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Early Packed Red Blood Cell Transfusion and Acute Respiratory Distress Syndrome after Trauma

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Background: **Transfusion of packed red blood cells (PRBCs) is a risk factor for acute respiratory distress syndrome (ARDS) in trauma patients. Yet, there is a paucity of information regarding the risk of ARDS with incremental PRBCs exposure.**

Methods: **For this retrospective analysis, eligible patients from National Study on Costs and Outcomes of Trauma were included. Our main exposure was defined as units of PRBCs transfused during the first 24 h after admission. The main outcome was ARDS.**

Results: **A total of 521 (4.6%) of 14070 patients developed ARDS, and 331 patients (63.5%) who developed ARDS received PRBCs transfusion. Injury severity, thoracic injury, polytrauma, and pneumonia receiving more than 5 units of fresh frozen plasma and 6–10 units of PRBCs were independent predictors of ARDS. Patients receiving more than 5 units of PRBCs had higher risk of developing ARDS (patients who received 6–10 units: adjusted odds ratio 2.5, 95% CI 1.12–5.3; patients who received more than 10 units: odds ratio 2.6, 95% CI 1.1–6.4). Each additional unit of PRBCs transfused conferred a 6% higher risk of ARDS (adjusted odds ratio 1.06; 95% CI 1.03–1.10).**

Conclusions: **Early transfusion of PRBCs is an independent predictor of ARDS in adult trauma patients. Conservative transfusion strategies that decrease PRBC exposure by even 1 unit may be warranted to reduce the risk of ARDS in injured patients.**

ANNUAL blood product use is estimated to be 14,182,000 units of packed red blood cells (PRBCs) and whole blood combined, with an estimated cost of $201.07 per unit of PRBCs and $63.67 per unit of whole blood per year.[1] Research over the past decade has demonstrated that allogeneic blood transfusion is associated with detrimental immunomodulatory effects,[2,3] which may result in acute respiratory distress syndrome (ARDS) in trauma patients.[4–6] Alterations in immunomodulation and proinflammatory mediators may be responsible for the development of ARDS after trauma.[7–9]

Transfusion of PRBCs, platelets, and fresh frozen plasma are all associated with the development of ARDS in trauma patients.[4,6,10–12] Although transfusion of more than 10 units of PRBCs within a 12- to 48-h interval has been identified as a risk factor for ARDS in trauma patients,[13–15] some smaller studies demonstrated that the transfusion of even a single unit of PRBCs is associated with increased mortality and ARDS.[4,16] However, Sadis *et al.*[11] recently reported that ARDS was less related to early large volume PRBCs transfusion than to circulatory shock, polytrauma, or thoracic trauma. Therefore, it remains unknown how much of the relationship between blood transfusion and ARDS is a result of the transfusion itself *versus* other confounders such as injury severity, chest trauma, circulatory shock, pneumonia, and/or long bone fractures.[11,17,18] Most studies investigating these questions are single center and are statistically underpowered to definitively answer this question.[4,6,10,11,14,19] Using the National Study on Cost and Outcomes of Trauma (NSCOT) database, we examined the relationship between volume of early PRBC transfusion and ARDS.

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Materials and Methods

Study Design

This study used data from the NSCOT, a multicenter, prospective cohort study of injured patients treated in 18 trauma centers and 51 large nontrauma centers in 14 states across the United States.[20] All of the participating centers received approval for the study from their institutional review boards. Patients were recruited into the study during an 18-month period: July 1, 2001 to November 30, 2002. The inclusion criteria for the patients were 18 to 84 yr of age and at least one injury of Abbreviated Injury Scale score of 3 or greater. Patients were excluded if they presented with no vital signs and were pronounced dead within 30 min of arrival, had injury occurring more than 24 h before hospital arrival, had major burns, had primary diagnosis of hip fracture for patients 65 yr of age or older, spoke neither English nor Spanish, were non-US residents, or were incarcerated or homeless at the time of injury. Patient recruitment details have been previously described.[20] The eligible patients who died during the index hospitalization were identified through medical record review. Eligible

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patients who lived to discharge were selected on the basis of a sampling scheme with a goal of enrolling evenly distributed among centers, age groups (18–64 yr of age, 65–84 yr of age), groups defined by injury severity, and area of injury. Every in-hospital death but only a random sample of patients discharged alive who had completed medical record data were included, yielding a total of 5,191 eligible participants (of whom 1,104 died in the hospital and 4,087 were discharged alive). It was necessary to weight data on the 5,191 patients for 2 reasons. First, the sampling protocol selected all patients who died in the hospital but only a proportion of patients discharged alive. Second, not all patients selected for inclusion in the study were enrolled. The resulting sampling weights consist of the reciprocal product of two probabilities: the conditional probability of being selected and the probability of being enrolled and having data abstracted from the medical records, given that the patient was selected. An extensive description of the sampling strategy and weighting scheme is described in our previous study.[20] The reference population to which inferences are made for the NSCOT study consists of 15,400 eligible patients. There were 924 patients who received care at a non-NSCOT hospital before transfer to a participating center who were further excluded. This yielded 14,476 patients. Furthermore, 406 patients who died within the first 24 h at NSCOT hospitals were excluded, resulting in 14,407 patients enrolled in this study. We were primarily interested in the PRBCs transfusion administered within the first 24 h (early) after hospital admission.

Measurements

For this study, 14,070 patients were included. Our main exposure was as the number of units of PRBCs received within the first 24 h of presenting to hospital; this was analyzed both as a continuous variable and categorized into four groups: 0, 1–5, 6–10, and > 10 units of transfused PRBCs. Outcomes were the development of ARDS and in-hospital mortality. The diagnosis of ARDS was made by the attending physicians at the index hospitals. ARDS was defined by the American-European Consensus Conference definition[21]: $Pao_2/Fio_2 < 200$ mmHg, bilateral infiltrates seen on frontal chest radiograph and pulmonary capillary wedge pressure ≤ 18 mmHg when measured, or no clinical evidence of left atrial hypertension. Patients were deemed to have a diagnosis of pneumonia if they met all the following criteria within 3 days: (1) radiologic - new infiltrate or cavitation with air-fluid level persisting for at least 24 h; (2) clinical – fever (≥ 38.3°C) or hypothermia (≤ 36.0°C) and white blood count greater than 10^5 or less than 4×10^3 or greater than 25% increase above last value or bands greater than 10%; (3) bacteriologic confirmation (demonstrated by at least one) – positive blood culture with same organism as identified in sputum or other respiratory culture OR protected brush specimen with at least 10^3 cfu/ml pathogen OR BAL with greater than 10^4 cfu/ml pathogen OR nonbronch BAL with greater than 10^3 cfu/ml pathogen OR positive Gram stain with at least 3+ of one type of bacteria OR positive semiquantitative sputum culture with at least 3+ growth of one type of pathogenic organism (if not quantitative, then must have moderate or heavy growth).

Statistical Analyses

All analyses were performed using sampling weights to obtain the population of eligible patients, which accounted for being selected and enrolled in the study.[20] Data missing were fewer than 5% of patients except for platelets transfusion (6.1%), cryoprecipitate (7.2%), and the first score for the Glasgow coma scale (13.4%). We performed the multiple imputations of missing values using the sequential regression imputation method.[22] Ten multiple imputation data sets were used to account for the missing covariates. Estimates and standard errors were combined using Rubin's rules.[23] Robust standard errors were computed to account for clustering within hospitals. We determined the associations among patient's characteristics and ARDS and PRBCs transfusion units using chi-square statistics and *t* test for categorical and continuous variables, respectively.

To determine which characteristics were independently associated with development of ARDS, we developed an adjusted logistic regression model. All of the covariates that were statistically significant at $P \leq 0.15$ in the unadjusted analyses except age were entered simultaneously into the model. Backwards elimination was then used to individually remove the most nonsignificant ($P > 0.05$) characteristic, and the model was refit. The adjusted model contained only statistically significant variables. All variables that were significant in the unadjusted regressions, but not included in the final model, were tested again for statistical significance in this adjusted model. No other characteristics were found to be statistically significant. The covariates tested were not collinear with each other; the variance inflation factor was between 1.1 and 2.5.

To determine the effects of PRBC transfusion on the development of ARDS and in-hospital death, we used multivariate weighted logistic regression models for development of ARDS and in-hospital mortality with the robust error variance procedure.[24] Both continuous and categorical PRBCs transfusion units were used. Confounding variables were chosen for inclusion in these models by using a change in estimates approach. Briefly, if the addition of a variable to the model changed the estimate of the main effect (PRBCs transfusion) by more than 10%, then the variable was considered to be an important confounder and was kept in the model.[25] To

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check the linearity of continuous transfused units of PRBCs in logit with the outcomes, we explored the lowess-smoothed univariate graphs and also added the Box-Tidwell transformed PRBCs in to the models. There was no evidence to suggest anything other than a linear logit relationship between PRBCs and outcomes.

Adjusted confounders for the categorical PRBCs transfusion on the development of ARDS included new injury severity score (NISS), injury mechanism, first emergency department Glasgow Coma motor score (ED GCS), maximum thorax Abbreviated Injury Severity score, pneumonia, polytrauma, other blood products units, including fresh frozen plasma and trauma center designation (table 1 and table 2). Adjusted confounders for the continuous PRBCs transfusion on the development of ARDS included NISS, race, injury mechanism, first ED GCS, maximum thorax Abbreviated Injury Severity score, pneumonia, polytrauma, other blood products units, including fresh frozen plasma, platelet, and cryoprecipitate and trauma center designation (table 1 and table 2). Adjusted confounders for the categorical PRBCs transfusion on the in-hospital death included age, NISS, Charlson comorbidity index score, first ED GCS, first ED measurement of systolic blood pressure less than 90 mmHg, maximum thorax Abbreviated Injury Severity score, maximum head Abbreviated Injury Severity score, long bone fracture, pneumonia, ARDS, other blood products transfusion units, including fresh frozen plasma, platelet, and cryoprecipitate (table 1 and table 2). Adjusted confounders for the continuous PRBCs transfusion on the in-hospital death included age, NISS, injury mechanism, Charlson comorbidity index score, first ED GCS, first ED measurement of systolic blood pressure less than 90 mmHg, maximum head Abbreviated Injury Severity score, pneumonia, ARDS, and other blood products transfusion units, including fresh frozen plasma, platelet, and cryoprecipitate (table 1 and table 2). We did not find any sizable collinearity among the covariates adjusted in the models. Adjusted odds ratios of PRBCs transfusion are reported along with their 95% confidence intervals. The data were analyzed using SAS 9.1 (SAS institute, Cary, NC) and STATA 10 software (Stata Corporation, College Station, TX).

Results

Study Population

A total of 14,476 eligible NSCOT patients were enrolled. Among the patients who met the enrollment criteria, 406 patients who died within the first 24 h were excluded. Consequently, 14,070 patients were included in this analysis (table 1). Patients were primarily male (n = 9637, 68.5%) with blunt trauma (n = 12,188, 86.6%). Most patients were non-Hispanic whites (60.2%). The average age was 43.3 ± 30 yr with a mean injury severity score of 29.9 ± 22.

Patients who received more units of PRBCs were significantly younger and male, had greater injury severity, suffered more penetrating injuries, and had lower ED GCS and Charlson comorbidity index score (table 1). Shock was present more often in patients who received a greater number of blood transfusions. Similarly, pneumonia, polytrauma, thoracic injuries, and long bone fractures were associated with greater PRBC transfusion. The majority of patients who received PRBCs were treated in trauma centers (> 80% in each group). Hospital and intensive care unit length of stay were greater in patients who received higher units of PRBCs ($P < 0.001$). Patients who received the greatest number of transfused PRBCs also received greater quantities of other blood products, including fresh frozen plasma, platelets, and cryoprecipitate (table 1).

ARDS

ARDS developed in 521 patients (4.6%); 504 eligible patients (11%) had pulmonary artery catheters, and pulmonary artery catheters were performed in 122 patients (57%) who had a diagnosis of ARDS. A total of 331 (63.5%) received early PRBCs transfusion. Patients who developed ARDS received significantly greater quantities of PRBCs during the first 24 h after admission (6 ± 12.2 *vs.* 1.1 ± 6.1 units; $P < 0.001$; table 2). The prevalence of ARDS increased with the higher units of early PRBCs transfusion (table 1).

Baseline characteristics between ARDS patients and non-ARDS patients are shown in table 2. ARDS patients were primarily men and had higher injury severity and lower ED motor GCS score. The incidence of ED shock, thoracic injury, head injury, and polytrauma was higher in the ARDS group. Most ARDS patients also had pneumonia and received more non-PRBCs transfusions. Age, race, mechanism of injury, Charlson comorbidity index score, and the presence of long bone fracture were not associated with the development of ARDS. The majority of patients who developed ARDS were treated in a trauma center.

Table 3 demonstrates the clinical predictors for ARDS in the final logistic regression model. Mean NISS, presence of thoracic injury, polytrauma, pneumonia, and receiving more than 5 units of fresh frozen plasma and 6–10 units of PRBCs were independent predictors for ARDS.

To investigate the effect of early PRBC transfusion on ARDS, two multivariate logistic regression analyses were performed. First, we examined the effects of the number of units of PRBCs transfused in the initial 24 h after hospital admission categorized into four predetermined groups, with group 1 serving as a reference group (table 4). There was a greater risk for the developing ARDS if patients received more than 5 units of PRBCs (group 3: adjusted odds ratio 2.48, 95% CI 1.17–5.26; group 4 *vs.* group 1: adjusted odds ratio 2.62, 95% CI 1.08–6.37).

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Table 1. Patients Characteristics Stratified by Requirements of PRBCs Transfusion During the Initial 24 h

		PRBCs Transfusion, Units				
	n (weighted n)	0 (Group 1), 3,638 (11,136)	1–5 (Group 2), 635 (1,899)	6–10 (Group 3), 194 (534)	> 10 (Group 4), 178 (501)	*P*
Age, yr, mean (SD)	4,645 (14,070)	44.1 (34.2)	43.0 (32.0)	38.7 (27.2)	> 38.8 (25.2)	0.001
Gender, %						0.01
Male	3,061 (9,636)	68.4	65.5	69.2	81	
Female	1,584 (4,434)	31.6	34.5	30.8	19	
NISS, mean (SD)*	4,645 (14,070)	20.9 (21.7)	29.1 (23.9)	32.3 (22.1)	37.1 (23.4)	< 0.0001
Race, %						0.04
Hispanic	664 (2,348)	16.1	20.2	22	10.8	
Non-Hispanic, white	3,013 (8,463)	61.4	55.3	54.3	56.4	
Non-Hispanic, non-white	969 (3,259)	22.5	24.6	23.8	32.8	
Mechanism of injury, %						< 0.0001
Penetrating	492 (1,882)	11	17.8	29	33.5	
Blunt	4,153 (12,188)	89	82.2	80	66.5	
Charlson comorbidity index score†						0.002
0	3,008 (10,010)	70	71.4	82.2	83.5	
1	719 (2,065)	15.2	15.4	6.9	8.8	
2	384 (900)	6.5	6.5	5.8	4.3	
≥3	534 (1,095)	8.3	6.7	5.2	3.4	
First ED assessment of GCS motor score‡						< 0.0001
6	3,612 (11,287)	84.3	69.3	61.5	50.1	
4–5	332 (922)	5.5	10.4	9.9	12.8	
2–3	76 (174)	0.9	2.8	2	1.9	
1, not chemically paralyzed	231 (474)	2.6	4.2	5.6	14	
1, chemically paralyzed	394 (1,213)	6.7	13.2	21	21.2	
First ED measurement of SBP < 90 mmHg, %						< 0.0001
No	4,455 (13,613)	98.9	93.4	82	76.7	
Yes	190 (457)	1.1	6.6	18	23.3	
Maximal AIS score, thorax %§						< 0.0001
< 3	3,149 (9,434)	71.6	56.4	40.6	35	
≥ 3	1,496 (4,636)	28.4	43.6	59.4	65	
Maximal AIS score, head %§						0.65
< 3	2,844 (9,351)	65.9	68.5	71	67.2	
≥ 3	1,801 (4,719)	34.1	31.8	29	32.8	
Long bone fracture, %						< 0.0001
No	4,332 (12,960)	95.3	81.9	76.9	77.3	
Yes	313 (1,110)	4.7	18.1	23.1	22.7	
Pneumonia, %						< 0.0001
No	4,150 (12,676)	93.1	83.6	75.4	64.3	
Yes	495 (1,394)	6.9	16.4	24.6	35.7	
Polytrauma, %						< 0.0001
No	3,330 (9,920)	78.3	46.1	38.3	23.7	
Yes	1,315 (4,150)	21.7	53.9	61.7	76.4	
Trauma center designation, %						< 0.0001
No	1,921 (3,961)	32	16.2	11.7	5.9	
Yes	2,724 (10,110)	68	83.8	88.3	94.1	
ICU admission						< 0.0001
No	2,074 (7,220)	60.2	24.4	7.4	2.2	
Yes	2,571 (6,850)	39.8	75.6	92.6	97.8	

(*continued*)

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Table 1. Continued

	n (weighted n)	PRBCs Transfusion, units: 0 (Group 1), 3,638 (11,136)	1–5 (Group 2), 635 (1,899)	6–10 (Group 3), 194 (534)	> 10 (Group 4), 178 (501)	P
ICU length of stay, days, mean (SD)	2,571 (6,850)	6.4 (12.7)	9.6 (18.7)	11.4 (26.5)	15.3 (22.4)	< 0.0001
Hospital length of stay, days, mean (SD)	4,645 (14,070)	7.9 (15.5)	16.8 (28.2)	19.6 (37.9)	24.0 (32.2)	< 0.0001
Fresh frozen plasma units						< 0.0001
0	4,084 (12,523)	97.9	76.1	26.4	7.3	
1– 5	365 (1,071)	1.8	22.0	57.4	29.3	
> 5	196 (476)	0.3	1.9	16.1	63.3	
Platelets units						< 0.0001
0	4,320 (13,135)	99.3	88.0	52.3	25.7	
1-5	100 (341)	0.1	4.1	18.5	30.2	
>5	225 (594)	0.6	8.0	29.3	44.1	
Cryoprecipitate units						< 0.0001
No	4,552 (13,780)	99.97	98.5	92.6	56.4	
Yes	93 (290)	0.03	1.5	7.4	43.6	
Outcomes						
ARDS, %						< 0.0001
No	4,431 (13,549)	98.3	92.7	85.9	76.7	
Yes	214 (521)	1.7	7.3	14.1	23.3	
In-hospital mortality, %						< 0.0001
No	3,958 (13,368)	96.2	92.7	88.4	84.9	
Yes	687 (702)	3.8	7.3	11.6	15.1	

* NISS can range from 1 to 75, with higher scores indicating more severe injury. † Scores for the Charlson comorbidity index can range from 0 (no serious coexisting conditions) to 17, with higher scores indicating a greater number of coexisting conditions. ‡ Motor scores for the GCS can range from 1 to 6, with higher numbers indicating better function. § Scores for the AIS can range from 1 to 6, with higher scores indicating more severe injury.

AIS = Abbreviated Injury Scale; ARDS = acute respiratory distress syndrome; ED = emergency department; GCS = Glasgow Coma Scale; ICU = intensive care unit; NISS = New Injury Severity Score; PRBC = packed red blood cell; SBP = systolic blood pressure.

We then evaluated the units of PRBCs transfused during the first 24 h categorized as a continuous variable when controlling for all confounding variables. The effect of units of PRBCs transfused during the first 24 h after hospital admission remained significant for ARDS (adjusted odds ratio 1.06, 95% CI 1.03–1.10). There was a 6% higher risk of ARDS for additional unit of PRBCs transfused.

In-hospital Mortality

Patients with higher PRBC transfusion rates during the initial 24 h had a higher in-hospital mortality rate, independent of injury severity (group 4, 15.1%; group 3, 11.6%; group 2, 7.3%; $P < 0.001$). The mortality rate was 3.8% in patients who did not receive PRBC transfusion (table 1). In addition, 21% of the patients who had ARDS died, compared with only 4% of the patients who did not develop ARDS ($P < 0.001$) (table 2).

To identify the effect on in-hospital mortality of total units of transfused PRBCs (categorized into our four predetermined groups) during the initial 24 h, multivariate logistic regression analysis was performed after adjusting for all confounding variables. There was no association between the number of transfused units and in-hospital mortality (table 4). Nevertheless, the effect of the number of units of PRBCs (categorized as a continuous variable) becomes significant for hospital mortality, with an odds ratio of 1.05 (95% CI 1.0–1.1, $P = 0.04$) after controlling for all confounding variables (an approximately 5% increased risk of hospital mortality with each additional unit of transfused PRBCs).

Discussion

Transfusion therapy is common in trauma patients. Injury is the fifth leading cause of death in patients over 18 yr of age,[26] and PRBCs are the most commonly transfused blood products in hospital.[27,28] We conducted this study to better understand the relationship between early PRBC transfusion and ARDS in trauma patients. The main findings of our study are that, independent of injury type, injury severity, or pneumonia, (1) early PRBCs transfusion of more than 5 units during the first 24 h of hospital admission predicted ARDS and (2) each unit of PRBCs transfused early after admission increased the risk of ARDS by 6%. This large multicenter study quantifies and confirms the increased risk of ARDS with early PRBC transfusion in trauma patients.

Causal relationships between transfusion products and the development of ARDS include but are not limited to[17] (1) host reactions to antigranulocyte antibodies,[29] (2) interactions between nonspecific systemic inflammatory mediators induced by either cellular or soluble fac-

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Table 2. Potential Risk Factors for ARDS

	n (weighted n)	Non-ARDS Patients, 4,431 (13,549)	ARDS Patients, 214 (521)	*P*
Age, yr, mean (SD)	4,645 (14,070)	43.5 (33.7)	43.1 (26.3)	0.63
Gender, %				0.003
Male	3,061 (9,637)	68.2	76.6	
Female	1,584 (4,434)	31.8	23.4	
NISS, mean (SD)*	4,645 (14,070)	22.4 (22.9)	37.5 (21.1)	< 0.0001
Race, %				0.58
Hispanic	664 (2,349)	16.8	14.3	
Non-Hispanic, white	3,013 (8,463)	59.8	68.3	
Non-Hispanic, non-white	969 (3,259)	23.4	17.4	
Mechanism of injury, %				0.8
Penetrating	492 (1,882)	13.4	12.4	
Blunt	4,153 (12,188)	86.6	87.6	
Charlson comorbidity index score†				0.77
0	3,008 (10,010)	71	73.7	
1	719 (2,066)	14.7	14.2	
2	384 (900)	6.4	5.6	
≥ 3	534 (1,095)	7.8	6.4	
First ED assessment of GCS motor score‡				< 0.0001
6	3,612 (11,287)	81.6	43	
4–5	332 (922)	6.3	13	
2– 3	76 (174)	1.2	1.9	
1, not chemically paralyzed	231 (474)	3	11.9	
1, chemically paralyzed	394 (1,213)	7.8	30.1	
First ED measurement of SBP < 90 mmHg, %				0.002
No	4,455 (13,613)	97.1	88.8	
Yes	190 (457)	2.9	11.2	
Maximal AIS score, thorax %§				< 0.0001
< 3	3,149 (9,434)	68.4	32.4	
≥ 3	1,496 (4,636)	31.6	67.6	
Maximal AIS score, head %§				0.001
< 3	2,844 (9,351)	67	51.3	
≥ 3	1,801 (4,719)	33	48.7	
Long bone fracture, %				0.25
No	4,332 (12,960)	92.3	88.2	
Yes	313 (1,110)	7.7	11.8	
Pneumonia, %				< 0.0001
No	4,150 (12,676)	92	39.9	
Yes	495 (1,394)	8	60.1	
Polytrauma, %				< 0.0001
No	3,330 (9,920)	72.4	21.5	
Yes	1,315 (4,150)	27.6	78.5	
ICU admission				
No	2,074 (7,220)	53.3	0	< 0.0001
Yes	2,571 (6,850)	46.7	100	
ICU length of stay, days, mean (SD)	2,571 (6,850)	7.1 (15.2)	20.0 (21.1)	< 0.0001
Hospital length of stay, days, mean (SD)	4,645 (14,070)	9.3 (19.1)	31.3 (25.3)	< 0.0001
PRBC transfusion, units, mean (SD)	4,645 (14,070)	1.1 (6.1)	6.0 (12.2)	< 0.0001
PRBC transfusion, units		%	%	< 0.0001
0	3,638 (11,136)	80.8	36.5	
1–5	635 (1,899)	13	26.7	
6–10	194 (534)	3.4	14.4	
> 10	178 (501)	2.8	22.4	
Fresh frozen plasma transfusion, units				< 0.0001
0	4,084 (12,523)	90.4	52.2	
1–5	365 (1,071)	6.9	25.7	
> 5	196 (476)	2.7	22.1	
Platelets transfusion, units				< 0.0001
0	4,320 (13,135)	94.2	72.0	
1–5	100 (341)	2.1	10.8	
> 5	225 (594)	3.7	17.2	

(*continued*)

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Table 2. Continued

	n (weighted n)	Non-ARDS Patients, 4,431 (13,549)	ARDS Patients, 214 (521)	*P*
Cryoprecipitate transfusion, units				< 0.0001
No	4,552 (13,780)	98.4	86.0	
Yes	93 (290)	1.6	14.0	
Trauma center designation, %				< 0.0001
No	1,921 (3,961)	28.9	8.1	
Yes	2,724 (10,110)	71.1	91.9	
In-hospital death				< 0.0001
No	3,958 (13,368)	95.6	79.3	
Yes	687 (702)	4.4	20.7	

* NISS can range from 1 to 75, with higher scores indicating more severe injury. † Scores for the Charlson comorbidity index can range from 0 (no serious coexisting conditions) to 17, with higher scores indicating a greater number of coexisting conditions. ‡ Motor scores for the GCS can range from 1 to 6, with higher numbers indicating better function. § Scores for the AIS can range from 1 to 6, with higher scores indicating more severe injury.

AIS = Abbreviated Injury Scale; ARDS = acute respiratory distress syndrome; ED = emergency department; GCS = Glasgow Coma Scale; ICU = intensive care unit; NISS = New Injury Severity Score; PRBC = packed red blood cell; SBP = systolic blood pressure.

tors such as interleukin-8 and tumor necrosis factor-α, and (3) depressed immune responses leading to a higher risk of infection.[30] Antigranulocyte antibodies from donors play an important role in the classic immune-mediated transfusion-related acute lung injury (TRALI). Donor exposure to alloantigens typically occurs during pregnancy, approximately 10% of female donors test positive for leukocyte alloantibodies, with a rate as high as 27% in those with a number of greater pregnancies.[31,32] Recently, a randomized crossover study demonstrated a greater decrease in Pa_{O_2}/F_{IO_2} and higher levels of circulating tumor necrosis factor-α after receiving blood transfusion from multiparous donors when compared to nulliparous donors.[33] Initially, TRALI was thought to be primarily mediated by antibody-antigen interactions with leukocytes, leading to complement fixation, neutrophil activation, and resulting lung injury.[34] It is now recognized that neutrophils primed by other insults such as trauma, surgery, sepsis and ischemia–reperfusion can be subsequently activated by allogenic transfusion by both antibody- and non–antibody-mediated processes can be causative.[35] Neutrophils isolated from trauma patients who received allogeneic PRBCs transfusions demonstrate neutrophil priming as per measured increase in surface expression of CD11b/CD18 receptor sites, superoxide production, and elastase release, all of which may predispose to ALI and ARDS.[36] Biologically active agents thought to activate neutrophils are primarily related to blood storage and include lipids, antileukocyte antibodies, cytokines, and platelet-derived CD-40 ligand.[37] Priming may well be attenuated by prestorage leukoreduction, but clinical data are conflicting regarding effects on decreasing the incidence of TRALI.[38] Observational studies reported a number of associations between prolonged storage and adverse clinical outcomes, such as length of stay and mortality in a variety of populations, including critically ill and trauma patients.[39,40] However, results from randomized controlled trials assessing clinical consequences of prolonged storage are controversial, and a definitive clinical trial will be necessary to explore this association.[41,42]

Of the commonly used blood component therapy, cryoprecipitate and fresh frozen plasma have the highest rate of antibodies and are more associated with the development of both TRALI and ARDS compared to PRBCs.[11,17,36,43–45] In the original description of TRALI by Popovsky and Moore,[46] PRBCs were implicated in only 10 of 36 confirmed cases of TRALI; in a separate investigation, Holness *et al.*[47] implicated fresh frozen plasma as the cause in 50% of TRALI-associated deaths. Although, these studies were performed in all critically

Table 3. Independent Predictors of ARDS

Risk factor	Odds Ratio (95% CI)
Age, yr	1.02 (1.00–1.03)
NISS	1.02 (1.01–1.04)
Thoracic injury	1.57 (1.07–2.31)
Pneumonia	7.52 (4.48–12.60)
Polytrauma	2.77 (1.62–4.74)
PRBC transfusion units	
0	Ref
1–5	1.70 (0.72–4.03)
6– 10	2.24 (1.06–4.73)
>10	2.18 (0.93–5.11)
Fresh frozen plasma transfusion units	
0	Ref
1–5	1.66 (0.88–3.15)
> 5	2.55 (1.17–5.55)

ARDS = acute respiratory distress syndrome; NISS = New Injury Severity Scores; PRBC = packed red blood cell.

Table 4. Effect of the Amount of Transfused PRBCs on ARDS and In-hospital Mortality Adjusted for Significant Confounders

	ARDS, aOR (95% CI)	In-hospital Death, aOR (95% CI)
PRBC units		
1–5	1.88 (0.77–4.62)	1.13 (0.64–2.02)
6–10	2.48 (1.17–5.26)*	1.52 (0.82–2.83)
> 10	2.62 (1.08–6.37)*	0.93 (0.27–3.17)

* $P < 0.05$; Referent group = 0 PRBC units.

aOR = adjusted odds ratio; ARDS = acute respiratory distress syndrome; PRBC = packed red blood cell.

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ill patients, including trauma patients, our study within only trauma patients also demonstrated that receiving more than 5 units of fresh frozen plasma in the first 24 h had higher risk of developing ARDS.

Blood transfusion therapy depresses immune function[48,49] and is known to increase in intensive care unit length of stay[50] and postoperative infection.[51] Although we did not have leukoreduction data, adoption of PRBCs leukoreduction strategies remains controversial. Leukoreduction of PRBCs has been associated with reduction in late-onset ARDS[52] and has also had variable success decreasing mortality[38,53] However, a randomized controlled trial of 2780 medical and surgical patients found no benefit in in-hospital mortality, hospital length of stay, or total hospital costs when randomized to receive unmodified blood components or leukoreduced PRBCs and platelets.[54] In addition, Phelan and colleagues[55] demonstrated no impact of leukoreduction on mortality in trauma patients. Recently, a double-blind randomized controlled trial has demonstrated that prestorage leukoreduction had no effect on the incidence or timing of lung injury or on plasma measures of systemic alveolar and endothelial inflammation in trauma patients requiring transfusion.[56] We cannot comment on the effect of leukoreduction on the relationship between PRBCs transfusion and ARDS in this study because these data were not collected as part of the NSCOT database.

Recently, Hebert *et al.* recommended a transfusion trigger of 7 g/dL for most critically ill patients, and adherence to such recommendation may decrease the exposure of PRBCs to trauma patients. A recent quandary may be the reemergence of "early goal-directed therapy," which includes administration of PRBCs to increase global oxygen delivery by measuring central venous saturation with the goal of achieving a saturation of 70% as a surrogate.[57] While this strategy has been demonstrated to increase survival in patients with severe sepsis and septic shock when implemented during the initial 6 h of diagnosis, direct application to the trauma patient has not been routinely adopted. However, a recent trial in high-risk perioperative patients demonstrated efficacy as per reduced postoperative complications and reduced hospital length of stay when early goal-directed therapy was implemented, possibly lending itself to being one step closer to trials in the trauma patient population.[58] The consistent finding when early goal-directed therapy is applied is that transfusion rates with PRBCs are significantly increased compared to patients in the control limb. However, most literature has supported this concept in so far as outcomes go, thus the balance of when to administer and when to refrain from PRBCs administration may be being clarified. Importantly, one must not overstate the positive results of early goal-directed therapy being attributable to only transfusion of PRBCs; the algorithm involves several therapeutic steps to employ to achieve the algorithms stated goals, making it extremely difficult to tease out which one is most beneficial.

Early blood transfusion in critically ill patients is associated with multiorgan failure and increased mortality.[14,59,60] A published *post hoc* analysis from "Transfusion Requirements in Critical Care Trial" showed no differences in all-cause mortality and multiorgan failure between the restrictive and liberal transfusion groups, supporting a restrictive red blood cell transfusion strategy.[61] Similarly, we demonstrated that there is approximately 5% increased risk of hospital mortality with each additional unit of transfused PRBCs, although we did not find this correlation when we considered PRBCs as predetermined groups.

Several limitations of our study should be considered. We cannot determine the timing of ARDS onset except to say that the criteria were met at some point during hospitalization. Consequently, we cannot separate cases of TRALI from ARDS using the consensus definition[62] and determine the association between early transfusion and late onset of ARDS. However, receipt of PRBCs increases the risk of ARDS due to reasons such as directly infecting the patient due to the blood harboring a particular pathogen or possibly by immunosuppressing the patient in a way that lowers the threshold for the occurrence of ARDS when an additional "hit" is incurred. In addition, we obtained the diagnosis of pneumonia from data recorded in the NSCOT database; given the size and intent of the initial study, details as to the timing of pneumonia are not available. As a result, we are unable to state that pneumonia was associated with an increased risk of developing ARDS. However, the association between transfusion and ARDS existed in the multivariate regression model after adjusting for pneumonia. With regard to the independent predictors of ARDS, the lack of the effect of more than 10 units of PRBCs on ARDS may be the result of other unmeasured factors influencing ARDS in patients who received larger transfusions, such as the more complex critically injured patient.

The number of geriatric patients with severe trauma was small and excluded children and adolescents, and we cannot extrapolate our findings to these populations. Because the NSCOT is a study of the effectiveness of trauma centers in urban and suburban America, these results cannot be readily extrapolated to rural areas of the country. One concern is that some unmeasured variables and confounders might have been missed, although we have carefully considered the indications for early PRBCs transfusion and risk factors for the development of ARDS. Furthermore, we did not have information about whether PRBCs were leukoreduced or about the gender of donors, and neither did we know the age of transfused PRBCs. Multiparous female donors have shown to have higher antileukocyte antibodies and circulating concentrations of tumor necrosis factor–α,

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which can aggravate cognate antigen-antibody interactions in the development of TRALI. However, the effects of leukoreduced or the prolonged storage PRBCs on outcomes remain controversial.

In summary, early PRBCs transfusion is an independent risk factor for ARDS in trauma patients, and each unit of PRBCs transfused increases the risk of ARDS by 6%. Conservative PRBC transfusion strategies early after trauma may need to be considered as part of early goal-directed therapy protocols.

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