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Incidence and clinical characteristics of TACO using an active surveillance algorithm

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Abstract

Background—The concordance of hemovigilance criteria developed for surveillance of transfusion-associated circulatory overload (TACO) with its clinical diagnosis has not been assessed. In a pilot study to evaluate an electronic screening algorithm, we sought to examine TACO incidence and application of hemovigilance criteria in patients with post-transfusion pulmonary edema.

Study Design and Methods—From June to September 2014, all transfused adult inpatients at four academic hospitals were screened with an algorithm identifying chest radiographs ordered within 12 hours of blood component release. Patients with post-transfusion pulmonary edema underwent case adjudication by an expert panel. TACO incidence was calculated and clinical characteristics were compared with other causes of post-transfusion pulmonary edema.

Results—Among 4,932 transfused patients, there were 3,412 algorithm alerts, 50 cases of TACO and 47 other causes of pulmonary edema. TACO incidence was 1 case per 100 patients transfused. TACO classification based on two sets of hemovigilance criteria (National Healthcare Safety Network and proposed revised International Society for Blood Transfusion) was concordant with

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expert panel diagnosis in 57% and 54% of reviewed cases, respectively. Although, the majority of clinical parameters did not differentiate expert-panel adjudicated TACO from other cases, improved oxygenation within 24 hours of transfusion did (p=.01).

Conclusions—The incidence of TACO was similar to that observed in prior studies utilizing active surveillance. Case classification by hemovigilance criteria was frequently discordant with clinical diagnoses of TACO in patients with post-transfusion pulmonary edema. Improvements in oxygenation within 24 hours of transfusion merit further evaluation in the diagnosis of TACO.

INTRODUCTION

Severe, non-infectious adverse transfusion reactions are receiving greater attention with an increased focus on their prevention.[1] Systematic data gathering efforts have improved our understanding of the incidence of pulmonary transfusion reactions such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). In this regard, both the International Society of Blood Transfusion (ISBT) and the US National Healthcare Safety Network (NHSN) have provided criteria for surveillance of pulmonary reactions (see Appendix 1) and each has promulgated a system of data gathering. [2-4]

While national hemovigilance systems are valuable and contribute to our understanding of transfusion reactions, a significant limitation is that reactions are captured by a passive reporting system thereby underestimating true incidence.[5-7] Active surveillance for severe transfusion reactions may offer a more accurate assessment of the incidence and characterization of severe transfusion-related acute adverse events, and provide insight on how to refine hemovigilance criteria to be more sensitive and specific. [8, 9]

With the rapid expansion of electronic medical records, algorithms to screen for and identify cases of post-transfusion pulmonary edema are becoming more common.[8-11] However, distinguishing the etiology of pulmonary transfusion reactions often poses a diagnostic challenge. [12, 13] The utility of applying hemovigilance system definitions developed for surveillance of pulmonary transfusion reactions to all transfused patients has not been examined, although there are ongoing efforts to re-evaluate and improve the specificity of these definitions. [4, 14, 15]

Our first objective in this multi-center study was to implement and validate an automated screening algorithm for post-transfusion pulmonary edema among all transfused patients in order to estimate TACO incidence. Our additional objectives were to compare clinical and surveillance definitions for TACO and to identify additional relevant clinical variables captured in this process which might improve the classification of pulmonary reactions as TACO.

METHODS

Study design and subjects

As part of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III), prospective surveillance for cases of pulmonary transfusion reactions was conducted

between June and September 2014 at four tertiary care hospitals. Cases of pulmonary transfusion reactions were identified by active surveillance of all adult hospitalized patients transfused with red blood cells, platelets, or plasma. The protocol was approved, including a waiver of consent, by institutional review boards of all participating sites (Aurora St. Luke's Medical Center (ASLMC), University of California San Francisco (UCSF), University of Pittsburgh Medical Center (UPMC), and Yale New Haven Hospital (YNHH)).

The study design involved four hierarchical layers of screening and diagnosis: i) an electronic algorithm flagged cases where a chest radiograph was ordered within 12 hours of blood product release ; ii) research nurses reviewed all alerted cases for new or worsening hypoxia and suspected pulmonary edema based on radiography reports within 12 hours of transfusion; iii) a pulmonary physician (NHR) triaged the coordinators' cases and ruled out exclusionary diagnoses; and iv) cases were then reviewed by a three-member expert panel consisting of critical care specialists with expertise in transfusion medicine (DJK, MRL, MAM). Screening, record review, data entry, and case adjudication occurred via a centralized Study Management System (SMS) managed by RTI, the REDS-III Data Coordinating Center.

Subjects were excluded from further screening if they did not receive a transfusion i.e., blood was issued but not transfused. Further exclusion criteria included 1) no chest radiograph (ordered but not performed); 2) no evidence for pulmonary edema on chest radiograph; 3) improvement or no change in pre-existing pulmonary edema; 4) no increase in supplementary oxygen; or 5) presence of conditions that could be mistaken for pulmonary edema on chest radiograph (e.g., recent lung transplantation, pulmonary fibrosis). Additionally subjects receiving extracorporeal membrane oxygenation (ECMO), in whom measures of oxygenation would be confounded, and routine post-cardiac surgery patients without significant pulmonary edema or increased oxygen requirements, were excluded. The disposition/classification of each screened case including inclusion and exclusion criteria was recorded in the SMS.

Research nurses completed extensive standardized study data forms and prepared standardized narrative reports from electronic medical record data. The case synopses included the clinical context and timeline of events, number and volumes of transfused blood components as well as fluids, chest radiograph images and reports, respiratory and hemodynamic monitoring data, echocardiography, and laboratory results. These summaries were provided to the expert panel to determine the etiology of possible pulmonary transfusion reactions. Each case was initially reviewed by two experts who independently classified it as TACO, TRALI including Possible TRALI, TACO/TRALI, or "Other" when an alternative diagnosis was identified. If the two experts independently agreed on a diagnosis, the classification was final. If the two experts did not agree, the third expert reviewed the case. If two of the three panel members agreed on a final diagnosis, the case was considered adjudicated. On periodic conference calls, all three members of the expert panel reviewed cases without two experts in agreement to discuss the case in more depth and assign a consensus determination.

A clinical diagnosis of TACO was derived from criteria used in the NHSN surveillance definition, namely with pulmonary edema developing within 6 hours of transfusion characterized by clinical, echocardiographic, or laboratory evidence of left atrial hypertension along with clinical judgment using other case information (See Appendix 2 for listing of available data). [2] TRALI was defined as new acute lung injury (ALI) that developed within 6 hours of transfusion, and there was no temporal relationship to an alternative risk factor for ALI (See Appendix 2). Cases designated as Possible TRALI in this study were patients where the expert panel believed that the underlying ALI risk factor was likely to have played a significant role in the development of pulmonary edema. Lastly, cases were designated as TACO/TRALI when the expert panel could not distinguish between the two diagnoses. Case classification by the expert panel was compared with strict application of NHSN and proposed revised ISBT hemovigilance criteria (See Appendix 1).

Statistical analysis

For incidence calculations, the total number of transfused components and number of unique transfused patients during the study period were captured from the hospital transfusion service. Individual transfusion episodes were defined as blood components released within 6 hours of one another. Distributions and proportions of demographic and clinical data were tabulated for groups of pulmonary transfusion reactions. Data were expressed as mean values ± standard deviation (SD), medians, or proportions and were compared using chi square tests, t-test, and Wilcoxon rank sum test, as appropriate. A multivariate logistic regression model was developed to identify how risk factors (demographics and clinical variables in Appendix 3) were associated with TACO and non-TACO cases. The initial model was refined using backward elimination at the $p = 0.05$ level to retain significant variables. After the final covariates were selected, interactions were investigated. Receiver operating characteristic curves (ROC) and area under the curve (AUC) were generated to compare the models' predictive accuracy and select the optimum model. The final model was also subjected to the Hosmer-Lemeshow test for goodness of fit. A two-tailed p value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SAS/STAT software, Version 9.4, Cary, NC.

RESULTS

Among 14,300 transfusion episodes during the study period, electronic surveillance generated 3,412 alerts from a total of 4,982 patients transfused 30,837 blood components (Figure 1, Appendix Table 1). The automated algorithm at each hospital was audited against transfusion reactions reported to the blood bank as well as through a review of 50 randomly selected transfusion episodes. 2.8% (97/3,412) of alerts were reviewed by the expert panel who diagnosed 50 cases of TACO and 47 cases of other diagnoses ("non-TACO"). These non-TACO diagnoses included 29 cases of Possible TRALI or TRALI, 2 cases of TACO/TRALI, and 16 cases of alternative causes of bilateral pulmonary opacities (Table 1). Etiologies of these 16 "Other" cases included: atelectasis (4), pneumonia (4), aspiration (2), mild post-cardiac surgery edema (2), neurogenic pulmonary edema (1), cardiogenic shock (1), negative pressure pulmonary edema (1), and diffuse alveolar hemorrhage (1).

1.5% (50/3,412) of alerts did not meet the exclusion criteria (Figure 1) and resulted in a diagnosis of TACO. Using the denominator of all unique patients transfused at each hospital over the study period, we estimated an incidence of 1 TACO cases per 100 patients transfused (50 / 4,982). Incidence rates were similar across the four hospitals (Range: 0.9-1.1 case per 100 patients transfused). Across all four centers, there were 3.5 TACO cases per 1000 transfusion episodes (50 / 14,300).

Clinical data corresponding to parameters included in the NHSN and proposed revised ISBT hemovigilance criteria for TACO were extracted from extended form data (Appendix Table 2) and case classification using these criteria were compared to expert panel diagnoses. Of the 97 patients with pulmonary edema referred for expert panel review, NHSN and proposed revised ISBT consensus criteria resulted in 23 (46%) and 22 (44%) more cases of TACO, respectively; and hemovigilance system classifications were concordant with expert panel review in 57% and 54% of cases, respectively (See Table 2). Using either of the hemovigilance criteria, we estimated an incidence of 1.4 TACO cases per 100 patients transfused. Hospital mortality was higher for cases classified as TACO using NHSN (28%) or ISBT (29%) criteria relative to that of expert panel diagnosis (14%; p=0.05).

Tables 3 and 4 provide a description of the clinical characteristics and comorbid conditions in cases of expert panel adjudicated TACO compared to those with other causes of post-transfusion pulmonary edema. Patients with TACO were older and had a greater prevalence of cardiac disease (congestive heart failure and coronary artery disease) as well as a history of COPD. There were no differences in the number of units transfused in 6 and 24 hours prior to developing pulmonary edema, nor was there a difference in overall fluid balance. Total volumes of transfused blood components were non-statistically higher in cases of TACO, and TACO was more common in patients receiving plasma alone or with RBC's (p 0.04) though not in those receiving both platelets and plasma (p 0.39).

The frequency of obtaining diagnostic tests that are included as part of hemovigilance criteria for TACO was as follows: echocardiogram data was available in 67% of cases – either prior to or following transfusion; central venous pressure and BNP levels were measured in 39% and 5% of cases, respectively. Table 5 provides oxygenation and hemodynamic characteristics of patients with TACO compared with other diagnoses. There were no significant differences in the proportion of patients receiving mechanical ventilation at the time of pulmonary edema. The severity of pulmonary edema based on chest radiograph reports (mild / moderate / severe) was also similar in cases of TACO vs. other diagnoses. In TACO cases, signs and symptoms of pulmonary edema (dyspnea, tachypnea, or increased oxygen requirements) were more likely to resolve within the first 24 hours following transfusion (p 0.01). Oxygenation, as measured either by PaO2/FiO2 or SpO2/FiO2 ratios within 24 hours of pulmonary edema as well as the change in oxygenation from the time of edema, was higher in cases of TACO vs. other diagnoses (p 0.05 & 0.01, respectively). In our multivariable regression analysis, only a history of congestive heart failure, a history of chronic obstructive pulmonary disease, and the PaO2/FiO2 ratio within 24 hours of pulmonary edema were significant in the final model of TACO vs. non-TACO cases (AUC 0.74; Hosmer Lemeshow Goodness-of-Fit test p=0.34)

DISCUSSION

For this study, we successfully implemented a system of active surveillance using electronic medical record screening and case review for pulmonary transfusion reactions. TACO incidence was similar across four academic hospitals and was similar to prior studies utilizing other active surveillance systems. Application of hemovigilance criteria to all cases of transfusion related pulmonary edema showed a substantial rate of discordance with the expert panel's clinical diagnoses of TACO. Notably, TACO cases identified using hemovigilance criteria had a higher mortality rate. Diagnostic tests used as part of hemovigilance criteria, such as BNP levels, were uncommonly utilized clinically. Many clinical risk factors – including transfusion volumes and fluid balance – did not distinguish TACO from other causes of transfusion associated pulmonary edema. However, improvement in readily available measures of oxygenation occurred more frequently in TACO and merits further evaluation in its diagnosis.

We developed our automated screening algorithm with the intent of having excellent sensitivity but not necessarily high specificity in four different hospital settings. Our limited auditing indicated that this algorithm did not miss any TACO cases; however, we recognize that the high number of cases generating alerts for further review (e.g., 24% of all transfusion episodes) makes its use impractical outside of a research setting. Subsequent modifications of the automated algorithm to exclude alerts without transfusion or chest radiographs and to include measures of oxygenation improved the specificity modestly from 2.8% to 10% in a pilot at one site. However, further modifications would be needed to decrease the false positive alert rate if this approach is to be considered for surveillance of pulmonary transfusion reactions. Our study found a per patient incidence rate of TACO similar to that of other prospective cohorts with some degree of active surveillance but lower compared to studies focused on a specific patient population or blood component type. [6, 9, 16] We also utilized a new metric – a per transfusion episode incidence - which we believe is meaningful as it reflects each opportunity for a patient to develop TACO. We found that TACO incidence per transfusion episode was one-third that of per patient incidence.

A notable finding was that relevant diagnostic data were often not available clinically at the time of a pulmonary transfusion reaction. Echocardiography which can provide useful noninvasive information regarding the pathogenesis of post-transfusion pulmonary edema was utilized in approximately two thirds of the study population. Measurement of central venous pressure was only sporadically utilized even in critically ill patients with central venous catheters. Most striking was the infrequent ordering of brain-natriuretic peptide (BNP), occurring in only 5% of cases. This finding parallels a review of TACO which found that BNP levels were only measured in 3% (3/98) and 11% (11/98) of cases prior to and following the development of pulmonary edema, respectively. [17] Studies have found higher BNP and NT-proBNP levels in TACO patients in comparison to those of patients with TRALI and Possible TRALI, and more recently, elevations in inflammatory cytokines have been recognized in TRALI but not in TACO. [8, 18-21] Whether increased use of BNP alone or in combination with other inflammatory markers would be beneficial in the differential diagnosis of transfusion-associated pulmonary edema remains unclear and merits further study. [20, 22]

The vast majority of the 97 subjects evaluated by the expert panel had acute respiratory distress, radiographic evidence of pulmonary edema, and a positive fluid balance – sufficient for diagnosis of TACO using NHSN criteria but not by clinical criteria used by our panel.[2] Our study, as others have reported, found that fluid balance was not useful in differentiating TACO from other forms of transfusion related pulmonary edema. [10, 18, 20, 23] Incorporating the clinical context, chest radiograph images, invasive hemodynamic monitoring data, and echocardiography data likely provided the expert panel with additional details in determining the most likely etiology of the pulmonary edema. When applied strictly, two hemovigilance definitions for TACO were frequently discordant with expert panel review and resulted in inclusion of additional cases of TACO. The impact of these additional cases on our reported incidence of TACO was relatively small, with incidence using either clinical diagnosis or hemovigilance criteria in line with what has been reported in studies of active surveillance. However, mortality rates using hemovigilance criteria were higher than that of expert panel diagnoses and what has been reported in prior studies.[24, 25] Strict application of hemovigilance criteria for TACO resulted in the inclusion of cases which were clinically classified by the expert panel as Other or Possible TRALI; the latter which is known to have a higher mortality rate than TACO.[11] While differences between the mortality rates by hemovigilance classification and those reported in the literature in clinical case series may be due to specific comorbidities or concurrent risk factors, future studies should specify the methodology used in case classification when reporting clinical outcomes.

It is well known that distinguishing pulmonary transfusion reactions requires clinical data that are labor intensive to extract and require experience to interpret. In an effort to improve the sensitivity and specificity of hemovigilance criteria, the ISBT Working Party on Haemovigilance has endeavored to revise the ISBT definition of TACO.[4, 14] However, given that the currently utilized diagnostic criteria for TACO contain data variables that are only obtained sporadically or lack specificity, others need to be identified and examined for their potential utility. Variables considered in the revised diagnosis of TACO, including the presence of cardiomegaly on chest radiographs or the impact of diuretics (at least net negative 1 liter within 24 hours) were infrequently available in our study and not different in TACO from other cases of pulmonary edema.[4, 14] The use of diuretics as a treatment for TACO (60%) was higher compared to two prior studies (29% and 27%), but in our cohort their use was also common for other causes of pulmonary edema (45%). [17, 23]

We also found that the severity of pulmonary edema as graded on chest radiograph reports and by measures of oxygenation was similar in cases of TACO and other forms of pulmonary edema. However within 24 hours of transfusion, measures of oxygenation had improved significantly in cases of TACO, and these improvements were independently associated with a diagnosis of TACO in our multivariable regression analysis. These improvements in oxygenation may correlate with resolution of pulmonary edema radiographically. Radiographic changes in pulmonary edema were included as part of the adjudication process and time to improvement in symptomatic, radiographic, or oxygenation parameters after transfusion may be useful in the *post-hoc* diagnosis of TACO.

This study has both strengths and limitations. Strengths include the use of active surveillance in a multicenter study population composed of both medical and surgical patients, the use of an electronic screening algorithm, the collection of detailed clinical data, and expert panel review for outcome adjudication. However, despite the high sensitivity of case identification, the accuracy of estimated incidence rates of pulmonary transfusion reactions may be limited by the short study period. An ongoing case-control study of TACO at the study hospitals will address this limitation by including a larger sample size and imputability criteria, and will additionally examine the role of BNP in classifying cases where adequate clinical data is not available. [26]

Given the advent of electronic medical record surveillance of pulmonary transfusion reactions, we can expect increased identification of complex cases of post-transfusion pulmonary edema. While providing some guidance in their identification, surveillance definitions of pulmonary transfusion reactions would benefit from enhanced specificity to help differentiate complicated clinical cases. Identifying additional clinical or biomarker predictors which further incorporate the pathophysiology of these specific clinical entities will hopefully improve classification of pulmonary transfusion reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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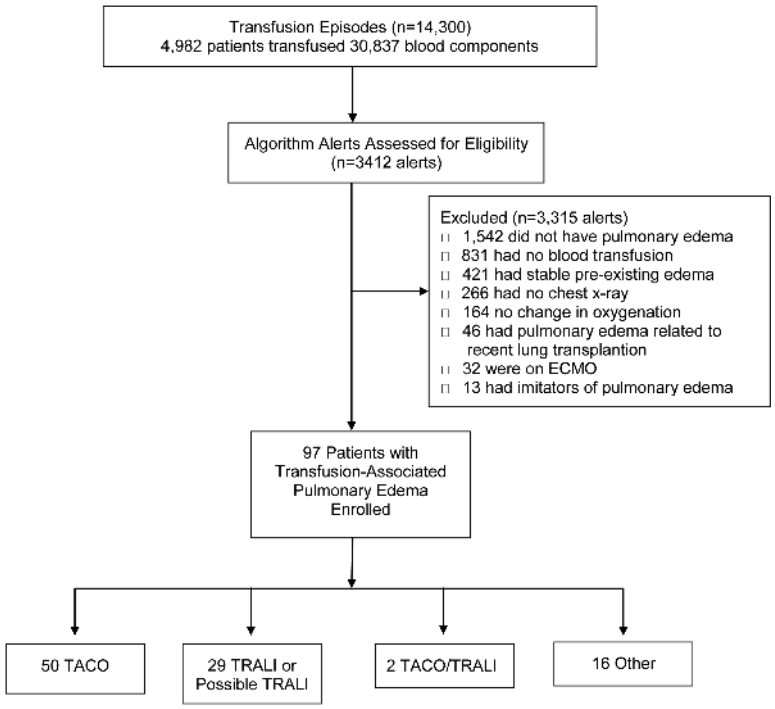

Figure 1.
Patient Flow Diagram

Table 1

Screening, Extended Form & Outcome Summary by Site

	Alerts Screened	Total Extended	TACO	TRALI or Possible TRALI	TACO/TRALI	Other
Site 1	1109	24	11	8	0	5
Site 2	1065	31	15	11	2	3
Site 3	724	20	11	5	0	4
Site 4	514	22	13	5	0	4
Total	**3412**	**97**	**50**	**29**	**2**	**16**

Table 2

Expert Panel Diagnosis of TACO Compared to Hemovigilance Criteria

Table 2a

NHSN Criteria for TACO	STRIPE Expert Panel Diagnosis of TACO			
		Yes	No	
	Yes	40	32	72
	No	10	15	25
		50	47	
Concordance of clinical and hemovigilance TACO diagnoses – 57%				

Table 2b

Proposed Revised ISBT Criteria for TACO	STRIPE Expert Panel Diagnosis of TACO			
		Yes	No	
	Yes	39	34	73
	No	11	13	24
		50	38	
Concordance of clinical and hemovigilance TACO diagnoses – 54%				

Table 3

Demographic and Transfusion Characteristics

Patient Characteristics	TACO (N=50)	Non-TACO (N=47)	P-value
Age †	66 ± 13	58 ± 16	0.01
Sex			
Female	24 (48%)	17 (36%)	0.30
Race			0.33
White	28 (56%)	25 (53%)	
Non-White	8 (16%)	13 (28%)	
Missing/Not reported	14 (28%)	9 (19%)	
Patient Alert location			0.09
Ward	11 (22%)	5 (11%)	
Intensive care unit	28 (56%)	36 (76%)	
Operating room	10 (20%)	5 (11%)	
Emergency department	0	1 (2%)	
Transfusion Strata			0.85
1-2 units	24 (48%)	24 (51%)	
3-9 units	20 (40%)	17 (36%)	
10+ units	6 (12%)	6 (13%)	
Component Type			0.10
RBC Only	22	20	
Plasma +/- RBC	11	3	
Platelets +/- RBC	3	17	
Platelet & Plasma	14	17	
Transfused volume (L)	0.9	0.4	0.14
Blood Units – 6 hrs *	2	2	0.45
Blood Units – 24 hrs *	4	3	0.56
Blood Infusion Rate L / Hr	0.3	0.3	0.95
Fluid balance (L) – 6 hrs	0.8	0.7	0.61

† The ages are presented as mean values ± SD.

* Number of blood components given in the 6 or 24 hours prior to development of pulmonary edema

Table 4

Comorbid Risk Factors

Risk Factor	TACO N=50	Non-TACO N=47	P-value
History of congestive heart failure	16 (32%)	5 (11%)	0.01
Coronary artery disease	20 (40%)	9 (19%)	0.03
Hypertension	33 (66%)	25 (53%)	0.22
Acute renal failure	9 (18%)	16 (34%)	0.10
Chronic renal failure	13 (26%)	12 (26%)	1.00
Hemodialysis	8 (16%)	6 (13%)	0.78
COPD	9 (18%)	2 (4%)	0.05
Severe liver disease	9 (18%)	12 (26%)	0.46
Recent surgery	21 (42%)	14 (30%)	0.29
Cardiac bypass	12 (24%)	7 (15%)	0.31

COPD=chronic obstructive pulmonary disease

Table 5

Clinical Characteristics & Outcomes

Characteristic	TACO N=50	Non-TACO N=47	P value
Mechanical Ventilation at edema	32 (64%)	35 (75%)	0.24
Pulmonary edema			0.83
Mild	50%	53%	
Moderate	40%	34%	
Severe	2%	2%	
Cardiomegaly	14 (28%)	9 (19%)	0.31
Pleural effusion at edema	26 (52%)	18 (38%)	0.39
Oxygenation at edema †	184	205	0.95
Oxygenation within 24 hrs of edema †	310	228	0.05
Change in oxygenation at 24 hrs †#	82	14	0.01
Diuretics pre-edema	15 (30%)	13 (28%)	0.83
Diuretics at edema	30 (60%)	21 (45%)	0.16
Vasopressors pre edema	14 (28%)	18 (38%)	0.19
Vasopressors at edema	19 (38%)	25 (53%)	0.13
Antihypertensive medications	29 (62%)	21 (42%)	0.07
Onset of Signs & Symptoms *			
During Transfusion	11 (22%)	10 (21%)	.53
Within 6 hours	31 (62%)	27 (57%)	.60
Between 6-24 hours	8 (8%)	10 (21%)	.32
Resolution of Signs & Symptoms			
Within 6 hours of Transfusion	1 (2%)	1 (2%)	1.0
Between 6-24 hours	18 (38%)	7 (15%)	.01
Between 24-72 hours	20 (42%)	19 (40%)	.87
Greater than 72 hours	3 (6%)	8 (17%)	.11
Hospital Outcomes ^			
ICU length of stay after edema	**3**	**5**	**0.07**
Hospital length of stay after edema	**8**	**11**	**0.25**
Hospital Mortality	**7 (14%)**	**15 (32%)**	**0.04**

† Data are presented as median values of PaO2/FiO2 or SpO2/FiO2 if arterial blood gas was not available

Difference in PaO2/FiO2 or SpO2/FiO2 from 24 hours following edema to the time of edema

* Signs and Symptoms defined as dyspnea, tachypnea, or increased oxygen requirements

^ Length of stay duration presented in days as median value