The Epidemiology of Transfusion-related Acute Lung Injury Varies According to the Applied Definition of Lung Injury Onset Time

Lisa K. Vande Vusse¹, Ellen Caldwell¹, Edward Tran², Laurie Hogl¹, Steven Dinwiddie², José A. López^{2,3}, Ronald V. Maier⁴, and Timothy R. Watkins^{1,2}

¹Division of Pulmonary and Critical Care Medicine, ³Division of Hematology, and ⁴Department of Surgery, University of Washington, Seattle, Washington; and ²Research Institute, Puget Sound Blood Center, Seattle, Washington

Abstract

Rationale: Research that applies an unreliable definition for transfusion-related acute lung injury (TRALI) may draw false conclusions about its risk factors and biology. The effectiveness of preventive strategies may decrease as a consequence. However, the reliability of the consensus TRALI definition is unknown.

Objectives: To prospectively study the effect of applying two plausible definitions of acute respiratory distress syndrome onset time on TRALI epidemiology.

Methods: We studied 316 adults admitted to the intensive care unit and transfused red blood cells within 24 hours of blunt trauma. We identified patients with acute respiratory distress syndrome, and defined acute respiratory distress syndrome onset time two ways: (1) the time at which the first radiographic or oxygenation criterion was met, and (2) the time both criteria were met. We categorized two corresponding groups of TRALI cases transfused in the 6 hours before acute respiratory distress syndrome onset. We used Cohen's kappa to measure agreement between the TRALI cases and implicated blood components identified by the two acute respiratory distress syndrome onset time definitions. In a nested case-control study, we examined potential risk factors for

each group of TRALI cases, including demographics, injury severity, and characteristics of blood components transfused in the 6 hours before acute respiratory distress syndrome onset.

Measurements and Main Results: Forty-two of 113 patients with acute respiratory distress syndrome were TRALI cases per the first acute respiratory distress syndrome onset time definition and 63 per the second definition. There was slight agreement between the two groups of TRALI cases ($\kappa = 0.16$; 95% confidence interval, -0.01 to 0.33) and between the implicated blood components ($\kappa = 0.15$, 95% confidence interval, 0.11 – 0.20). Age, Injury Severity Score, high plasma-volume components, and transfused plasma volume were risk factors for TRALI when applying the second acute respiratory distress syndrome onset time definition but not when applying the first definition.

Conclusions: The epidemiology of TRALI varies when applying two plausible definitions of acute respiratory distress syndrome onset time to severely injured trauma patients. A TRALI definition that standardizes acute respiratory distress syndrome onset time might improve reliability and align efforts to understand epidemiology, biology, and prevention.

Keywords: blood transfusion; lung injury; trauma

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Correspondence and requests for reprints should be addressed to Timothy R. Watkins, M.D., M.Sc., Harborview Medical Center, Campus Box 359762, 325 9th Avenue, Seattle, WA 98104. E-mail: timw@medicine.washington.edu

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Transfusion-related acute lung injury (TRALI) is a severe and sometimes fatal complication of blood component transfusion (1). Effective preventive strategies are needed, which requires an understanding of TRALI epidemiology and pathobiology. TRALI risk factors consistently identified by epidemiologic studies include blood transfusions from female donors and receipt of components containing cognate antibodies against human leukocyte antigen or human neutrophil antigen (2–5). Shock, sepsis, transfusion of blood components stored for extended periods, and transfusion of bioactive lipids from stored blood components are associated with TRALI in specific settings (4, 6–8). TRALI is likely underrecognized (9), particularly in critically ill patients with multiple coexisting risk factors for lung injury (3).

To promote consistent research, the Canadian Consensus Conference and National Heart, Lung, and Blood Institute working group proposed standardized TRALI definitions (10–12). Both define TRALI as new-onset acute respiratory distress syndrome (ARDS) occurring within 6 hours of a blood component transfusion. Both definitions allow for the possibility that blood component transfusions contribute to lung injury in patients with preexisting risk factors. However, neither standardized definition specifies how ARDS onset time should be defined. Applying varied methods to determine ARDS onset time could reduce the reliability of the TRALI definition and lead to false conclusions about its risk factors and biology. In this study, we identified ARDS cases in a population of patients transfused after severe blunt trauma. We applied two plausible definitions of ARDS onset time and examined agreement between the two corresponding groups of TRALI cases transfused in the 6 hours before ARDS onset. We also examined agreement between the blood components implicated in these TRALI cases and determined clinical risk factors for each group of TRALI cases. We hypothesized that the use of different definitions for ARDS onset time would affect the epidemiology of consensus-defined TRALI, including the distribution of cases, characteristics of implicated blood components, and clinical risk factors.

Methods

Study Design

The Age of Transfused blood and Lung injury After transfusion Study (ATLAS) is an ongoing prospective cohort study at Harborview Medical Center (Seattle, WA) designed to examine clinical risk factors and biomarkers for transfusion-associated ARDS. The cohort includes patients aged 18 years or older who receive a red blood cell transfusion and are admitted to the intensive care unit within 24 hours of blunt trauma. We exclude patients who are not expected to survive more than 24 hours from injury, meet ARDS criteria before red blood cell transfusion, arrive at our emergency department more than 24 hours after injury, were transfused in the 6 months before injury or between injury and arrival at our hospital, or receive more than 15 red blood cell components within 24 hours of injury, and patients who are pregnant, in police custody, have isolated head injury, or refuse consent. We collect data on baseline characteristics, clinical interventions, complications, and outcomes from the time of emergency department arrival through hospital discharge. In order of priority, we record the start time of each blood transfusion from a barcode scanned in real time in the operating suite, the transfusion report that accompanies each unit, and nursing documentation in the electronic medical record. We obtain blood component and donor data from Puget Sound Blood Center (Seattle, WA), which supplies all blood components. Additional details on data collection and study definitions are included in the data supplement. All study participants consented to inclusion in the parent study.

The current secondary analysis of the ATLAS cohort included all patients enrolled between January 2010 and August 2013. We prospectively identified the incidence of ARDS according to the Berlin definition (13). Two trained observers reviewed all chest radiographs and computed tomography scans to determine the presence of bilateral infiltrates consistent with pulmonary edema. When observers disagreed, the decision was adjudicated by a third observer. We required that radiographic and oxygenation criteria both occur within a 24-hour period. We defined the timing of ARDS

onset two ways (Figure 1). The first definition identified ARDS onset as the time when the first of two criteria, oxygenation or radiographic, was fulfilled. The second definition identified ARDS onset as the time when both criteria were fulfilled. We considered all patients who received one or more blood transfusions within 6 hours before ARDS onset to be TRALI cases (10, 12). As a result, we identified two groups of TRALI cases—one corresponding to each ARDS onset time definition.

This study was approved by the University of Washington Institutional Review Board. Part of this study was previously published in abstract form (14).

Statistical Methods

We used Cohen's kappa (15) to measure agreement between the TRALI cases and implicated blood components identified by the two ARDS onset time definitions. We performed two nested case-control studies, applying the following steps separately for each group of TRALI cases. TRALI cases were matched to three control subjects on time-from-injury. We considered patient characteristics associated with ARDS in prior trauma studies (16, 17) as potential TRALI risk factors, including: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Injury Severity Score, direct chest injury (flail chest and/or lung contusion), shock (systolic blood pressure < 90 mm Hg) in the emergency department, current or former smoking, and alcohol use (defined as any amount of alcohol detected in the blood on admission). Transfusion-specific potential risk factors included the number of red blood cell units, high plasma-volume components (HPVC; sums included platelet, plasma, and cryoprecipitate units), and total plasma volume transfused in the 6 hours before TRALI onset. We also examined the percent of units from female donors and the proportion of transfused plasma obtained from female donors. Plasma volume was measured for platelet units and was estimated per local standards as 30 ml per red blood cell unit, 200 ml per plasma unit, and 15 ml per cryoprecipitate pool.

We used multivariable conditional logistic regression (18) to examine potential TRALI risk factors. To minimize bias, we constructed models to avoid covariate pairs with high multicollinearity (19). As a result, potential TRALI risk factors were

Figure 1. Conceptual diagram of two study definitions of acute respiratory distress syndrome onset time. ABG = arterial blood gas; ARDS = acute respiratory distress syndrome; CXR = chest X-ray or CT scan; TRALI = transfusion-related acute lung injury.

examined across four models. Collinearity analyses and final regression models are described in the data supplement. Finally, we performed a third nested case-control study using similarly designed models to identify specific risk factors for ARDS cases who received no transfusions in the 6 hours before meeting all ARDS criteria. We refer hereafter to these cases as “Non-TRALI ARDS.” Non-TRALI ARDS cases could be transfused between the time of trauma and 6 hours before fulfilling all ARDS criteria. As such, these patients could also fulfill criteria for TRALI when applying the first ARDS onset time definition.

A two-sided P less than 0.05 indicated statistical significance. We used StataIC 12.0 software (Stata Corp, College Station, TX) for all analyses.

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Results

Three hundred sixteen subjects were enrolled at the time of this analysis (Figure 2). Overall, 113 (36%) met ARDS criteria. Compared with patients who never developed ARDS, those who developed ARDS were older, had higher Injury Severity Scores, more commonly experienced a direct chest injury, and were more frequently in shock on presentation (see Table E1 in the online supplement). Patients with ARDS also had higher international normalized ratio, lower platelet count, and lower temperature at the

time of hospital arrival and received more red blood cell transfusions, HPVC transfusions, and crystalloid within 24 hours of injury.

Among the 113 subjects with ARDS, forty-two (37%) met TRALI criteria when applying the first ARDS onset time definition. Sixty-three subjects (56%) met TRALI criteria when applying the second/ later ARDS onset time definition. Fifty subjects (44%) met criteria for Non-TRALI ARDS. Twenty-eight of the 77 individuals who met TRALI criteria under either ARDS

onset time definition were TRALI cases under both ARDS onset time definitions (Figure 3). The resulting kappa coefficient was 0.16 (95% confidence interval [CI], −0.01 to 0.33). Compared qualitatively to TRALI cases identified under the first ARDS onset time definition, those meeting TRALI criteria under the second ARDS onset time definition were more often men and white, with more shock and alcohol use at the time of hospital arrival (Table 1).

The median time to TRALI onset under the first ARDS onset time definition was

Figure 2. Cohort enrollment. Enrollment of the Age of Transfused blood and Lung injury After transfusion Study (ATLAS) from January 2010 through August 2013. ARDS = acute respiratory distress syndrome; RBC = red blood cells.

Figure 3. Overlap of patients meeting criteria for acute respiratory distress syndrome (ARDS) and transfusion-related acute lung injury (TRALI). The overlapping circles represent the number of patients among the 316-person cohort who developed ARDS or TRALI according to two plausible definitions of ARDS onset time. ARDS = acute respiratory distress syndrome; TRALI by definition 1 = transfusion-related acute lung injury that begins when the first of two Berlin criteria are met; TRALI by definition 2 = transfusion-related acute lung injury that begins when all Berlin criteria are met.

5.9 hours from injury. The median time to TRALI onset under the second ARDS onset time definition was 7.0 hours from injury (Table E2). The median time between meeting the two ARDS criteria was 6.1 hours (interquartile range [IQR], 2.7–14.1). In the interval between meeting both ARDS criteria, patients were transfused a median of 1 RBC unit (IQR, 0–3; range, 0–15) and 1 HPVC unit (IQR, 0–4; range, 0–20). In contrast, among the 50 subjects with Non-TRALI ARDS, the median time to fulfilling both ARDS criteria was 42.9 hours after injury. Patients with Non-TRALI ARDS experienced longer durations of mechanical ventilation and intensive care unit/hospital length of stay. In-hospital mortality was similar between TRALI cases fulfilling the first ARDS onset time definition (26%), TRALI cases fulfilling the second ARDS onset time definition (21%), and Non-TRALI ARDS cases (24%).

Blood Component Transfusions Implicated in TRALI

Patients with ARDS received 958 blood component transfusions before meeting

both ARDS criteria, including 511 red blood cell (53%), 360 plasma (38%), 65 platelet (7%), and 22 cryoprecipitate units (2%). A total of 156 blood components were implicated in TRALI cases identified under the first ARDS onset time definition. A total of 372 components were implicated in TRALI cases identified under the second timing definition. Seventy-one (16%) of the 457 unique components implicated under either ARDS onset time definition were implicated by both definitions (kappa, 0.15; 95% CI, 0.11–0.20) (Figure E1). When examining only the 28 patients with TRALI according to both ARDS onset time definitions, 71 (32%) of the 220 unique components implicated under either ARDS onset time definition were implicated by both definitions (kappa, 0.22; 95% CI, 0.13–0.31) (Figure E2).

When qualitatively comparing all implicated blood components, a higher percentage were red blood cell units in TRALI cases according to the first ARDS onset time definition than the second (Table E3). Red blood cell and platelet units implicated in TRALI cases under the first

ARDS onset time definition were more likely to be leukoreduced, and platelets were more likely to be irradiated when compared with components implicated in TRALI cases under the second ARDS onset time definition. Blood donor age, days of storage between donation and transfusion, and percent of units from a female donor were similar between the two groups of TRALI cases.

TRALI Risk Factor Analyses

In bivariate analyses, TRALI cases identified under the first ARDS onset time definition had significantly higher APACHE II scores and Injury Severity Scores than matched control subjects. TRALI cases identified under the second ARDS onset time definition also had higher Injury Severity Score and APACHE II scores than matched control subjects; they were also significantly older and more likely to be men, have direct chest injury, and be in shock than matched control subjects. The quantity of red blood cell and plasma units, the total plasma volume, and the volume of female-donor plasma transfused in the 6 hours before TRALI onset were greater for cases identified under the first ARDS onset time definition than matched control subjects (Table 2). In addition to these factors, TRALI cases identified under the second ARDS onset time definition received significantly more platelet and cryoprecipitate transfusions than matched control subjects.

In multivariable analyses, APACHE II score and number of red blood cell transfusions in the prior 6 hours were the only factors significantly associated with the development of TRALI under the first ARDS onset time definition (Table 3). APACHE II score and number of red blood cell transfusions were also associated with TRALI under the second ARDS onset time definition. In addition, age, Injury Severity Score, and number of HPVC units or plasma volume transfused in the prior 6 hours were significant risk factors under the second ARDS onset time definition. Due to high multicollinearity, shock was excluded from all regression models. Results of sensitivity analyses that included shock as a model covariate were not meaningfully different.

APACHE II score was the only statistically significant risk factor for Non-TRALI ARDS in multivariable analyses (Table E4).

Table 1. Characteristics of transfusion-related acute lung injury cases and control subjects

Subject Characteristics	TRALI by First Timing Definition			TRALI by Second Timing Definition		
	Control Subjects (n = 126)	Cases (n = 42)	P Value	Control Subjects (n = 189)	Cases (n = 63)	P Value
Age, yr	49 (19)	51 (21)	0.51	40 (20)	55 (20)	0.04
Men, n (%)	87 (69)	26 (62)	0.39	119 (63)	50 (79)	0.02
White race, n (%)	112 (89)	35 (83)	0.36	167 (88)	57 (90)	0.65
APACHE II score	20.6 (6.2)	26.5 (6.4)	<0.001	20.1 (7.6)	27.5 (5.6)	<0.001
Injury Severity Score	29.2 (14.8)	38.4 (13.7)	0.002	29.6 (16.1)	39.7 (13.9)	<0.001
Direct chest injury	35 (28)	20 (48)	0.02	46 (24)	34 (54)	<0.001
Multiple fractures	38 (30)	14 (33)	0.71	48 (25)	19 (30)	0.47
Shock in ED	84 (67)	33 (79)	0.18	132 (70)	54 (86)	0.02
Alcohol use	35 (28)	9 (21)	0.44	58 (31)	16 (25)	0.42
Smoking	33 (26)	10 (24)	0.76	47 (25)	12 (19)	0.42
Diabetes	15 (12)	9 (21)	0.11	15 (8)	11 (17)	0.03
Moderate transfusion	11 (9)	6 (14)	0.06	19 (10)	17 (27)	0.001
Massive transfusion	14 (11)	10 (23)	0.07	12 (6)	8 (13)	0.11
Transfused units,* median (IQR)						
Red blood cells	1 (0–3)	3 (1–5)	0.01	2 (0–3)	3 (2–6)	<0.001
Platelets	0 (0–0)	0 (0–0)	0.17	0 (0–0)	0 (0–1)	0.001
Plasma	0 (0–2)	0 (0–3)	0.14	0 (0–2)	2 (0–5)	<0.001
Cryoprecipitate	0 (0–0)	0 (0–0)	0.99	0 (0–0)	0 (0–0)	0.005
HPVCs	0 (0–2)	0.5 (0–3)	0.15	0 (0–3)	2 (0–6)	<0.001

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ED = emergency department; HPVCs = high plasma-volume components; IQR = interquartile range; TRALI = transfusion-related acute lung injury.

Results are expressed as mean (SD) unless otherwise specified.

*Blood components transfused from time of injury until death or hospital discharge.

Discussion

Although it is generally accepted that ARDS exists, there is no consensus on when it starts, which has implications for TRALI research. Our study shows that variations in how ARDS onset time is defined lead to significant differences in the epidemiology of TRALI. When we applied two plausible definitions of ARDS onset time to a single prospective cohort of transfused trauma patients with ARDS, there was only slight agreement (20) between identified TRALI cases and fair agreement between blood components implicated in TRALI cases. The distribution and characteristics of the blood components implicated in TRALI development varied substantially between the definitions. Finally, different clinical risk factors emerged across the TRALI groups and for the group of patients with ARDS who were transfused but did not meet consensus TRALI criteria.

Our results suggest that investigators using different methods to determine ARDS onset time may study meaningfully different TRALI populations. This variability could lead to different conclusions about TRALI

incidence, clinical risk factors, and linked biomarkers. Although not examined in our study, differing methods of monitoring oxygenation and varied frequencies of arterial blood gases and chest radiographs could similarly impact the reliability of the TRALI definition. Without the ability to reliably identify cases, our current understanding of TRALI epidemiology, pathogenesis, and the effects of mitigation strategies may be inaccurate. Importantly, research of other critical care syndromes, such as ARDS and acute kidney injury, likely faces similar challenges. Specifically, interstudy differences in operationalizing standard definitions and institution-specific differences in the frequency of measuring determinative data points may produce unreliable results.

Prior clinical studies of TRALI performed in critical care settings largely do not address how ARDS onset times were operationalized in relation to case assessment. Only one (21) of seven contemporary studies examining patient-related TRALI risk factors (4, 6–8, 21–23) details how the investigators determined ARDS onset time. Other studies found that expert investigators frequently do not agree on the radiographic definition of

ARDS (24, 25), which further adds to the concern of unreliability of the TRALI definition raised by our study.

Notably, both standardized TRALI definitions term ARDS that occurs within 6 hours of a blood component transfusion in the setting of concurrent risk factors “possible TRALI” (10, 12). Our study population included only severely injured trauma patients; therefore, all TRALI cases fall in the “possible” category. We cannot determine if each ARDS event in our study would have occurred in the absence of transfusion; therefore, it is possible that some patients with ARDS are misclassified as TRALI. The threshold theory of TRALI suggests that blood component transfusions mechanistically contribute to TRALI in an otherwise at-risk individual (26). Conversely, since we required red blood cell transfusion for study entry we cannot exclude that blood components contributed to all ARDS cases.

It is possible that blood component transfusions modify the inflammatory response to injury in a fashion that facilitates ARDS development. Alternatively, blood components administered for bleeding after injury may simply coincide with early ARDS

Table 2. Distribution and characteristics of blood components transfused to cases and control subjects

Transfusion Sums and Characteristics*	Non-TRALI Acute Respiratory Distress Syndrome [†]	TRALI by First Timing Definition			TRALI by Second Timing Definition		
	Cases (n = 50)	Control Subjects (n = 126)	Cases (n = 42)	P Value	Control Subjects (n = 189)	Cases (n = 63)	P Value
Red blood cell units	4 (2–7)	0 (0–1)	2 (1–3)	<0.001	1 (0–2)	2 (2–4)	<0.001
Plasma units	2 (0–4)	0 (0–0)	0 (0–2)	0.02	0 (0–1)	1 (0–4)	<0.001
Platelets units	0 (0–1)	0 (0–0)	0 (0–0)	0.06	0 (0–0)	0 (0–1)	<0.001
Cryoprecipitate units	0 (0–0)	0 (0–0)	0 (0–0)	0.29	0 (0–0)	0 (0–0)	0.002
% Units from female donor	20 (12–40)	29 (0–50)	33 (0–67)	0.94	24 (0–50)	27 (0–50)	0.69
Plasma volume, ml × 10 ⁻¹	69 (12–155)	0 (0–3)	9 (3–40)	0.01	0 (0–28)	31 (6–108)	<0.001
Female donor plasma, ml × 10 ⁻¹	12 (3–27)	0 (0–0)	3 (0–6)	0.03	0 (0–3)	3 (0–20)	<0.001
% Plasma [‡] from female donor	13 (3–35)	15 (0–50)	20 (0–63)	0.003	13 (0–50)	12 (0–38)	0.71
Days of storage							
Red blood cell transfusions	13 (10–17)	11 (9–17)	11 (8–14)	0.16	11 (8–17)	11 (7–17)	0.44
Platelet transfusions	4 (3–5)	4 (3–5)	4 (3–5)	0.99	5 (4–5)	4 (3–5)	0.50

Definition of abbreviations: TRALI = transfusion-related acute lung injury.

Results are presented as median (interquartile range).

*Transfusions received while remaining at risk. The at-risk time period differs by acute respiratory distress syndrome onset time definition as follows: Non-TRALI acute respiratory distress syndrome, time from injury to meeting all acute respiratory distress syndrome criteria; TRALI by first timing definition, the 6 hours before meeting the first of two acute respiratory distress syndrome criteria; TRALI by second timing definition, the 6 hours before meeting all acute respiratory distress syndrome criteria.

[†]Non-TRALI acute respiratory distress syndrome refers to patients with acute respiratory distress syndrome who were not transfused in the 6 hours before meeting all acute respiratory distress syndrome criteria.

[‡]Percentage of plasma volume transfused while at risk that came from female donors.

development. In our study, Non-TRALI ARDS started days later than TRALI, reflecting the concentration of blood transfusions early after trauma. The quantity of transfusions administered after injury was not a significant risk factor for Non-TRALI ARDS. A prior cohort study showed that the association between red blood cell transfusions and ARDS in trauma patients is strongest in the first 24 hours after injury and varies over time (27). Reilly and colleagues showed that markers of biologic mechanisms hypothesized to cause ARDS also differ when comparing ARDS that begins within 24 to 48 hours of trauma to later-onset ARDS (28). In the context of these consistent studies, our results support that lung injury mediated by blood component transfusions may be a distinct subphenotype of ARDS.

This study has several potential limitations. We only examined two of the many ways that ARDS onset time could be defined. The TRALI risk factors meeting statistical significance in multivariable analyses may not have differed between our two study definitions after accounting for differences in power. Additionally, we did not evaluate all potential TRALI risk factors.

For example, calculation of a resuscitation ratio was only possible in patients who received both red blood cell and plasma transfusions in the 6 hours before ARDS onset. As a result, we had insufficient power to analyze this potential risk factor. Due to similar sample size restrictions, power was too limited to examine component-specific risk factors like red blood cell storage time, platelet irradiation, and leukoreduction. Although mechanistic links between blood transfusions and ARDS are supported by many studies (2, 29–37), the potential for residual confounding in this observational research prevents us from concluding that the risk factors we identified directly cause lung injury. In addition, in some cases transfusion start times may have been inaccurately documented and therefore be misclassified as implicated or not implicated in TRALI events. We were also unable to assess how institution-specific practices, such as transfusion strategies and the frequency of arterial blood gas measurements and chest imaging, affect TRALI research. For example, it is possible that the differences in the pretransfusion processing of blood components transfused to our two sets of TRALI cases reflect variations in transfusion practice at our

center as time-from-injury lengthened. Finally, we examined TRALI risk factors in a cohort of severely injured trauma patients at a single center. Therefore, our results may not be applicable to critically ill patients with different ARDS risk profiles or generalizable outside critical care of trauma patients.

Our work highlights limitations of the consensus definition of TRALI when applied in critical care settings where multiple ARDS risk factors coexist and the timing of ARDS onset is difficult to accurately determine. Our understanding of the role blood transfusions play in inflammatory lung injury may be biased by applying a TRALI definition that does not account for the breadth of mechanisms by which transfusions may contribute to inflammation. To achieve the goal of mitigating TRALI risk in critically ill patients, we need research that focuses on mechanisms by which bioactive substances in blood components modify inflammation in patients with primed immune systems and the duration of effect. Such research should consider the role of transfusions received throughout the period of critical illness rather than conforming to arbitrary time definitions (38).

Table 3. Associations between potential risk factors and transfusion-related acute lung injury

	TRALI					
	First Timing Definition			Second Timing Definition		
	Adjusted Odds Ratio	95% Confidence Interval	P Value	Adjusted Odds Ratio	95% Confidence Interval	P Value
Baseline variables*						
Age, yr	1.01	0.98–1.03	0.66	1.02	1.0–1.05	0.05
Male sex	0.36	0.12–1.07	0.07	1.55	0.59–4.7	0.37
APACHE II score	1.21	1.06–1.39	0.005	1.14	1.06–1.22	<0.001
Injury Severity Score	1.03	0.99–1.06	0.15	1.04	1.01–1.07	0.02
Direct chest injury	2.08	0.81–5.34	0.13	1.70	0.66–4.41	0.28
Transfusions while at risk†						
Per red blood cell unit‡	1.42	1.10–1.82	0.007	1.84	1.36–2.47	<0.001
Per high plasma-volume component‡	1.14	0.94–1.38	0.19	1.31	1.11–1.54	0.002
Per % of units from female donors*	0.55	0.04–7.45	0.66	2.92	0.37–22.85	0.31
Per 100 ml of transfused plasma						
All plasma	1.07	0.98–1.17	0.12	1.01	1.0–1.02	0.002
Female donor plasma§	1.07	0.66–1.74	0.78	0.96	0.69–1.32	0.79

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; TRALI = transfusion-related acute lung injury.

*Model included age, sex, APACHE II score, Injury Severity Score, direct chest injury, sums of red blood cell and high plasma-volume component units transfused during risk window, and percent of transfused units from female donors.

†The at-risk time period differs by acute respiratory distress syndrome onset time definition as follows: first timing definition, the 6 hours before meeting the first of two acute respiratory distress syndrome criteria; second timing definition, the 6 hours before meeting all acute respiratory distress syndrome criteria.

‡Model included age, sex, APACHE II score, Injury Severity Score, direct chest injury, and percent of transfused units donated by a female.

§Estimated from the adjusted model with separate terms for total plasma and total female plasma.

Conclusions

We propose that a new standard definition of transfusion-mediated acute lung injury specific to critically ill patients is needed to perform rigorous research. A revised TRALI definition would need to consider the potential cumulative effect of blood transfusions as proinflammatory stimuli in patients with coexisting ARDS risk factors,

akin to the threshold theory of Bux and Sachs (26). In addition, a revised definition could avoid arbitrary time frames by requiring evidence of respiratory deterioration after transfusion using data collected at prespecified intervals. Future studies that uniformly operationalize this new standard definition may further elucidate modifiable mechanistic links between blood transfusions and ARDS in

critically ill patients and strengthen efforts to develop preventive strategies. ■

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