

Short Communication

# Analysis of food allergy history of patients who developed mild allergic transfusion reactions

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## ABSTRACT

We examined the history of food allergy (FA) in patients at the University of Yamanashi Hospital who were hospitalized from 2019 to 2021 and developed allergic transfusion reactions (ATRs). One hundred fifty-seven patients developed mild ATRs, among which 22 patients had a history of FA. Out of the 157 patients, 30 patients received red blood cell (RBC) transfusion, among which 20.0% (6/30) had FA. Thirty patients received fresh frozen plasma (FFP) transfusion, and 23.3% (7/30) of them had FA. Ninety-seven patients received platelet concentrate (PC) transfusion, and 9.3% (9/97) of them had FA. The FA history-positive rate was 21.7% (13/60) in patients who developed mild ATRs after RBC or FFP transfusion, which was significantly higher than that (11.1%, 4,380/39,473) in all patients hospitalized and that in patients without any adverse transfusion reactions (3.1%) during the same periods. We suggest the possibility that allergic food antigens included in blood products might partly (maximally 10%) be involved in the occurrence of mild ATRs after RBC or FFP transfusion. Despite the higher incidence of ATRs after PC transfusion, the involvement of FA was not demonstrated probably because more multimodal factors are implicated in ATRs after PC transfusion.

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## Key Words

allergic transfusion reactions, food allergy history, allergic predisposition

## I. Introduction.....

Transfusion adverse reactions are classified as hemolytic side effects, non-hemolytic side effects, and infections. Non-hemolytic transfusion reactions are classified as allergic transfusion reaction (ATR), febrile nonhemolytic transfusion reaction (FNHTR), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory

overload (TACO), hypotension, bacterial sepsis, and others<sup>1), 2)</sup>.

Among them, allergy (allergic transfusion reactions; ATRs) is the most frequent and mild-symptomatic transfusion reaction<sup>1)</sup>. An allergy occurs if the immune response shows excessive reactions to eliminate foreign antigens. However, most of the causes of allergy to transfusions have not been elucidated. The only known cause

of allergy to blood transfusions is in patients deficient of plasma proteins (IgA or haptoglobin), who produce antibodies to these proteins due to previous blood transfusions<sup>3, 4</sup>. Food allergy (FA) is also an allergy elicited through antigen-specific immunological mechanisms induced by food.

In this study, we investigated the association between allergy after blood transfusion and a history of food allergy in patients who underwent blood transfusion at the University of Yamanashi Hospital.

**II. Methods and subjects**.....

This study was judged by the Ethics Committee of the University of Yamanashi School of Medicine as not requiring ethical review. For a period of three years from January 2019 to December 2021, we studied patients who underwent blood transfusion and developed transfusion adverse reactions at the University of Yamanashi Hospital. During this period, 14,146 red blood cell (RBC) products, 7,896 fresh frozen plasma (FFP) products, and 6,595 concentrated platelet (PC) products were transfused to the patients. All blood products including RBC, FFP, and PC were transfused based on Guideline for the use of RBC products<sup>5</sup>, FFP<sup>6</sup>, and PC<sup>7</sup>, respectively. As a result, 247 patients developed transfusion adverse reactions. Some patients developed the adverse reactions following transfusion of more than one product (i.e., FFP, RBCs, and platelets). We observed 157 patients who developed allergy after transfusion of a single product.

Classification of adverse transfusion reactions was de-

termined by a physician based on the guideline of the Japan Society on Transfusion Medicine and Cell Therapy as shown in **Supplemental Table 1**<sup>8</sup>. “Allergic adverse reactions (ATRs)” refer to adverse transfusion reactions with 4) pruritus, 5) flushing, 6) urticaria. When patients are served allergen-free meals during hospitalization, they are assumed as patients with food allergies.

We compared the FA history of these 157 patients who developed allergy reactions with that of all hospitalized patients (39,473 patients). For this, the statistical method chi-square test was used (p < 0.05 was considered to show a significant difference).

The all-inpatient data including ages, gender, and their afflicted disease were from the hospital statistics of University of Yamanashi Hospital shown in the homepage (<https://www.hosp.yamanashi.ac.jp/wp-content/uploads/2022/12/17d3e528c13ac6d071ec4dbf0a9b801d-1.pdf>).

**III. Results**.....

**Breakdown of adverse blood transfusion reactions**

Among 247 patients who developed transfusion reactions, no hemolytic adverse reactions were observed, and all were non-hemolytic. Excluding patients who underwent transfusion of multiple products, 200 patients (339 cases) developed adverse transfusion reactions (**Table 1A**). Among these 339 cases, 0.44% (62 cases) developed adverse reactions after RBC transfusion, 0.72% (57 cases) after FFP transfusion, and 3.34% (220 cases) after PC transfusion. Furthermore, among the 339 cas-

**Table 1A** Types of Adverse Blood Transfusion Reactions

	No. of cases	No. of patients*1	No. of patients by blood transfusion products		
			RBC	FFP	PC
Non-hemolytic blood transfusion reactions*2	339	200	57 (62 cases)	37 (57 cases)	106 (220 cases)
of the above minor reactions	330	193	55 (96.5%)	33 (89.2%)	105 (99.1%)
of the above allergy	286	157	30 (54.4%)	30 (90.9%)	97 (92.4%)
of the above allergy with FA	58	22 (14.0%)	6/30 (20.0%)	7/30 (23.3%)	9/97 (9.3%)
			13/60 (21.7%)		

\*1 Patients who had separate reactions with different blood products were counted as separate patients.

\*2 Excluding compound blood product administration

RBC; red blood cells, FFP: fresh frozen plasma, PC; platelet concentrates, FA; food allergy

**Table 1B** Percentage of FA patients in patients without adverse transfusion reactions and in all in-patients (2019 – 21)

	All patients	FA patients	Percentage
Patients without adverse transfusion reactions	2830	89	3.1 %
All in-patients	39473	4380	11.1%

es (200 patients), 330 cases (193 patients) were mild. Among the mild 330 cases (193 patients), 286 cases (157 patients) were allergic (mild ATRs) (Table 1A).

**Association between FA history and adverse reactions to blood transfusion**

Among the 157 patients who developed allergy reactions after transfusion, 14.0% (22/157) have an FA history. Furthermore, among these 157 patients, 30 patients received RBC transfusion and 20.0% (6/30) of them had a history of FA. Thirty patients received FFP transfusion, and 23.3% (7/30) of them had a history of FA. Ninety-seven patients received PC transfusion, and 9.3% (9/97) of them also had a history of FA (Table 1A).

During the study period, the total number of hospitalized patients was 39,473, among which 11.1% (4,380/39,473) had an FA history (Table 1B). Compared with this, the percentage of patients with a history of FA in RBC transfused or FFP transfused patients (21.7%) was significantly higher (p = 0.042). FA history rate of the patients who underwent blood transfusion without any adverse transfusion reactions was also investigated (Table 1B), and was 3.1% (89/2830), much lower than the FA rate of the ATR patients with FFP/RBC transfusion (21/7%) (p = 2.12 × 10<sup>-13</sup>). On the other hand, there was no significant difference in the FA history rate between the PC transfused patients and all hospitalized patients.

Table 2 shows a list of foods (the number of patients in parentheses) excluded from allergen-free meals during their hospitalization.

**Baseline characteristics**

Baseline characteristics of the patients with ATRs and all the hospitalized patients were shown in Supplemental Figures 1 and 2. Age structure in increments of 5 years of the ATR patients (157) and all inpatients from 2019 to 2021 are shown in Supplemental Figure 1A, B. we found no difference of the ratios of 0 ~ 4 years old patients between the 2 groups (p = 0.981, proportion z-test

with Yates' continuous correction). Moreover, there is no statistical significance of all the patient age compositions between the 2 groups (p = 0.999, paired T test). Therefore, higher percentage of FA in the ATR patients is not because of higher percentage of infants.

As for gender, the male ratio was not different between in the ATR group and in the all-inpatient group (p = 0.262, proportion z-test with Yates' continuous correction) (Supplemental Figure 1C).

Supplemental Figure 2 shows that disease compositions of the 2 groups are different from each other. Sixty-nine % of the ATR patients was malignant neoplasm patients, whereas only 31% in the all-inpatient group. As expected, most of malignant tumor in the ATR group is hematological tumor. This is followed by hematologic disease except for neoplasm, which is included in others due to only a limited percentage in the all inpatient group.

**IV. Discussion**.....

Although ATRs are the most frequent transfusion-related adverse reactions, the search for the cause is not usually carried out in mild cases, and thus the mechanism is not fully understood<sup>9</sup>. However, previous reports suggest that allergic constitution such as bronchial asthma, hay fever, atopic dermatitis, and food allergy are closely related to the development of ATRs<sup>10-12</sup>.

The prevalence of FA in Japan is reported to be 4.0 - 16.7% in infancy, 1.3 - 4.5% in school-age children, and less than 5% after school age<sup>13</sup>. However, after the school age, infants with FA often find it possible to ingest the food they are allergic to. Ebisawa et al. reported that the cumulative food allergy incidence was 64.5% in 2-year-old children, 80.3% in 5-year-old children, and 90.1% in 10-year-old children based on a survey of 2,954 cases<sup>14</sup>. On the other hand, the precise percentage of those with a history of FA in the general population is unknown. In this study, by examining the number of patients who were served allergen-free meals, we found

**Table 2** A list of foods excluded from allergen-free meals during the hospitalization (the number of patients)

Fruits (5)	Soybeans (1)	Fish (1)
Peach (1)	Soy milk (1)	Mackerel (4)
Grapefruits (5)	Fermented soybeans (1)	Shrimps, crabs (4)
fresh vegetables (1)	Nuts (1)	
Tomato (2)	Egg white (2)	
Mushrooms (1)	dairy products (2)	
Bracken (1)	Cow milk (2)	

\*With duplicate entries

that approximately 10% of inpatients at the University of Yamanashi Hospital have a history of FA.

There is no difference in the infant ratios between the ATR patient and all inpatient groups (**Supplemental Figure 1A, B**). Therefore, higher percentage of FA in the ATR patients is not because of higher percentage of infants.

The FA history-positive rate was 3.1% (89/2830) in patients who did not develop adverse transfusion effects after blood transfusion, which was significantly lower than that in patients who developed ATRs after RBC or FFP transfusion (21.7%, 13/60) ( $p = 2.12 \times 10^{-13}$ ). This rate (3.1%) is also significantly lower than the ratio in all patients in (11.1%, 4,380/39,473) ( $p = 3.88 \times 10^{-40}$ ). These findings further support that food allergy is at least one of the causes of ATR.

Despite allergen-free meals, if the patient remains sensitized, the allergic reaction may be triggered when the allergen in the food enters the body from blood donors through blood transfusion. However, there have only been a few reports on ATR, probably because of the difficulty in identifying the causative food. Previous case reports identified that blood recipients with a history of allergy to peanuts or shrimp suffered ATR and anaphylaxis due to the transmission via blood products of the antigens ingested by blood donors<sup>15), 16)</sup>. In this study, we reported that the rate of FA history in patients who developed mild ATRs after receiving RBCs/FFP was significantly higher than that in other hospitalized patients. We suggest that some (up to 10%) of RBC- and FFP-related ATRs may have been induced by food antigens in the donor serum. On the other hand, the pathogenic mechanisms of PC-related ATRs, which have a very high incidence, are more diverse (e.g., involvement of blood cell-derived cytokines). The involvement of food antigens was relatively low.

Ebisawa et al. reported that most frequent causative foods for immediate food allergy were hen's egg (39.0%), cow's milk (21.8%), and wheat (1.7%)<sup>14)</sup>. However, in this study the most frequent causative foods were grapefruits, shrimps/crabs, and mackerel (**Table 2**), which may be due to differences in age groups.

In conclusion, we found that the FA history-positive rate was 21.7% in patients who developed mild ATRs after RBC/FFP transfusion, which was significantly higher than that in all hospitalized patients (11.1%) and that in hospitalized patients without any adverse transfusion reactions (3.1%). We suggest the possibility that allergic food antigens included in blood products might partly be involved in the occurrence of mild ATRs, although a

large-scale study is required to clarify the role of FA in the development of mild ATRs.

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