

Relationship between allergic transfusion reactions and allergic predisposition among pediatric patients with hematological/oncological disease



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Abstract

Background: Allergic transfusion reactions (ATRs) manifest frequently as transfusion reactions, and their onset may be related to a patient's allergic predisposition. Moreover, although pediatric patients with hematological/oncological disease are more susceptible to ATRs, the relationship between allergic predisposition and ATRs remains to be fully clarified.

Study Design and Methods: Patients who were diagnosed with pediatric hematological/oncological disease and received transfusion at the study institutions were included. We determined patient background information related to their allergy history, measured the levels of allergen-specific immunoglobulin E (IgE) using sera obtained on diagnosis, and analyzed their associations with ATR onset.

Results: Of the 363 patients analyzed, 144 developed ATRs. Multivariate analysis identified cases with high basophils in the peripheral blood, and *Dermatophagoides pteronyssinus*- and egg white-specific IgEs were involved in the development of ATR in all age groups. Meanwhile, a history of food allergies, and positivity for Japanese cypress- and *D. pteronyssinus*-specific IgEs were risk factors for developing ATRs in the <5 years age group. Moreover, patients aged 5–<10 years with a history of asthma, allergic rhinitis, pollinosis, or atopic dermatitis, and those aged ≥10 years with positivity for dog dander-specific IgE were at risk for developing ATRs.

Conclusion: The allergic constitution of patients plays a role in ATR onset even in pediatric hematological/oncological diseases. Therefore, advance confirmation of a patient's allergic constitution may partly predict the onset of ATRs. However, since multiple allergic predispositions within complex mechanisms may be involved in the onset of ATRs, further verification is required.

KEYWORDS

allergic rhinitis, allergic sensitization, asthma, atopic dermatitis, hay fever, pollinosis

1 | INTRODUCTION

Allergic transfusion reactions (ATRs) are one of the most frequently occurring transfusion reactions.^{1,2} ATRs can manifest in varying degrees, from mild to severe anaphylaxis; however, the cause of many mild ATRs, the predominant form of ATRs, has not been established. Thus, prediction of ATR development before transfusion is difficult. If an ATR occurs without an improvement in the symptoms with medications, it may be necessary to discard the relevant blood product and reorder another blood product.³ Previous studies have suggested that ATR onset cannot be attributed to a single factor, but is caused by a combination of various factors, including donor- and product-derived factors as well as patient-related factors.²⁻⁴

With respect to patient-related factors, pediatric patients have been reported to show a higher incidence of ATRs than adults.^{5,6} Furthermore, patients' disease, age, sex, number of transfused products, and past history of ATRs are related to the onset of ATRs in children.^{3,7,8} Especially in patients with hematological and oncological disease, ATRs may occur with a particularly high frequency after transfusion of both platelet and red blood cell products.^{3,7} Interestingly, ATRs have been shown to occur frequently in patients with hematological diseases, even in adults.⁹ Therefore, despite the presence of risk factors specific to children, some risk factors, such as the presence of underlying disease, are common for adults and children.

Type I immunoglobulin E (IgE)-mediated hypersensitivity is considered to be the main pathogenic mechanism underlying ATRs.^{1,2} Basophil activation in an IgE-dependent manner has been confirmed in a basophil activation test using a blood product that causes ATRs.¹⁰ Confirmation of the presence of allergic history is an important step in medical care for allergic diseases. Even in blood transfusion therapy, the relationship between allergic predisposition and ATRs has been shown mainly in adult patients.¹¹⁻¹⁴ However, to date, no clear association has been found between allergic history and ATRs in pediatric patients.^{7,8,15} Nevertheless, recent studies on pediatric hematological and oncological diseases have reported that allergic sensitization-associated single-nucleotide polymorphisms associated with the development of ATRs may exist.¹⁶ Therefore, even in children, the patient's allergic predisposition may be involved in the development of ATRs. However, pediatric ATRs may show no association with a history of allergies for various reasons, including the inability of retrospective analyses to accurately reflect the patient's allergic history, the absence of clinical symptoms even in the presence of an allergic predisposition, and multiple other patient factors involved in the onset of ATRs that may not be easily reflected in the analyzed results.

Therefore, in this study, to examine the relationship between allergic predisposition and the onset of ATRs in children, we decided to evaluate the total IgE level and multiple allergen-specific IgE levels in addition to the confirmation of patients' allergic history. In addition, to reduce other patient-related factors that can affect the analysis, the target cases were limited to hematological and oncological diseases that are considered to show a high incidence of ATRs.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We retrospectively analyzed data from pediatric patients (aged ≤ 20 years) who had hematological disease or oncological disease and had been transfused multiple times with a red blood cell concentrate and/or platelet concentrate at Nagano Children's Hospital or Shinshu University Hospital between April 2003 and March 2020. All occurrences of ATRs in both institutions during the study period were analyzed. The current study included cases reported in previous studies.^{7,16-21} This study was approved by the institutional ethical review board in each institution (approval number: 31-59 [in Nagano Children's Hospital], 4610 [in Shinshu University]).

2.2 | Transfused blood products

All transfused blood products were obtained from the Japanese Red Cross Blood Society. Platelet concentrates were derived from single-donor apheresis. Red blood cell concentrates were prepared from 200 or 400 mL of whole blood obtained from single donors. All platelet and red blood cell concentrates were of donor origin with ABO and RhD blood types identical products. Pre-storage leucocyte reduction and diversion of the first aliquot of blood were performed for each blood product according to the passage of time, as previously described.⁷ The products were subsequently irradiated prior to transfusion.

2.3 | Definitions of ATR and severity

ATR was defined as in previous studies: ATR was diagnosed when at least one symptom, such as rash, pruritus, urticaria, flushing, and respiratory distress, had occurred during the transfusion or within 4 h of its completion.¹⁷ The severity of ATR was determined as follows based on a previous report: grade I, only transient symptoms corresponding to a minor ATR; grade II, an ATR requiring discontinuation of blood transfusion but showing

recovery with symptomatic treatment; grade III, anaphylaxis with symptomatic bronchospasm with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension.¹⁷

2.4 | Analysis of total IgE and allergen-specific IgE

For each case, total IgE and allergen-specific IgE were analyzed using stored serum collected at the time of diagnosis of hematological disease or oncological disease. Patients were stratified according to the total IgE level; an IgE level > 360 IU/mL was indicated as the reference standard range of the measurement kit (IATRO-ACE IgE II, LSI Medience Corporation, Tokyo, Japan). Allergen-specific IgE levels were analyzed using a panel IgE test (View Allergy 39®, Thermo Fisher Diagnostics K.K., Tokyo, Japan).^{22,23} The results of each allergen-specific IgE, analyzed with View Allergy 39®, were classified into seven stages from classes 0 to 6. An index value of <0.27 was considered to be negative and categorized in class 0; values between 0.27 and 0.50 were considered to be false-positive and categorized in class 1; and index values of ≥0.50 were considered to be positive; values of ≥0.50 and <1.80 were categorized in class 2; values of ≥1.80 and <7.05 were categorized in class 3; values of ≥7.05 and <17.35 were categorized in class 4; values of ≥17.35 and <29.31 were categorized in class 5; and values of ≥29.31 were categorized in class 6.

2.5 | Statistical analysis

Candidate risk factors for patients with ATR were evaluated using Fisher's exact test and logistic regression analysis. Potential factors with at least borderline significance ($p < .100$) in the univariate analysis were included in the multivariate analysis. Total IgE values were compared by age group and ATR grade category using the Kruskal-Wallis test. The relationship between severe ATRs and the related allergen-specific IgEs or their classification was examined using Fisher's exact test. All statistical analyses were performed using the EZR software.²⁴ Statistical significance was defined as $p < .05$.

3 | RESULTS

3.1 | Assessment of the relationship between patients' background factors and ATRs by univariate analysis

The total number of patients included in this study was 363. Of these, 144 (39.7%) developed ATRs. Table 1(A)

shows the results of univariate analysis of the relationship between the development of ATRs and common patient background factors at the time of diagnosis of the underlying disease. There was no association between ATR development and patient age, sex, and the nature of the underlying disease (hematological or oncological). However, the incidence of ATRs was higher in patients with a history of allergy-related diseases such as asthma, allergic rhinitis, pollinosis, and atopic dermatitis than that in those without these diseases. However, no association was found between ATR onset and a history of allergies to medical drugs and foods.

At the time of diagnosis of underlying diseases, patients with ATR tended to have higher basophil counts in the peripheral blood, but there was no difference in eosinophil counts. Furthermore, many patients with ATRs showed higher total IgE levels than those without ATR. However, total IgE levels also increased as the children became older (Figure 1). Regarding transfusion-related parameters, many patients with ATR received more blood products than those without ATR. However, no difference was observed between the patients with and without premedication.

3.2 | Assessment of the relationship between allergen-specific IgE and the onset of ATRs with univariate analysis

Next, we investigated the relationship between positivity for allergen-specific IgE and ATR occurrence. Figure 2 shows the breakdown of the classes from 0 to 6 for each allergen-specific IgE in all patients. Table 1(B) shows the results of a univariate analysis of the relationship between ATR onset and the positivity of each allergen-specific IgE (i.e., class II or higher). Several pollen-specific IgEs (orchard grass, timothy, ragweed, mugwort, Japanese cedar, Japanese cypress, and Japanese white birch) had higher positive rates in patients with ATR-onset than those without. Furthermore, in patients with ATRs, the positive rates of perennial aeroallergen-specific IgEs for *Dermatophagoides pteronyssinus*, house dust, *Malassezia*, cat dander, dog dander, and cockroach were higher compared to those without ATR. Furthermore, in patients with ATRs, the positive rate of food allergen-specific IgE for egg white was higher than that in those without ATRs.

3.3 | Assessment of the risk factors involved in the onset of ATRs with multivariate analysis

Multivariate analysis using items showing $p < .100$ in Tables 1 (A) and (B) for all patients suggested that

TABLE 1 Univariate analysis of the relationship between ATR development and clinical parameters

Clinical parameters		ATR (n = 144)	Non-ATR (n = 219)	p value
(A) Patient background at diagnosis				
Age	<5 y:5 to <10 y:≥10 y	56:37:51	98:55:66	.479
Sex	Male:female	85:59	110:109	.107
Disease	Hematological disease:solid tumor	103:41	168:51	.270
Past history ^a	Asthma, allergic rhinitis, pollinosis, and atopic dermatitis:none	41:103 (28.5%)	33:186 (15.1%)	.002
Allergic history ^a	Drug allergy:none	36:108 (25.0%)	42:177 (19.2%)	.194
	Food allergy:none	30:114 (20.8%)	31:188 (14.2%)	.114
Eosinophil (/μL) ^b	≤300:>300	125:19	195:24	.513
Basophil (/μL) ^b	≤100:>100	125:19	204:15	.064
Total IgE (IU/mL) ^{b,c}	≤360:>360	89:50	184:31	<.001
Premedication with antihistamines	Yes:None	134:10	205:14	.832
Number of times receiving RBC products (number)	≤20:>20 to 40:>40	98:33:13	192:20:7	<.001
Number of times receiving PLT products (number)	≤20:>20 to 40:>40	67:29:48	154:42:23	<.001
(B) Allergen-specific IgE at diagnosis ^{c,d}				
Pollen allergen	Orchard grass	45:99 (31.3%)	33:186 (15.1%)	<.001
	Timothy	40:104 (27.8%)	31:188 (14.2%)	.002
	Ragweed	38:106 (26.4%)	27:192 (12.3%)	<.001
	Mugwort	31:113 (21.5%)	25:194 (11.4%)	.011
	Japanese cedar	68:76 (47.2%)	63:156 (28.8%)	<.001
	Japanese cypress	50:94 (34.7%)	49:170 (22.4%)	.011
	Alder	28:116 (19.4%)	29:190 (13.2%)	.140
	Japanese white birch	31:113 (21.5%)	26:193 (11.9%)	.018
Perennial aeroallergen	<i>Dermatophagoides pteronyssinus</i>	79:65 (54.9%)	57:162 (26.0%)	<.001
	House dust	80:64 (55.6%)	63:156 (28.8%)	<.001
	<i>Candida</i>	9:135 (6.3%)	5:214 (2.3%)	.091
	<i>Alternaria</i>	19:125 (13.2%)	23:196 (10.5%)	.503
	<i>Aspergillus</i>	7:137 (4.9%)	4:215 (1.8%)	.122
	<i>Malassezia</i>	30:114 (20.8%)	24:195 (11.0%)	.015
	Cat dander	30:114 (20.8%)	22:197 (10.0%)	.006
	Dog dander	32:112 (22.2%)	17:202 (7.8%)	<.001
	Cockroach	17:127 (11.8%)	12:207 (5.5%)	.046
	Moth	20:124 (13.9%)	18:201 (8.2%)	.114
Food allergen	Kiwi fruits	19:125 (13.2%)	16:203 (7.3%)	.071
	Bananas	24:120 (16.7%)	22:197 (10.0%)	.076
	Apples	20:124 (13.9%)	21:198 (9.6%)	.236
	Peanuts	22:122 (15.3%)	19:200 (8.7%)	.062
	Wheat	22:122 (15.3%)	20:199 (9.1%)	.093
	Soybeans	12:132 (8.3%)	12:207 (5.5%)	.290
	Rice	13:131 (9.0%)	12:207 (5.5%)	.208
	Sesame	23:121 (16.0%)	20:199 (9.1%)	.067
	Tuna	6:138 (4.2%)	4:215 (1.8%)	.204
	Salmon	5:139 (3.5%)	4:215 (1.8%)	.492
	Mackerel	1:143 (0.7%)	2:217 (0.9%)	1.000
	Shrimp/lobster	6:138 (4.2%)	11:208 (5.0%)	.803
	Crab	4:140 (2.8%)	6:213 (2.7%)	1.000
	Milk	8:136 (5.6%)	6:213 (2.7%)	.264
	Beef	4:140 (2.8%)	4:215 (1.8%)	.718
	Chicken	4:140 (2.8%)	2:217 (0.9%)	.220

TABLE 1 (Continued)

Clinical parameters		ATR (n = 144)	Non-ATR (n = 219)	p value
	Pork	2:142 (1.4%)	3:216 (1.4%)	1.000
	Egg white	16:128 (11.1%)	11:208 (5.0%)	.040
	Ovomucoid	6:138 (4.2%)	3:216 (1.4%)	.164
	Buckwheat	16:128 (11.1%)	17:202 (7.8%)	.351
Other allergens	Latex	10:134 (6.9%)	10:209 (4.6%)	.354

Abbreviations: ATR, allergic transfusion reaction; IgE, immunoglobulin E; PLT, platelet; RBC, red blood cell.

^aPercentages of applicable patients within each group are shown in parentheses.

^bPeripheral blood levels at diagnosis.

^cData obtained from serum stored at diagnosis.

^dData are presented as the number of positive patients: number of negative patients (percentage of allergen-specific IgE-positive patients).

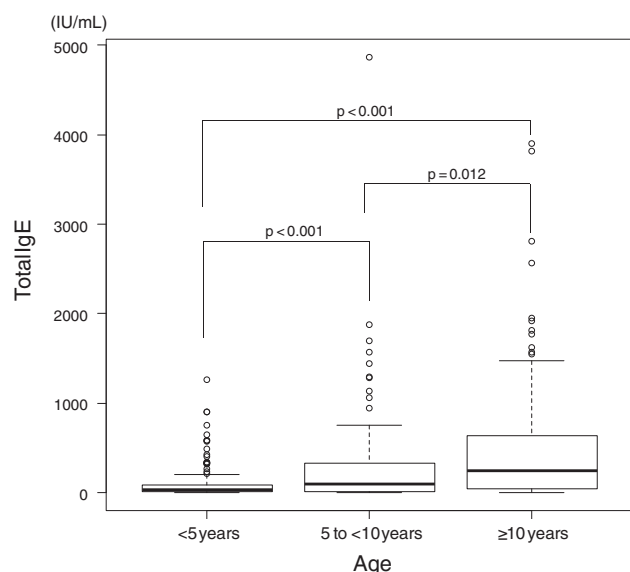


FIGURE 1 Comparison of total IgE level in the three different age groups

positive results for *D. pteronyssinus* and egg white-specific IgEs were risk factors for the onset of ATRs, in addition to a high basophil count in peripheral blood and several of platelet transfusions (Table 2).

3.4 | Assessment of the risk factors involved in the onset of ATRs according to different age groups

As shown in Figure 1, the total IgE levels could change depending on the age group. We also examined the risk factors for ATR development across different age groups. Univariate and multivariate analyses showed that in patients under 5 years of age, a history of food allergy and positive results for Japanese cypress- and *D. pteronyssinus*-specific IgEs were the risk factors for ATRs. In contrast, in patients who were aged 5–<10 years, a

history of asthma, allergic rhinitis, pollinosis, or atopic dermatitis were the risk factors for ATR development. Similarly, in patients who were aged ≥ 10 years, positive allergen-specific IgE for dog dander was the risk factor for ATR development. In addition, in all age groups, having several platelet transfusions was a risk factor for the development of ATR (Table 2).

3.5 | Association of total IgE levels and classes of allergen-specific IgE with severe ATRs

Based on the classification of ATRs in previous reports,¹⁷ we compared the total IgE levels by ATR grades based on severity, but no difference was observed between grades I and III ATRs. (Figure 3) In addition, no significant association was found between the presence of grade III ATR and the positivity of allergen-specific IgE or the presence of a higher classified level of allergen-specific IgE.

4 | DISCUSSION

A previous study that was mainly conducted in adults showed that the total IgE level was higher in patients with ATR-onset.^{12–14} Similar to these results, many pediatric cases with ATR in this study also had higher total IgE levels. Therefore, an allergic predisposition may be involved in the onset of ATR, even in children. However, it is difficult to set a cut-off level for total IgE level in children because total IgE levels vary depending on various factors such as age and sex.^{25–27} Therefore, it may be difficult to use total IgE as a diagnostic parameter for allergies²⁷ and predict the onset of ATR on the basis of the total IgE value alone. However, aeroallergen-specific IgE levels have also been reported to be higher in patients with ATR than that in those without.^{12,13} In these studies, multiple allergen-specific IgEs were analyzed for two

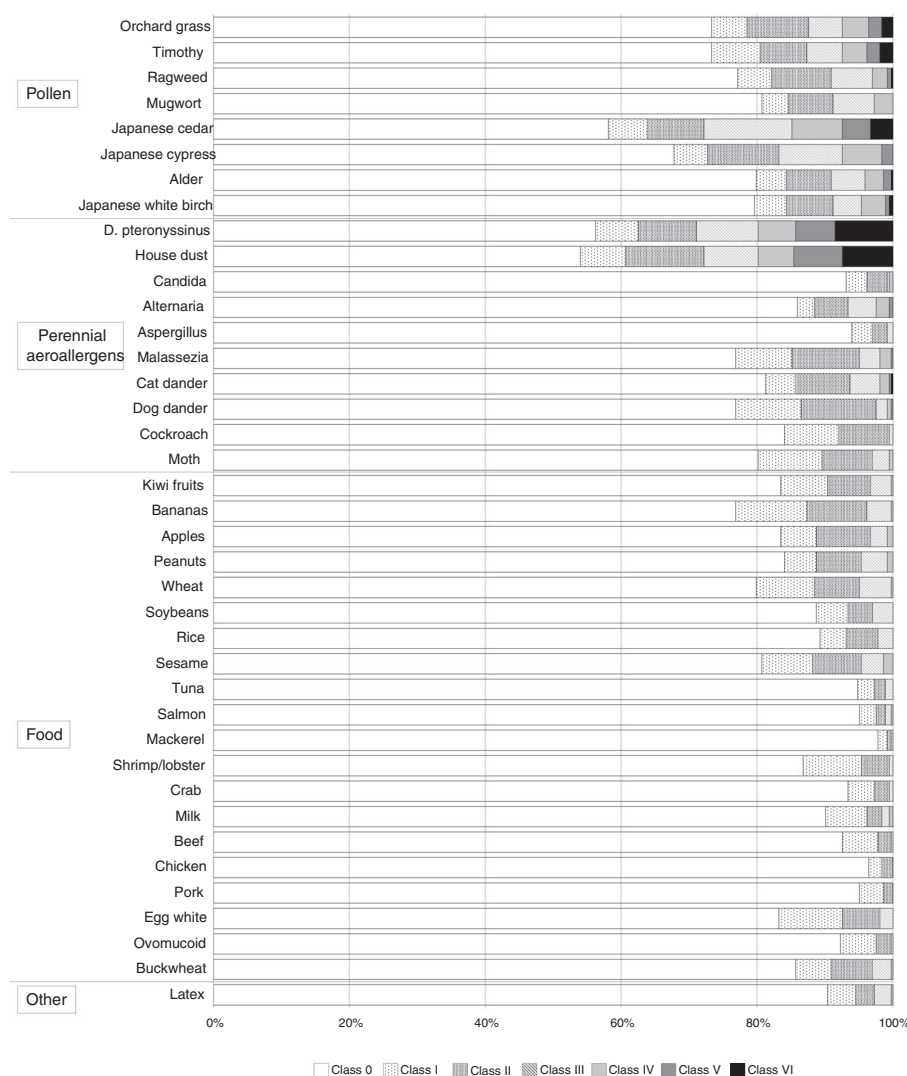


FIGURE 2 Breakdown of the cases included for the analyzed allergen-specific IgEs

types of allergens (i.e., aeroallergens and food allergens). Aeroallergens include weed, grass, and tree pollen; pet epidermis; dust mites; and mold allergens, while food allergens include cow's milk, chicken egg, peanut, soybean, wheat, and codfish.^{12,13} Although it was not possible to identify detailed allergens, the patients showed sensitization. Many patients with hay fever were also shown to develop ATR. Therefore, pollen-specific allergic predisposition may be a particularly important factor. However, food allergens were not associated with the development of ATR.¹³

In our study, Japanese cypress pollen-specific IgE positivity was a risk factor involved in the onset of ATR in patients <5 years of age, which was similar to the results of previous studies.^{12,13} However, in addition to a history of food allergy in patients <5 years and a history of allergy-related diseases in those aged 5–<10 years, the findings suggested that aeroallergens other than pollen, such as *D. pteronyssinus*– and dog dander–specific IgEs, or food allergens (egg white–specific IgE) were also

involved in the onset of ATR. According to a Japanese report, the highest incidence of immediate type of food allergy occurred in children who were aged <1 year; food allergy occurred 64.5% of patients who were aged ≤2 years and 80.3% of patients who were aged ≤5 years.²⁸ Nevertheless, the prevalence of childhood wheezing peaked at 2 years of age (24.2%) and then decreased; however, it maintained a 10% or higher rate of illness until 8 years.²⁹ Allergic dermatitis was more frequent in children who were aged 6–8 years than older children (13–15 years), while allergic rhino-conjunctivitis was more common in older children.^{30,31} Thus, age is strongly associated with several allergy-related diseases. Furthermore, sensitization to some food and pollen allergens increases in early childhood in Japan, and sensitization to environmental allergens, such as *D. pteronyssinus*, may also increase simultaneously.^{32,33} Furthermore, sensitization to Japanese cypress is common in children, and allergic sensitization to dog dander, in particular, is more frequent in children than in adults.³⁴ Therefore, the

TABLE 2 Multivariate analysis of risk factors for ATR development across patient age groups

Age categories	Clinical parameters		Odds ratio	95% CI	p value
All patients	Basophil	>100/ μ L	2.520	(1.140–5.570)	.023
	Number of PLTs products received	>40	5.540	(3.030–10.100)	<.001
	Perennial aeroallergen-specific IgE	<i>Dermatophagoides pteronyssinus</i>	4.060	(2.490–6.620)	<.001
	Food allergen-specific IgE	Egg white	2.770	(1.150–6.680)	.023
<5 years	Number of PLTs products received	>40	9.980	(3.110–32.000)	<.001
	Allergic history	Food allergy	4.630	(1.670–12.900)	.003
	Pollen allergen-specific IgE	Japanese cypress	5.730	(1.210–27.000)	.028
	Perennial aeroallergen-specific IgE	<i>Dermatophagoides pteronyssinus</i>	8.640	(3.390–22.000)	<.001
5–<10 years	Number of PLTs products received	>40	3.470	(1.110–10.900)	.032
	Allergic history	Asthma, allergic rhinitis, pollinosis, and atopic dermatitis	4.160	(1.500–11.600)	.006
≥ 10 years	Number of PLTs products received	>40	4.310	(1.710–10.900)	.002
	Perennial aeroallergen-specific IgE	Dog dander	6.040	(2.140–17.000)	.001

Abbreviations: ATR, allergic transfusion reaction; CI, confidence interval; IgE, immunoglobulin E; PLT, platelet.

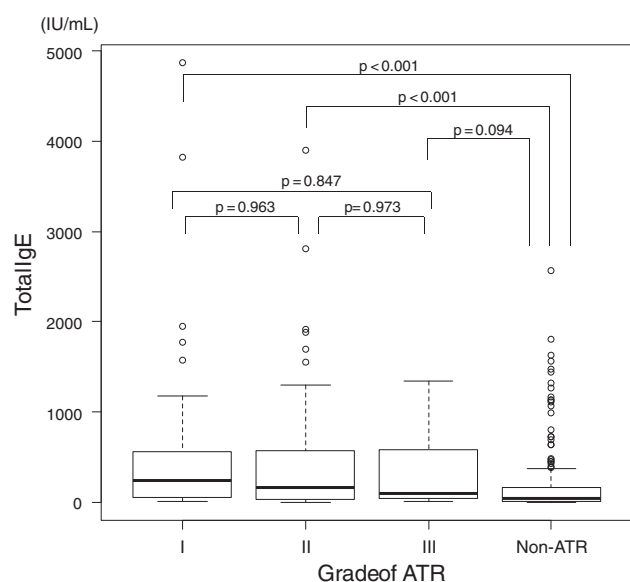


FIGURE 3 Comparison of total IgE level according to the severity of ATR or non-ATR groups

results of this study well reflect the background of pediatric allergic sensitization in Japan.

Allergic predisposition accompanied by high allergen-specific IgE levels is thought to indicate a primed state to ATRs or primary drivers for ATRs.^{2,12} ATRs can develop by adding additional factors to this state, although the mechanism underlying ATRs is still largely unknown. To

date, peanuts, fish, beans, shrimp, etc. have been reported as food allergens that cause ATRs.^{35–40} There were two patterns of ATR development caused by food allergens. The first pattern was that the patient originally had a food allergy. If the donor donates blood after ingesting the appropriate food, the blood product contains the allergen, and the patient develops allergies.^{35,36} In another onset pattern, donors possess food allergies, and donor-derived allergen-specific IgE is infused into patients during blood transfusion, resulting in a state of passive IgE sensitization.^{41–43} Subsequently, when the patient ingests the corresponding food, allergic symptoms develop.^{37,44,45} Although analysis of donors or blood products has not been conducted in this study, it is possible that such a mechanism was involved in our study, especially in patients who had food allergies in advance. This is thought to be important when evaluating especially severe ATR, and analysis of the allergic predisposition of donors in addition to patients is necessary.⁴⁶

Nevertheless, in cases with sensitization to pollen-allergens, oral allergy syndrome may develop when ingesting foods containing an allergen structure common to pollen, which is called pollen-food allergy syndrome.^{47–49} Many combinations of pollen and food allergens that cause the onset of allergy syndrome have been reported. Although it is currently unclear whether ATRs can develop as a result of a reaction between pollen-specific IgE in the patient's body and food-derived allergen contained in the blood product, it may be necessary to

verify this in the future. Furthermore, pollen-derived miRNAs have been recently reported to be present in human blood. This process was mediated by the ability of platelets to uptake sub-pollen particles and their nucleic acids.⁵⁰ Even if the donor or the product shows these characteristics, it is completely unknown if factors derived from pollen can react with the patient's pollen-specific IgE in any way. However, it is interesting to note that pollen may be directly involved in ATR development. This concept may also be useful in elucidating the clinical mechanism of ATRs, which develop particularly frequently due to platelet products.^{3,7}

Through this study, we were able to identify the possibility that allergic predisposition is also involved in the onset of ATRs in pediatric patients. However, this study has some limitations. First, since this study was conducted as a retrospective analysis, the method of collecting patient samples and clinical information was not completely unified. All ATRs that occurred during the study period were reported at both participating institutions, but there may be some ATRs that were under-reported over the extended observation period. In addition, accurate assessment may have been difficult in pediatric patients who could not complain of symptoms or those were intubated. Although premedication had no effect in this analysis, the number of blood transfusions in patients was closely related to the development of ATR. Thus, several unknown biases may have been involved in this analysis. Furthermore, the onset of allergic symptoms and sensitization to environmental allergens has been reported to differ depending on the age of the survey, and the distribution of allergens has been shown to vary across regions.^{30,34} Therefore, the generalizability of these results to other regions and countries may be limited. Furthermore, since the target diseases in this study were limited to hematological and oncological diseases, further study is needed to determine whether the analysis results also apply to many other pediatric diseases. Finally, in this study, we could not present a method to distinguish severe ATR cases, such as anaphylaxis, which is a particular problem. Recently, it has been reported that an immuno-basophil activation test may be useful in detecting ATR, including severe cases.⁵¹ Our study also showed that ATRs tend to frequently occur in patients with high basophils in the peripheral blood. In the future, we hope that allergen-specific IgE sets that are useful for predicting the onset of severe ATR will be selected and used as cost effective and highly accurate predictors in combination with other test items.

In conclusion, this study confirmed that allergic predisposition in patients is involved in the development of ATRs in pediatric hematological and oncological diseases. However, in children, the risk factors for

developing ATRs differ depending on the age group, and various allergens are actually involved in allergic predisposition and act as risk factors for ATR development. Therefore, it is important to collect detailed information on the patient's background, such as the patient's age, environment, and medical history. However, in children, it is not always easy to judge the allergic predisposition status only by interviews. Measurement of allergen-specific IgE levels is one of the methods used to determine the presence or absence of allergic predisposition, and may be useful for predicting the onset of ATRs. Furthermore, it may be a means to obtain useful information to elucidate the pathogenic mechanism of ATRs.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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