Early View

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Pulmonary disease as a risk factor for transfusion-related acute lung injury

Akira Yokoyama¹, Yukiyo Sakamoto¹, Taisuke Jo¹,²*, Hirokazu Urushiyama¹, Hiroyuki Tamiya¹, Goh Tanaka¹, Hiroki Matsui³, Kiyohide Fushimi⁴, Hideo Yasunaga³, Takahide Nagase¹

¹Department of Respiratory Medicine, Graduate School of Medicine, ²Department of Health Services Research, Graduate School of Medicine, ³Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan, and ⁴Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author: Taisuke Jo, Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

E-mail: jo-taisuke@umin.ac.jp
Short summary: Physicians should be aware of the risk of developing transfusion-related acute lung injury when performing a blood transfusion in patients with interstitial lung disease.
**Abstract**

Transfusion-related acute lung injury (TRALI) is a severe condition characterized by noncardiogenic pulmonary edema that develops within 6 hours after blood transfusion. Patient factors and blood products have both been implicated in the development of TRALI; however, the role of pulmonary disease has not been investigated. We aimed to determine whether pulmonary disease is a risk factor for TRALI. We conducted a nested case-control study using data from the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan, between July 2010 and March 2015. Case patients who developed TRALI were 1:4-matched with control patients for sex, age, and same hospital for receipt of blood transfusion. We conducted a multivariable conditional logistic regression analysis to evaluate the associations of TRALI with various factors including comorbidities, body mass index (BMI), and plasma-containing blood products. We identified 2,019,501 hospitalized patients who received a blood transfusion. Among these patients, 72 developed TRALI. The 72 case patients had higher proportions of hematological malignancy, trauma, and interstitial lung disease (ILD) than the 288 matched control patients. The multivariable conditional logistic regression analysis showed that occurrence of TRALI was associated with ILD (odds ratio, 3.88; 95% confidence interval, 1.11–13.6), BMI ≥25.0 kg/m² (2.10; 1.05–4.24),
and plasma-containing blood products (1.94; 1.10–3.42), but not with infectious lung
disease or obstructive airway disease. In conclusion, ILD was an independent risk factor
for the development of TRALI. Physicians should be aware of the increased risk of
TRALI in patients with ILD.

Introduction

Transfusion-related acute lung injury (TRALI) is one of the adverse events associated
with blood transfusion and is characterized by noncardiogenic pulmonary edema that
develops within 6 hours after blood transfusion [1]. The proportions of patients who
developed TRALI were reported to vary from 0.08% to 15.0% [2]. Previous studies
identified several risk factors for TRALI, including sepsis, chronic alcoholism, and
surgery for liver transplantation [3-5]. Anti-white blood cell antibody was identified as
another risk factor for the development of TRALI [5]. Efforts were thus undertaken to
reduce the risk of TRALI by avoiding the use of blood donated by women, especially
pregnant women [6].

Regarding the underlying mechanism for TRALI, a two-event model has been
proposed [7]. In this model, both patient factors and blood products are involved in the
development of TRALI. The first event is related to patient clinical conditions that lead
to activation of the pulmonary endothelium by polymorphonuclear leukocytes (PMNs).
This process occurs when PMNs become primed and functionally hyperactive due to the background disease. The second event is related to infusion of blood products containing specific antibodies or mediators that affect PMNs. As a result, activated PMNs cause endothelial damage and capillary leakage leading to the development of TRALI. Pulmonary diseases (infectious lung disease, obstructive airway disease, and interstitial lung disease [ILD]) can activate endothelial cells via PMNs [8].

Acute and severe deterioration of the lungs can lead to fatal outcomes in patients with pulmonary disease. Therefore, it is essential to determine whether pulmonary disease is a risk factor for TRALI. However, no studies to date have evaluated the risk of TRALI in patients with pulmonary disease. In the present study, we aimed to determine whether pulmonary disease was a risk factor for TRALI in patients who required blood transfusion by conducting a nested case-control study using a Japanese inpatient database.

Methods

Data source

We conducted a nested case-control study using data from the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan, between July 2010 and
March 2015. The database includes data for more than 1,000 hospitals in Japan, and covers more than 90% of all tertiary-care emergency hospitals. The number of hospitalized patients in participating hospitals reaches about 7 million per year, comprising more than 50% of all hospitalized patients in Japan [9].

The database includes data on patient age, sex, body height and weight, smoking history, main diagnoses, comorbidities on admission, complications occurring during hospitalization, discharge status, medications, and treatments. The study was approved by the Institutional Review Board of The University of Tokyo. The board waived the requirement for informed patient consent because of the anonymous nature of the data.

Patient selection

We identified patients who were discharged during the study period and who received blood products for transfusion (whole blood, red blood cells, platelets, or fresh-frozen plasma), but not autologous blood transfusion, during hospitalization. We used the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code for TRALI (J708) to identify case patients who developed TRALI.
Patient characteristics and blood products

The following patient characteristics were collected: sex; age; body mass index (BMI); smoking history; comorbidities; and blood products used for transfusion.

Patients were categorized into four age groups (<39, 40–59, 60–79, and ≥80 years).

BMI (kg/m²) was categorized into four groups (<18.5, 18.5–24.9, ≥25, and missing).

Comorbidities included: hematopoietic disorder (ICD-10 codes, D50–D77); hematological malignancy (C81–C96); other malignancy (C00–C80, C97–D48); trauma (S00–T98); gastroenterological disorder (K00–K93); sepsis (A400–A403, A408–A415, A418, A419); hepatic dysfunction including liver disease (K70–K77), alcoholism (F101, F102, F105, F107, G312, K701, K703, K704, K709, K852, K860), and liver surgery; heart failure (I20–I25, I34–I37, I42, I43, I48, I50); infectious lung disease (J09–J22, J85, J86); obstructive airway disease (J40–J47); and ILD (J80–J82, J84, J990, J991).

Obstructive airway disease included chronic obstructive pulmonary disease, chronic bronchitis, bronchial asthma, and bronchiectasis.

Blood products included whole blood, red blood cells, platelets, and fresh-frozen plasma. All of these blood products except for red blood cells were grouped into plasma-containing products.
Treatments and outcomes

We evaluated the frequencies of ICU admission, emergency intubation, systemic corticosteroid administration, and use of sivelestat after initial blood transfusion during hospitalization in case patients and control patients to better understand the disease severity in the examined patients. We evaluated all-cause in-hospital mortality because the database did not provide data on causes of death.

Statistical analysis

For this study, a nested case-control design was adopted to evaluate risk factors for the development of TRALI. Case patients who developed TRALI were 1:4-matched with control patients for sex, age, and same hospital for receipt of blood transfusion. Sex and age were matched because they are variables associated with both the exposure (lung disease) and the disease (TRALI), and are commonly used for matching. Hospitals were matched because individual hospitals may have different practices for lung disease, transfusion, and diagnosis of TRALI. We considered these three variables to be strong confounders and therefore used them for case-control matching. We matched four control patients to one case patient to preserve the control patients and increase the sample size, which can improve the statistical power and the precision of
the findings [10]. Patient characteristics were compared using the chi-square test for binominal and categorical variables. Student’s t-test or the Mann–Whitney U test was used to compare numerical variables, depending on the distribution of each variable. We conducted a multivariable conditional logistic regression analysis to evaluate risk factors for TRALI. Independent variables included potential risk factors based on previous studies (sepsis, liver dysfunction), pulmonary disease (infectious lung disease, obstructive airway disease, ILD), other comorbidity (heart failure), and BMI. We also included plasma-containing products in the independent variables. Independent variables were chosen from risk factors that were identified in previous studies and available in the DPC database. Variance inflation factors were estimated for the variables used in the model and checked for multicollinearity. The results derived from the multivariable model were shown as odds ratio, 95% confidence interval, and P-value for each independent variable. Values of $P<0.05$ were considered significant. All analyses were conducted using SPSS version 23.0 (IBM SPSS, Armonk, NY) or Stata version 16.0 (StataCorp, College Station, TX).

**Results**

Patient characteristics and blood products
The patient characteristics are shown in Table 1. We identified 2,019,501 hospitalized patients who received a blood transfusion. Among these patients, 72 developed TRALI (38 men, 34 women; mean age ± standard deviation, 69.4 ± 2.03 years). The 72 case patients were 1:4-matched with 288 control patients who received a blood transfusion during hospitalization but were not diagnosed as TRALI. No significant differences were observed in sex and age distribution between the two groups. A higher proportion of patients with BMI ≥25 kg/m² was observed in the case patients compared with the control patients after matching (25.0% vs. 14.6%). Patients with smoking history did not differ significantly between the case patients and control patients after matching (37.5% vs. 39.6%, P=0.746). Regarding comorbidities, the case patients had higher proportions of hematological malignancy, trauma, and ILD than the control patients.

The blood products used for blood transfusion are shown in Table 2. Only a very small fraction of patients received whole blood for transfusion. Red blood cells were most commonly used in both the case patients and control patients, with no significant difference. Platelets and fresh-frozen plasma were used more often in the case patients than in the control patients (38.9% vs. 21.2% and 41.7% vs. 29.9%, respectively). As a result, the proportion of patients who received plasma-containing products was
significantly higher in the case patients compared with the control patients (55.6% vs. 39.9%, \(P=0.017\)).

Treatments and outcomes

The frequencies of the treatments required after initial blood transfusion during hospitalization are shown in Table 3. After matching, the case patients were more likely to undergo ICU admission, receive emergency intubation, require systemic corticosteroid administration, and use sivelestat. In-hospital mortality was not significantly higher in the case patients than in the control patients (20.8% vs. 16.7%, \(P=0.405\)).

Multivariable conditional regression model

The results of the multivariable conditional regression model are shown in Table 4. Occurrence of TRALI was significantly associated with ILD (odds ratio, 3.88; 95% confidence interval, 1.11–13.6), BMI ≥25.0 kg/m\(^2\) (2.10; 1.05–4.24), and plasma-containing blood products (1.94; 1.10–3.42), but was not significantly associated with infectious lung disease or obstructive airway disease. The variance
inflation factors for all variables were less than two, which indicates that multicollinearity is unlikely to exist among the variables.

Discussion

We evaluated three pulmonary disease categories (infectious lung disease, obstructive airway disease, and ILD) as potential risk factors for the development of TRALI. Of these, only ILD was significantly associated with the development of TRALI.

In our cohort, the proportion of patients who developed TRALI was as low as 0.0036%. The reported incidence of TRALI has varied widely (0.01%–5.1%) among previous studies because they had different study populations [4, 11, 12]. The occurrence of TRALI in our real-world database study was much lower compared with these previous studies. There are several possible explanations for this discrepancy. First, TRALI may have been underdiagnosed because no biomarkers have been identified to assist with its diagnosis. Consequently, it can be difficult to distinguish TRALI from other diseases that resemble TRALI, such as transfusion-associated circulatory overload (TACO), acute respiratory distress syndrome (ARDS), and acute exacerbation of ILD. Second, there may be differences in the blood products used for transfusion. In Japan, blood donation during pregnancy and until 6 months after delivery is prohibited, mainly from the viewpoint of safety during maternity care. The
percentage of male-derived fresh-frozen plasma production reached almost 100% in April 2011 [13]. Blood products from women, particularly pregnant women, have a higher prevalence of anti-HLA antibodies that can increase the incidence of TRALI. The male-predominant plasma transfusion strategy in Japan may have successfully mitigated the impact of donor anti-HLA antibodies. In fact, the cumulative numbers of patients with TRALI, possible TRALI, and TACO from 2010 to 2015 reported by the Japan Red Cross Society were 47, 52, and 162, respectively [14]. Given that the database used in the present study covers 50% of all hospitalized patients in Japan, the number of patients with TRALI captured in our study may be reasonable.

The all-cause in-hospital mortality in patients with TRALI was 20.8% in our study. This was higher than the mortalities reported in previous studies [15-17] as well as in a document on hemovigilance published by the Japan Red Cross Society [14] that reported only 4 patients who may have died from TRALI from 2010 to 2015. In-hospital mortality in the matched control patients was as high as 16.7%, suggesting the presence of critical clinical conditions in the patients in our cohort. The high mortality in our study can be interpreted as a consequence of the high mortality in the patient population examined.
Recently, risk factors for the development of TRALI have been extensively studied with respect to blood products used for transfusion [18]. The studies demonstrated the involvement of anti-HLA antibodies and/or anti-HNA antibodies in the development of TRALI. Based on the results, use of these products has been avoided, resulting in a reduced incidence of TRALI [6].

Our results identified ILD as a risk factor for the development of TRALI. It could be argued that patients with TRALI may have been simultaneously diagnosed with ILD because TRALI cannot be easily distinguished from acute ILD exacerbation. To avoid such contamination in the present study, patients with ILD were defined as those who were diagnosed with ILD at admission.

The ICD-10 codes used to identify ILD included collagen vascular disease, hypersensitivity pneumonitis, and idiopathic interstitial pneumonia. The common feature of patients with these diseases and patients with other pulmonary diseases evaluated in this study is chronic systemic inflammation. The production of cytokines that induce the inflammation associated with pulmonary diseases, such as IL-6 and IL-8, has been intensively studied [19-21]. A previous study on TRALI showed the involvement of these pro-inflammatory cytokines in the development of TRALI [5, 22, 23]. However, it remains unclear why ILD was the only pulmonary disease identified as
a risk for the development of TRALI. Further studies exploring the mechanisms for the development of TRALI in patients with ILD are warranted to determine the differences among patients with various pulmonary diseases.

Limitations of the present study should be acknowledged. First, we were unable to validate the diagnoses used in the study because the database did not contain the results of laboratory tests and imaging examinations, or medical records. Furthermore, a validation study to specifically evaluate the diagnosis of TRALI is unrealistic because of the rarity of the disease. However, although sensitivity of diagnoses was reported to be relatively low, the specificity of diagnoses was preserved in the database [24]. With regard to the diagnosis of TRALI, much effort has been devoted to the discrimination of TRALI from other conditions such as TACO and ARDS in previous studies [1, 25]. In the present study, diagnosis of TRALI was based solely on the judgement of the attending physicians. It may be possible that TRALI was contaminated with TACO or ARDS. However, considering that all three conditions are undesirous and serious conditions after blood transfusion, and particularly because TRALI and ARDS are pathophysiologically similar to one another, we think that the message of our study is not weakened by the contamination. Second, owing to a lack of data, we were unable to evaluate antibodies that can mediate TRALI in detail. Finally, because this was a
retrospective study, the results are prone to bias owing to unmeasured confounders, such as high peak airway pressure while undergoing mechanical ventilation [5].

In conclusion, in this nested case-control study using a nationwide inpatient database in Japan, we showed that ILD was an independent risk factor for the development of TRALI. Physicians should be aware of the increased risk of TRALI in patients with ILD.

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Table 1. Characteristics and comorbidities of patients with and without TRALI

| Characteristics | Control (N=2,019,501) | All | TRALI (N=72) | Control (N=288) | After matching (N=72) | After matching (N=72) |
|-----------------|-----------------------|-----|-------------|-----------------|----------------------|----------------------|
|                 | n                     | %   | n           | %               | n                     | %                     |
| Sex (male)      | 1,052,795             | 52.1| 38          | 52.8            | 152                   | 52.8                  | 1.000                |
| Age (years)     |                       |     |             |                 |                      |                      |                      |
| <39             | 135,759               | 6.72| 4           | 5.56            | 16                    | 5.56                  | 4                    |
| 40–59           | 258,474               | 12.8| 8           | 11.1            | 34                    | 11.8                  | 8                    |
| 60–79           | 992,584               | 49.2| 39          | 54.2            | 171                   | 59.4                  | 39                   |
| ≥80             | 632,612               | 31.3| 21          | 29.2            | 67                    | 23.3                  | 21                   |
| Body mass index |                       |     |             |                 |                      |                      |                      |
| <18.5           | 1,103,086             | 54.6| 36          | 50.0            | 167                   | 58.0                  | 36                   |
| 18.5–24.9       | 429,990               | 21.3| 12          | 16.7            | 60                    | 20.8                  | 12                   |
| ≥25             | 306,249               | 15.2| 18          | 25.0            | 42                    | 14.6                  | 18                   |
| Missing         | 180,104               | 8.92| 6           | 8.33            | 19                    | 6.60                  | 6                    |
| Smoking history | 774,301               | 38.3| 27          | 37.5            | 114                   | 39.6                  | 27                   |
| Comorbidities   |                       |     |             |                 |                      |                      |                      |
| Hematopoietic disorder | 724,501 | 35.9| 32          | 44.4            | 108                   | 37.5                  | 32                   |
| Hematological malignancy | 182,971 | 9.1 | 12          | 16.7            | 24                    | 8.3                   | 12                   |
| Other malignancy | 718,948               | 35.6| 26          | 36.1            | 110                   | 38.2                  | 26                   |
| Trauma          | 302,636               | 15.0| 24          | 33.3            | <0.001                | 42                    | 14.6                 |
| Gastroenterological disorder | 824,421 | 40.8| 16          | 22.2            | 0.001                 | 128                   | 44.4                 |
| Heart failure   | 486,578               | 24.1| 21          | 29.2            | 66                    | 22.9                  | 21                   |
| Liver dysfunction | 135,856              | 6.7 | 5           | 6.9             | 24                    | 8.3                   | 5                    |
| Infectious lung disease | 86,310  | 4.3 | 6           | 8.3             | 0.089                 | 15                    | 5.2                  |
| Interstitial lung disease | 22,049  | 1.1 | 5           | 6.9             | <0.001                | 6                     | 2.1                  |
| Condition              | Cases | Rate | Age | Score | Severity | Age | Severity | Score | Mortality Rate |
|------------------------|-------|------|-----|-------|----------|-----|----------|-------|----------------|
| Obstructive airway     | 71,602| 3.6  | 4   | 5.6   | 0.356    | 13  | 4.5      | 4.5   | 0.709          |
| Sepsis                 | 94,048| 4.7  | 5   | 6.9   | 0.357    | 17  | 5.9      | 5.9   | 0.741          |

TRALI, transfusion-related acute lung injury.
Table 2. Blood products used for transfusion

| Blood products               | All Control (N=2,019,501) | All TRALI (N=72) | After matching Control (N=288) | After matching TRALI (N=72) | P-value |
|------------------------------|-----------------------------|------------------|-------------------------------|----------------------------|---------|
| Red blood cells              | 1,881,694 (93.2)            | 71 (98.6)        | 273 (94.8)                    | 71 (98.6)                  | 0.068   |
| Plasma-containing products   | 673,202 (33.3)              | 40 (55.6)        | 115 (39.9)                    | 40 (55.6)                  | <0.001  |
| Whole blood                  | 1,153 (0.1)                 | 0 (0)            | 0 (0)                         | 0 (0)                      | 0.839   |
| Platelets                    | 424,662 (21.0)              | 28 (38.9)        | 61 (21.2)                     | 28 (38.9)                  | <0.001  |
| Fresh-frozen plasma          | 412,556 (20.4)              | 30 (41.7)        | 86 (29.9)                     | 30 (41.7)                  | <0.001  |

TRALI, transfusion-related acute lung injury.
Table 3. In-hospital treatments and outcomes of patients with or without TRALI

| Treatments          | All            | After matching |   |   |   |   |
|---------------------|----------------|----------------|----------------|---|---|---|---|
|                     | Control (N=2019501) | TRALI (N=72) | Control (N=288) | TRALI (N=72) |   |   |   |
|                     | n  | %  | n  | %  | P-value | n  | %  | n  | %  | P-value |
| ICU admission       | 278,920 | 13.8 | 33 | 45.8 | <0.001 | 65 | 22.6 | 33 | 45.8 | <0.001 |
| Emergency intubation| 91,180  | 4.5  | 19 | 26.4 | <0.001 | 24 | 8.3  | 19 | 26.4 | <0.001 |
| Corticosteroid      | 411,378 | 20.4 | 56 | 77.8 | <0.001 | 102 | 35.4 | 56 | 77.8 | <0.001 |
| Sivelestat          | 55,421  | 2.7  | 26 | 36.1 | <0.001 | 13  | 4.5  | 26 | 36.1 | <0.001 |
| Outcomes            |               |               |               |               |               |               |               |               |               |               |
| All-cause in-hospital mortality | 313,253 | 15.5 | 15 | 20.8 | 0.212 | 48 | 16.7 | 15 | 20.8 | 0.405 |

TRALI, transfusion-related acute lung injury.
Table 4. Multivariable conditional logistic regression analysis for the development of TRALI after blood transfusion

|                                    | Odds ratio | 95% Confidence interval | P-value |
|------------------------------------|------------|--------------------------|---------|
| Plasma-containing blood products   | 1.94       | 1.10–3.42                | 0.022   |
| Body mass index (kg/m²)            |            |                          |         |
| <18.5                              | 0.84       | 0.39–1.80                | 0.655   |
| 18.5–24.9 Reference                |            |                          |         |
| ≥25.0                              | 2.10       | 1.05–4.24                | 0.037   |
| Missing                            | 1.71       | 0.57–5.10                | 0.336   |
| Sepsis                             | 0.81       | 0.25–2.62                | 0.727   |
| Liver dysfunction                  | 0.79       | 0.27–2.36                | 0.678   |
| Heart failure                      | 1.49       | 0.80–2.79                | 0.212   |
| Infectious lung disease            | 1.87       | 0.65–5.44                | 0.248   |
| Obstructive airway disease         | 1.32       | 0.39–4.51                | 0.656   |
| Interstitial lung disease          | 3.88       | 1.11–13.61               | 0.034   |

TRALI, transfusion-related acute lung injury.