

# Transfusion and Pulmonary Morbidity After Cardiac Surgery

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**Background.** True lung injury is among the leading causes of transfusion-related mortality. Pulmonary morbidity after cardiac surgery has been related to damaging effects of cardiopulmonary bypass and transfusion, but is confounded by cardiac-related events that may not reflect true lung injury. Thus, cardiac surgery poses unique challenges to criteria-specific diagnosis of transfusion-related acute lung injury (TRALI). Our objective was to determine the prevalence of pulmonary morbidity related to transfusion and whether TRALI consensus-criteria are applicable to cardiac surgery.

**Methods.** A total of 16,847 patients underwent on-pump, coronary artery bypass grafting (CABG), valve, or CABG-valve surgery from September 1998 to February 1, 2006. We performed four propensity-score-matching analyses with logistic regression on probability of receiving a transfusion: total hospital red blood cell (RBC) and fresh frozen plasma (FFP) transfusion and intraoperative RBC and FFP transfusion. Outcomes included traditional cardiac-surgery-defined pulmonary morbidity and ratio of arterial partial pressure of oxygen to fractional in-

spired oxygen concentration ( $P_{aO_2}/F_{iO_2}$ ), a criterion for TRALI.

**Results.** Patients receiving RBC transfusion had more risk-adjusted pulmonary complications: respiratory distress 4.8% vs 1.5%,  $p < 0.001$ ; respiratory failure 2.2% vs 0.39%,  $p < 0.0001$ ; longer intubation times, 9.9 hours vs 7.5 hours,  $p < 0.0001$ ; acute respiratory distress syndrome, 0.64% vs 0.21%,  $p = 0.015$ ; and reintubation, 5.6% vs 1.3%,  $p < 0.0001$ . The FFP was similarly related to more pulmonary complications after surgery. By TRALI criteria, the majority manifested "lung injury" ( $P_{aO_2}/F_{iO_2}$  ratio  $< 300$ ) but unrelated to transfusion (65% vs 64%).

**Conclusions.** Transfusion is associated with many measures of postoperative pulmonary morbidity. Yet the  $P_{aO_2}/F_{iO_2}$  ratio as important criterion of TRALI is unrelated to transfusion. Thus, due to the nature of cardiac surgery, application of consensus guided diagnosis of TRALI is problematic.

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Various measures of pulmonary morbidity after cardiac surgery have been related to cardiopulmonary bypass [1] and blood product administration [2–4]. True lung injury as it relates to transfusion of blood products is termed transfusion-related acute lung injury (TRALI), and has been characterized as adult respiratory distress syndrome (ARDS) due to transfusion [4, 5]. Patients undergoing cardiac surgery pose a unique challenge when attempting to apply standard definitions of TRALI, in part because measures of pulmonary morbidity may not reflect lung injury but cardiac events that prolong intubation support [6]. Current criteria for diagnosis of TRALI [7, 8] characterize it as onset of acute respiratory distress, evidence of hypoxemia, as reflected in arterial partial pressure of oxygen to fractional inspired oxygen concentration ( $P_{aO_2}/F_{iO_2}$ ) ratio less than 300, presence of bilateral lung infiltrates on chest radiograph, and all temporally related to transfusion within a 6 hour time

period. Other manifestations of TRALI include fever and mild to moderate hypotension [3, 4, 9].

In cardiac surgery, approximately half of transfusions occur in the operating room and the remainder in the postoperative period, thus making the timing of temporal relationships of transfusion to lung injury difficult. A majority of cardiac surgical patients arrive to the intensive care unit (ICU) on ventilatory support; consequently, clinical symptoms of dyspnea and acute respiratory distress are absent. In addition, patients arrive to the ICU mildly hypothermic; hence, increases in patient temperature are also not evident. Therefore, some suggest that, for a definitive diagnosis of TRALI, specific lung injury risk factors such as use of cardiopulmonary bypass [8] should be absent.

In order to better understand whether we could reasonably apply standard TRALI criteria or components of consensus criteria in the context of the cardiac surgical population we performed the following: (1) examined pulmonary morbidity related to transfusion both intraoperatively and postoperatively in a large cohort of patients undergoing cardiac surgery with use of cardiopulmonary bypass; (2) determined whether transfusions of red blood cell (RBC) and fresh frozen plasma (FFP)

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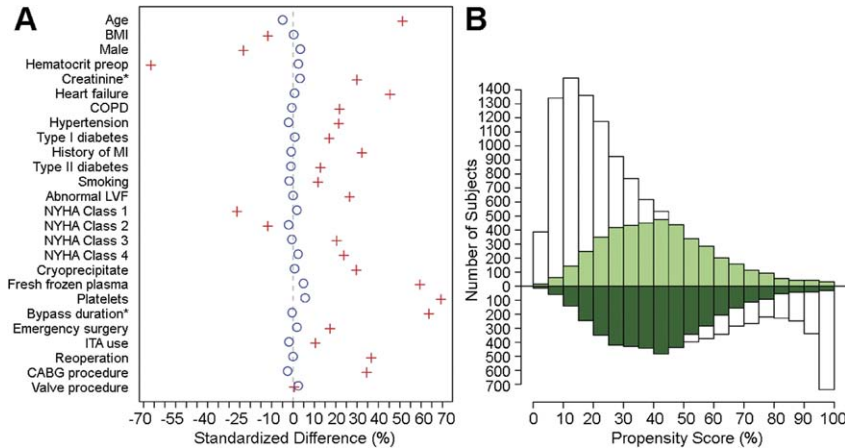


Fig 1. (A) Standardized differences of variables between patients who received red blood cell transfusions during the hospital stay and those who did not. Red crosses symbolize differences before propensity matching and blue open circles symbolize differences after propensity matching. Propensity matching effectively reduced heterogeneity among variables between the two patient populations in comparison. (\* log transformed prior to the analysis). (B) Mirror histogram of propensity scores for patients who received red blood cell transfusion during the hospital stay (below the horizontal line at zero) and those who did not (above the horizontal line at zero). Matched patients are a subset of the original patient population and their volumes are highlighted in color. Matched groups have similar propensity score distributions. (BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ITA = internal thoracic artery; LVF = left ventricular function; NYHA = New York Heart Association.)

were associated with “lung injury” using a surrogate measurement,  $P_{aO_2}/F_{iO_2}$ ; and (3) because of current consensus in England regarding female plasma donors, we investigated whether donor gender was associated with recipient pulmonary morbidity or lung injury.

## Patients and Methods

### Patients

Between September 1998 and February 2006, 16,847 patients underwent coronary artery bypass grafting

(CABG), a valve procedure, or combination of CABG and valve surgery at Cleveland Clinic. Baseline demographics and perioperative variables were obtained from the Department of Cardiothoracic Anesthesia Registry. Registry information was prospectively collected concurrent with patient care by trained database personnel. The Cardiovascular Information Registry, a similar prospective registry, was also accessed for additional variables. Data from these registries are approved for use in research by the Institutional Review Board with patient consent waived. To examine the impact of donor gender on lung

Fig 2. (A) Standardized differences of variables between patients who received fresh frozen plasma transfusion during the hospital stay and those who did not. Red crosses symbolize differences before propensity matching and blue open circles symbolize differences after propensity matching. Propensity matching effectively reduced heterogeneity among variables between the two patient populations in comparison. (\* log transformed prior to the analysis.) (B) Mirror histogram of propensity scores for patients who received fresh frozen plasma transfusion during the hospital stay (below the horizontal line at zero) and those who did not (above the horizontal line at zero). Matched patients are a subset of the original patient population and their volumes are highlighted in color. Matched groups have similar propensity score distributions. (BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ITA = internal thoracic artery; LVF = left ventricular function; MI = myocardial infarction; NYHA = New York Heart Association.)

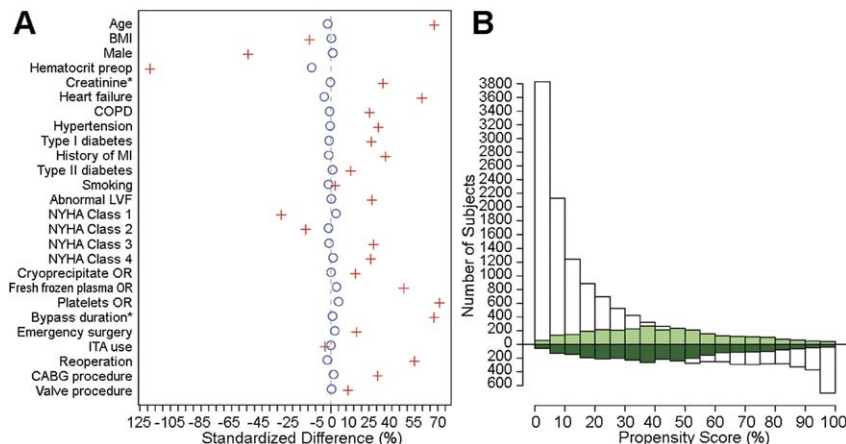


Fig 3. (A) Standardized differences of variables between patients who received red blood cell transfusion during the operation and those who did not. Red crosses symbolize differences before propensity matching and blue open circles symbolize differences after propensity matching. Propensity matching effectively reduced heterogeneity among variables between two comparison groups. (\* log transformed prior to the analysis.) (B) Mirror histogram of propensity scores for patients who received red blood cell transfusion during the operation (below horizontal line at zero) and those who did not (above horizontal line at zero). Matched patients are a subset of the original patient population and their volumes are highlighted in color. Matched groups have similar propensity score distributions. (BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ITA = internal thoracic artery; LVF = left ventricular function; MI = myocardial infarction; NYHA = New York Heart Association; OR = operating room.)

injury we received information from American Red Cross Biomedical Services on donor gender for products received from the American Red Cross supplier to Cleveland Clinic Blood Bank.

### Pulmonary Outcomes

Pulmonary morbidity outcomes analyzed included the following: prolonged postoperative ventilation beyond 72 hours; respiratory failure defined documented need for reintubation secondary to respiratory failure; respiratory

distress defined requirement for  $FiO_2$  greater than 80% for more than 24 hours or use of continuous positive airway pressure mask support; ARDS, defined as a clinical syndrome of  $Pao_2$  less than 60 mm Hg and significant infiltrate on chest radiograph, decreased lung compliance less than 0.5 mL/cm  $H_2O$ , and accurately documented by the infectious disease and the ICU teams; readmission to the ICU for respiratory failure; and total intubation time (initial intubation and reintubation duration) and total length of ICU stay (primary admission

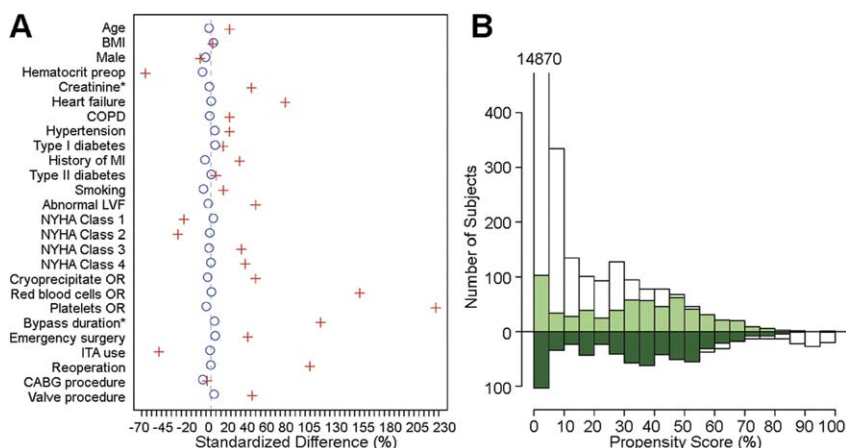


Fig 4. (A) Standardized differences of variables between patients who received fresh frozen plasma transfusion during the operation and those who did not. Red crosses symbolize differences before propensity matching and blue open circles symbolize differences after propensity matching. Propensity matching effectively reduced heterogeneity among variables between two groups. (\* log transformed prior to the analysis.) (B) Mirror histogram of propensity scores for patients who received fresh frozen plasma transfusion during the operation (below the horizontal line at zero) and those who did not (above the horizontal line at zero). Matched patients are a subset of the original patient population and their volumes are highlighted in color. Matched groups have similar propensity score distributions. (BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ITA = internal thoracic artery; LVF = left ventricular function; MI = myocardial infarction; NYHA = New York Heart Association; OR = operating room.)

**Table 1. Comparison Between Propensity-Matched Patient Groups With and Without Red Blood Cell Transfusion During the Hospital Stay. Descriptive Statistics Are Median (25th Quintile, 75th Quintile) for Continuous Variables and Count (Proportion) for Binary Variables**

Outcomes	Red Blood Cell Transfusion (n = 4,388)	No Red Blood Cell Transfusion (n = 4,388)	p Value
Respiratory distress/insufficiency	209 (4.8%)	64 (1.5%)	<0.0001
ICU intubation time (hours)	9.92 (5.93, 18.27)	7.50 (5.05, 13.00)	<0.0001
Respiratory failure	97 (2.2%)	17 (0.39%)	<0.0001
ARDS	28 (0.64%)	9 (0.21%)	0.0153
Intubation morbidity	334 (7.6%)	85 (1.9%)	<0.0001
Reintubation for pulmonary related reasons	244 (5.6%)	55 (1.3%)	<0.0001
Readmission to ICU for pulmonary related reasons	129 (2.9%)	36 (0.82%)	<0.0001
ICU length of stay (hours)	49.24 (26.81, 92.59)	27.42 (23.13, 48.50)	<0.0001

ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

and readmission to ICU). The outcome variable reflective of lung injury for operating room transfusion only was  $\text{PaO}_2/\text{FiO}_2$  ratio measured immediately after surgery on admission to the intensive care unit (ICU). ( $\text{PaO}_2/\text{FiO}_2$  ratio of 300 mm Hg or less was considered a measure of hypoxemia [8]). A ratio less than 300 mm Hg was considered to be reflective of lung injury secondary to intraoperative events in our patient setting.

#### Statistical Methods

Primary statistical analyses of this study included four propensity score matching analyses [10, 30]. We propensity-matched patients on baseline and perioperative variables [Figs 1–4]. Using this technique we compared pulmonary outcomes with the following: (1) patients with and without RBC transfusion during the hospital stay; (2) patients with and without FFP transfusion during the hospital stay; (3) patients with and without RBC transfusion restricted to operating room only; and (4) patients with and without FFP transfusion also limited to the operating room only.

For each of the four propensity score matching analyses, outcomes were compared between the two matched groups in a stratified analysis, with each pair of matched

patients as a stratum. There were missing values in preoperative creatinine (260), preoperative hematocrit (2,770), body mass index (9), hypertension (150), diabetes (285), smoking (274), and  $\text{PaO}_2/\text{FiO}_2$  ratio (902). All the statistical estimates and p values were adjusted for missing data using multiple imputation methods with five imputations. For parsimony of presentation, descriptive statistics were reported only for the first imputed data set when there were no substantial differences among the five imputed data sets.

We developed a linear prognostic model for the  $\text{PaO}_2/\text{FiO}_2$  ratio using the predictors considered in the propensity score analysis. Splines were used to account for nonlinearity in some continuous predictors. Because almost all predictors were statistically significant, no model selection was done.

We studied the effect of donor gender being female on the outcomes in an exploratory analysis. Details of that analysis are included in Appendix 1.

Significance level of all tests was set at 0.05. Analyses and plotting were carried out using SAS 9.1 (SAS Institute Inc, Cary, NC) and R 2.6.2 (<http://www.r-project.org>). Further details of overall statistical methodology can be found in Appendix 2.

**Table 2. Comparison Between Propensity-Matched Patient Groups With and Without Fresh Frozen Plasma Transfusion During the Hospital Stay. Descriptive Statistics Are Median (25th Quintile, 75th Quintile) for Continuous Variables and Count (Proportion) for Binary Variables**

Outcome	Fresh Frozen Plasma Transfusion (n = 964)	No Fresh Frozen Plasma Transfusion (n = 964)	p Value
Respiratory distress/insufficiency	93 (9.7%)	67 (7.0%)	0.0645
Intubation time (hours)	21.56 (13.15, 89.46)	15.55 (7.85, 35.45)	<0.0001
Respiratory failure	71 (7.4%)	43 (4.5%)	0.0076
ARDS	25 (2.6%)	16 (1.7%)	0.1383
Intubation morbidity	275 (28.5%)	153 (15.9%)	<0.0001
Reintubation for pulmonary related reasons	165 (17.1%)	104 (10.8%)	0.0002
Readmission to ICU for pulmonary related reasons	64 (6.6%)	32 (3.3%)	0.0020
ICU length of stay (hours)	93.00 (48.35, 208.6)	69.71 (35.92, 123.54)	<0.0001

ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

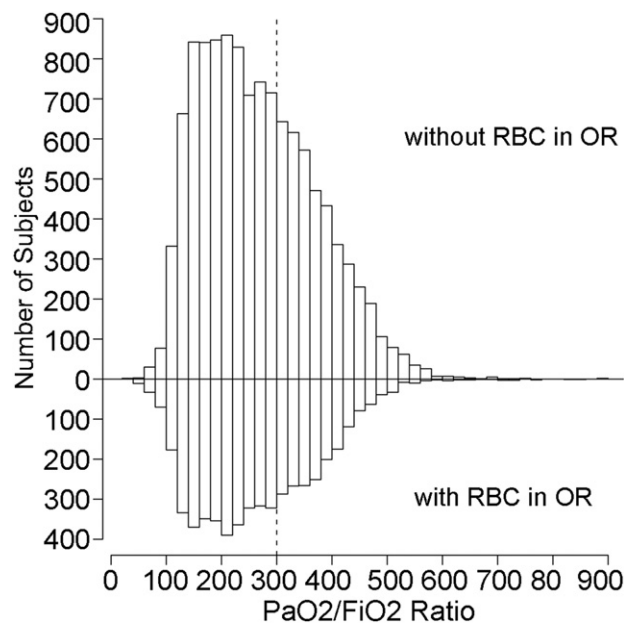


Fig 5. Frequency histograms of  $P_{aO_2}/F_{iO_2}$  ratio of those patients receiving red blood cell (RBC) transfusions in the operating room (OR) ( $P_{aO_2}/F_{iO_2} < 250$  [49.9%],  $P_{aO_2}/F_{iO_2} < 300$  [65%]), and those that did not ( $P_{aO_2}/F_{iO_2} < 250$  [49%],  $P_{aO_2}/F_{iO_2} < 300$  [64%]). ( $P_{aO_2}/F_{iO_2}$  = ratio of arterial partial pressure of oxygen to fractional inspired oxygen concentration.)

**Results**

*Pulmonary Morbidity and Transfusion*

A total of 79,530 red blood cell and component blood product units were transfused. Among propensity-matched patients, those who received RBC transfusion had more pulmonary morbidity postoperatively (Table 1). They had longer intubation time, higher prevalence of respiratory distress and failure, and more frequently required reintubation for pulmonary-related reasons. Prevalence of ARDS was higher. They also had more readmissions to the ICU, and longer overall ICU length of stay.

Among matched patients, those who received FFP had more pulmonary morbidity (Table 2). Total intubation time was longer, prevalence of respiratory failure was higher, and reintubation for pulmonary-related reasons was more frequent. They were more frequently readmitted to the ICU for pulmonary-related reasons and had longer overall ICU length of stay.

*Lung Injury and Transfusion*

Over 65% of patients who received an intraoperative RBC transfusion, and 64% of those who did not, had a  $P_{aO_2}/F_{iO_2}$  ratio after operation less than 300 (Fig 5). In addition, almost 50% of patients in both groups had a  $P_{aO_2}/F_{iO_2}$  ratio less than 250 on ICU admission.

The ICU admission  $P_{aO_2}/F_{iO_2}$  ratios among 2,941 pairs of propensity-matched patients were also similar; for those receiving intraoperative RBC transfusion versus no intraoperative RBC transfusion (median [25th quintile,

75th quintile]: 257 [185, 340] and 248 [182, 330]),  $p = 0.169$ , respectively. Similarly, among 625 propensity-matched pairs of patients between intraoperative FFP transfusion versus no intraoperative FFP transfusion, ICU admission  $P_{aO_2}/F_{iO_2}$  ratios were similar; median (25th quintile, 75th quintile): 227 (153,323), 238 (167,328),  $p = 0.25$ , respectively.

Emergency surgery, higher New York Heart Association (NYHA) functional class, longer cardiopulmonary bypass duration, and operating room FFP transfusion

Table 3. Prognostic Model of Square Root  $P_{aO_2}/F_{iO_2}$  Ratio

Variable	Estimate	Standard Error	p
<b>Demographics:</b>			
Male	-0.55	0.060	<0.0001
Age (<40 years)	-0.066	0.014	<0.0001
Age (>40)	-0.015	0.0024	<0.0001
BMI (<40 kg/m <sup>2</sup> )	-0.15	0.0052	<0.0001
BMI (>40 kg/m <sup>2</sup> )	0.030	0.019	0.11
<b>Products:</b>			
RBC operating room (yes/no)	0.13	0.066	0.041
FFP operating room (yes/no)	-0.43	0.16	0.0064
Platelets operating room (yes/no)	-0.18	0.11	0.087
Cryoprecipitate operating room (yes/no)	-0.65	0.43	0.13
<b>Laboratory values:</b>			
Log creatinine	-0.17	0.069	0.015
Preoperative hematocrit	0.0083	0.0059	0.16
<b>Clinical history:</b>			
Heart failure	-0.17	0.059	0.0037
Prior myocardial infarction	-0.17	0.056	0.0019
Hypertension	-0.35	0.057	<0.0001
Type I diabetes	0.61	0.085	<0.0001
Type II diabetes	0.26	0.063	<0.0001
Abnormal LVF	-0.17	0.051	0.0011
NYHA <sup>a</sup> class II	-0.14	0.065	0.028
NYHA class III	-0.22	0.081	0.0067
NYHA class IV	-0.43	0.10	<0.0001
Smoker	-0.37	0.052	<0.0001
COPD	0.33	0.062	<0.0001
<b>Clinical status:</b>			
Emergency	-1.04	0.25	<0.0001
<b>Procedure:</b>			
Reoperation	0.25	0.065	0.0001
CABG	-0.33	0.091	0.0002
Internal thoracic artery use	-0.28	0.082	0.0006
Valve	0.26	0.071	0.0003
Log cardiopulmonary bypass duration	-0.69	0.080	<0.0001

<sup>a</sup>NYHA = 1 is used as the reference for comparison with other levels.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; FFP = fresh frozen plasma; LVF = left ventricular function; NYHA = New York Heart Association;  $P_{aO_2}/F_{iO_2}$  = ratio of arterial partial pressure of oxygen to fractional inspired oxygen concentration; RBC = red blood cells.

were among a number of perioperative variables related to significantly lower the  $\text{PaO}_2/\text{FiO}_2$  ratio (see Table 3).

#### Donor Gender

Details from the donor gender analysis are presented in Appendix 1. There was no statistically significant difference in pulmonary morbidity between patients who received female and male donor units, possibly because the prevalence of those events was low. The  $\text{PaO}_2/\text{FiO}_2$  ratio ( $p = 0.56$ ), ICU length of stay ( $p = 0.68$ ), and intubation time ( $p = 0.38$ ) were also similar. We found it impossible to study donor gender of FFP in this study because we had insufficient donor gender information.

#### Comment

We report that transfusion was associated with a higher risk-adjusted prevalence of respiratory distress and failure, ARDS, reintubation for pulmonary-related reasons, longer total intubation time, more readmissions to the ICU for pulmonary-related reasons, and longer ICU length of stay. Similarly, FFP transfusion was associated with significantly more pulmonary complications in the postoperative period. Surprisingly, a substantial proportion of patients manifested ( $\text{PaO}_2/\text{FiO}_2 < 300$ ) for both transfused and nontransfused groups, which is considered to be a marker of lung injury. Important determinants for a lower  $\text{PaO}_2/\text{FiO}_2$  included duration of cardiopulmonary bypass, emergency surgery, clinical risk factors, and intraoperative FFP administration.

Cherry and colleagues [11] summarized current criteria for diagnosis of TRALI from the American-European Consensus Conference Definition of ALI [12], the National Heart, Lung and Blood Institute Definition of TRALI [8], and the European Haemovigilance Network Definition of TRALI [7]. Common among published criteria is the temporal relationship between transfusion and onset of clinical signs and symptoms. Acute onset of clinical symptoms commonly occurs within 1 to 2 hours of transfusion [4] with 100% of patients' clinical symptoms presenting within 6 hours of transfusion [5, 13]. Evidence of hypoxemia, bilateral pulmonary infiltrates, and absence of fluid overload are among TRALI criteria. In large case series, 72% necessitate ventilatory support and a majority have symptom resolution within 96 hours of presentation [13, 14]. Transfusion-related acute lung injury has been further differentiated as "possible TRALI" if the patient has an alternative risk factor for acute lung injury [8].

Patients who were transfused in our investigation had more pulmonary morbidity; however, lack of ability to apply clear-cut criteria for TRALI complicated our ability to diagnose true lung injury. Identification of TRALI in our investigation was complicated by lack of formal surveillance; inability to detect TRALI-specific symptoms in addition to mortality as a competing risk factor.

Differentiating TRALI from transfusion-associated circulatory overload (TACO), is also problematic, but probably pertinent to the cardiac surgery setting. Although TRALI can be considered "permeability edema" versus

"hydrostatic edema" from TACO, clinical and radiographic manifestations are similar and both may coexist [15]. Patients come to surgery with cardiovascular disease, multiple comorbidities, in heart failure, and with poor left ventricular function and are precisely the high-risk patients receiving blood products. In addition, use of cardiopulmonary bypass exposes these patients to risk for acute lung injury. Others have had difficulty differentiating TRALI from TACO in the clinical practice setting [16]. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic (NT-pro-BNP) have been used in an attempt to differentiate these two in critically ill patients; however, neither test reliably distinguished these [17]. Popovsky [18] noted the overlap of hypoxemia and signs and symptoms between TACO and TRALI which complicated differentiation. However, the author highlighted problematic clinical consequences of TACO: need for ICU care and longer hospital length of stay [18, 19].

Furthermore, it is difficult to differentiate lung injury related to transfusion with  $\text{PaO}_2/\text{FiO}_2$  TRALI criteria measures. Over 60% of our patients with and without transfusion manifested a ratio less than 300 on ICU admission and almost 50% of patients in the transfused and nontransfused groups manifested  $\text{PaO}_2/\text{FiO}_2$  less than 250. Pulmonary dysfunction after cardiac surgery is well recognized. Contributing factors are use of cardiopulmonary bypass, general anesthesia, breach of pleura, and cessation of ventilation while on cardiopulmonary bypass [20, 21]. However, others have attributed lung injury to RBC transfusion rather than cardiopulmonary bypass duration as measured by a rise in pulmonary vascular permeability as measured with  $^{67}\text{Ga}$ -transferrin pulmonary leak index [22].

#### Characterizing TRALI

All plasma-containing blood components have been implicated in TRALI [2–4]. In its most severe presentation, it appears clinically similar to ARDS; however, it has lower mortality and shorter time to clinical resolution [4, 23]. Silliman and colleagues [24] reported prevalence of TRALI as 1 in 1,120 cellular components, suggesting TRALI may be more common than previously recognized. In an investigation of recipients of blood components from a donor with a granulocyte antibody, Kopko and colleagues [14] suggested that TRALI may present with mild signs and symptoms such as dyspnea and oxygen desaturation without pulmonary edema. These authors noted lack of recognition and spectrum of clinical presentation may result in inappropriate treatment.

While the causative pathogenesis of lung injury in TRALI is unknown, the end result is increased vascular permeability and pulmonary edema [23]. One theory is that TRALI is immune-mediated with antibodies from donor plasma acting against recipient leukocyte antigens, resulting in recipient leukocyte activation [4, 23]. Another proposed theory is the "two-hit model" characterized by a "first hit" such as cardiac surgery which activates leukocytes; the "second hit" occurs with transfusion which initiates release of leukocyte cytotoxic contents [5, 25]. The immune-mediated and two-hit model of TRALI

are not mutually exclusive and both are supported by clinical and experimental observations [26]. Other mechanisms include immune complex formation with complement activation and cytokine network activation [23].

#### *Role of Gender and HLA antigens*

In a review of 58 TRALI-related transfusion fatalities reported to the Center for Biologics Evaluation and Research from 1997 to 2002, Holness and colleagues [2] reported that FFP was the most common blood component implicated in the development of TRALI; followed by RBC, platelets, and cryoprecipitate-reduced plasma. Forty-eight of the 63 donors implicated in these TRALI deaths were tested for antihuman leukocyte antigen (HLA) and (or) antigranulocyte antibodies; 83% were found to be positive. Parity, particularly multiparity, was a risk factor for antibody development and a frequent finding among implicated female donors. Insunza and colleagues [27] reported that HLA antibodies were present in 18% of previously pregnant apheresis donors. Rates of HLA alloimmunization for parous women range from 17% to 40% [23, 28]. Current recommendations for TRALI risk reduction include reducing the use of plasma products from female donors and screening female and other at risk donors for anti-HLA antibodies, including HLA class II and antigranulocyte antibodies [2, 29]. Although there has been an observation that the majority of blood donors implicated in these reactions are females who have been sensitized to fetal antigens by multiple pregnancies, there are many blood products from multiparous donors that contain such antibodies and do not cause clinically apparent TRALI reactions [14, 23, 24]. We reported similar outcomes among gender groups; however, our investigation of donor gender was limited by the small number of morbid outcomes.

#### *Limitations*

This was an observational cohort investigation and the presence of unknown confounders could certainly influence the observed study results. Lack of formal TRALI surveillance was problematic; however, should a surveillance system been in place, the ability to apply TRALI consensus-specific criteria would have been challenging due to the nature of our patient population. Timing of transfusion as it relates to outcome is difficult because exact timing of transfusion is not a measured variable. Lung injury as expressed by the  $\text{PaO}_2/\text{FiO}_2$  ratio was measured only on ICU admission; we were unable to determine the impact of transfusion on  $\text{PaO}_2/\text{FiO}_2$  further into the postoperative period. However, the  $\text{PaO}_2/\text{FiO}_2$  ratio as one of the metrics of TRALI is insensitive in the setting of cardiac surgery. Furthermore, our ability to examine the impact of donor gender was hindered by insufficient donor gender information and lack of information on parity of female donors.

#### *Conclusion*

Cardiac surgical patients with poor cardiopulmonary reserve, who received transfusion, had more risk-adjusted pulmonary morbidity after surgery. Whether

increased pulmonary morbidity was related to TRALI, TACO, or both is uncertain in part because current consensus-criteria for TRALI are insufficient for the cardiac surgical population. Almost 80,000 units of blood products were transfused in our subset of cardiac surgical patients in a period of less than 10 years. According to current prevalence estimates, TRALI could have been identifiable in approximately 72 patients. While lack of formal surveillance was problematic, current consensus criteria is insensitive to the diagnosis of TRALI.

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## Appendix 1

Among the 16,847 patients in the study sample, 4,020 of them (23.86%) did not receive transfusion of any blood products (RBC, FFP, cryoprecipitate, and platelets). The 12,827 (76.14%) patients that had transfusions received a total of 79,530 units of blood products, among which 38,613 (48.55%) units had missing donor gender, 18,556 (23.33%) units came from female donors, and 22,361 (28.12%) units came from male donors. Among the 12,827 patients that received a transfusion, 1,365 (10.64%) had complete information on donor gender of all the units they received; 5,698 (44.42%) did not have any information on donor gender of all the units they received.

Among 1,365 patients with complete donor gender information of all the transfused units, 310 received exclusively female units, and 542 patients received exclusively male units. Because the donor gender is independent of a patient's condition, these two groups are similar in preoperative and intraoperative variables (this is confirmed in a two-group comparison of these variables, results not shown). Therefore, any difference in the outcomes can be attributed to the effect of donor gender. However, we did not find any difference between female donor versus male donor comparison in arterial partial pressure of oxygen to fractional inspired oxygen concentration ( $\text{PaO}_2/\text{FiO}_2$ ) (median [25th quintile, 75th quintile]: 257 (197, 328), 250

(187,332),  $p = 0.56$ , respectively; ICU length of stay (median [25th quintile, 75th quintile]: 28.8 (24.4, 51.9), 30.0 (24.5, 55.3),  $p = 0.68$ , respectively; and intubation time (median [25th quintile, 75th quintile]: 8.25 (5.67, 13.1), 8.58 (5.72, 14.7),  $p = 0.38$ , respectively. Wilcoxon rank sum tests were used here for the first imputed data set. Because no statistical significance was found, we expected that the multiple imputation adjusted  $p$  values were not significant either. We did not find any difference in the binary morbid event because the incident rates of those events were very low and did not show up in these two small groups.

## Appendix 2

In this Appendix, we provide a more detailed account of the statistical analysis plan used in this study. Primary analyses of this study included four propensity score matching analyses. To conduct the propensity score analysis, we first performed a logistic regression to calculate the predictive probability of a patient receiving a transfusion, given that patient's set of preoperative and intraoperative variables; this probability is the propensity score for that patient. It has been shown [Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55] that patients with similar propensity scores have similarly distributed pre- and intraoperative variables, regardless of whether they received a transfusion or not. Therefore, assuming that all relevant confounders are considered, identification of a subset of patients from the transfusion and nontransfusion groups with similar propensity scores allows differences in outcomes between the two subsets to be attributed to transfusion itself.

A greedy match [Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. *Proceedings of the 26th Annual SAS Users Group International Conference*. Cary NC: SAS Institute 2001:214–26] algorithm was used to perform 1:1 matching between the transfusion and nontransfusion groups. In order to evaluate the quality of matching for each confounding variable, we calculated the standardized differences between the transfusion and nontransfusion groups, before and after matching. Good matching removes or reduces standardized differences in confounders between comparison groups. Standardized difference was defined to be the difference in means between the groups divided by the average standard deviation.

The analysis involved a summation of all RBC and FFP therapy transfused for the hospital stay and a number of outcomes reflective of lung injury in the postoperative period. This analysis included an examination of the following.

- (1) Patients with and without RBC transfusion during the hospital stay; and
- (2) patients with and without FFP transfusion during the hospital stay.

Outcomes reflective of lung injury in the second analysis included the following: pulmonary morbidity as defined by prolonged postoperative ventilation beyond 72 hours; respiratory failure defined by patients who were extubated after the surgical procedure with documented need for reintubation secondary to respiratory failure; respiratory distress was defined as a patient requiring an  $\text{FiO}_2$  of greater than 80% for more than 24 hours, or use of continuous positive airway pressure mask support; acute respiratory distress syndrome (ARDS), was defined as acute onset with clinical diagnosis of  $\text{PaO}_2$  less than 60 mm Hg, significant infiltrate on chest radiograph, decreased lung compliance less than 0.5 mL/cm water and documented by the infectious disease and the ICU teams; readmission to the

ICU for respiratory failure; and total intubation time (initial intubation and reintubation duration) and total length of ICU stay (primary admission and readmission to ICU).

Propensity matching between patients with ( $n = 6,459$ ) and without ( $n = 10,388$ ) RBC transfusion during the hospital stay resulted in 4,388 matched-pairs. Propensity matching resulted in a similar distribution of perioperative variables between the two groups (Figs 1A and 1B). Propensity matching between patients with ( $n = 1,238$ ) and without ( $n = 15,609$ ) FFP transfusion during the hospital stay resulted in 964 matched pairs. Propensity matching resulted in a similar distribution of baseline variables between the two groups. (Figs 2A and 2B).

- (3) Patients with and without RBC transfusion restricted to operating room only.
- (4) Patients with and without FFP transfusion also limited to the operating room only.

The outcome variable was the ratio of arterial partial pressure of oxygen to fractional inspired oxygen concentration ( $P_{aO_2}/F_{iO_2}$ ) measured immediately after surgery on admission to the intensive care unit (ICU). ( $P_{aO_2}/F_{iO_2}$  ratio of  $\leq 300$  mm Hg was considered a measure of hypoxemia [Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004;44:1774–89].). A ratio less than 300 mm Hg was considered to be reflective of lung injury secondary to intraoperative events in our patient setting.

Propensity matching between patients with ( $n = 5,237$ ) and without ( $n = 11,610$ ) intraoperative RBC transfusion during the hospital stay resulted in 2,941 matched-pairs. Propensity matching effectively reduced the heterogeneity among perioperative variables between the two groups. (Fig 3A; B) Propensity matching between patients with ( $n = 728$ ) and without ( $n = 16,119$ ) an intraoperative FFP transfusion resulted in 625 matched pairs. Following propensity matching baseline variables were comparable between the two groups (Fig 4A; B).

Descriptive statistics were calculated and compared between matched groups. Effect of transfusion was tested in a stratified regression model for the outcome, with each matched-pair as a stratum. For continuous outcomes, we used general linear model with cluster-specific random effects. Proper transformations on the continuous outcomes were used to meet the model

assumptions. For binary outcomes, we used conditional logistic regression.

There were missing values in preoperative creatinine (260), preoperative hematocrit (2,770), body mass index (9), hypertension (150), diabetes (285), smoking (274), and  $P_{aO_2}/F_{iO_2}$  ratio (902). We imputed the missing values five times using the multiple imputation method (SAS PROC MI). All analyses described above, including the development of the propensity score, greedy matching, and post-matching analysis, were repeated for each of five imputed data sets and results were combined by multiple imputation formula for proper inference and  $p$  values (SAS PROC MIANALYZE). The  $p$  values from the combined analysis were in general a little larger than the  $p$  values obtained from the analysis of a single imputed data set, which reflects the proper adjustment for the uncertainty in the missing data. Unless otherwise stated, all  $p$  values were adjusted for multiple imputations. For parsimony of presentation, descriptive statistics were reported only for the first imputed data set when there were no substantial differences between the five imputed data sets.

We developed a linear prognostic model for  $P_{aO_2}/F_{iO_2}$  ratio using the predictors considered in the propensity score analysis. The  $P_{aO_2}/F_{iO_2}$  ratio was square root transformed to make the residual assumptions of the model satisfied. The model building process started with a semiparametric generalized additive model in which all the continuous predictors were assumed to have a smooth but otherwise unrestricted relationship with the mean outcome variable. If the effect of the predictor appeared to be nonlinear, we took a monotone transformation of that predictor or approximated it with a low rank regression spline to reflect such nonlinear relationship in broad strokes. Hence, the final model was a parametric linear model with predictors and their spline terms. The estimates, standard errors and  $p$  values in the final model were adjusted appropriately to account for the uncertainty of multiple imputations. Since almost all predictors are significant, no model selection was done.

Significance level of all tests was set at 0.05. No  $p$  value adjustment for multiple statistical tests was made; however, all the endpoints were predefined during the planning stage of this study. The analyses and plotting were carried out using SAS 9.1 and R 2.6.2 (<http://www.r-project.org>).