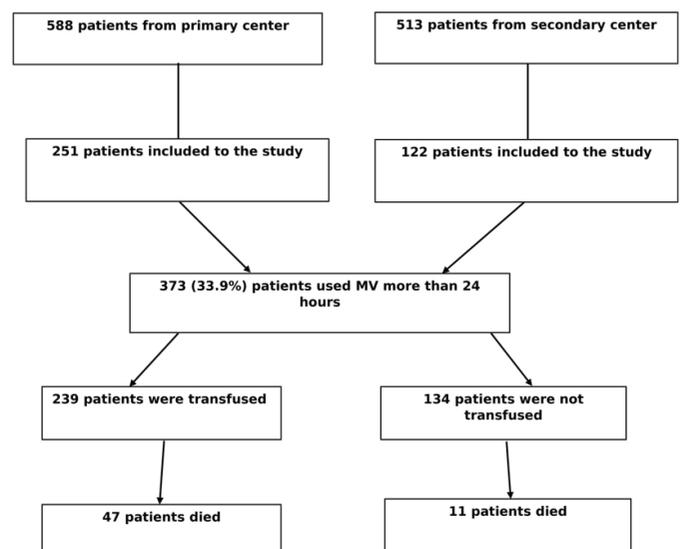


Figure 1. Cohort flow

Criteria of Transfusion

In this study, restrictive RBC transfusion policy was used. The threshold hemoglobin value was 7 g/dL for stable patients that had no shock symptoms and didn't need inotropes, high oxygen, high ventilator support. The patients having major surgery, intracranial pathology, shock, gastrointestinal hemorrhage, heart failure, and similar situations were transfused if they had hemoglobin ≤ 10 g/dL.

Laboratory Analysis

The initial hemogram and biochemical results were recorded. For measurement of hemogram and biochemistry, peripheral blood was collected into vacutainer tubes.

Statistical Analysis

We used the IBM SPSS 21.0 (version 21.0; IBM Corp., Armonk, NY, USA) software to perform statistical analysis. Continuous and categorical data were expressed as median (range) and number (percentage), respectively. We compared the continuous variables using Student's t-test and Mann-Whitney U test for parametric and non-parametric data, respectively. Categorical variables were compared using chi-squared test or Fisher's exact test. Multivariate binary logistic regression models were used to calculate the relationship between risk factors and RBC transfusion in mechanically ventilated patients reported as ORs and 95% Cis. The receiver-operator characteristic (ROC) curve was used to assess the RBC transfusion and laboratory findings. For all tests, $p < 0.05$ was considered to be statistically significant.

Table 1. Demographic characteristics of patients

Number of patients	n=373 (%) / Mean \pm SD
Sex (Male)	203 (54.4%)
Respiratory tract disorders	114 (30.6%)
Neurologic and metabolic diseases	101 (27.1%)
Septicemia	62 (16.6%)
Cardiovascular disease	28 (7.5%)
Hematology-oncology	32 (8.6%)
Others	36 (9.7%)
Age (years)	3.86 \pm 4.86
Acute kidney injury	132 (35.4%)
Inotropic drug usage	176 (47.2%)
Continuous renal replacement treatment (CRRT)	58 (15.5%)
Length of mechanical ventilator usage (day)	8.84 \pm 13.74
Length of pediatric intensive care unit stay (day)	13.90 \pm 16.91
PRISM score	18.16 \pm 14.54
Mortality	58 (15.5%)
Number of patients administered RBC transfusion	239 (64.1%)
Number of RBC transfusion sessions	507
PRISM: Pediatric Risk of Mortality, RBC: Red blood cell, CRRT: Continuous renal replacement treatment	

The cut-off and area under the curve (AUC) values were interpreted using the ROC analysis in accordance with the methods of Dirican⁷. An AUC value of 0.5 corresponded to random chance, and an AUC value of 1.0 indicated perfect accuracy of the ROC curve.^{8,9}

Results

Cohort flow

Of the 1101 children admitted to the PICUs, 588 patients were from the primary center and 513 from the secondary center. We included 373 for this study. Of them, 239 patients were transfused. Patient mortality was 19.7 % (47 patients) in transfused group (Figure 1).

Demographics

We selected 373 patients for the present study with 203 (54.4%) boys and 170 (45.6%) girls. Their ages were distributed between 1 month and 17.8 years, with a mean 3.86 \pm 4.86 years. The most frequent diagnosis at admission was primary respiratory disease and disorders (30.6%), followed by neurologic or metabolic diseases (27.1%). Respiratory system diseases were most commonly lower respiratory tract infections such as bacterial or viral pneumonia. The mean duration of intensive care unit stay was 13.90 \pm 16.91 days. Mean MV duration was 8.84 \pm 13.74 days. AKI developed in 132 (35.4%) patients while in PICU, and 58 (15.5%) of these patients underwent CRRT, while others received supportive treatments. We treated 176 (47.2%) patients with inotropic drugs. Mean PRISM score was 18.16 \pm 14.54 and mortality rate was 15.5% (58 patients). Number of patients administered RBC transfusion was 217 (58.7%) (Table 1).

Relationship Between RBC Transfusion and Prognostic Factors in MV Patients

There was a statistically significant relationship between RBC transfusion and each of the following: inotropic drug use ($p < 0.001$), CRRT ($p < 0.001$), AKI ($p < 0.001$), mortality ($p = 0.003$), length of MV usage ($p < 0.001$), length of stay in PICU ($p < 0.001$), and PRISM scores ($p < 0.001$) (Table 2). The initial calcium ($p < 0.001$), mean platelet volume (MPV) ($p = 0.016$), alanine transaminase (ALT) ($p < 0.001$), aspartate aminotransferase (AST) ($p < 0.001$), prothrombin time (PT) ($p = 0.019$), international normalised ratio ($p = 0.028$), lactate dehydrogenase (LDH) ($p < 0.001$), hemoglobin ($p < 0.001$), uric acid ($p = 0.003$), and platelet count ($p = 0.013$) were significantly different in the group receiving blood component transfusion (Table 2).

Logistic Regression Analysis of Risk Factors for RBC Transfusion

Odds ratios of RBC transfusions were 1.341 [95% confidence interval (CI), 0.707-2.543] for AKI; 2.804 (95% CI, 1.069-

7.357) for CRRT; 5.168 (95% CI, 2.865-9.324) for inotropic drug usage; 1.273 (95% CI, 0.555-2.920) for mortality (Table 3).

Analysis of Laboratory Findings by ROC Analysis for RBC Transfusion in the Mechanically Ventilated Patients

The analysis of ROC curves revealed that an PRISM score with a cut off value of 11.5 had a sensitivity of 73.3% and a specificity of 60.0%. Additionally, the lower hemoglobin

value had a 74.5% sensitivity and 59.4% specificity (cut off: 9.95), the lower platelet counts a 63.6% sensitivity and 54.3% specificity (cut off: 267,500), the MPV value a 63.6% sensitivity and 48.5% specificity (cut off: 8.3), AST a 70.9% sensitivity and 55.4% specificity (cut off: 32.5), ALT a 69.6% sensitivity and 51.2% specificity (cut off: 18.5), LDH a 67.5% sensitivity and 52.9% specificity (cut off: 331.5) (Table IV). The relationships between the laboratory findings and RBC transfusion are presented in Figures 2.

Table 2. Evaluation of blood component transfusion and the prognostic factors

	RBC transfusion during the MV		p	
	Yes (n=239), Median (min-max)	No (n=134) Median (min-max)		
Sex (Male)	130 (51.1%)	73 (51.2%)	0.987	
Age, year	1.0 (31 days - 17.58)	2.0 (33 days - 16.50)	0.192	
Inotropic drug usage	149 (72.3%)	27 (48.8%)	<0.001	
Continuous renal replacement treatment	52 (78.7%)	6 (47.9%)	<0.001	
Acute kidney injury	108 (95.7%)	24 (71.1%)	<0.001	
Mortality	47 (29.8%)	11 (9.1%)	0.003	
Length of MV usage	6.0 (28 h - 110 d)	3.0 (26 h - 28 d)	<0.001	
Duration of stay in PICU	11.0 (28 h - 122 d)	4.5 (26 h - 35 d)	<0.001	
PRISM score	17 (6 - 58)	8 (4-65)	<0.001	
Length of mechanical ventilator usage				
<2 days	42 (17.6%)	64 (47.7%)	<0.001	
2-7 days	102 (42.7%)	52 (38.8%)		
>7 days	95 (39.7%)	18 (13.4%)		
Respiratory tract disorders	68 (28.5%)	46 (34.3%)	0.013	
Neurologic-metabolic diseases	57 (23.8%)	44 (32.8%)		
Septicemia	52 (21.8%)	10 (7.5%)		
Cardiovascular disease	18 (7.5%)	10 (7.5%)		
Hematology-oncology	22 (9.2%)	10 (7.5%)		
Other	22 (9.2%)	14 (10.4%)		
Laboratory findings	Sodium (mmol/L)	139.0 (111.0-182.0)	140.0 (128.0-173.0)	0.174
	Chlorine (mmol/L)	102.0 (75.8-150.0)	102.0 (92.0-126.0)	0.752
	Calcium (mg/dL)	9.0 (5.1-11.8)	9.4 (4.4-11.2)	<0.001
	MPV	8.7 (4.8-13.0)	8.3 (6.1-11.7)	0.016
	RDW	15.7 (5.5-36.2)	15.1 (11.9-27.4)	0.094
	ALT (IU/L)	29 (5-1816)	17 (4-203)	<0.001
	AST (IU/L)	47 (6-1895)	30 (6-695)	<0.001
	Prothrombin time (s)	14.5 (11.3-82.0)	13.1 (10.8-35.8)	0.019
	aPTT (s)	35.1 (18.8-142.2)	32.7 (19.8-118.0)	0.116
	INR	1.21 (0.90-5.40)	1.00 (0.90-2.80)	0.028
	LDH (IU/L)	423 (112-5424)	328.5 (120-1180)	<0.001
	CRP (ml/dL)	3.6 (0.10-405.9)	2.0 (0.05-239.4)	0.163
	Leucocyte count (mm ³)	11100 (130-31300)	12200 (200-111800)	0.980
	Haemoglobin (g/dL)	9.5 (3.6-19.3)	11.2 (5.4-15.9)	<0.001
	Uric acid (mg/dL)	3.6 (0.6-17.8)	3.4 (0.5-13.8)	0.003
Platelet count (10 ³ /μL)	244.9 (6-84)	307 (33-742)	0.013	

RBC: Red blood cell, MV: Mechanical ventilation, PICU: Pediatric intensive care unit, PRISM: Pediatric risk of mortality, MPV: Mean platelet volume, RDW: Red blood cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine transaminase, aPTT: Active partial thromboplastin time, INR: International normalised ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein, min: Minimum, max: Maximum

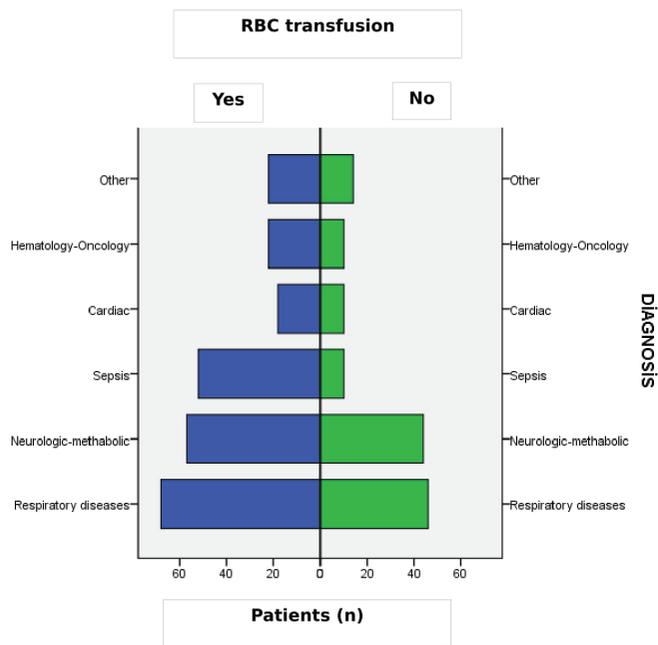


Figure 2. Correlation between the admission diagnosis and RBC transfusion rate
RBC: Red blood cell

Discussion

This retrospective study describes several associations between RBC transfusions and clinical outcomes in mechanically ventilated children. Inotrope drug usage, AKI, CRRT, and mortality were higher in the patients undergoing RBC transfusion. However, logistic regression analysis showed that RBC transfusion was only associated with CRRT and inotrope drug usage. The most significant relationship with RBC transfusion was determined by inotropic drug use. In addition, the initial liver enzymes and anemia were associated RBC transfusion. The patients who received RBC transfusion during the PICU stay had higher PRISM score and lower initial hemoglobin than non-transfused patients.

The indications of blood product transfusion in pediatric patients are similar with adults, however, the settings of transfusion guidelines change according to age and body weight of the child. The RBC suspension administration is frequently used in PICUs. Approximately 15-23% of patients in PICU need to receive RBC suspension at least once and the rate can increase to 50% for patients who have hospitalization more than 48 hours.^{1,4,10}

The RBC suspension is commonly administered to improve oxygenation in pulmonary deficiencies during hypoxemia. However, the immunomediators released after the RBC transfusion can cause pulmonary damage and clinical deterioration in critically ill patients.^{11,12} Thus, the duration of mechanical ventilation increases. Similar to the previous reports the duration of stay in PICU and the duration of

MV usage were higher in our patients who used to receive RBC transfusion. As seen in Figure 3, the frequency of RBC transfusion increased significantly after 48 hours. In addition, transfusion was performed in the majority of the patients who were ventilated more than 7 days. In an adult study showed that RBC transfusion was used 51% in patients who stayed more than 7 days.¹² Unlike this study, we were included children who only used have MV in our study. Therefore, our RBC transfusion rate can be higher compared to literature. The transfusion rate was 84.1% in patients who had ventilation more than 7 days.

The frequency of transfusion was significantly higher in the sepsis group. As shown in Figure 2, 52 of 62 patients with sepsis had RBC transfusion. There are several reasons for this result. Much more blood sampling is performed in patients with sepsis and close laboratory follow-up is required. Extracorporeal support such as CRRT and plasma exchange are used for organ failure during sepsis. In addition, as indicated in the Survival Sepsis Campaign, it was recommended to

Table 3. Logistic regression analysis of RBC transfusion for prognostic factors in the mechanical ventilated children

Risk factors	p value	Odds ratio	95% confidence interval
Acute kidney injury	0.368	1.341	0.707-2.543
Continuous renal replacement therapy	0.036	2.804	1.069-7.357
Inotropic drug usage	<0.001	5.168	2.865-9.324
Mortality	0.570	1.273	0.555-2.920

RBC: Red blood cell

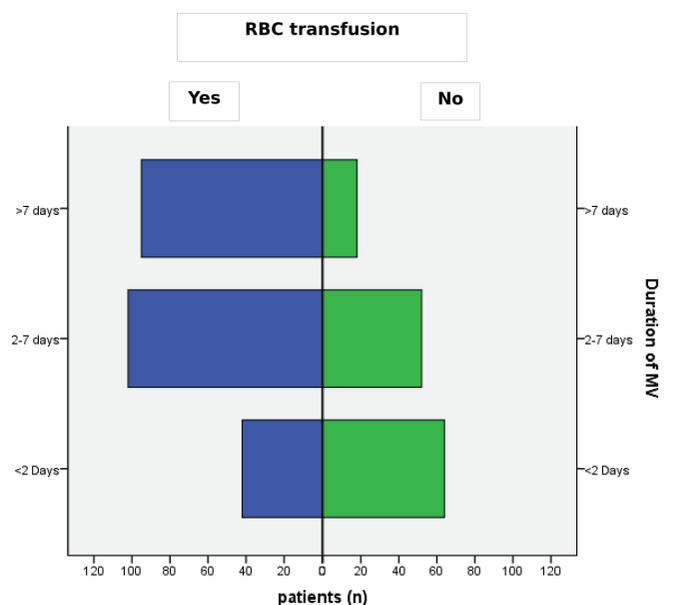


Figure 3. Correlation between the duration of the mechanical ventilation time and RBC transfusion rate
RBC: Red blood cell

Table 4. ROC Analysis of laboratory findings for RBC transfusion in mechanical ventilated patients

Parameter	AUC	SE	p	95% CI		Cut-off value	Sensitivity	Specificity
				Lower limit	Upper limit			
PRISM score	0.701	0.040	<0.001	0.622	0.780	11.5	73.3%	60.0%
Leucocyte (10 ³ /μL)	0.447	0.031	0.093	0.387	0.507	11330	48.9%	43.6%
Haemoglobin (g/dL)	0.721	0.033	<0.001	0.657	0.784	9.95	74.5%	59.4%
Neutrophil (10 ³ /μL)	0.571	0.037	0.063	0.498	0.644	5950	63.4%	49.0%
Lymphocyte (10 ³ /μL)	0.532	0.032	0.322	0.470	0.595	1990	61.5%	45.2%
Platelet count (10 ³ /μL)	0.595	0.029	0.003	0.537	0.653	267,500	63.6%	54.3%
MPV	0.585	0.030	0.007	0.525	0.644	8.3	63.6%	48.5%
RDW	0.545	0.031	0.069	0.484	0.606	14.95	63.6%	45.5%
AST (IU/L)	0.683	0.029	<0.001	0.627	0.740	32.5	70.9%	55.4%
ALT (IU/L)	0.644	0.029	<0.001	0.586	0.702	18.5	69.6%	51.2%
LDH (IU/L)	0.684	0.030	<0.001	0.624	0.743	331.5	67.5%	52.9%
Calcium (mg/dL)	0.621	0.030	<0.001	0.563	0.679	9.0	64.6%	56.0%
Prothrombin time (s)	0.673	0.042	<0.001	0.590	0.756	13.3	67.7%	62.3%

RBC: Red blood cell, PRISM: Pediatric Risk of Mortality, MPV: Mean platelet volume, RDW: Red blood cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

keep hemoglobin 10 or over in patients with septic shock.¹³ Hemodilution from fluid resuscitation in sepsis is another important reason for decreased hemoglobin levels. Especially, excessive volume infusion during resuscitation can cause dilutional anemia. Therefore, our transfusion rates may be high in the septic patients.

A similar relationship was found between inotropic drug usage and RBC transfusion. The patients who were treated with inotropic drugs had significantly need more RBC transfusion than those who did not have inotropic support. The patients having thrombocytopenia and coagulation disorders such as thrombocytopenia-associated multiple organ failure (TAMOF) in case of shock and multi-organ failure are used to have inotropic drugs that increase the need of transfusion. The hemoglobin level also should be kept around 10g/dl in patients with shock. All these risk factors increase the RBC transfusion.

Likewise, there was a significant relationship between PRISM score and RBC requirement and ROC analysis showed a moderate correlation. In the literature, transfusion requirement was associated with higher mortality scores.¹²

In a recent study AKI was considered as an independent risk factor in the worse prognosis of critically ill children.¹⁴ In our study, logistic regression analysis showed that need of RBC transfusion was not associated AKI. In critically ill children, CRRT is commonly used treatment modalities for AKI which may increase the RBC requirement.¹⁵ We experienced a statistically significant relationship between the CRRT and

RBC transfusion. Appropriate and effective anticoagulation is required for CRRT.¹⁵ The most common of anticoagulation used was systematic application of unfractionated heparin in our study. Heparin usage can cause bleeding and blood loss. In addition, hemodilution due to fluid overload might have influenced the frequency of transfusion in patients undergoing CRRT.

Hemoglobin level was the most sensitive parameter in ROC analysis. There was a moderate correlation between RBC transfusion and anemia on admission. Anemia at admission increased the need for blood transfusion in patients in need of MV. In the literature, there are a few adult studies demonstrating that initial hemoglobin level is associated with RBC transfusion, like our study.^{16,17} There was a significant relationship between RBC transfusion requirement and liver function tests such as ALT, AST, LDH, and PT elevation. In case of liver dysfunction, major blood losses occur during and after surgical processes such as catheterization.¹⁸ There was no severe bleeding in our patients during catheterization. We only experienced leak style bleeding in these patients.

The present study has some limitations. First, this study was a retrospective. Second, transfusion related complications were not included. These complications can effect outcome, duration of MV use and duration of PICU stay. Third, the amount of blood losses was not measured. Fourth, serial measurements of the hemoglobin levels were missing. Fifth, other transfusions such as platelet were not recorded. Sixth, our PICU does not have a trauma and a cardiovascular

division. Therefore, there were a few number of hemorrhagic or hemorrhagic shock patients in our study. It may have affected our study results. The strengths of our study are that the data was acquired from two centers having large number of pediatric. There is not any published similar PICU studies that commend on duration of mechanical ventilation specifically for children.

Conclusion

The present multicenter study revealed that the need for RBC transfusion was high in patients receiving MV support, and almost all patients required transfusion especially after the 7th day. Hemoglobin and liver function tests during admission to PICU can be used to predict the RBC transfusion needing. RBC transfusions were associated with higher severity score, longer lengths of stay and MV usage, higher CRRT usage and higher inotrope requirement. Therefore, RBC transfusion is associated worse outcome in critically ill children and blood-saving measures should improve in PICU patients. In conclusion, it should be remembered that patients who need RBC transfusion should be followed up more carefully and closely.

Ethics

Ethics Committee Approval: Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee, ethical committee no. 29430533903.99-113999, August 2019.

Informed Consent: As this is a retrospective study, the patient data were extracted from electronic and written medical records. Therefore, there is no informed consent received from the cases individually.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: F.A., C.D., Data Collection or Processing: F.A., F.V., Analysis or Interpretation: F.A., H.S.Ş., A.K., Literature Search: F.A., C.D., M.T.P., Writing: F.A.

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