Transfusion of Leukocyte-Depleted RBCs Is Independently Associated With Increased Morbidity After Pediatric Cardiac Surgery*

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Objective: To test the hypothesis that transfusion of leukocyte-depleted RBC preparations within the first 48 hours of PICU stay was independently associated with prolonged duration of mechanical ventilation, irrespective of surgery type and disease severity.

Design: Retrospective, observational study.

Setting: Single-center PICU in The Netherlands.

Patients: Children less than 18 years consecutively admitted after pediatric cardiac surgery between February 2007 and February 2010.

Interventions: None.

Measurements and Main Results: Data from 335 patients were used for analysis of whom 86 (25.7%) were transfused during the first 48 hours of PICU stay. Duration of mechanical ventilation (115 ± 19 hours vs. 25 ± 4 hours, $p < 0.001$) was longer among transfused patients. Ventilator-associated pneumonia (10.5% vs. 1.6%, odds ratio 7.2; 95% confidence interval 1.92–32.47; $p < 0.001$) was more frequent among transfused patients. New acute kidney injury after 48 hours of PICU admission (23.9% vs. 15.4%, $p = 0.18$) and mortality were comparable (2.3% vs. 4%, $p = 0.16$). The number of discrete transfusion events was significantly correlated with the duration of mechanical ventilation (Spearman's rho 0.617, $p < 0.001$). Transfusion remained independently associated with prolonged duration of mechanical ventilation after adjusting for confounders using Cox proportional hazards regression analysis.

Conclusions: Transfusion of leukocyte-depleted RBCs within the first 48 hours of PICU stay after cardiac surgery is independently associated with prolonged duration of mechanical ventilation. (*Pediatr Crit Care Med* 2013; 14:298–305)

Key Words: child; critical care; outcome; pediatric cardiac surgery; RBC transfusion

***See also p. 330.**

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Transfusion of RBCs is inextricably linked with PICU supportive care after pediatric cardiac surgery (PCS) (1). Children admitted after PCS are more likely to be transfused even when no (severe) anemia is present (2). However, in non-PCS patients, RBC transfusions are independently associated with increased morbidity and mortality (2–4). In addition, a prospective randomized trial showed a restrictive transfusion strategy to be feasible and safe in non-PCS children (5).

Postcardiac surgery, RBC transfusion in adults has been linked with increased morbidity, such as infectious complications or prolonged length of ventilatory support, as well as increased mortality (6, 7). Data have now emerged from two pediatric studies that postoperatively transfused PCS patients also experienced prolonged ventilatory support and increased likelihood of postoperative infections (8, 9). However, the findings cannot easily be extrapolated to the general PCS patient population because of two issues. First, a transfusion algorithm was not available in both studies leading to *confounding by indication*. This means that it is possible that the sickest patients are exposed to RBC transfusion much more liberally. Second,

standard RBC preparations were used instead of leukocyte-depleted preparations. Although not free from scientific debate, it has been proposed that leukocytes present in standard RBC preparations are responsible for immunodulation, leading to immunosuppression and the development of multiple system organ failure (10–12). As of January 2002, leukocyte-depleted RBC preparations are used in the Netherlands. Despite this, we noted an independent association between transfusion of leukocyte-depleted RBC preparations and increased morbidity and mortality in a heterogeneous group of critically ill children (4). These findings could not be explained by length of RBC prestorage or increased prevalence of nosocomial infections (13, 14). Our previous study did not include patients admitted after PCS. It would therefore be interesting to study the effects of transfusion of leukocyte-depleted RBC preparations on outcome in this specific patient population. Hence, the objective of this observational study using propensity score analysis (to limit confounding by indication) was to test the hypothesis that transfusion of leukocyte-depleted RBC preparations within the first 48 hours of PICU stay is independently associated with prolonged duration of mechanical ventilation (MV), irrespective of type or surgery.

METHODS

Study Design

The study was designed as a retrospective, single-center observational study. The Institutional Review Board waived the need for informed consent.

Patients and Setting

Medical records from all children aged 0 months to 18 years consecutively admitted to our 20-bed medical-surgical tertiary care PICU after PCS between February 2007 and February 2010 were obtained, irrespective of pretransfusion hemoglobin concentration. Children admitted to the neonatal ICU or adult ICU after PCS were not considered for analysis. Children with chronic anemia (i.e., anemia greater than or equal to 6 weeks), hemoglobinopathies, or active blood loss (i.e., drain production greater than 2 mL/kg/hour for 3 consecutive hours) prompting surgical reintervention were excluded. Anemia was defined as hemoglobin < 9.6 g/dL as previously done (15, 16). As of January 2002 in The Netherlands, all RBC preparations are leukocyte depleted.

Routine Management in the PICU

Cardiovascular drugs used in the PICU included dopamine (5–20 μg/kg/minute), dobutamine (5–20 μg/kg/minute), milrinone (0.5–1 μg/kg/minute), epinephrine, and norepinephrine. There was no clinical algorithm when to use which particular drug, but usually dopamine and milrinone were concurrently used in our PICU. Prespecified fluid intake was targeted to be 65% to 75% of normal at the day of surgery and subsequently increased over 48 hours to 100% of normal fluid intake. Patients were ventilated with a time-cycled, pressure-limited mode of ventilation (Evita 4/XL, Draeger Medical, Lubeck, Germany). In general, targets of gas exchange included transcutaneously measured oxygen saturation (Spo_2) greater than 92% with F_{IO_2} less than 0.4 for patients with normal physiology after surgery (i.e., a two-ventricle circulation without cyanosis) and normocapnia unless acute lung injury or acute respiratory distress syndrome was present. In all patients, perioperative antimicrobial prophylaxis was used for 24 hours. Enteral feeding was achieved through nasogastric tube feeding. Sedation and analgesia were achieved with continuous infusion of midazolam and opioid drugs (morphine and fentanyl).

The decision to transfuse a patient during PICU stay was left at the discretion of the attending physician. Routinely, the quantity per RBC transfusion amounted to 10–15 mL/kg.

Data Collection

For each patient, demographical data were collected, including gender, age in days, and weight. The cardiac surgical procedures were classified in accordance with the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) method (17). This method ranks the complexity of the surgical intervention from 1 to 6. Additional perioperative data included duration of surgery, aortic cross-clamp time, use of cardiopulmonary bypass (CPB), duration of CPB, and transfusion of RBC preparations during surgery and presence of normal physiology (i.e., a two-ventricle circulation without cyanosis) after surgery. Disease severity upon PICU admission was assessed by the Pediatric Risk of Mortality II (PRISM II) score (18, 19). PICU data recorded included the use and duration of MV (DMV), length of PICU stay and PICU mortality. For each patient, the number of discrete transfusion events during PICU stay, as well as the amount per transfusion in mL was noted. Transfusion of CPB machine blood in the PICU was also recorded (i.e., the patient's own blood was collected from the CPB machine and transfused in the PICU if deemed necessary by the attending physician). The lowest hemoglobin (g/dL) per day was recorded. For patients with complete repair, the lowest Pa_{O_2}/F_{IO_2} ratio and oxygenation index (OI) per day were recorded. The OI was calculated as follows: (mean airway pressure [mPaw] × F_{IO_2}) / Pa_{O_2} (mm Hg). The daily cumulative index of inotropic support was calculated as described elsewhere (20, 21). Acute kidney injury (AKI) was defined by the pediatric Risk, Injury, Failure, Loss of kidney function, End-renal disease (pRIFLE) criteria as described elsewhere (22). A ventilator-associated pneumonia (VAP) was identified if the patient met all of the following criteria: a) new onset of fever (greater than 38.3°C), b) new elevation in C-reactive protein (CRP) and/or newly developed leukocytosis (more than 15,000 mm^{-3}) or leucopenia (less than 5000 mm^{-3}), c) positive culture from or endotracheal aspirate, d) new consolidation or infiltrative disorder on chest radiograph (identified by a pediatric radiologist), and e) an increase in ventilatory parameters (23).

Definition of Outcome

DMV (hour) was defined as the primary outcome. In general, children are extubated as early as possible in our unit. Hence, the decision to extubate is not influenced by the decision to transfuse a patient or the use of inotropes. Secondary outcomes included use and duration of inotropic support (DIS), occurrence of AKI during PICU admission, and occurrence of VAP during PICU admission.

Statistical Analysis and Sample Size Calculation

Data are expressed as mean ± SD or SEM for continuous data and proportions for categorical data. In the bivariate analysis, demographical and clinical data were compared for the primary and secondary outcome measures between patients who were transfused within the first 48 hours of PICU admission (RBCTx48) and those who were not. The Mann-Whitney *U* test was used for continuous variables, whereas for categorical variables the chi-square test was used or Fisher's exact test when the expected value of a cell was less than 5. Correlations were assessed calculating the Spearman correlation coefficient. A propensity score was calculated to limit confounding by indication. This score estimated the likelihood for an individual patient to be or not be transfused within the first 48 hours of PICU admission. It is derived from a multiple logistic regression analysis in which variables that most likely influence the likelihood of transfusion were entered. In this study, the propensity score was based upon the type of surgery defined by the RACHS category, hemoglobin less than 9.6 g/dL during the first 48 hours of PICU admission, cumulative drain production, transfusion with CPB machine blood in the PICU, age of the patient, and repair status (normal physiology) after surgery. These variables were chosen based on clinical experiences by the team that takes daily care of children after cardiac surgery (i.e., the intensivist, cardiologist, and cardiothoracic surgeon).

We performed two bivariate analyses, one including all patients and an additional one including only patients with normal physiology after surgery. The reason for this was that it is common daily practice to achieve higher hemoglobin levels in patients who do not have normal cardiac physiology.

Next, using regression analysis, we wanted to estimate the independent contribution of RBCTx48 to the primary outcome measure (i.e., DMV). Regression analysis estimates how confounders are related to the outcome and produces an adjusted estimate of the intervention effect (24). Cox proportional hazards regression analysis was used to adjust for disease severity (PRISM II score), type of surgery (RACHS category), duration of surgery, and occurrence of VAP. The RBCTx48 propensity score was also forced into this model. VAP has been identified as a predictor for prolonged DMV in PCS patients (25). Nonsurvivors and patients who were not ventilated were censored. All statistical analyses were performed with SPSS version 18 (Chicago, IL). We calculated beforehand that a minimum sample size of 270 patients with a 1:3 ratio between transfused and nontransfused patients would be needed to detect a statistically significant (hazard ratio [HR]) of 1.5 with a standard deviation of 0.5 and a correlation with other covariates in the Cox regression model with a power of 0.80 and alpha 0.05. *p* values below 0.05 were accepted as statistically significant.

RESULTS

Patient Characteristics

Figure 1 shows the study profile. A total of 404 patients were admitted to the PICU after cardiac surgery. Data of 335 patients (82.9%) were usable for analysis. The majority of patients were characterized as RACHS-2 or -3.

A total of 111 patients (33.1%) received one or more RBC transfusions of whom 86 (77.5%) were transfused within the first 48 hours of PICU admission. Seventy-nine patients (71.1%) were transfused only once. The mean amount of transfusion volume was 13.7 ± 0.32 mL/kg bodyweight (range 10.8–15.6). The median (27% to 75% interquartile range) propensity score (i.e., the likelihood of a patient being assigned to RBC transfusion) was 0.64 (0.33–0.81) and 0.16 (0.06–0.38) for, respectively, transfused and nontransfused patients. It was well calibrated (Hosmer and Lemeshow test, $p = 0.417$) and discriminated well between transfused and nontransfused patients (*c* index = 0.861 (26)).

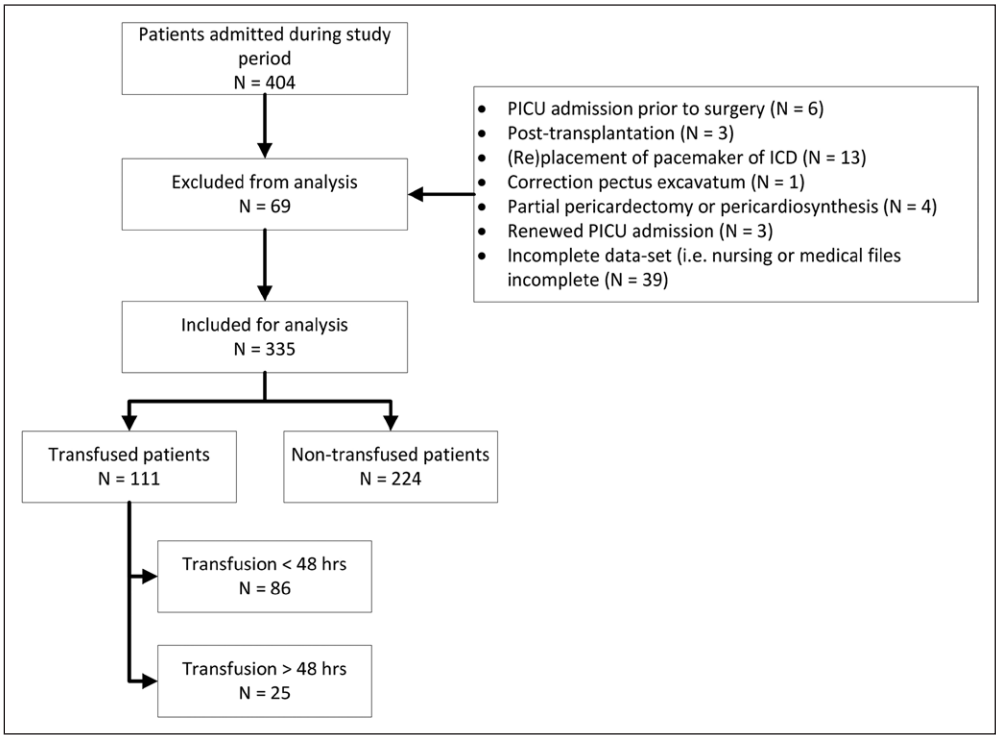


Figure 1. Study profile.

Association of RBCTx48 With Patient Outcome–Unadjusted Analysis

Table 1 summarizes the baseline characteristics. Transfused patients were significantly younger (19.4 ± 30.5 days vs. 48.0 ± 52.5 days, $p < 0.001$),

TABLE 1. Baseline Characteristics of Transfused and Nontransfused Pediatric Cardiac Surgery Patients During the First 48 Hours of PICU Stay

	All Patients			Patients With Normal Physiology After Surgery		
	RBCTx ($n = 86$)	No RBCTx ($n = 249$)	p	RBCTx ($n = 66$)	No RBCTx ($n = 205$)	p
Demographics						
Male/female (%)	61.6/38.4	53.8/46.2	0.208	59.1/40/9	51.0/49.0	0.250
Age (days)[a]	19.4 ± 30.5	48.0 ± 52.5	< 0.001	20.1 ± 28.2	50.3 ± 54.8	< 0.001
Weight (kg)	8.6 ± 6.4	16.8 ± 15.4	< 0.001	9.0 ± 6.6	17.7 ± 16.5	< 0.001
Pediatric Risk of Mortality II score	10.1 ± 7.1	5.7 ± 4.4	< 0.001	9.2 ± 6.5	5.5 ± 4.4	< 0.001
Propensity score[b]	0.64(0.33–0.81)	0.16(0.06–0.38)	NA	ND	ND	NA
Characteristics of surgical procedure						
Risk Adjustment for Congenital Heart Surgery category (%)[a]						
I	4.6	22.3				
II	23.3	41.5				
III	54.6	29.9				
IV	14.0	4.5				
V	0	0				
VI	3.5	1.8				
Duration (min)	305 ± 107	240 ± 73	< 0.001	316 ± 101	240 ± 72	< 0.001
Use of CPB (%)	84.8	74.3	0.044	97.0	84.0	0.006
Time on CPB (min)	126 ± 59	80 ± 43	< 0.001	124 ± 56	80 ± 42	< 0.001
Priming of CPB with RBC (%)	3.5	2.5	0.594	4.5	2.9	0.519
RBCTx during surgery (%)	8.1	5.2	0.325	9.1	6.3	0.441
Clinical characteristics during PICU stay						
Hemoglobin < 9.6 g/dL the first 48 hr (%)[a]	87.2	65.5	< 0.001	89.4	72.3	0.004
Total drain production (mL/kg)[a]	33 ± 4	13 ± 1	< 0.001	34 ± 43	12 ± 17	< 0.001
CPB blood transfused (%)[a]	9.3	27.3	< 0.001	12.1	31.6	0.002

RBCTx = red blood cell transfusion; ND = not determined; NA = not applicable; CPB = cardiopulmonary bypass.
Data are expressed as mean ± SD or percentage of total unless otherwise stated.
[a]Used to calculate the propensity score.
[b]Data expressed as median (25% to 75% interquartile range).

weighed less (8.6 ± 0.7 kg vs. 16.8 ± 1.0 kg, $p < 0.001$), and had a higher PRISM II score (10.1 ± 0.8 vs. 5.7 ± 0.3, $p < 0.001$) compared with nontransfused patients. Duration of surgery (305 ± 11 minutes vs. 240 ± 5 minutes, $p < 0.001$) and CPB (126 ± 8 minutes vs. 80 ± 3 minutes, $p < 0.001$) was significantly longer among transfused patients. Priming of the CPB system with blood as well as transfusion of RBC preparations during surgery was comparable between the two groups.

The association of RBCTx48 with patient outcome is shown in T**able 2**. Transfused patients had prolonged mean ventilatory time (119.5 [95% CI 79.5–159.4] hours vs. 25.8 [95% CI 18.4–33.3] hours, log-rank test $p < 0.001$) (unadjusted HR 2.6, 95% CI 2.0–3.4) (**Fig. 2**). There was also a significant correlation between the number of discrete transfusion events and length of ventilatory support (Spearman's rho 0.617, $p < 0.001$. Transfused patients also showed prolonged DIS (141 ± 20 hours vs. 55 ± 8 hours, $p < .001$) and a longer stay in the PICU (8.3 ± 0.9 days vs. 3.5 ± 0.2 days, $p < 0.001$). There was a higher VAP rate among transfused patients (10.5% vs. 1.6%, OR 7.2, 95% CI 1.92–32.47, $p < 0.001$). New AKI after 48 hours of PICU admission (23.9% vs. 15.4%, $p = 0.18$) and mortality were not different between the two groups (2.3% vs. 4%, $p = 0.16$).

TABLE 2. Results From the Unadjusted Analysis Evaluating the Effect of Transfusion of Lleukocyte-Depleted RBC Preparations During the First 48 Hours of PICU Admission on Patient Outcome

	All Patients			Patients With Normal Physiology After Surgery		
	RBCTx ($n = 86$)	No RBCTx ($n = 249$)	p	RBCTx ($n = 66$)	No RBCTx ($n = 205$)	p
Mechanical ventilation (%)	100	97.6	0.146	100	98.1	0.254
Time on ventilator (hr)	115 ± 19	25 ± 4	< 0.001	117 ± 193	24 ± 58	< 0.001
Use of inotropes (%)	79.1	36.1	< 0.001	84.8	33.0	< 0.001
Time on inotropes (hr)	141 ± 20	55 ± 8	< 0.001	139 ± 171	55 ± 23	0.001
Acute kidney injury (%)[a]	23.9	15.4	0.178	22.6	17.4	0.470
Ventilator-associated pneumonia (%)	10.5	1.6	< 0.001	12.1	1.0	< 0.001
Length of PICU stay (d)	8.0 ±.9	3.5 ±.2	< 0.001	8.0 ± 8.5	3.3 ± 3.6	< 0.001
PICU mortality (%)	2.3	0.4	0.163	0	0	Not determined

RBCTx = red blood cell transfusion.
Data are expressed as mean ± SEM or percentage of total unless otherwise stated.
[a]During PICU admission.

Similar findings were made when only patients with a normal physiology after surgery were studied (Tables 1 and 2).

Association of RBCTx48 with Patient Outcome–Adjusted Analysis

After adjusting for PRISM II score, RACHS category, duration of surgery, occurrence of VAP, repair status, and the RBCTx48 propensity score, RBCTx48 remained independently associated with the DMV (HR 1.41, 95% CI 1.06–1.88) (**Table 3** and **Fig. 3**).

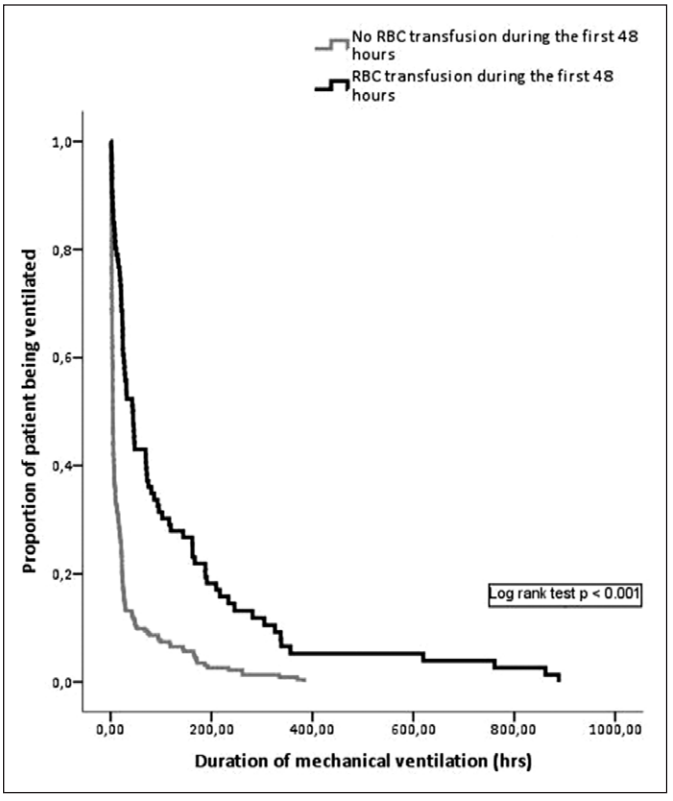
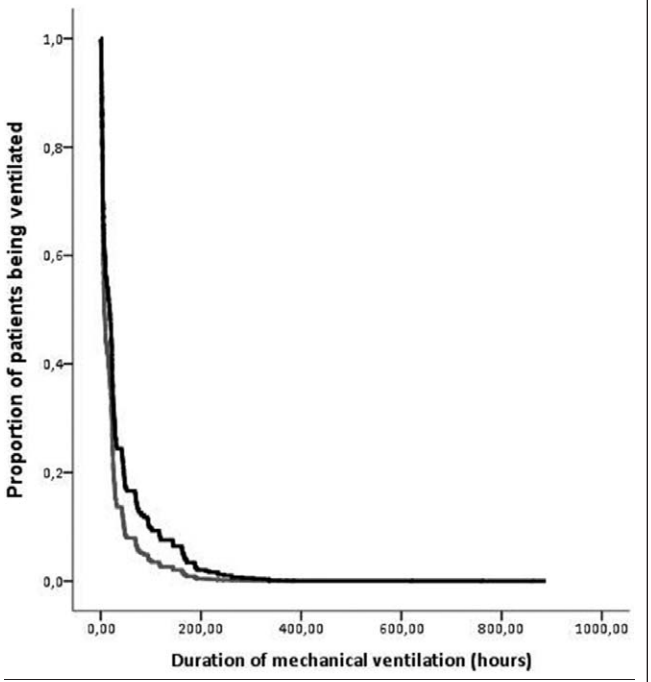


Figure 2. Survival curve of the duration of mechanical ventilation of all transfused ($n = 111$) and nontransfused patients ($n = 224$).

DISCUSSION

The main finding of this study is that transfusion of leukocyte-depleted RBC preparations during the first 48 hours of PICU stay after PCS was independently associated with prolonged DMV, irrespective of type and duration of surgery or severity of illness.

To our best of knowledge, we are the first to establish such independent association with the use of leukocyte-depleted RBC preparations. Data are also now emerging from other pediatric institutions, evaluating the effect of standard RBC preparations after admission to the PICU for PCS. Kipps et al (8) performed a secondary analysis of data from 275 infants enrolled in two trials of hematocrit strategy during CPB. They found that infants who were transfused had prolonged DMV, especially when the transfusion volume did not exceed 15 mL/kg. As acknowledged by the authors themselves, the major criticism toward this study is the fact that no attempt was made to minimize confounding by indication (i.e., using



Time interval	Transfusion during the first 48 hours	No transfusion during the first 48 hours
0	86	243
24	57	45
48	37	28
72	33	23
96	27	19
120	24	15
144	24	14
168	18	11
192	15	7
216	14	6
>240	11	5

Figure 3. Adjusted survival curve of the duration of mechanical ventilation of patients with or without RBC transfusions during the first 48 hours of PICU stay.

propensity score analysis). Furthermore, their study included more complex patients than ours as 40.0% of their patients could be classified as category 4 of the RACHS-1 method. Nonetheless, our data confirm their findings on DMV. Another group of investigators reviewed their PCS patients in 2003 (27). Out of 802 patients, 46.2% were transfused with irradiated, leukocyte-reduced RBC preparations. Length of hospital stay (LOS) was independently prolonged in patients in their predefined high-exposure group (transfusion volume more than 15 mL/kg). From their analysis, it was unclear if also DMV was independently associated with blood transfusion. Importantly, one could question the use of LOS as primary outcome measure as it is a subjective parameter and influenced by many (intentionally or not) unforeseen circumstances.

Observational studies such as the present one are only designed to identify associations and not causative mechanisms. We can therefore only speculate about possible physiologic explanations why RBC transfusions prolonged the DMV. It has been proposed that leukocytes present in RBC preparations are accountable for suppression of the host immune response, thus rendering an individual more susceptible for (severe) infections such as VAP, although the benefits of RBC prestorage leukoreduction have not been identified (10–12, 28). Nonetheless, we therefore adjusted for VAP in the multiple regression analysis. Alternatively, immunomodulatory effects of the RBCs themselves or from inflammatory mediators contained within a RBC unit may contribute to a prolonged postoperative proinflammatory status (29–31). This phenomenon needs to be evaluated in future studies. One group of investigators has shown that washing of RBCs was associated with reduced inflammatory biomarkers and number of transfusions in PCS patients (29).

Blood loss with subsequent anemia and hypovolemia is most likely the main reason for RBC transfusion after PCS. By doing so, it is often thought that systemic oxygen consumption will be improved and the potentially detrimental effects of anemia-induced tachycardia reduced. However, this concept is not supported by strong recommendations and needs to be confirmed (16, 32). Also, neonatal and more complex PCS may be transfused more liberally. This clinical practice was reflected in our propensity score as we had incorporated hemoglobin less than 9.6 g/dL during the first 48 hours of PICU admission, cumulative drain production, age, and the RACHS-1 category.

The use of a restrictive transfusion strategy in PCS patients may be considered based upon our findings. Such a strategy has been evaluated in 125 PCS patients (< 60% RACHS-1 category 2 and 3) with a hemoglobin less than 9.5 g/dL enrolled in the TRIPICU trial (33). The main conclusion from this analysis was that a restrictive transfusion strategy (transfusion threshold hemoglobin 7.0 g/dL) was as safe as a liberal transfusion strategy assessed by the occurrence of multiple organ dysfunction, length of PICU stay or 28-day mortality. Recently, the results from the adult Transfusion Requirements After Cardiac Surgery trial were reported (34). In this trial, 253 patients were randomized to a liberal transfusion strategy (targeted hematocrit greater than or equal to 30%) vs. 249 to a restrictive strategy (targeted hematocrit greater than or equal to 24%). Overall, 30-day mortality and serious morbidity were comparable in both groups, suggesting that a restrictive strategy was safe. However, because of the heterogeneity in PCS patients, we think that it is important that future pediatric investigations should be directed toward defining a justifiable threshold when and which PCS patients to transfuse, especially when managing more complex PCS patients. Of interest, one group of investigators has found that RBC transfusions were not associated with improved outcomes in 94 infants less than 6 weeks with hypoplastic left heart syndrome undergoing staged Norwood operations (31).

TABLE 3. Results From the Cox Proportional Hazards Regression Analysis Evaluating the Effect of Transfusion of Leukocyte-Depleted RBC Preparations During the First 48 Hours of PICU Admission on Duration of Mechanical Ventilation

Variable	Hazard Ratio[a]	95% Confidence Interval	*p*
Pediatric Risk of Mortality II score	0.96	0.94–0.098	< 0.001
Risk Adjustment for Congenital Heart Surgery category	0.95	0.81–1.11	0.481
Duration of surgery	0.999	0.99–1.00	0.423
Ventilator-associated pneumonia[b]	3.470	1.80–6.69	< 0.001
RBC transfusion during the first 48 hr	1.41	1.06–1.88	0.018
RBC transfusion propensity score	0.14	0.08–0.24	< 0.001

[a]For continuous or ordinal variables (Pediatric Risk of Mortality, duration of surgery, and propensity score), a hazard ratio (HR) < 1 signifies an increased duration of mechanical ventilation (DMV). For dichotomous variables (Risk Adjustment for Congenital Heart Surgery category, ventilator-associated pneumonia [VAP], and RBC transfusion during the first 48 hours), an HR > 1 signifies an increased DMV. Thus, the probability to still being ventilated at a given time point is 1.41 times higher in the transfused group than in the nontransfused group.

[b]VAP at any time during pediatric ICU admission following RBC transfusion.

There are limitations to this study that need to be addressed. First, its retrospective character could have influenced the availability of the data collected. Nonetheless, data on both primary and secondary outcomes could be retrieved for all included patients. Second, the decision to transfuse was at the discretion of the attending physician. The decision to transfuse is often made on a subjective basis when no transfusion algorithm is available. Subjective criteria often include being on a ventilator or on vasoactive support. This leads to confounding by indication (i.e., severely ill patients or patients with a low hemoglobin are more easily transfused), a matter that can ultimately only be resolved by a randomization although regression analysis also minimizes confounding in cohort studies (35). However, in order to minimize the effect of confounding by indication, we have adjusted our observations using propensity score analysis. The propensity score calculates for each patient the likelihood of receiving a specific intervention based upon preselected variables. Therefore, as with any propensity score analysis, it is conceivable that variables predictive for a transfusion were not identified and hence not used when calculating the score (35). Also, there must be significant overlap in the distribution of the propensity scores between the index and the control group. Indeed we did observe this in our study (**Fig. 4**). Also, ideally the propensity score needs to be externally validated but this was not done in our study. Third, our study reflects a single-center experience. This may limit the generalizability of our study although our PICU is most likely comparable to other European and North-American PCS centers. Fourth, as with any multivariate analysis, causality between an event and the outcome cannot be determined as there might very well be a confounder that is associated with the outcome and not picked up by estimates of severity such as the PRISM II score used in this study. Fifth, our definition of VAP was not in full agreement with the CDC definition. As a consequence, we may have overestimated the number of VAPs. Also, because of the significantly shorter length of PICU stay in the control group, the VAP rate may have been underestimated (follow-up bias). However, there is no minimum period of time defined for a pneumonia to be considered VAP (36). Sixth, we used the RACHS method instead of more new and improved scoring systems such as the one proposed by O'Brien et al (37) to allow comparison with previously published papers. The RACHS-1 categories cover a wide range of diagnosis. Hence, it cannot be estimated if there is a link between bleeding, transfusion, and anatomy within a certain category. However, the RACHS-1 method has been used by others (9). Finally, in line with national registration, we used the PRISM II score to assess the severity of illness of the patient. However, this score is designed to assess the likelihood of death. Hence, its suitability in studies such as ours for estimating severity of illness is questionable. Furthermore, PRISM II is generally replaced by PRISM III nowadays and has not been validated as an appropriate severity of illness score in PCS patients.

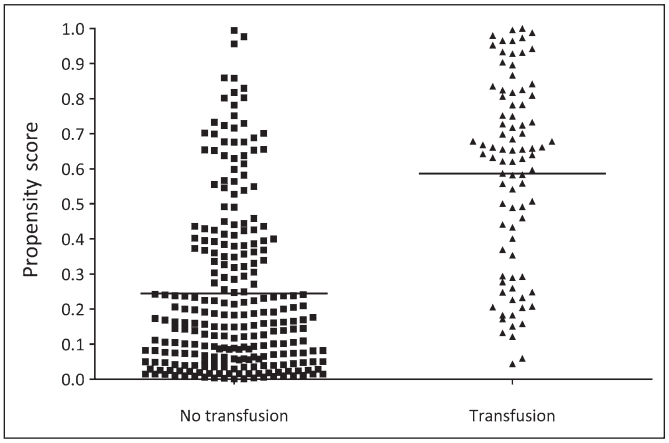


Figure 4. Distribution of propensity scores between all transfused ($n = 111$) and nontransfused patients ($n = 224$).

CONCLUSIONS

In this retrospective, single-center observational study transfusion of leukocyte-depleted RBC preparations during the

first 48 hours of PICU admission after PCS was independently associated with prolonged DMV. The number of discrete transfusion events was significantly correlated with the DMV. These findings need to be confirmed by others.

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