

# Transfusion-Related Acute Lung Injury (TRALI) Occurrence, Risk Factors, and Outcome: A Nested Case- Control Study

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## Abstract

### Background and Objectives:

Transfusion-Related Acute Lung Injury (TRALI) is a serious complication of blood transfusion characterized by hypoxemia and pulmonary edema. Our study assessed TRALI occurrence, potential risk factors using a large administrative database and medical charts.

### Materials and Methods:

This nested case-control study identified individuals with claims evidence of transfusion and TRALI occurrence from 1/1/07 through 12/31/09 using HealthCore's Integrated Research Database (HIRDSM). Potential cases were ascertained by ICD-9-CM diagnosis code 518.7 and matched to controls who were transfused individuals without TRALI. Medical charts were evaluated and univariate conditional logistic regression was used to compare cases and controls by potential risk factors.

### Results:

The study identified 346,972 transfused individuals with majority being females (59.8%), elderly (53.3%), and in the inpatient setting (85.3%). TRALI rates were higher in the inpatient setting, and lower for persons 80 years and over. TRALI rates by blood components ranged from 0.7 to 21.4 per 10,000 persons, with highest rate for platelets and plasma recipients (95% CI, 0.5-119.3). Of 10 confirmed cases, 2 persons died of TRALI. Confirmed cases were more likely to have direct or indirect lung injuries, cardiac surgeries, hematologic malignancies, other malignancies, and history of smoking.

### Conclusion:

Our study highlights an important role that large administrative databases with medical charts can have in assessing TRALI occurrence and potential risk factors. Overall, this hypothesis-generating study suggests the need for further population-based investigations in the inpatient hospital setting to assess the effects of aging, health conditions, and other potential risk factors on TRALI occurrence.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to Internet Journal of Hematology.

## INTRODUCTION

Transfusion-Related Acute Lung Injury (TRALI) is a serious, life threatening complication of blood transfusion

defined as acute lung injury occurring within the first six hours of transfusion and characterized by respiratory distress, hypoxemia, and dyspnea [1-5]. According to the FDA's Summary Fatality reports following Blood Collection and Transfusion, during the six-year period, 2005-2010, nearly half (about 47%) of all transfusion-related fatalities reported to Center for Biologics Evaluation and Research (CBER) were due to TRALI [1].

TRALI is thought to be caused by two major immune-mediated mechanisms, which lead to neutrophil activation, damage to endothelial cells and pulmonary edema that are responsible for the clinical presentation of TRALI. Leukocyte antibodies, biologically active substances

including lipids and cytokines as well as underlying recipient conditions have been implicated in the major development mechanisms for TRALI [6-8]. One hypothesis is that leukocyte antibodies in donors, mainly multiparous women [2] who may have developed these due to exposure to fetal blood, can activate recipient's neutrophils in pulmonary capillaries and cause pulmonary damage and capillary leak [6-8]. Another hypothesis for TRALI occurrence is the 'two-hit mechanism' with the first hit being underlying patients conditions (e.g., active infection, malignancy, surgery) at the time of transfusion that may prime and attract neutrophils to the endothelial surface of the lung followed by the second event, transfusion of the recipient-specific leukocyte antibodies or release of other biologically active substances (e.g. lipids, cytokines) leading to pulmonary damage and TRALI occurrence [6-8]. The reported U.S. incidence of TRALI is based mostly on single and multi-center non-population-based studies and therefore, varies considerably across studies, with critically ill persons having the highest TRALI rates [9-14]. In contrast, a population-based study among elderly Medicare beneficiaries (age 65 and over) suggested that TRALI is an infrequent complication of outpatient transfusions, which may be due to lower likelihood of potentially predisposing recipient factors in the outpatient setting [15]. Underdiagnosis and underreporting of TRALI may have also contributed to the variation in the reported TRALI occurrence. Literature suggests that increased TRALI rates in critically ill persons are likely due to the underlying recipient conditions, which currently are not well defined [16,17]. To our knowledge, no past studies have used large administrative claims and medical chart data to study TRALI occurrence and risk factors. Therefore, we conducted a nested-case control study to assess TRALI occurrence and potential transfusion (e.g., blood components, units, product expiration) as well as recipient (e.g., underlying health conditions and procedures) risk factors using a large administrative database and medical charts.

## **MATERIALS AND METHODS**

### **Study Design**

HealthCore Integrated Research Database (HIRDSM), a longitudinal health care claims database, which includes automated computerized claims data and enrollment information for over 69 million members in the United States with medical eligibility from 16 Blue Cross and/or Blue Shield licensed plans, was used to assess the incidence and risk factors for TRALI. Claims data captures medical

services rendered, including patient diagnoses and procedures, during a visit to either the physician office or a hospital, while enrollment data helps to ascertain coverage eligibility and provides information on demographic characteristics. Based on data from the HIRD, a study cohort of patients with claims evidence of blood and blood component transfusion were identified. Blood and blood components (e.g., whole blood, red blood cells, platelets and plasma) were identified using International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) procedure codes, Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and UB92 revenue codes in the time period between 01/01/2007 and 12/31/2009.

### **Selection of Cases and Controls**

Potential TRALI cases were determined by the occurrence of at least one claim with an International Classification of Disease, 9th revision, (ICD-9) diagnosis code 518.7. Controls were selected from individuals who had claims evidence of transfusion without claims suggestive of TRALI. Specifically, potential controls were excluded if they had claims with ICD-9 diagnosis codes for TRALI (518.7), acute respiratory failure (518.81), acute and chronic respiratory failure (518.84) and other pulmonary insufficiency (518.82) within 0-3 days following a transfusion. Exclusion of potential controls with claims evidence of acute respiratory failure conditions in close proximity to the time of transfusion ensured that true TRALI cases were not included in the control group.

Controls were matched at a 4:1 ratio to the cases by age, gender, facility and timing of transfusion. During the chart retrieval process, medical charts for the four matching controls identified from the claims data for each case were not always available due to various reasons (e.g. facility not willing to participate, charts not available). Therefore some cases had less than four matching controls in the final analyses. Matching on age was based on categories of 0-4, 5-9, 10-18, 19-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85+ years. Matching by facility was based on the identification number and setting (i.e. outpatient or inpatient) of the TRALI diagnosis. When TRALI diagnosis occurred on a physician claim, the controls were identified from the same facility. When TRALI diagnosis occurred on a physician claim and no transfusion facility identified, the facility reported on the most recent service date prior to TRALI diagnosis was used to identify controls. Matching by timing of transfusion was through selection of controls with the nearest transfusion service dates after all other matching

criteria were applied. All controls had transfusion service dates within  $\pm 365$  days from the service date of the matched case.

#### Data collection

Administrative claims data was used to ascertain the characteristics of persons who were transfused and the occurrence of TRALI by gender, age, blood components, U.S regions, and settings. Patients were classified into mutually exclusive categories according to the specific type of blood and blood components transfused and compared by demographic and other characteristics. Inpatient and outpatient hospital claims were used to identify transfusions and TRALI occurrence; while demographic variables (age, gender, and region) were determined from the enrollment files.

Claims-based reports of TRALI were more closely examined using medical chart data. We created a chart abstraction form to collect specific clinical information related to exposure to blood and blood products, transfusion-related adverse effects, patient characteristics, potential risk factors and outcomes (e.g., mortality) for the TRALI cases and their matched controls. The form collected information on each blood product transfused, including date and time of transfusion, type and volume transfused, underlying reasons for transfusion, and occurrence of transfusion-related adverse effects. Detailed information pertaining to vital signs, laboratory, and radiology information was abstracted for a period of 3 days immediately prior to and following transfusion. Patient characteristics including a history of diagnoses and surgical procedures considered potential risk factors for TRALI (e.g., cardiopulmonary bypass, direct or indirect lung injury, aspiration, pneumonia, toxic inhalation, lung contusion, lung surgery, malignancies, smoking) as well as demographic information were also abstracted. Confirmation of TRALI cases was performed by a board-certified physician with expertise in transfusion medicine. Medical chart data for the claims-based TRALI cases were reviewed by the physician to determine whether the patient had TRALI. The Canadian Consensus Panel TRALI definition was applied as the gold standard during physician case confirmation [3]. Confirmed cases and their matched controls were used for the nested case-control study analysis (Figure 1).

#### Statistical analysis

The claims-based crude incidence rates and 95% confidence intervals (CIs) for TRALI were calculated per 10,000 persons exposed overall and for the mutually exclusive blood and blood product categories. Additionally, the overall

crude incidence rates by age, gender, region, and setting were calculated and comparisons were made between the mutually exclusive categories using chi-square test for categorical variables and ANOVA for continuous variables. As it was difficult to ascertain code validity through medical chart review, TRALI rate estimates (per 10,000 transfused persons) with corresponding 95% confidence intervals were based on all the potential TRALI cases as identified using the claims-based algorithm. Demographics and other potential transfusion (e.g., blood volume, blood components) and recipient risk factors (e.g., health conditions, procedures) identified from medical chart data were compared between TRALI cases and controls.

Due to the small sample size, univariate conditional logistic regression was used to estimate the odds ratios (ORs) and 95% CIs for potential TRALI risk factors, after controlling for the matched potential confounders. All analyses were conducted using SAS version 9.2 and all tests were two-sided.

## RESULTS

Based on claims data analysis, we identified 346,972 persons with recorded transfusion of blood and blood components during the study period 2007-2009 (Table 1). A majority of the blood or blood component users were female (59.8%), elderly (53.3%), and in the inpatient setting (85.3%). Comparison of all the mutually exclusive transfusion categories by demographic and other characteristics shows significant differences among users of various blood components (Table 1). Among all individuals transfused, 35 (1.0 per 10,000 persons) had TRALI recorded in the claim. As shown in Table 1, TRALI rates per 10,000 varied by gender, age, region, and setting, with the higher rates among males, for persons ages 40-64 and 65-79, in the Midwest, and in the inpatient setting; and with lower TRALI rates for persons 80 and over and in the outpatient setting. Also, the claims-based TRALI rates ranged from 0.7 to 21.4 per 10,000 persons depending on the blood component category, with wide confidence intervals due to small sample sizes in some of the mutually exclusive categories (Table 2).

A total of 35 TRALI cases were identified from the administrative claims data. After excluding patients with no medical record data available, lack of provider participation and patients with minimal chart information, a confirmation chart sample of 28 TRALI cases was available for physician review. The chart evaluation by the physician resulted in a cohort of 10 confirmed TRALI cases with the corresponding chart-based overall TRALI rate of 0.29 per 10,000 persons



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**Table 2**

Claims-based TRALI rates among beneficiaries by blood or blood components transfused during 2007-2009

Categories	Number of persons transfused	TRALI cases	TRALI rates per 10,000 persons	95% Confidence Intervals
Total	346,972	35	1.0	0.7-1.4
RBC only	113,094	13	1.1	0.6-2.0
Plasma only	10,243	3	2.9	0.6-8.6
Platelets only	4,031	0	N/A*	N/A
RBC and Plasma	6,597	0	N/A*	N/A
RBC and Platelets	7,496	2	2.7	0.3-9.6
Platelets and Plasma	467	1	21.4	0.5-119.3
RBC, Platelets and Plasma	1,398	1	7.2	0.2-39.9
Whole blood only	810	0	N/A*	N/A
Other combinations	17,434	2	1.1	0.1-4.1
Unspecified	185,402	13	0.7	0.4-1.2

\*TRALI rate is likely not reflected due to a relatively small sample size

**Table 4**

Transfusion and other characteristics for cases and matched controls as recorded in medical charts

Characteristics	Total		Cases		Controls	
	N	%/SD	N	%/SD	N	%/SD
Sample Size	44	100.0%	10	100.0%	34	100.0%
Admission type						
Outpatient	6	13.6%	0	0.0%	6	17.6%
Inpatient	38	86.4%	10	100.0%	28	82.4%
Reason for transfusion*						
Anemia	33	75.0%	7	70.0%	26	76.5%
Bleeding/Hemorrhage	12	27.3%	3	30.0%	9	26.5%
Thrombocytopenia	1	2.3%	1	10.0%	0	0.0%
Surgery	5	11.4%	1	10.0%	4	11.8%
Other	7	15.9%	4	40.0%	3	8.8%
Patient blood type						
Blood typing done	44	100.0%	10	100.0%	34	100.0%
Major blood group						
A+	17	38.6%	0	0.0%	17	50.0%
B+	2	4.5%	2	20.0%	0	0.0%
B-	1	2.3%	0	0.0%	1	2.9%
O+	22	50.0%	7	70.0%	15	44.1%
O-	1	2.3%	1	10.0%	0	0.0%
AB+	1	2.3%	0	0.0%	1	2.9%
Antibody test	35	79.5%	7	70.0%	28	82.4%
Atypical antibodies	1	2.3%	1	10.0%	0	0.0%
Mutually exclusive product type						
RBC only	29	65.9%	5	50.0%	24	70.6%
Plasma only	2	4.5%	1	10.0%	1	2.9%
Platelets only	5	11.4%	2	20.0%	3	8.8%
RBC and Plasma	0	0.0%	0	0.0%	0	0.0%
RBC and Platelets	3	6.8%	1	10.0%	2	5.9%
Platelets and Plasma	0	0.0%	0	0.0%	0	0.0%
RBC, Platelets and Plasma	1	2.3%	1	10.0%	0	0.0%
Other	4	9.1%	0	0.0%	4	11.8%
At least one leukoreduced component transfused	32	72.7%	8	80.0%	24	70.6%
All transfused components leukoreduced	24	54.5%	6	60.0%	18	52.9%
Average number of blood components transfused per person	2.8	2.7	3.0	2.4	2.8	2.8
Average number of units transfused per person	3.1	4.1	3.0	2.4	3.1	4.5
Average number of days to the RBC's expiration†	20.6	9.4	28.7	6.0	19.8	8.5
Median number of days to the RBC's expiration†	24.0	N/A	30.0	N/A	21.5	N/A

\*Patients may be counted in more than one category

†5 TRALI cases and 16 controls with data available were used

**Table 3**

Patient characteristics for cases and matched controls as recorded in the medical charts

Characteristics	Total		Cases		Controls	
	N	%/SD	N	%/SD	N	%/SD
Sample Size	44	100.0%	10	100.0%	34	100.0%
Age	75.2	14.4	74.4	15.9	75.4	14.2
Age groups						
Under 40	1	2.3%	0	0.0%	1	2.9%
40 to 49	2	4.5%	1	10.0%	1	2.9%
50 to 64	9	20.5%	2	20.0%	7	20.6%
65 and Over	32	72.7%	7	70.0%	25	73.5%
Gender						
Male	20	45.5%	4	40.0%	16	47.1%
Female	24	54.5%	6	60.0%	18	52.9%
Race						
Caucasian	34	77.3%	9	90.0%	25	73.5%
Non-Caucasian	3	6.8%	1	10.0%	2	5.9%
Unknown	7	15.9%	0	0.0%	7	20.6%
Ethnicity						
Hispanic	2	4.5%	0	0.0%	2	5.9%
Non-Hispanic	4	9.1%	1	10.0%	3	8.8%
Not Specified	38	86.4%	9	90.0%	29	85.3%
Region						
West	15	34.1%	4	40.0%	11	32.4%
NorthEast	15	34.1%	3	30.0%	12	35.3%
South	5	11.4%	1	10.0%	4	11.8%
MidWest	9	20.5%	2	20.0%	7	20.6%
Serious outcome after transfusion-related adverse event						
Death	2	4.5%	2	20.0%	0	0.0%



**Table 5**

Pre-transfusion patient characteristics as recorded in the medical charts for cases versus matched controls

Characteristics	Total N %	Cases N %	Controls N %
Sample Size	44 100.0%	10 100.0%	34 100.0%
Pre-transfusion lung injury recorded in the chart			
Direct lung injury	5 11.4%	2 20.0%	3 8.8%
Pneumonia	2 4.5%	1 10.0%	1 2.9%
Lung surgery	2 4.5%	0 0.0%	2 5.9%
Other direct lung injury	1 2.3%	1 10.0%	0 0.0%
Small cell carcinoma of lung	1 2.3%	1 10.0%	0 0.0%
Indirect lung injury	18 40.9%	7 70.0%	11 32.4%
Sepsis	3 6.8%	1 10.0%	2 5.9%
Shock	1 2.3%	1 10.0%	0 0.0%
Cardiopulmonary bypass	3 6.8%	1 10.0%	2 5.9%
Long bone/pelvis fracture	4 9.1%	1 10.0%	3 8.8%
Other indirect lung injury	7 15.9%	3 30.0%	4 11.8%
Chest tumor excision	1 2.3%	0 0.0%	1 2.9%
Lupus	1 2.3%	1 10.0%	0 0.0%
Old granulomatous lung disease	1 2.3%	1 10.0%	0 0.0%
Pulmonary hypersensitivity	1 2.3%	1 10.0%	0 0.0%
Pulmonary hypertension, CHF*			
COPD*	1 2.3%	0 0.0%	1 2.9%
Right chest tube	1 2.3%	0 0.0%	1 2.9%
Right chronic pleural effusion	1 2.3%	0 0.0%	1 2.9%
Surgical procedures			
Any surgery	40 90.9%	10 100.0%	30 88.2%
Cardiopulmonary bypass	3 6.8%	1 10.0%	2 5.9%
Other cardiac surgery	11 25.0%	3 30.0%	8 23.5%
Lung surgery	2 4.5%	0 0.0%	2 5.9%
Diagnoses			
Trauma	4 9.1%	0 0.0%	4 11.8%
Septic shock	1 2.3%	1 10.0%	0 0.0%
CHF*	12 27.3%	5 50.0%	7 20.6%
MI*	4 9.1%	1 10.0%	3 8.8%
Cardiac insufficiency	5 11.4%	1 10.0%	4 11.8%
Asthma	6 13.6%	2 20.0%	4 11.8%
COPD*	13 29.5%	3 30.0%	10 29.4%
Allergy	6 13.6%	2 20.0%	4 11.8%
Diabetes	13 29.5%	3 30.0%	10 29.4%
Hypertension	28 63.6%	6 60.0%	22 64.7%
Hematologic malignancy	4 9.1%	2 20.0%	2 5.9%
Other malignancy	15 34.1%	5 50.0%	10 29.4%
Liver disease	2 4.5%	0 0.0%	2 5.9%
History			
Smoking	15 34.1%	4 40.0%	11 32.4%
Alcoholism	1 2.3%	1 10.0%	0 0.0%
Pregnancy*	8 33.3%	2 33.3%	6 33.3%
Pre-transfusion ventilation procedures			
Mechanical ventilation	13 29.5%	2 20.0%	11 32.4%
Tracheostomy performed	0 0.0%	0 0.0%	0 0.0%
Supplemental oxygen given	24 54.5%	4 40.0%	20 58.8%

aCHF-Congestive heart failure; MI-Myocardial infarction;

COPD-Chronic obstructive pulmonary disease

bPercentages calculated out of a total of 24 females of which 6 were cases and 18 were controls

**Table 6**

Univariate conditional logistic regression models comparing TRALI cases and matched controls by transfusion and recipient characteristics as recorded in medical charts

Characteristics	Crude OR*	95% Confidence Intervals	p-value
Direct lung injury	2.89	0.38 22.23	0.31
Indirect lung injury	3.49	0.80 15.15	0.10
Direct or indirect lung injury	4.86	0.92 25.76	0.06
Cardiac surgery	1.41	0.28 7.14	0.68
Hematologic malignancy	3.37	0.47 24.46	0.23
Other malignancy	2.04	0.49 8.41	0.33
History of smoking	1.67	0.33 8.50	0.54
Pre-transfusion mechanical ventilation or supplemental oxygen	0.48	0.13 1.77	0.27
Transfusion of RBCs only	0.41	0.10 1.67	0.21
Average number of days to the RBCs expiration	1.05	0.96 1.15	0.29

\*Unadjusted crude odds ratios comparing TRALI cases vs. controls by possible risk factors for TRALI occurrence

## DISCUSSION

To our knowledge, this nested case-control study for the first time utilized a large administrative database in combination with medical chart review to assess transfusion of blood and blood components, TRALI occurrence, potential risk factors

and outcomes. During the three-year study period, the use of blood and blood components were more likely to occur in the elderly, females, and in the inpatient setting. The study suggested that TRALI occurrence may vary by age, gender, blood components transfused, recipient conditions and procedures, as well as service settings. Overall, the study found lower unadjusted TRALI rates in the very old (ages 80 and above) and higher TRALI rates in males, persons ages 40-79, and in the inpatient setting. The potential age difference in TRALI occurrence could be explained by a number of factors, including the possibility of increasing difficulties in diagnosing TRALI among older patients with multiple comorbidities. Additionally, the age-related decline in innate immunity and consequent impairment of neutrophil function, a major effector cell in TRALI, could contribute to the potential TRALI decline in the very elderly and requires further investigation [18-21]. The study also found the lowest rate of TRALI for persons transfused with RBCs only and the highest rate of TRALI for persons transfused with platelets and plasma, which is supported by the literature [2,9,11,22,23]. The study's finding of approximately 94% of all possible TRALI claims-based cases in the inpatient setting may be due to the greater number of comorbidities (i.e. predisposing factors) among persons transfused in the inpatient setting as compared to the outpatient setting. This finding is supported by the literature, which shows much higher TRALI rates in the critically ill hospital patients as opposed to lower TRALI rates in the outpatient setting where patients are likely to have fewer comorbidities and thus fewer predisposing factors [15-17]. Although numbers were small, the medical chart evaluation showed a high TRALI case-fatality rate of 20%. This outcome suggests that TRALI is a severe condition among the cases we confirmed, and is in agreement with the existing literature [9,11,14]. Our study, in support of current literature and using medical chart data, suggested a potentially higher TRALI risk in persons with underlying direct or indirect lung injuries, hematologic malignancies, history of smoking, and cardiac surgeries [9,12-14,24-27]. Meanwhile, the study findings did not suggest an increased TRALI risk with the component storage and with pre-transfusion ventilation procedures, which could be due a very small number of cases evaluated. The review of medical chart data also found a substantially higher proportion of patients with blood type O+ among cases compared to controls, which indicates the need for further research to understand a possible role of blood group in TRALI occurrence. The finding of a predominantly blood group type O in cases may have caused our study's result of

longer time to RBCs expiration for cases versus controls as type O blood may be in higher demand. All confirmed TRALI cases occurred in the inpatient setting, thus suggesting a need for greater healthcare provider awareness and for the future TRALI studies that focus on the inpatient setting. In addition, the medical chart evaluation showed a potentially inappropriate use of diuretics in a majority of TRALI cases, highlighting the need for greater awareness by physicians of appropriate TRALI management. Overall, our study findings suggest the need for future population-based TRALI investigations to evaluate the effect of potential recipient risk factors for acute lung injury (ALI) on TRALI occurrence in the inpatient setting. Such studies could include conditions that may cause direct or indirect lung injuries, such as: aspiration of gastric contents, pneumonia, toxic inhalation, lung contusion, near drowning, sepsis (including severe sepsis), septic shock, multiple trauma, burn injury, cardiopulmonary bypass, drug overdose, as well as other lung and non-lung diseases and conditions which can increase risk of ALI and therefore potentially increase TRALI risk as well [3,5,26].

Our population-based study assessed data from a large administrative database complemented by medical chart review. Therefore, limitations may include potential under- or misrecording of the risk factors and TRALI outcome. As an example of potential limitations, the study's claims-based blood component categorization showed a large group of transfused persons categorized into an unspecified transfusion category, suggesting under-recording of component-specific procedures in the institutional medical settings, which could be due to a lack of reimbursement incentives for transfusions performed. Although medical records were used to complement and inform the claims-based analyses, obtaining the requested charts for the encounters of interest and finding all the relevant information from the medical charts were challenging. Consequently, the study identified only 10 confirmed TRALI cases, a sample size too small to conduct multivariable analysis adjusting for potential confounders. TRALI rate estimates by component type had relatively large confidence intervals and thus may not necessarily reflect true rate estimates as TRALI has a complex clinical definition and can be either misdiagnosed or misrecorded in the claims data. As potential risk factors may be related to the matching variables, our nested case-control study results may have been biased toward null. Our study, therefore, suggests the need for multiple additional years of data to help increase the precision of the study estimates and

improve ability to identify potential risk factors for TRALI occurrence. Future population-based studies are needed to assess validity of the TRALI code in the inpatient setting, where TRALI is more likely to occur and medical records are more likely to be complete.

To our knowledge, this is the first nested case-control study to assess TRALI occurrence, potential risk factors and outcomes, using both a very large administrative database and medical chart review. Our study suggested that TRALI occurrence may vary by age, gender, blood components, recipient conditions, regions and setting, as well as indicated a potentially increased TRALI risk with direct or indirect lung injury, cardiac surgeries, malignancies and history of smoking. Despite the study limitations, this hypothesis-generating study highlights the importance of using large administrative databases in TRALI research and shows the need for future population-based investigations to assess the effects of aging, direct and indirect lung injuries, hematologic malignancies and other potential recipient and transfusion factors on TRALI occurrence. The study also suggests the need for a greater awareness by medical providers of higher TRALI rates in the inpatient setting, appropriate TRALI management, and of potential recipient conditions and procedures that may increase TRALI risk. The increased healthcare provider awareness of TRALI, its potential underlying risk factors and appropriate management should help reduce risk of TRALI occurrence and its complications (e.g., mortality), especially in a high-risk hospital inpatient population. Overall, our study demonstrates the importance of large administrative databases and medical chart review in assessment of TRALI and potential risk factors, and suggests the need for additional population-based studies with multiple years of data, larger sample sizes, and with a focus on the inpatient hospital setting, in order to better ascertain recipient and transfusion risk factors for TRALI occurrence and mortality.

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