Title
Differentiating pulmonary transfusion reactions using recipient and transfusion factors.

Journal
Transfusion, 57(7)

ISSN
0041-1132

Authors
Roubinian, Nareg H
Looney, Mark R
Keating, Sheila
et al.

Publication Date
2017-07-01

DOI
10.1111/trf.14118

Peer reviewed

HHS Public Access

Author manuscript

Transfusion. Author manuscript; available in PMC 2018 January 08.

Published in final edited form as:

Transfusion. 2017 July ; 57(7): 1684–1690. doi:10.1111/trf.14118.

Differentiating pulmonary transfusion reactions using recipient and transfusion factors

Nareg H. Roubinian[1,2], **Mark R. Looney**[2], **Sheila Keating**[1], **Daryl J. Kor**[3], **Clifford A. Lowell**[1], **Ognjen Gajic**[3], **Rolf Hubmayr**[3], **Michael Gropper**[2], **Monique Koenigsberg**[2], **Gregory A. Wilson**[3], **Michael A. Matthay**[2], **Pearl Toy**[2], **Edward L. Murphy**[1,2], and **the TRALI Study Group**

[1]Blood Systems Research Institute, San Francisco, California

[2]University of California at San Francisco, San Francisco, California

[3]Mayo Clinic, Rochester, Minnesota

Abstract

BACKGROUND—It is increasingly recognized that recipient risk factors play a prominent role in possible transfusion-related acute lung injury (pTRALI) and transfusion-associated circulatory overload (TACO). We hypothesized that both transfusion and recipient factors including natriuretic peptides could be used to distinguish TRALI from TACO and pTRALI.

STUDY DESIGN AND METHODS—We performed a post hoc analysis of a case-control study of pulmonary transfusion reactions conducted at the University of California at San Francisco and Mayo Clinic, Rochester. We evaluated clinical data and brain natriuretic peptides (BNP) levels drawn after transfusion in patients with TRALI (n = 21), pTRALI (n = 26), TACO (n = 22), and controls (n = 24). Logistic regression and receiver operating characteristics curve analyses were used to determine the accuracy of clinical and biomarker predictors in differentiating TRALI from TACO and pTRALI.

RESULTS—We found that pTRALI and TACO were associated with older age, higher fluid balance, and elevated BNP levels relative to those of controls and TRALI. The following variables were useful in distinguishing cases of pTRALI and TACO from TRALI: age more than 70 years, BNP levels more than 1000 pg/mL, 24-hour fluid balance of more than 3 L, and a lower number of transfused blood components. Using the above variables, our logistic model had a 91% negative predictive value in the differential diagnosis of TRALI.

CONCLUSIONS—Models incorporating readily available clinical and biomarker data can be used to differentiate transfusion-related respiratory complications. Additional studies examining recipient risk factors and the likelihood of TRALI may be useful in decision making regarding donor white blood cell antibody testing.

Causes of pulmonary edema as a complication of transfusion include transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and possible TRALI (pTRALI). Pulmonary edema in these reactions has often been divided into

Address reprint requests to: Nareg H. Roubinian, MD, MPHTM, Blood Systems Research Institute, 270 Masonic Avenue, San Francisco CA 94118; nroubinian@bloodsystems.org.

hydrostatic (TACO) and permeability etiologies (TRALI and pTRALI).[1] The distinction between permeability etiologies is the temporal relationship of pTRALI to risk factors for acute respiratory distress syndrome (ARDS). There is growing evidence that recipient rather than transfusion factors predominate in the pathogenesis of pTRALI.[2] Supporting findings include the decline in TRALI but not pTRALI with implementation of plasma transfusion from male donors and the lack of correlation of pTRALI to human leukocyte antigen (HLA) antibody status.[3–6]

Despite advances in our understanding of the epidemiology and pathogenesis of TACO, TRALI, and pTRALI, differentiating them clinically remains a diagnostic challenge. Distinguishing these clinical syndromes requires the interpretation of clinical, radiographic, and hemodynamic data that are not always available and are labor-intensive to extract.[7] Furthermore, the diagnoses of pulmonary transfusion reactions are based on clinical criteria that lack specificity.[8]

Several studies have shown that cytokines and biomarkers may have utility in differentiating pulmonary transfusion reactions.[2,3,9] Aberrations in inflammatory cytokines have been recognized in patients who develop TRALI and pTRALI but not TACO.[10] In addition, brain natriuretic peptides (BNP) levels have been found to be useful in characterizing TACO relative to controls.[11,12] One study found limited diagnostic value in the use of BNP to distinguish TRALI and pTRALI from TACO.[13] However, this same study found elevated cardiac filling pressures and BNP levels in pTRALI and TACO patients compared to those of TRALI. Given these and the above differences in the epidemiology of TRALI and pTRALI, clinical and biomarker predictors may be useful in their discrimination. We hypothesized that recipient factors, including BNP levels, could be used to differentiate TRALI from TACO and pTRALI.

MATERIALS AND METHODS

Study design

We performed a post hoc analysis of a prospective observational study of pulmonary transfusion reactions that was conducted between 2006 and 2009 at the University of California at San Francisco Medical Center and the Mayo Clinic in Rochester, Minnesota. Cases of posttransfusion hypoxemia were identified by active surveillance using a real-time alert system that screened arterial blood gas results in all hospitalized patients older than 6 months who received blood transfusion, as previously described.[3,14] The protocol was approved, including a waiver of consent, by the University of California at San Francisco Medical Center and Mayo Clinic institutional review boards.

Trained study coordinators with critical care experience screened all alerts for potential cases of possible transfusion reactions based on findings of new or worsening bilateral opacities on the chest radiograph, triggering the collection of standardized clinical data via chart review. Cases were then adjudicated by two critical care physicians on a four-member expert panel. Each expert independently classified a case as TRALI, TACO, pTRALI, or TACO and TRALI when there was evidence for both diagnoses or as “other” when an alternative diagnosis was identified. If the two experts did not agree, a third reviewer

reviewed the case and provided input. On periodic conference calls, members of the expert panel reviewed cases without two experts in agreement to discuss it in more depth and assign a consensus determination.

TRALI was defined as new acute lung injury that developed within 6 hours of transfusion where there was no temporal relationship to risk factors for ARDS.[15] pTRALI was defined as new acute lung injury where there was a clear temporal relationship to an alternative risk factor for ARDS (see Appendix, available as supporting information in the online version of this paper, for list of risk factors). A diagnosis of TACO was based on criteria used in the National Healthcare Safety Network definition, with pulmonary edema developing within 6 hours of transfusion and being characterized by clinical, echocardiographic, or laboratory evidence of left atrial hypertension.[16]

Transfusion strata were developed a priori based on the number of blood components transfused in a 6-hour period before the development of a pulmonary transfusion reaction (1 to 2, 3 to 9, and 10 or more). Controls, matched to cases by 6-hour transfusion strata, were randomly selected from among all transfused patients at the same hospitals concurrent with enrollment of cases. Controls did not have evidence of hypoxemia or evidence of bilateral infiltrates on chest radiography within 12 hours of transfusion of the last unit.

Patient sample collection and biomarker assays

Residual pre- and posttransfusion recipient blood samples were collected from the clinical laboratory in a subset of cases and controls from the parent case-control study (Appendix Figure 1, available as supporting information in the online version of this paper). Samples were stored at 4°C until cases were adjudicated, and median times that blood was drawn before and after transfusion were 20 and 16 hours, respectively. Plasma fractions were separated from whole blood EDTA tubes and stored at −80°C before measurement of biomarkers. Samples tested were those collected closest to transfusion. Biomarker testing was performed after case adjudication.

Biomarkers were measured after expert panel review and classification using microarray kits from R&D Systems on the Luminex platform (Luminex Corp.). BNP levels were measured in available samples for cases of TACO, TRALI, pTRALI, and controls. In a further subset of cases of TACO (n = 14), pTRALI (n = 22), and controls (n = 15) we also measured cystatin C, ST-2, growth differentiation factor-15 (GDF-15), angiopoietin-2, and tissue inhibitor of metallopeptidase inhibitor 3 (TIMP-3).

Statistical analysis

Distributions and proportions of demographic and clinical data were tabulated for groups. Data are expressed as mean values ± standard deviation (SD), median (inter-quartile range [IQR]), or as proportions as appropriate. Statistical tests comparing groups were performed using chi-square tests for categorical data and analysis of variance or Kruskal-Wallis test when appropriate for continuous variables. Biomarker data were imported into a statistical analysis package (Stata Version 12.1, StataCorp). Because the distribution of biomarker results was skewed, the Wilcoxon test was used to compare biomarker levels in samples between groups of TRALI, TACO, pTRALI, and control patients. Logistic regression was

performed to determine individual associations between risk factors and outcomes of interest. A multivariable model of risk factors was developed by including variables significant in the initial analyses ($p < 0.2$). Given parallel elevations in age, cardiac filling pressures, and BNP levels in prior studies of patients with TACO and pTRALI, we grouped these subjects to evaluate whether recipient risk factors would differentiate them from patients with TRALI. Receiver operator characteristic curves were constructed and area under the curve (AUC) was calculated to determine the discriminative capacity and best threshold levels of clinical predictors and biomarkers in differentiating TRALI from TACO and pTRALI (n = 69). Sensitivity, specificity, and positive and negative predictive values were calculated. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit (HLGOF) test. A two-tailed p value of less than 0.05 was considered significant.

RESULTS

Tables 1 and 2 provide a description of the demographics, comorbid risk factors, and clinical characteristics of cases of TACO, TRALI, pTRALI, and controls in which clinical blood samples were available. As previously reported, patients with TACO were older, had a greater prevalence of cardiac and renal comorbidities, and had recent surgery while pTRALI patients had a greater prevalence of mechanical ventilation and need for vasopressors at the time of pulmonary edema.[2,17] APACHE II scores were similar among the three groups.

Comparison of pre- and posttransfusion BNP values in TRALI, TACO, and pTRALI and in control patients is summarized in Table 3 and Appendix Table 1 (available as supporting information in the online version of this paper). Before and after transfusion, BNP levels were higher in patients with TACO and pTRALI relative to those in TRALI and control patients ($p < 0.01$ for all). However, BNP levels after transfusion were not significantly different between TACO and pTRALI patients (p 0.80) or between TRALI and control patients (p 0.21). The total number of blood components transfused during or within 6 hours did not differentiate TRALI from pTRALI or TACO; however, patients with TRALI were more likely to have received more than 20 blood components within 6 hours. Comparisons of additional posttransfusion biomarker values in TACO, pTRALI, and control patients are summarized in Appendix Table 2 (available as supporting information in the online version of this paper). Notably, cystatin C levels were higher in TACO relative to pTRALI patients and ST-2 and TIMP-3 levels were higher in pTRALI relative to TACO (all $p < 0.05$).

Diagnostic accuracy of BNP to differentiate TACO from TRALI was excellent with an AUC of 0.88 (HLGOF, 0.11). Using a diagnostic cut point of 750 pg/mL, BNP had a sensitivity of 88%, specificity of 81%, and positive and negative predictive values of 85% in the differential diagnosis of TACO versus TRALI. Adjustment for a history of chronic renal failure and creatinine levels did not impact the diagnostic accuracy of BNP. However, BNP alone had only moderate diagnostic accuracy in differentiating TRALI from pTRALI (AUC, 0.73) and was not useful in differentiating TACO from pTRALI (AUC, 0.52).

Table 4 shows associations of clinical and biomarker factors in our multivariable risk model of pTRALI and TACO relative to TRALI. Recipient factors associated with TACO and pTRALI relative to TRALI included age greater than 70, a positive fluid balance greater

than 3 L in the 24 hours before transfusion, and BNP levels greater than 1000 pg/mL. The combination of the above recipient factors and number of units transfused had excellent performance in differentiating TRALI from pTRALI or TACO (AUC, 0.88; HLGOF, 0.65). Using the above predictors, our logistic model had 96% sensitivity and 92% positive predictive value in ruling out TRALI and correctly classified 91% of cases. A BNP level of greater than 1000 pg/mL alone had lower sensitivity (86%) but similar predictive value (91%) in excluding TRALI compared to cases of TACO and pTRALI.

Sensitivity analyses were performed to compare the subjects in the parent case control study with the subset studied in which clinical samples were available (Appendix Table 3, available as supporting information in the online version of this paper). Compared to the parent study, the subset had similar age ($p = 0.88$), sex ($p = 0.95$), receipt of red blood cells (RBCs; 0.71), plasma ($p = 0.26$), or platelets (PLTs; $p = 0.66$), as well as the mean number of units transfused ($p = 0.32$). While comorbidities were also similar, compared to the full cohort, the subset studied was less likely to have had recent surgery (36% vs. 50%; $p = 0.01$) or require vasopressors (27% vs. 38%; $p = 0.04$).

DISCUSSION

In this case-control study of pulmonary transfusion reactions, we examined the role of blood component characteristics and clinical predictors, including BNP levels, in differentiating TRALI from pTRALI and TACO. We found that age, fluid balance, and BNP levels were significantly higher in subjects who developed TACO and pTRALI relative to those with TRALI and transfused controls. In fact, we found only very small elevations in BNP levels after the development of pulmonary edema in cases of TRALI, and this mild elevation was not different compared to that of transfused controls without pulmonary edema. Finally, our regression model suggests that BNP alone or in a combination with other clinical predictors may have utility in excluding a diagnosis of TRALI from other pulmonary transfusion reactions.

Both TRALI and pTRALI are considered to have inflammatory etiologies of pulmonary edema and are associated with elevated plasma levels of interleukin (IL)-6 and IL-8.[2,3,9,10] In this study, we found that pTRALI and not TRALI was associated with elevations in BNP levels. Given the association of ARDS risk factors and positive fluid balance, many cases of pTRALI may have a hydrostatic component in addition to an inflammatory etiology of pulmonary edema. Similar findings have been reported in clinical trials of ARDS where 29% of clinically defined ARDS cases had pulmonary capillary wedge pressure readings that were consistent with concomitant elements of hydrostatic edema.[18] In fact, BNP levels in this ARDS cohort were similarly elevated to our pTRALI subjects, and it was hypothesized that in addition to stretch-induced release by cardiomyocytes, BNP elevations in ARDS may be related to catecholamine release or altered pulmonary secretion or clearance of BNP.[19] Recognition of similarities in pathophysiology and clinical outcomes of these causes of pulmonary edema has led to the proposed renaming of pTRALI to transfused ARDS.[20] More recently, a combination of inflammatory markers and clinical characteristics were useful in characterizing distinct endotypes of ARDS with different mortality outcomes related to specific ventilator and fluid management strategies.[19,21,22] Inflammatory

cytokines or cardiopulmonary biomarkers may provide similar insights into the appropriate management and outcomes of patients with pulmonary transfusion reactions.

Antibody-mediated TRALI is related to the presence of antibodies directed toward HLA or human neutrophil antigens.[1,3] HLA antibody status has been found to be a risk factor for TRALI but not pTRALI in several studies.[4–6] Our finding that recipient factors are common in pTRALI does not exclude a role for transfusion in causing or exacerbating inflammatory lung edema. Continued work to understand the epidemiology and mechanism of non–antibody-mediated TRALI may have relevance to the potential inflammatory role of transfusion in pTRALI or even TACO.[23] However, elevated BNP levels or the predominance of recipient factors may have utility in excluding TRALI and the need to evaluate for HLA antibodies in blood donors.

While elevations of BNP levels and cytokine levels may have utility in characterizing specific pulmonary transfusion reactions, some limitations need to be highlighted. Criticism regarding the utility of BNP relate to its nonspecificity in patients with renal insufficiency or obesity.[24,25] Indeed, significant elevations in BNP may be seen in patients with chronic renal insufficiency and heart failure without pulmonary edema or prior to transfusion and may not be useful in excluding TRALI. Similarly, inflammatory cytokines may not improve discrimination of transfusion reactions in postoperative cases where elevations related to surgery may be expected.[26] Recent studies suggest that additional biomarkers have increased specificity for forms of hydrostatic and permeability pulmonary edema, and these markers could have utility in differentiating pulmonary transfusion reactions.[27–29] For example, cystatin C, a renal biomarker associated with cardiovascular complications, was differentially elevated in TACO relative to pTRALI and controls in our cohort. Conversely, markers of endothelial injury, such as angiopoietin-2 and TIMP-3, have been associated with cases of ARDS, and in our series, the latter was elevated in cases of pTRALI relative to that of TACO and controls. These markers of endothelial injury merit further study and may provide additional insight regarding the role of recipient factors, such as sepsis or pneumonia, relative to transfusion in the pathogenesis of pTRALI.

Given the advent of electronic medical record surveillance and focus on noninfectious adverse outcomes related to transfusion, we can expect increased identification of complex cases of transfusion-related respiratory complications.[30,31] While providing some guidance in their identification, definitions of pulmonary transfusion reactions require more specific criteria to help differentiate complex clinical cases. The International Society of Blood Transfusion (ISBT) working party on hemovigilance has endeavored to revise their definition of TACO to improve its sensitivity and specificity.[32,33] Identifying and validating key clinical and biomarker predictors and developing algorithms that better incorporate the pathophysiology of these specific clinical entities will hopefully assist clinicians in the diagnosis and management of patients with pulmonary complications of transfusion.

This study has both strengths and limitations. Major strengths include the use of active surveillance in a study population composed of both medical and surgical patients, the detailed collection of granular clinical data, and expert panel review to ensure accuracy of the outcome adjudication. However, several limitations should also be noted. Plasma

samples were only available on a subset of the parent case-control cohort and may have limited our ability to detect between-group differences and precluded development of a validation cohort. While there were no differences in age, sex, or transfusion characteristics in our cohort, there were modestly lower rates of surgery and need for vasopressors than in the parent study. Therefore, our conclusions may be limited in perioperative populations or those in shock where fluid balances and BNP levels may differ. However, the relative infrequency of TRALI after plasma mitigation makes studies of particular patient populations that include biomarker analyses challenging. The advantage of BNP is that it is a routinely available laboratory test in clinical care though other biomarkers may prove to be more useful in the characterization of pulmonary transfusion reactions. Additional studies are needed to assess whether a combination of inflammatory and cardiopulmonary biomarkers aid in the classification of cases without diagnostic certainty (TACO and TRALI overlap cases) or where sufficient clinical data are not available.

In conclusion, the elevation of BNP levels in addition to fluid balance in pTRALI and TACO supports the hypothesis that recipient characteristics play a significant role in their pathogenesis. A prediction model utilizing both clinical predictors and BNP levels provided excellent discrimination allowing a high rate of appropriate classification of pulmonary transfusion reactions. If cut points for clinical predictors and biomarkers are validated in future studies, these findings may prove useful in determining the etiology of transfusion-related pulmonary complications and decision making regarding donor white blood cell antibody testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by NHLBI SCCOR Grant P50-HL-O81027 (PT) and intramural funding from Blood Systems Research Institute (NHR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or the NIH.

The Transfusion-Related Acute Lung Injury Study Group consists of the following:

Steering committee

Pearl Toy, MD (Principal Investigator), Ognjen Gajic, MD, Mark Looney, MD, Rolf Hubmayr, MD, Michael A. Gropper, MD, PhD, Michael A. Matthay, MD, Richard B. Weiskopf, MD, Edward L. Murphy, MD, MPH, and Clifford Lowell, MD, PhD

Clinical site coordinators and research assistants

University of California San Francisco: Monique Koenigsberg, RN, Kelly Lang, RN, Christopher Chin, Deanna Lee, PhD, Lynda Bartek, RN

Mayo Clinic: Gregory Wilson, CCRC, Tami Krpata, Deborah Rasmussen, Cindy Medcalfe

Blood banks and investigators

Blood Centers of the Pacific: Nora Hirschler, MD

Blood Systems Research Institute: Rosa Sanchez Rosen, MD, Philip Norris, MD, Dan Hindes

University of California at San Francisco: Pearl Toy, MD

Mayo Clinic: S. Breandan Moore, MD, Jeffrey L. Winters, MD, Manish Gandhi, MD

ABBREVIATIONS

ARDS	acute respiratory distress syndrome
AUC	area under the curve
BNP	brain natriuretic peptides
HLGOF	Hosmer-Lemeshow goodness-of-fit
IQR	interquartile range
pTRALI	possible transfusion-related acute lung injury
TACO	transfusion-associated circulatory overload
TIMP-3	tissue inhibitor of metallopeptidase inhibitor 3

References

1. Popovsky MA. Pulmonary consequences of transfusion: TRALI and TACO. Transfus Apher Sci. 2006; 34:243–4. [PubMed: 16872902]
2. Looney MR, Roubinian N, Gajic O, et al. Prospective study on the clinical course and outcomes in transfusion-related acute lung injury*. Crit Care Med. 2014; 42:1676–87. [PubMed: 24776608]
3. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood. 2012; 119:1757–67. [PubMed: 22117051]
4. Kleinman SH, Triulzi DJ, Murphy EL, et al. The Leukocyte Antibody Prevalence Study-II (LAPS-II): a retrospective cohort study of transfusion-related acute lung injury in recipients of high-plasma-volume human leukocyte antigen antibody-positive or -negative components. Transfusion. 2011; 51:2078–91. [PubMed: 21446938]
5. van Stein D, Beckers EA, Sintnicolaas K, et al. Transfusion-related acute lung injury reports in the Netherlands: an observational study. Transfusion. 2010; 50:213–20. [PubMed: 19694998]
6. Hashimoto S, Nakajima F, Kamada H, et al. Relationship of donor HLA antibody strength to the development of transfusion-related acute lung injury. Transfusion. 2010; 50:2582–91. [PubMed: 20667042]
7. Skeate RC, Eastlund T. Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol. 2007; 14:682–7. [PubMed: 17898575]
8. Gajic O, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. Crit Care Med. 2006; 34(5Suppl):S109–13. [PubMed: 16617253]
9. Vlaar AP, Hofstra JJ, Determann RM, et al. Transfusion-related acute lung injury in cardiac surgery patients is characterized by pulmonary inflammation and coagulopathy: a prospective nested case-control study. Crit Care Med. 2012; 40:2813–20. [PubMed: 22824931]
10. Roubinian NH, Looney MR, Kor DJ, et al. Cytokines and clinical predictors in distinguishing pulmonary transfusion reactions. Transfusion. 2015; 55:1838–46. [PubMed: 25702590]
11. Tobian AA, Sokoll LJ, Tisch DJ, et al. N-terminal pro-brain natriuretic peptide is a useful diagnostic marker for transfusion-associated circulatory overload. Transfusion. 2008; 48:1143–50. [PubMed: 18298592]
12. Zhou L, Giacherio D, Cooling L, et al. Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. Transfusion. 2005; 45:1056–63. [PubMed: 15987348]
13. Li G, Daniels CE, Kojicic M, et al. The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung

injury and transfusion-related circulatory overload in the critically ill. Transfusion. 2009; 49:13–20. [PubMed: 18954397]

14. Finlay HE, Cassorla L, Feiner J, et al. Designing and testing a computer-based screening system for transfusion-related acute lung injury. Am J Clin Pathol. 2005; 124:601–9. [PubMed: 16146824]
15. Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med. 2005; 33:721–6. [PubMed: 15818095]
16. Division of Health Quality Promotion, National Center for Preparedness Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual Biovigilance Component Protocol, Hemovigilance Module. Atlanta: Centers for Disease Control and Prevention; 2009.
17. Murphy EL, Kwaan N, Looney MR, et al. Risk factors and outcomes in transfusion-associated circulatory overload. Am J Med. 2013; 126:357e29–38.
18. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564–75. [PubMed: 16714767]
19. Semler MW, Marney AM, Rice TW, et al. B-type natriuretic peptide, aldosterone, and fluid management in ARDS. Chest. 2016; 150:102–11. [PubMed: 27018313]
20. Toy P, Kleinman SH, Looney MR. Proposed revised nomenclature for transfusion-related acute lung injury. Transfusion. 2016; 56:709–13.
21. Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med. 2017; 195:331–8. [PubMed: 27513822]
22. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med. 2014; 2:611–20. [PubMed: 24853585]
23. Lannan KL, Sahler J, Spinelli SL, et al. Transfusion immunomodulation—the case for leukoreduced and (perhaps) washed transfusions. Blood Cells Mol Dis. 2013; 50:61–8. [PubMed: 22981700]
24. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. Am J Kidney Dis. 2005; 46:610–20. [PubMed: 16183415]
25. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. Circulation. 2005; 112:2163–8. [PubMed: 16203929]
26. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery. 2015; 157:362–80. [PubMed: 25616950]
27. Agrawal A, Matthay MA, Kangelaris KN, et al. Plasma angiopoietin-2 predicts the onset of acute lung injury in critically ill patients. Am J Respir Crit Care Med. 2013; 187:736–42. [PubMed: 23328529]
28. Shah KS, Maisel AS. Novel biomarkers in heart failure with preserved ejection fraction. Heart Fail Clin. 2014; 10:471–9. [PubMed: 24975910]
29. Arpino V, Mehta S, Wang L, et al. Tissue inhibitor of metalloproteinases 3-dependent microvascular endothelial cell barrier function is disrupted under septic conditions. Am J Physiol Heart Circ Physiol. 2016; 310:H1455–67. [PubMed: 26993226]
30. Clifford L, Jia Q, Subramanian A, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. Anesthesiology. 2015; 122:12–20. [PubMed: 25611652]
31. Clifford L, Singh A, Wilson GA, et al. Electronic health record surveillance algorithms facilitate the detection of transfusion-related pulmonary complications. Transfusion. 2013; 53:1205–16. [PubMed: 22934792]
32. International Society of Blood Transfusion Working Party on Haemovigilance in collaboration with The International Haemovigilance Network Prepublication Draft December 2014 [Internet]. Amsterdam: ISBT Central Office; 2014. Transfusion-associated circulatory overload (TACO) 2014

revision. [cited 2016 Aug 30]. http://www.isbtweb.org/fileadmin/user_upload/files-2015/haemovigilance/TACO_definition_validation_form_jan2015_haemovigilance.pdf

33. Proposed standard definitions for surveillance of non infectious adverse transfusion reactions. International Society of Blood Transfusion Working Party on Haemovigilance in collaboration with The International Haemovigilance Network. Jul. 2011 [cited 2016 Aug 30]. http://www.isbtweb.org/filead-min/user_upload/files-2015/haemovigilance/definitions/Proposed%20definitions%202011%20surveillance%20non%20infectious%20adverse%20reactions%20haemovigilance%20incl%20TRALI%20correction%202013.pdf

TABLE 1

Characteristics of cases and controls *

Patient characteristics	TACO (n = 22)	TRALI (n = 21)	pTRALI (n = 26)	Controls (n = 24)
Age (years)	61 ± 18	56 ± 17	59 ± 25	53 ± 23
Sex				
Female	13 (59)	9 (43)	11 (42)	12 (50)
Race				
White	18 (82)	18 (86)	16 (62)	15 (62)
Nonwhite	0 (0)	1 (5)	4 (15)	4 (17)
Missing or not reported	4 (18)	2 (9)	6 (23)	5 (21)
Transfusions (number of units)				
1–2	12 (54)	11 (52)	13 (50)	12 (50)
3–9	6 (27)	7 (33)	8 (31)	5 (21)
10+	4 (18)	3 (14)	5 (19)	7 (29)
Component types				
RBCs	80	71	58	71
Plasma	40	43	65	42
PLTs	44	42	41	34

* Data are reported as mean values ± SD, number (%), or percent.

TABLE 2

Comorbid risk factors *

	TACO (n = 22)	TRALI (n = 21)	pTRALI (n = 26)	Control (n = 24)
Risk factor				
History of congestive heart failure	10 (45)	5 (24)	2 (8)	3 (13)
Coronary artery disease	8 (36)	3 (14)	3 (12)	3 (13)
Acute renal failure	7 (31)	7 (33)	6 (23)	3 (13)
Chronic renal failure	5 (23)	3 (14)	3 (12)	2 (8)
Hemodialysis	3 (14)	3 (14)	1 (4)	3 (13)
Recent surgery	12 (55)	8 (38)	7 (27)	7 (29)
Clinical characteristics				
Ventilation at edema	8 (36)	4 (19)	12 (46)	5 (20)
Vasopressors at edema	7 (31)	7 (33)	11 (42)	1 (4)
PaO_2/FiO_2 ratio at edema	139 ± 64	143 ± 72	133 ± 76	374 ± 46
APACHE II scores	15 ± 7	14 ± 6	16 ± 7	13 ± 5
Fluid balance pre-edema (L)	2.0 (0.7–3.3)	1.5 (0.8–2.2)	3.6 (1.1–6)	1.0 (0–2)

* Data are reported as number (%), mean values ± SD, or median values (IQR).

TABLE 3

Recipient and transfusion risk factors for TRALI, pTRALI, and TACO

	TRALI (n = 21)	pTRALI (n = 26)	TACO (n = 22)	p value*
% Age ≥ 70 years	19	38	32	0.02
BNP level (pg/mL)				
Posttransfusion (IQR) *†‡	271 (137–638)	686 (379–1431)	1934 (1552–3000)	< 0.01
% > 1000 pg/ml	14	50	84	
Fluid balance pre-transfusion				
Number > 3 L/24 hr (%)	3 (15)	14 (56)	6 (24)	0.04
Number of transfused units				
Mean ± SD	7.4 ± 13.2	5.2 ± 6.0	4.6 ± 5.0	0.15
Median (IQR)	2 (2–3)	2.5 (2–6)	2 (1–6)	0.04
Number transfused > 20 units/6 hr§	3 (14)	1 (4)	0 (0)	
Receipt of plasma or whole blood from female donor (%)	8 (38)	4 (11)	0 (0)	< 0.01

*p values for comparisons of TRALI relative to TACO and pTRALI.

†BNP levels between pTRALI and TRALI significantly different.

‡BNP levels between TRALI and TACO significantly different.

§Number of units of RBCs, plasma, or PLTs transfused in the 6 hours before development of pulmonary edema.

TABLE 4

Multivariate model of recipient and transfusion risk factors for TACO or pTRALI versus TRALI by logistic analysis (n = 69)

	Odds ratio (95% CI)	p value
Recipient factors		
Age > 70 years	14.1 (1.6–122)	0.02
Posttransfusion BNP level > 1000 (pg/mL)	40.3 (6.1–266)	0.001
Fluid balance > 3 L	64 (4.5–932)	0.002
Transfusion factors		
Number of units transfused during or within 6 hr	0.91 (0.81–1.02)	0.11