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Red blood cell transfusions are associated with prolonged mechanical ventilation in pediatric acute respiratory distress syndrome

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Abstract

Objective—Blood products are often transfused in critically ill children, although recent studies have recognized their potential for harm. Translatability to pediatric acute respiratory distress syndrome (PARDS) is unknown given that hypoxemia has excluded PARDS patients from clinical trials. We aimed to determine whether an association exists between blood product transfusion and survival or duration of ventilation in PARDS.

Design—Retrospective analysis of prospectively enrolled cohort.

Setting—Large, academic pediatric intensive care unit.

Patients—Invasively ventilated children meeting Berlin ARDS and PALICC PARDS criteria from 2011 to 2015.

Interventions—We recorded transfusion of red blood cells (RBC), fresh frozen plasma (FFP), and platelets within the first 3 days of PARDS onset. Each product was tested for independent association with survival (Cox) and duration of mechanical ventilation (competing risk regression with extubation as primary outcome and death as competing risk). A sensitivity analysis using 1:1 propensity matching was also performed.

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Measurements and Main Results—Of 357 PARDS patients, 155 (43%) received RBC, 82 (23%) received FFP, and 92 (26%) received platelets. Patients that received RBC, FFP, or platelets had higher severity of illness score, lower PaO_2/FiO_2, and were more often immunocompromised (all $p < 0.05$). Patients who received RBC, FFP or platelets had worse survival and longer duration of ventilation by univariate analysis (all $p < 0.05$). After multivariate adjustment for above confounders, no blood product was associated with survival. After adjustment for the same confounders, RBC were associated with decreased probability of extubation (subdistribution hazard ratio 0.65, 95% CI 0.51 to 0.83). The association between RBC and prolonged ventilation was confirmed in propensity-matched subgroup analysis.

Conclusions—RBC transfusion was independently associated with longer duration of mechanical ventilation in PARDS. Hemoglobin transfusion thresholds should be tested specifically within PARDS to establish whether a more restrictive transfusion strategy would improve outcomes.

Keywords

ARDS; PARDS; transfusions; outcome

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome of diverse etiologies of hypoxemic respiratory failure. In pediatrics, it is uncommon, representing only 1–4% of pediatric intensive care unit (PICU) patients (1, 2), but is associated with up to 30% of PICU deaths (3). At present, there are no specific therapies, and management in children (4) and adults focuses on supportive care with lung-protective mechanical ventilation (5) and fluid-restriction (6). Transfusion of red blood cells (RBC) is frequently prescribed in order to maximize oxygen delivery during hypoxemia. However, there is increasing recognition of the negative consequences of RBC transfusion in critical illness, with studies showing increased inflammatory mediator release (7), development or worsening of lung injury (7–9), and increased mortality (9, 10). Leukoreduction has been shown to decrease, but not eliminate, pro-inflammatory effects and transfusion-related complications (11). The 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) explicitly recommended further studies assessing the risk and benefits of transfusions in pediatric ARDS (PARDS), as well as testing of specific transfusion thresholds (12).

Trials in critically ill adults (13) and children (14) have shown that a more restrictive transfusion threshold has no difference in outcome compared with more liberal thresholds. However, PARDS patients may be underrepresented in these studies due to significant hypoxemia and hemodynamic instability, making it difficult to extrapolate results to this population. Therefore, we aimed to study the impact of blood product transfusion on outcomes of PARDS. We hypothesized that blood products would be associated with higher mortality and increased duration of mechanical ventilation.

METHODS

Patient Population

This was a retrospective analysis of a prospectively enrolled PARDS cohort. The cohort has been described in detail before (2). Briefly, patients were screened daily in the Children's Hospital of Philadelphia (CHOP) PICU for acute lung injury (American-European Consensus Conference definition)(15) between July, 2011 and June, 2015. As the study was initiated prior to the 2012 Berlin definition (16), a minimum positive end-expiratory pressure (PEEP) was not specified; however, as our institution does not utilize PEEP < 5 cmH2O, all patients met Berlin criteria for ARDS. Similarly, as the study was initiated prior to the 2015 PALICC definition for PARDS (4), we did not stratify severity using oxygenation index (OI), but by PaO_2/FiO_2; however, all patients met PARDS criteria by OI. This study was approved by the CHOP Institutional Review Board and requirement for informed consent was waived.

Specific inclusion criteria were 1) acute respiratory failure requiring invasive mechanical ventilation for more than 24 hours, 2) invasive arterial access, 3) age > 1 month and < 18 years, 4) $PaO_2/FiO_2 \leq 300$ on two consecutive arterial blood gases separated by at least 1 hour, and 5) bilateral parenchymal infiltrates on radiograph. Exclusion criteria were 1) respiratory failure from cardiac failure (determined by echocardiography), 2) exacerbation of underlying chronic respiratory disease, 3) chronic ventilator dependence, 4) intracardiac shunt, 5) mechanical ventilation for more than 7 days before $PaO_2/FiO_2 \leq 300$, and 6) PARDS established outside of the CHOP PICU.

Data Collection

RBC, fresh frozen plasma (FFP), and platelet transfusions were retrospectively abstracted during the first 3 days after PARDS diagnosis. Products were ordered at the discretion of the physicians caring for the patients with no pre-determined protocol. RBC and platelets were leukoreduced pre-storage, and irradiated prior to transfusion. All platelets were obtained by apheresis.

Definitions

The designation "immunocompromised" was given for patients with a potentially immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy, or a congenital immunodeficiency, as we have previously done (17). Vasopressor score (18) was: dopamine (μg/kg/min) x 1 + dobutamine (μg/kg/min) x 1 + epinephrine (μg/kg/min) x 100 + norepinephrine (μg/kg/min) x 100 + phenylephrine (μg/kg/min) x 100 + vasopressin (U/kg/min) x 10,000 + milrinone (μg/kg/min) x 10. Non-pulmonary organ failures at time of PARDS diagnosis were identified using accepted pediatric definitions (19). Severity of illness score used was the Pediatric Risk of Mortality (PRISM) III at 12 hours.

Outcomes

The co-primary outcomes were 28-day all-cause mortality and duration of mechanical ventilation. All mention of "mechanical ventilation" in this study implies invasive

ventilation, and non-invasive support was not counted toward total ventilator days. “Day 1” was initiation of invasive ventilation. Liberation from invasive ventilation for > 24 hours defined successful extubation. Ventilator-free days (VFD) at 28 days are also reported, and are equal to 28 minus the number of ventilator days, with non-survivors and ≥ 28 days of ventilation assigned VFD = 0.

Statistics

Analyses were performed in Stata 14. Data are expressed using either percentages or median values [IQR, inter-quartile ranges]. Differences between distributions of categorical variables were analyzed by Fisher’s exact test. Continuous variables were compared using Wilcoxon rank sum. A non-parametric test of trend was used to assess whether increasing volume of transfusion were associated with either higher mortality, duration of ventilation in survivors, or probability of extubation.

Multivariate Cox regression was used to test for an association between transfusions and 28-day mortality, after adjustment for PRISM III, immunocompromised status, and PaO_2/FiO_2 24 hours after PARDS onset. We have shown PRISM III and immunocompromised status to be associated with mortality and duration of ventilation (20), and PaO_2/FiO_2 at 24 hours accurately stratifies PARDS severity (2). Additional potential confounders with univariate association with mortality ($p < 0.10$, Table 1) were also considered. Non-pulmonary organ failures, vasopressor score, and fluid balance were all co-linear with PRISM III, and were not included given the low mortality rate and concerns for over-fitting. The proportional hazard assumption was tested by examination of scaled Schoenfeld residuals.

Because VFD is a composite endpoint incorporating both death and length of ventilation, it is a problematic endpoint from which to identify variables associated predominantly with ventilator duration. Thus, we did not analyze VFD. Additionally, using Kaplan-Meier or Cox regression analysis of time to extubation would censor a patient who dies before the end of the time period assuming non-informative censoring, which is likely a false assumption.

We therefore used competing risk regression to look at the association between blood product transfusion and duration of mechanical ventilation, using extubation as the primary outcome and death as the competing risk. Observations were censored at 28 days. As the two outcomes are interrelated (increased mortality decreases duration of ventilation), competing risk analysis using the Fine and Gray method (21) generates a cumulative incidence function and allows calculation of a subdistribution hazard ratio (SHR) to estimate the risk of extubation while accounting for the competing risk of death. This allows for an estimation of the hazard (the SHR) of transfusion on probability of extubation while explicitly accounting for the fact the mortality contributes to the decreased probability of extubation for patients who die. This is contrasted with traditional Cox regression, in which patients who die are censored, which is assumed (incorrectly in our case) to be non-informative. As with mortality analysis, the competing risk regression models were adjusted for PRISM III, immunocompromised status, and PaO_2/FiO_2 at 24 hours after PARDS onset. The proportional hazard assumption was assessed by testing for interaction with a time-dependent covariate.

Additionally, as we detected an association with RBC transfusion and outcome in our primary analyses, we performed propensity score matching to specifically examine the relationship of RBC transfusions and outcomes. We preferred propensity score matching over propensity score stratification due to the improved covariate balance with matching, even at the expense of reduced sample size and precision (22). We created a propensity score to estimate likelihood of RBC transfusion, using the variables age, PRISM III, immunocompromised status, non-pulmonary organ failures, vasopressor score, PaO_2/FiO_2 at PARDS onset and at 24 hours. Variables were chosen for univariate association with either RBC transfusion (Supplementary Table 1) or mortality (Table 1). Fluid balance at 72 hours was not included because it occurred entirely after the exposure (RBC transfusion in the first 72 hours). The vasopressor score (highest in first 24 hours) and PaO_2/FiO_2 at 24 hours were included because they were strongly associated with both RBC exposure and outcomes, and greatly improved the propensity score matching, despite being partly concurrent with RBC exposure. The C statistic for the propensity score was 0.78, suggesting good discrimination for probability of receiving RBC. The propensity scores were used to perform a 1:1 match using a greedy nearest-neighbor caliper (width 0.05) matching (without replacement) algorithm (23), with only successfully matched pairs used for analysis. Greedy nearest-neighbor cycles through subjects one at a time, matching an RBC transfused subject with the best available non-transfused, even if that non-transfused subject is a better match for a later RBC transfused subject. “Without replacement” implies that an RBC transfused subject is matched only to a single non-transfused subject. Balance of covariates was assessed after matching using both standardized mean differences (SMD) and *p* values.

RESULTS

Description of the Cohort

Between 2011 and 2015, 357 patients with PARDS were enrolled. Demographics of the cohort are summarized in Table 1. Infectious pneumonia, non-pulmonary sepsis, and aspiration pneumonia were the most common triggers for PARDS. Overall mortality was 13%, and 19% of patients were immunocompromised. As expected, non-survivors had a higher PRISM III score, were more likely to be immunocompromised, had more organ failures, and had worse PaO_2/FiO_2 at 24 hours.

Demographics of transfusion groups are shown in Supplementary Table 1. Of the 357 patients, 155 received RBC (43%), 82 received FFP (20%), and 92 received platelets (22%) within 72 hours of PARDS onset. Patients getting RBC, FFP, and platelets were all more likely to be immunocompromised ($p < 0.001$), have a higher PRISM ($p < 0.001$) and vasopressor scores ($p < 0.001$), more non-pulmonary organ dysfunction ($p < 0.001$), lower PaO_2/FiO_2 at 24 hours after PARDS diagnosis ($p < 0.05$), and worse outcomes (Supplementary Table 2). Of patients receiving RBC, the median pre-transfusion hemoglobin was 7.8 g/dL [7.1, 8.6] and the median post-transfusion hemoglobin was 11.0 g/dL [10, 12.1].

Primary Analysis of the Association between Transfusions and Outcomes

After controlling for confounders, neither RBC (HR 2.01, 95% CI 0.96 to 4.22, p = 0.063), FFP (HR 0.98, 95% CI 0.44 to 2.21, p = 0.963) nor platelet transfusion (HR 1.10, 95% CI 0.47 to 2.60, p = 0.822) demonstrated independent association with mortality (Table 2). In competing risk regression (Table 3), transfusion of RBC was associated with a decreased likelihood of being successfully extubated (SHR 0.65, 95% CI 0.51 to 0.83, p = 0.001; Figure 1). Neither FFP nor platelets showed independent association with likelihood of extubation. A dose-response curve was generated for RBC transfusion in 15 mL/kg increments (Figure 2), which showed stepwise increase in mortality (p < 0.001), increased ventilator days among survivors (p < 0.001) and decrease in SHR for successful extubation (p < 0.001) with greater incremental volume of transfusion. Transfused patients had significantly lower hemoglobin values than non-transfused patients (p < 0.001) but there were no differences between the different levels of transfusion either before transfusion (p > 0.05) or after transfusion (p > 0.05) (Supplementary Table 3).

Propensity Score Analysis

Additionally, we developed a propensity score for RBC transfusion and performed 1:1 matching. One hundred ninety-eight subjects (n = 99 per group) were matched. The matched cohort demonstrated good balance of covariates, with reduction in SMD after matching (Supplementary Tables 4 and 5). Unmatched patients (Supplementary Table 6) were older (6.2 years 3.5 years, p = 0.021), had lower vasopressor scores (8 versus 10, p = 0.036), fewer organ failures (1 versus 2, p = 0.012), shorter ventilator duration (9 versus 11 days, p = 0.030), and were over-represented at the lowest (least likely to receive RBC) and highest (most likely to receive RBC) propensity score distribution (Supplementary Figure 1). The 99 matched patient pairs demonstrated no difference in mortality (12% RBC versus 8% no RBC, p = 0.480; Supplementary Table 4 and Supplementary Figure 2). However, the RBC transfused cohort had longer duration of ventilation in survivors (12 versus 10 days, p =0.023), fewer VFD (15 versus 18 VFD, p = 0.025), and a decreased likelihood of extubation given the competing risk of death (SHR 0.73, 95% CI 0.54 to 0.99, p = 0.044; Supplementary Figure 2).

Sensitivity Analyses

Because of the possibility of ongoing bleeding confounding the relationship between RBC transfusion and outcomes, we excluded 14 patients in whom RBC transfusions were recorded for hemorrhage or post-operative bleeding. Results were consistent with the primary analysis: no association was seen with RBC transfusion and survival (HR 1.78, 95% CI 0.82 to 3.84, p = 0.148), whereas an association with reduced probability of extubation was confirmed (SHR 0.67, 95% CI 0.52 to 0.86, p = 0.002).

Finally, as patients with refractory PARDS requiring extracorporeal membrane oxygenation (ECMO) frequently require RBC transfusions at ECMO initiation, we excluded the 15 patients placed on ECMO and repeated the analyses. Results remained consistent, with a marginal association with increased mortality (HR 2.08, 95% CI 1.00 to 4.34, p = 0.050) and a consistent association with reduced probability of extubation (SHR 0.69, 95% CI 0.54 to 0.87, p = 0.002) with RBC transfusions.

DISCUSSION

In this PARDS cohort, there was an increase in duration of ventilation in patients transfused RBC compared with those patients who were not transfused after controlling for known risk markers for poor outcomes. There was no association of any blood product with mortality. Results were confirmed in propensity-matched subgroups and sensitivity analyses. Further, increasing amounts of RBC were associated with incrementally worse outcomes. This supports the notion that transfusion in an attempt to increase oxygen delivery early in the course of PARDS may have adverse effects on the overall disease course.

Previous literature has revealed conflicting results with regards to outcomes associated with transfusions of blood products in PARDS. One single center study showed a small worsening of oxygenation index after RBC transfusion, but as with our cohort, a longer duration of mechanical ventilation (24). An older single center study of transfusion in PARDS, on the other hand, showed increased mortality only in association with FFP, with only a trend toward mortality and increased duration of mechanical ventilation with RBC. However, multivariate adjustment was not done for severity of illness in that study (25).

There are several possible explanations for the results presented here. Previous studies in PARDS have shown that increasing fluid positivity early in PARDS patients is associated with increased mortality and fewer ventilator free days (26). In our cohort, those transfused blood products had a more positive fluid balance at 72 hours, but fluid balance was not independently associated with either mortality (HR 1.00, 95% CI 0.99 to 1.00, p = 0.907) or likelihood of successful extubation (SHR 1.00, 95% CI 0.99 to 1.00, p = 0.638), after adjusting for PRISM, immunocompromised status, and PaO_2/FiO_2.

Another possible explanation would be that RBC transfusion imparts additional injury to the lung. Transfusion related acute lung injury (TRALI) is a well described phenomenon in which respiratory distress develops within 6 hours post transfusion of blood products (27). Mechanistically, it is thought to occur via either a single hit involving donor antibodies that activate recipient neutrophils or via a double hit etiology in systemically inflamed patients. The first hit involves upregulation of vascular adhesion molecules on the pulmonary endothelium in the setting of systemic inflammation, leading to a setup for stimulus-induced pulmonary dysfunction via activation of sequestered neutrophils (27). When RBC are transfused, antibodies from the small amount of plasma transfused with red blood cells or biologic mediators such as microlipids produced as a result of the storage process induce these primed polymorphonuclear cells to release proinflammatory mediators such as IL-6, IL-8, phospholipase A2, and reactive oxygen species, leading to capillary leak syndrome, and lung injury (28). This could add additional hits to injured lungs, worsening existing PARDS early in the course of disease and thereby prolonging the duration of the disease and mechanical ventilation with it. If TRALI is the primary etiology for the demonstrated prolonged ventilation, it is notable that FFP and platelets did not demonstrate associations with outcomes, as FFP has a higher incidence of TRALI than RBC in prior studies (29). However, associations between FFP and TRALI are largely historical, and modern blood banking practices, such as limited use of female donors, have greatly reduced the incidence of TRALI (30). Additionally, it is possible we were underpowered to detect an association

between FFP or platelets and outcomes, as substantially fewer patients received these products, relative to RBC.

It seems possible, therefore, that transfused RBC may negatively influence PARDS through multiple mechanisms. Recently, it has been recognized that RBC play a significant role in the control of vasoactivity through release or sequestration of nitric oxide via compounds called S-nitrosothiols (SNOs) during oxygen loading and unloading (31). It has further been demonstrated that in a porcine model of hypoxemia, there is a deficiency of SNO-hemoglobin, which impairs vasodilator ability, manifested in the lung as worsening ventilation/perfusion (V/Q) mismatch and increased pulmonary vascular resistance due to unopposed vasoconstriction (32). Storage of RBC has a similar effect in depleting SNO-Hgb, with up to 80% lost by 7 days (33). It is possible that transfusion of low SNO-Hgb cells may exacerbate deficiencies in V/Q matching and PVR, leading to worsening oxygenation impairment and the need to provide further ventilator support to overcome this deficit, leading to the potential for further ventilator induced lung injury. In addition to preclinical data and data from adults with ARDS, there is accumulating evidence in critically ill pediatric patients that transfusion may negatively impact respiratory function. Two recent prospective studies showed in a cohort of critically ill PICU patients an association between transfusion of RBC and increased new or worsening respiratory dysfunction as measured by PaO_2/FiO_2, and an increased risk of new organ dysfunction, compared with those who were not transfused (34, 35).

These data question the safety of transfusing RBC in the PARDS population outside of the indication of severe anemia. The Transfusion Strategy for Patients in PICU (TRIPICU) study (14) showed no difference in development of subsequent multi-system organ dysfunction when comparing a liberal threshold and a restrictive transfusion threshold among pediatric patients with critical illness, though this study was not restricted to PARDS. The present data, in combination with these recent studies of blood transfusions early on in critical illness, suggests that it would be important to assess whether RBC transfusions actually improve tissue oxygenation in PARDS, and whether a more restrictive transfusion threshold would be appropriate even in the setting of the significant hypoxemia seen in PARDS.

Because of the retrospective nature of the study, indications for transfusions were not confidently recorded. It is possible that the association between RBC and prolonged ventilation reflects a reluctance to extubate patients with significant bleeding. However, we believe this not to sufficiently explain our findings. First, the exposure we tested was limited to the first 3 days after PARDS onset, whereas subjects were ventilated for a median 10 [IQR 6, 16] days. Second, only a minority of patients (14 of 155, 9%) exposed to RBC were transfused for bleeding, and results of our sensitivity analysis excluding these subjects were consistent with the primary analysis. A future prospective cohort study specifically querying the indication for RBC transfusion in PARDS could more appropriately address this limitation.

The present study represents the largest dataset to date examining an association between transfusion and respiratory outcomes in PARDS patients using modern blood banking practices and detailed data collection. However, several important limitations must be noted.

As this study was conducted at a single center, conclusions drawn from the data may not be generalizable, though it did provide for more homogeneity in management. Patient demographics, illness severity, and transfusion practices were also similar to other published data sets. Mortality in our cohort was low (13%), although consistent with that reported by recent PARDS cohorts (36, 37). This may have rendered us underpowered to confidently claim that RBC transfusion had no association with mortality. Analysis of the exposure (transfusions) was restricted to the first 3 days after PARDS onset, and we did not assess the impact of later transfusions. While this is consistent with prior analyses in critically ill children (9), this limits the generalizability of our conclusions regarding the association between RBC and prolonged ventilation. We also analyzed individual blood products recognizing that these patients received combinations of blood products, which complicates the ability to draw conclusions about the effect of transfusing individual blood products. This does, however, represent real world conditions as critically ill patients often receive multiple, sometimes simultaneous transfusions of blood products. Transfusion decisions were also left up to the judgment of the caring providers, leading to heterogeneous thresholds and indications. While this also represents real world practice, confounding by indication is a possibility. Transfused patients may represent the more severely ill, and while statistical methods cannot address unmeasured confounding, we attempted to minimize bias by performing a both multivariate analysis and propensity matching, as well as sensitivity analyses. While the conclusion regarding duration of ventilation was confirmed, the effect size was attenuated in the propensity-matched cohort. This should be interpreted with caution, as only 55% of patients could be matched, with only 20 deaths, thereby reducing both power and precision at the expense of improved covariate balance between RBC-transfused and non-transfused subjects. We also did not have detailed data regarding the age of blood for our patient population, though studies have thus far not shown a difference in outcomes with less fresh blood (38–40).

CONCLUSIONS

In PARDS patients, RBC transfusion is associated with prolonged duration of mechanical ventilation. Future studies should focus on whether tissue oxygenation improves after transfusion in PARDS and whether a lower transfusion threshold in PARDS patients would impact outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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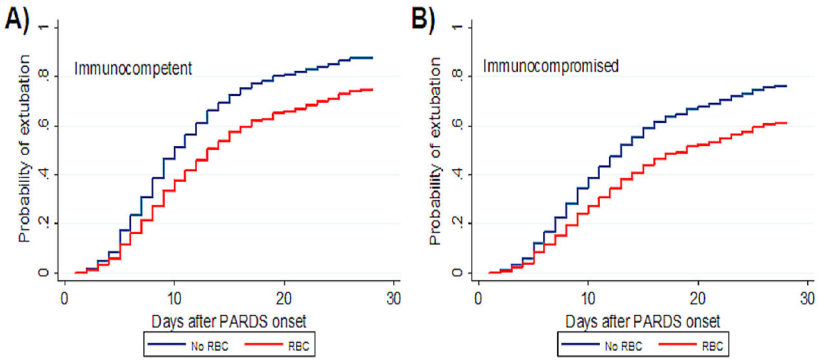

Figure 1.

Probability of successful extubation by 28 days after pediatric acute respiratory distress syndrome (PARDS) onset, given the competing risk of death (subdistribution hazard ratio 0.65, 95% CI 0.51 to 0.83). Patients that received red blood cells (RBC; red) and those that did not receive RBC (blue). Curves are adjusted for Pediatric Risk of Mortality (PRISM) III and PaO_2/FiO_2 at 24 hours after PARDS onset, and shown separately for (A) immunocompetent and (B) immunocompromised patients.

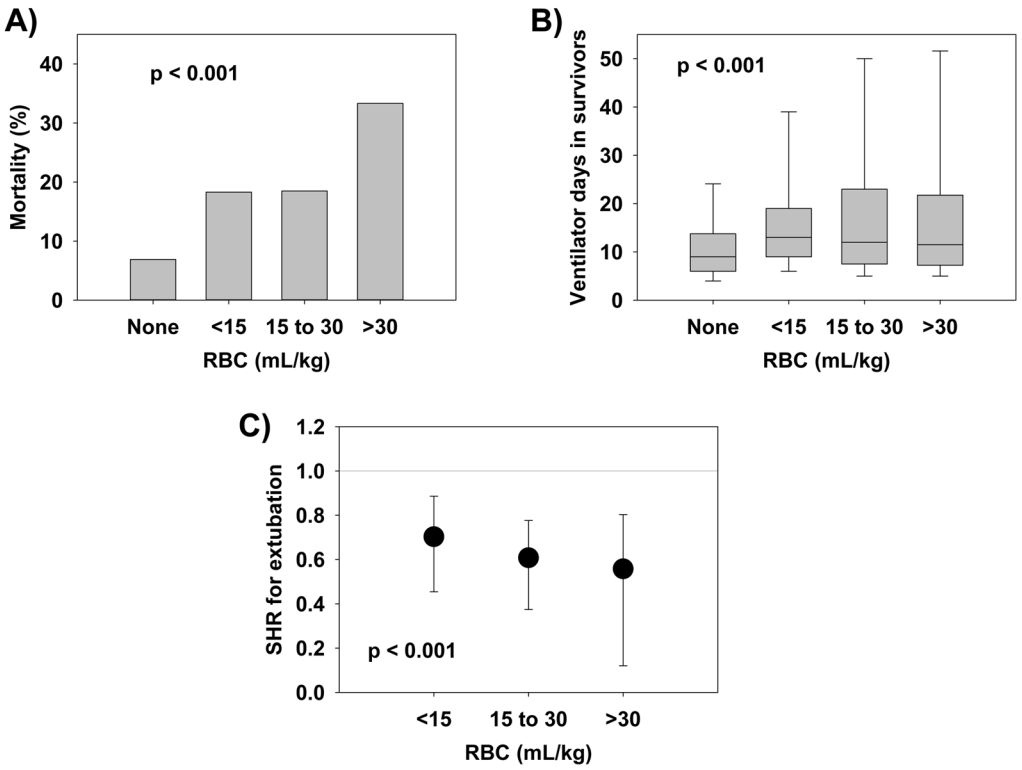

Figure 2.

Dose response curves showing the associations between increasing amounts of red blood cells (RBC) and (A) mortality, (B) ventilator days among survivors, and (C) subdistribution hazard ratio (SHR) from competing risk regression reflecting probability of extubation. RBC doses are expressed as milliliters per kilogram (mL/kg) of actual body weight.

Table 1

Characteristics of the PARDS Cohort

Variable	All patients (n = 357)	Survivors (n = 310)	Non-survivors (n = 47)	*p* value
Age (years)	4.1 [1.3, 12.1]	3.9 [1.3, 11.4]	6.3 [1.4, 15.1]	0.132
Female/male (%/%)	154/203 (43/57)	132/178 (43/57)	22/25 (47/53)	0.637
PRISM III at 12 hours	10 [5, 17]	9 [5, 15]	20 [11, 31]	< 0.001
Immunocompromised (%)	68 (19)	43 (14)	25 (53)	< 0.001
Cause of PARDS (%)				
Infectious pneumonia	203 (57)	180 (58)	23 (49)	
Aspiration pneumonia	34 (10)	30 (10)	4 (8.5)	
Non-pulmonary sepsis	73 (20)	62 (20)	11 (23)	0.572
Trauma	26 (7)	21 (7)	5 (11)	
Other	21 (6)	17 (5)	4 (8.5)	
Non-pulmonary organ dysfunctions at PARDS onset	2 [1, 3]	1 [1, 2]	3 [2, 4]	< 0.001
Vasopressor score	9 [3, 18]	8 [3, 16]	17 [5, 30]	0.004
Fluid balance at 72 hours (mL/kg)	90 [31, 175]	88 [30, 170]	121 [46, 265]	0.017
PARDS onset				
PaO_2/FiO_2	160 [113, 217]	161 [118, 218]	136 [81, 205]	0.099
OI	10 [7, 16]	10 [7, 15.5]	11.8 [6.6, 25]	0.107
PIP (cmH_2O)	30 [25, 35]	30 [25, 35]	30.5 [28, 36.8]	0.174
PEEP (cmH_2O)	10 [8, 12]	10 [8, 12]	10 [8, 12]	0.926
ΔP (cmH_2O)	21 [17, 25]	20 [17, 24]	21 [18, 26]	0.176
V_T (mL/kg)	7.5 [6.7, 8.5]	7.5 [6.7, 8.5]	7.6 [6.5, 8.3]	0.771
24 hours after PARDS onset				
PaO_2/FiO_2	226 [165, 280]	231 [172, 284]	174 [106, 236]	< 0.001
OI	6.8 [5, 10.9]	6.5 [4.8, 10.5]	9.2 [6.2, 19.6]	< 0.001
PIP (cmH_2O)	27 [24, 32]	27 [23, 31]	30 [26, 35]	0.005
PEEP (cmH_2O)	10 [8, 10]	10 [8, 10]	10 [8, 12]	0.051
ΔP (cmH_2O)	18 [14, 22]	17 [14, 22]	21 [15, 23]	0.020
V_T (mL/kg)	7.3 [6.5, 8.1]	7.3 [6.5, 8.1]	7.1 [6.2, 8]	0.617
Transfusions at 72 hours (%)				
Any	190 (53)	153 (49)	37 (79)	< 0.001
RBC only	71 (20)	67 (22)	4 (9)	0.048
FFP only	11 (3)	9 (3)	2 (4)	0.644
Platelets only	12 (3)	12 (4)	0	0.379
RBC + FFP	16 (4)	13 (4)	3 (6)	0.453
RBC + platelets	25 (7)	13 (4)	12 (26)	< 0.001
FFP + platelets	12 (3)	10 (3)	2 (4)	0.663
RBC + FFP + platelets	43 (12)	29 (9)	14 (30)	< 0.001

FFP: fresh frozen plasma; OI: oxygenation index; PARDS: pediatric acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; PICU: pediatric intensive care unit; PIP: peak inspiratory pressure; ΔP: driving pressure (PIP minus PEEP); PRISM: Pediatric Risk of Mortality; RBC: red blood cells; V_T: tidal volume; VFD: ventilator-free days

Table 2

Cox regression for 28-day survival (hazard ratio > 1 means associated with worse survival)

Model	Hazard ratio	95% CI	*p* value
Any transfusion			
PRISM III at 12 hours	1.08	1.05 to 1.11	< 0.001
Immunocompromised (yes)	2.83	1.45 to 5.56	0.002
PaO_2/FiO_2 at 24 h (per increase in 20)	0.92	0.84 to 1.00	0.045
Any transfusion (yes)	1.33	0.55 to 3.21	0.524
Any RBC			
PRISM III at 12 hours	1.08	1.05 to 1.10	< 0.001
Immunocompromised (yes)	2.83	1.49 to 5.40	0.002
PaO_2/FiO_2 at 24 h (per increase in 20)	0.93	0.86 to 1.02	0.110
Any RBC (yes)	2.01	0.96 to 4.22	0.063
Any FFP			
PRISM III at 12 hours	1.08	1.05 to 1.11	< 0.001
Immunocompromised (yes)	3.06	1.55 to 6.04	0.001
PaO_2/FiO_2 at 24 h (per increase in 20)	0.91	0.84 to 0.99	0.038
Any FFP (yes)	0.98	0.44 to 2.21	0.963
Any platelets			
PRISM III at 12 hours	1.08	1.05 to 1.11	< 0.001
Immunocompromised (yes)	2.92	1.39 to 6.13	0.030
PaO_2/FiO_2 at 24 h (per increase in 20)	0.91	0.84 to 1.00	0.039
Any platelets (yes)	1.10	0.47 to 2.60	0.822

FFP: fresh frozen plasma; PRISM: Pediatric Risk of Mortality; RBC: red blood cells

Table 3

Competing risk regression for successful extubation (subdistribution hazard ratio > 1 means associated with earlier extubation) by 28 days after pediatric acute respiratory distress syndrome onset

Model	Subdistribution hazard ratio	95% CI	*p* value
Any transfusion			
PRISM III at 12 hours	0.98	0.96 to 0.99	0.001
Immunocompromised (yes)	0.66	0.46 to 0.94	0.020
PaO_2/FiO_2 at 24 h (per increase in 20)	1.11	1.09 to 1.14	< 0.001
Any transfusion (yes)	0.79	0.63 to 1.01	0.056
Any RBC			
PRISM III at 12 hours	0.98	0.96 to 0.99	0.001
Immunocompromised (yes)	0.69	0.48 to 0.98	0.037
PaO_2/FiO_2 at 24 h (per increase in 20)	1.11	1.08 to 1.14	< 0.001
Any RBC (yes)	**0.65**	**0.51 to 0.83**	**0.001**
Any FFP			
PRISM III at 12 hours	0.97	0.96 to 0.99	< 0.001
Immunocompromised (yes)	0.62	0.43 to 0.89	0.009
PaO_2/FiO_2 at 24 h (per increase in 20)	1.11	1.09 to 1.15	< 0.001
Any FFP (yes)	0.99	0.72 to 1.37	0.970
Any platelets			
PRISM III at 12 hours	0.97	0.96 to 0.99	0.001
Immunocompromised (yes)	0.65	0.45 to 0.94	0.024
PaO_2/FiO_2 at 24 h (per increase in 20)	1.12	1.08 to 1.15	< 0.001
Any platelets (yes)	0.90	0.64 to 1.26	0.526

FFP: fresh frozen plasma; PRISM: Pediatric Risk of Mortality; RBC: red blood cells