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Analysis of clinical presentations of allergic transfusion reactions and febrile non-haemolytic transfusion reactions in paediatric patients

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Abstract

Background and objectives Like adults, children can have allergic transfusion reactions (ATRs) and febrile non-haemolytic transfusion reactions (FNHTRs). But published information about the incidence of paediatric ATR and FNHTR is scarce.

Materials and methods This retrospective study was conducted from April 2002 to June 2018 on children who had ATRs and/or FNHTRs to platelet (PLT), red blood cell (RBC) or washed PLT/RBC concentrate transfusions. We analysed ATR/FNHTR clinical presentations, such as severity, time of occurrence and other features when they occurred.

Results During the study, 2742 children received 23 444 bags of PLT and RBC concentrate (including washed products). ATRs occurred in 100 cases (3.6% of total patients), caused by 201 products (0.9% of total products). In contrast, 28 patients (1.0% of total patients) had 42 FNHTRs caused by 42 products (0.2% of total products). Upon analysis of cases with detailed clinical information, the median onset time for ATRs and FNHTRs was 2.0 h after the start of transfusion. Of the 40% of ATRs that necessitated the discontinuation of blood transfusions, 10% escalated to anaphylaxis. Compared with minor ATRs, anaphylaxis tended to develop quickly. Moreover, 96% of patients with FNHTRs had a fever less than 39°C. There were no associations between blood product types and numbers or occurrence patterns of these reactions.

Conclusion The occurrence of ATRs and FNHTRs in children was variable, although there are common features such as severity and time of occurrence.

Key words: anaphylaxis, ATR, children, FNHTR, occurrence pattern.

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Introduction

Although blood transfusion is an important supportive therapy, transfusion-related adverse reactions (TRARs), including allergic transfusion reactions (ATRs) and febrile

non-haemolytic transfusion reactions (FNHTRs), are a problem [1]. Reactions, such as ATRs and FNHTRs, occur more often in children than adults [2,3]. Some patients have severe symptoms, such as anaphylaxis [4]. Other severe side effects, such as transfusion-related acute lung injury and transfusion-associated circulatory overload, can also occur in children and require special attention [2,3]. Although it has been difficult to recognize the actual medical status of patients developing TRARs,

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haemovigilance systems in Europe and North America have brought about more thorough investigations [5–7]. However, many details remain unknown about the clinical background of TRAR. Therefore, medical staff must often oversee the transfusion of patients without sufficient medical background information and every medical institution must be alert to provide safe transfusion. Previous guidelines have outlined the care and monitoring of transfusion patients. According to one set of guidelines, severe reactions are most likely to occur within the first 15 min of the start of transfusion, and patients should be most closely observed during this period [8]. However, additional observations are made at the discretion of each clinical area and need to be noted only should the patient become unwell or show signs of a transfusion reaction [8]. Because children find it hard to describe their feelings to medical staff and cooperate in clinical examinations, monitoring paediatric patients is not easy for medical staff. Furthermore, there is less information about transfusion medications, protocols or procedures available for children than for adults, and more is needed.

We conducted a study of children who had ATRs and/or FNHTRs from platelet (PLT), red blood cell (RBC), or washed PLT/RBC transfusions in a single centre. We investigated the clinical features of ATRs/FNHTRs in clinical practice and considered the use of some helpful aids for observing paediatric patients during transfusion.

Materials and methods

Patient selection and types of transfusion products

From April 2002 to June 2018, we conducted a retrospective study on the clinical features of ATRs and/or FNHTRs due to PLT concentrate, RBC concentrate or washed PLT/RBC concentrate blood transfusion for paediatric patients (aged ≤ 20 years old) at Nagano Children's Hospital. In this study, the same patients analysed in previous studies were included [1]. All PLT concentrate products in this study were obtained from single-donor apheresis [9]. RBC concentrates were prepared from whole blood collection of 200 ml or 400 ml derived from random single donors based on blood type [10]. One or two units of RBC (each derived from 200 or 400 ml of whole blood donation) were given according to the patient's weight. Prestorage leucocyte reduction (LR), which is primarily used for the prevention of FNHTRs and diversion of the first aliquot of blood, was utilized for each blood product according to the passage of time, as previously described [1]. Specifically, LR for each PLT and RBC concentrate product were introduced in October 2004 and January 2007 [1]. Therefore, during this study period, both LR products and non-

LR existed. If a patient presented with a TRAR, washed products were prepared according to the number of TRARs or the severity of the reaction [11,12]. In the guidelines of the Japan Society of Transfusion Medicine and Cell Therapy, introduction of washed PLT concentrates is recommended when TRARs occur more than twice despite premedication. If serious TRARs such as anaphylactic shock occur even once, washed PLT concentrates are recommended [13]. For recurrent FNHTR, ATR or anaphylactic reactions associated with RBC transfusions, the use of washed RBCs is also considered. The Institutional Review Board of Nagano Children's Hospital approved this study (approval number: 30–32). Written informed consent was signed by each participating patient's parent or guardian before transfusion.

Assessment of vital signs and TRARs

At the beginning of all blood transfusions, at least 2 medical staff (physician or nurse) double-checked the transfusion initiation, and a nurse observed each patient's condition at the bedside for at least the first five minutes of the transfusion. Nurses monitored the patient's vital signs at 5 min, 15 min, and at the end of transfusion. Other factors were observed and monitored according to each patient's medical background and situation. Attending and other physicians diagnosed TRARs clinically and symptomatically. TRARs were reported to the Department of Laboratory Medicine of the institution during the study period. We assessed all reports of TRARs during the study period. If the information provided in these reports was insufficient, each patient's medical chart was checked. If ATRs and/or FNHTRs occurred multiple times in one patient, all reactions were assessed.

ATR and FNHTR evaluation methods

For ATRs, at least one symptom, such as rash, pruritus, urticaria, flushing and respiratory distress, occurred during transfusion or within 4 h of its end. [4,9,11]. The severity of each ATR was defined per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [14]. According to the 'infusion-related reaction' section, grades 1 and 2 are described as follows: grade 1, 'Mild transient reaction; infusion interruption not indicated; intervention not indicated'; and grade 2, 'therapy or infusion interruption indicated but responds promptly to symptomatic treatment'. In the 'Allergic reaction' section, grade 3 is described as 'bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated'. In contrast, in the 'Anaphylaxis' section, grade 3 is defined as 'symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-

related oedema/angioedema; hypotension'. Based on this information, we classified the severity of each ATR in this study as follows: grade 1, only transient symptoms corresponding to a minor ATR; grade II, an ATR requiring discontinuation of blood transfusion but recovering rapidly with symptomatic treatment; and grade III, anaphylaxis with 'symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension'. FNHTRs were characterized by fever ($\geq 1^\circ\text{C}$ elevation) that could be accompanied by chills, rigour, hypertension, tachycardia and dyspnoea without other clinical symptoms [1]. The symptoms occurred within 4 h after the end of transfusion, and no other causes, such as a haemolysis or bacterial infection, were indicated. When fever was accompanied by other indications of an ATR, it was considered to be associated with an ATR. The severity of an FNHTR was defined as follows: grade 1, fever $\leq 38.0^\circ\text{C}$; grade II, fever $< 39.0^\circ\text{C}$; grade III, fever $< 40.0^\circ\text{C}$; and grade IV, fever $> 40.0^\circ\text{C}$.

Statistical analysis

Fisher's exact test was used to analyse ATR severity. Pearson's chi-squared test was used only when calculations were difficult in Fisher's exact test due to sample conditions. The occurrence time of ATRs/FNHTRs and the level of fever in children with FNHTRs were analysed using the Mann-Whitney *U*-test for comparisons between two groups of continuous variables or the Kruskal-Wallis test for comparisons of 3 or more groups of continuous variables. All statistical analyses were carried out using the EZR statistical program [15]. A *P* value < 0.05 was considered statistically significant.

Results

Patient's characteristics and transfused products

In total, 23 444 PLT and RBC (including washed products) were transfused to 2742 children in the study period. For RBC (including washed), 15 053 products were transfused into 2662 patients, and for PLT (including washed), 8391 products were transfused into 1041 patients during the study period. The transfused children had a male to female ratio of 1406:1336, and median age at initial transfusion of 0.2 years (range 0–20 years). The departments for the 2742 transfusion patients were as follows: neonatology 1146, cardiology 841, paediatric intensive care 247, haematology/oncology 226, general surgery 145, neurosurgery 84, general paediatrics 30, neurology 17, orthopaedic surgery 4, plastic surgery 1 and urology 1. Detailed data from the children included in this study

are shown in Table 1. As previously described [1], the introduction period for LR products, including both PLT and RBC concentrate products, was short, and current LR techniques and diversion of the first aliquot of blood products have been used for a long time. Bias was observed in the breakdown of causal transfusion products, as shown in Table 1.

ATRs

During the study period, the onset of ATRs was observed in 100 cases (3.6%), and a total of 201 products (0.9%) transfused. From these ATRs, we analysed 93 patients with 188 products whose detailed or appropriate clinical information was available. The patients' age at onset ranged from 0 to 19 years old (median 6.0 years old), and the male to female ratio was approximately 1.9:1. Eighty-one of 93 (87.1%) patients with transfusion symptoms had haematological and/or malignant diseases. The reactions began 0.1–7.0 h after the start of transfusion, the median being 2.0 h. Fifty-four per cent of patients had only one ATR, while the remainder had many (including 5.4% who had more than five). Regarding severity, 58.5% were grade I. Grade II or higher ATRs, which required the discontinuation of blood transfusion, occurred in more than 41.5% of patients, and anaphylactic symptoms (grade III ATRs) were observed for 10.6% of the transfused products. Although 82% of the ATRs were associated with PLT concentrate products, they also occurred with washed products (14 PLT concentrates for six patients and 3 RBC concentrates for one patient, that had been prepared to prevent such reactions). Three out of six patients also had multiple ATR episodes even with washed PLT concentrates. Most ATRs manifested with multiple symptoms. All symptoms observed in ATRs are listed in Table 2, the most common being urticaria, followed by other skin-related symptoms, such as pruritus and rash. Fever was noted in 14 of 93 patients (15%) and 16 (8.5%) of 188 products.

FNHTRs

By contrast, 42 products (0.2% of total products) caused FNHTRs in 28 patients (1.0% of the total) in this study period. As with ATRs, we studied 34 products for 25 patients who had had FNHTRs. The patients' ages at onset ranged from 0 to 18 years (median 5.0). FNHTRs were more likely to occur in boys (approximately 2.6 times more than girls) and in those with haematological and/or malignant diseases (96% of patients who developed FNHTR). The reaction appeared 0.5 to 5.0 h after the transfusion began, the median onset time being 2.0 h.

Table 1 Clinical characteristics of ATR(s) and FNHTR(s) in paediatric patients

Variables	ATR	FNHTR
No. of patients	93	25
No. of causal transfused products	188	34
Patient's age		
Range, years (median)	0–19 (6.0)	0–18 (5.0)
Patient's sex		
Male-to-female ratio	61:32	18:7
Patient's disease		
Aplastic anaemia/myelodysplastic syndromes	3	1
Langerhans cell histiocytosis	1	0
Acute lymphoblastic leukaemia	18	5
Acute myeloid leukaemia	10	2
Malignant lymphoma	9	2
Brain tumour	14	1
Neuroblastoma	14	5
Rhabdomyosarcoma	6	5
Other solid tumours	6	3
Non-haematological and/or malignant diseases	12	1
Occurrence time after the initiation of transfusion		
Range, hours (median)	0.1–7.0, (2.0)	0.5–5.0, (2.0)
Number of each reaction per patient		
1	50 (53.8%)	18 (72.0%)
2	22 (23.7%)	6 (24.0%)
3	13 (14.0%)	0 (0%)
4	3 (3.2%)	1 (4.%)
≥5	5 (5.4%)	0 (0%)
Severity of each reaction per causal products		
Grade 1	110 (58.5%)	11 (32.4%)
Grade 2	58 (30.9%)	18 (52.9%)
Grade 3	20 (10.6%)	4 (11.8%)
Grade 4	Undefined	1 (2.9%)
Causal transfusion products developing ATR or FNHTR		
PLT products		
PLT	31 (16.5%)	7 (20.6%)
PLT-LR	9 (4.8%)	2 (5.9%)
PLT-LR/D	100 (53.2%)	7 (20.6%)
Washed PLT	14 (7.4%)	1 (2.9%)
RBC products		
RBC	12 (6.4%)	10 (29.4%)
RBC-LR/D	19 (10.1%)	5 (14.7%)
Washed RBC	3 (1.6%)	2 (5.9%)

ATR, allergic transfusion reaction; FNHTR, febrile non-haemolytic transfusion reaction; LR, prestorage leucocyte reduction; LR/D, prestorage leucocyte reduction and diversion of the first aliquot of blood; PLT, platelet concentrate; RBC, red blood cell concentrate.

Eighteen patients (72%) had an FNHTRs only once, whereas the remaining seven (28%) had many such reactions. One patient had four FNHTRs. Eighty-five per cent of fevers were grade 1 or 2, which was relatively minor. In contrast to ATRs, the number of products causing FNHTRs was the same for PLT and RBC concentrates. The washed products likewise caused FNHTRs (Table 1): one PLT product in 1 child and 2 RBC in another. The patient

who had FNHTR twice with washed RBC was the same who had four febrile reactions.

Analysis of ATR severity along with causal products and the number of ATR occurrences

We analysed the severity of ATR for each transfusion product that caused such a reaction. Although the total

Table 2 Clinical symptoms of ATRs

Symptoms	Number
Urticaria	141
Pruritus	39
Rash	29
Fever	16
Cough	13
Respiratory distress	10
Wheezing	6
Flushing	5
Vomiting	3
Abdominal pain	1
Chills	1
Diarrhoea	1
Hypotension	1
Nausea	1
Tachycardia	1

Number indicates the number of patients who developed each symptom of ATR. Multiple symptoms can be observed in an individual who presents with ATR.

number of ATRs differed for each product, the severity of reactions was similar in both PLT and RBC concentrates. For ATRs due to either PLTs or RBCs, more than half the reactions were grade 1. Among the remaining ATRs (grade II or higher), anaphylactic symptoms were more frequent when PLTs were transfused than with RBCs. Even for washed PLT/RBC concentrates that were primarily prepared to prevent ATRs, 30% of reactions were grade II (Fig. 1a). Next, we studied the relationship between the number of reactions and their severity, as shown in Fig. 1b. Most ATRs occurred up to twice, and the severity of the first and second reactions was similar. Although anaphylaxis (grade III) was not included after three ATRs, approximately 20–40% of ATRs were grade II.

Analysis of the occurrence time of ATRs after the initiation of a blood transfusion

Although ATRs occurred within a wide time window after each blood product was transfused, we saw no significant difference among products (Fig. 2a). Next, we analysed the relationship between the number of ATRs experienced by a patient and the time of occurrence after beginning a blood transfusion. As shown in Fig. 2b, no significant difference was observed. Comparing the occurrence time with the severity of ATRs revealed that grade III reactions occurred earlier than other milder ones. However, there was no difference between grade I and II ATRs (Figure 2c).

Analysis of the severity of fever in patients with FNHTRs along with the causal products and the number of reactions

We analysed the relationship of the severity of fever in patients with FNHTRs to the blood products used, with or without the LR procedure, and the number of such reactions. Although there was a significant difference among the three blood products (PLT, RBC and washed PLT/RBC concentrates), there was no difference between any two products (Fig. 3a) with or without the LR procedure (Fig. 3b,c) number of FNHTR occurrence (Fig. 3c).

Analysis of the occurrence time of FNHTRs after the initiation of a blood transfusion

Similarly, we analysed the occurrence time of these reactions after beginning the transfusion and found no significant difference (Fig. 4a–c).

Discussion

Children often have ATRs especially when they receive PLT concentrates [1,2]. Since washed platelets can prevent ATRs [9,16,17], allergens in plasma must be among the factors causing ATRs [17,18]. However, it is difficult to identify such allergens. Additionally, we saw some ATRs requiring the discontinuation of transfusion even after the administration of washed PLT and RBC concentrates that contain minimal plasma. Moreover, even a small transfusion amount can quickly cause anaphylaxis [19]. Therefore, in children, we must recognize that serious ATRs can occur at a constant frequency regardless of the type of blood products used and the amount of residual plasma. However, even if the patient develops multiple ATRs, the severity of the reaction does not always change. One possible reason is factors, such as premedication and blood product washing, that affect repeated ATRs. However, in adults, the incidence of adverse events does not always increase, even when repeated PLT transfusions are given [20,21]; severe urgent reactions are not always constant, and these types of reactions occur most frequently during the first five transfusions [22]. No reliable paediatric data comparing the number and severity of ATRs have been reported. Further investigation is necessary to determine whether severe ATRs are more likely to develop during the first few transfusions, similar to those in adult populations, or whether severe ATRs develop on a constant basis regardless of the number of transfusions.

The median time required for the onset of an ATR varied little according to the type of transfusion products and the number of reactions. There are no available previous

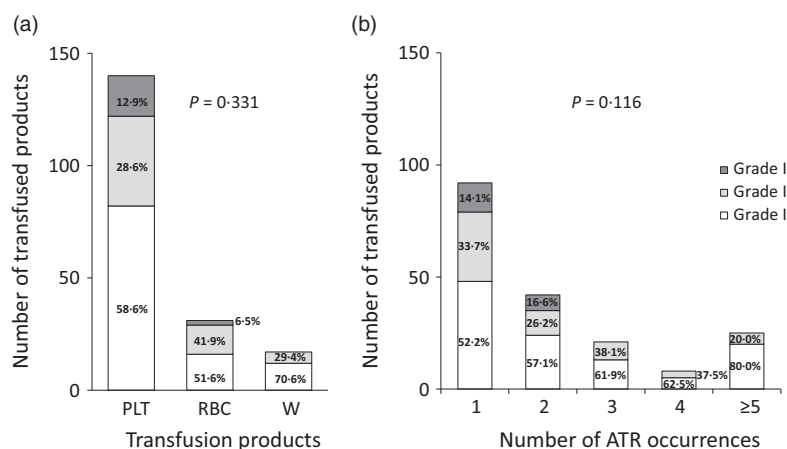


Fig. 1 Analysis of ATR grades. (a) Comparison of the severity of reactions according to the type of blood product. (b) Comparison of the severity of reactions according to the number of ATR occurrences. % indicates the ratio per products with grade I, II and III ATRs. PLT, platelet concentrate; RBC, red blood cell concentrate; W, washed products.

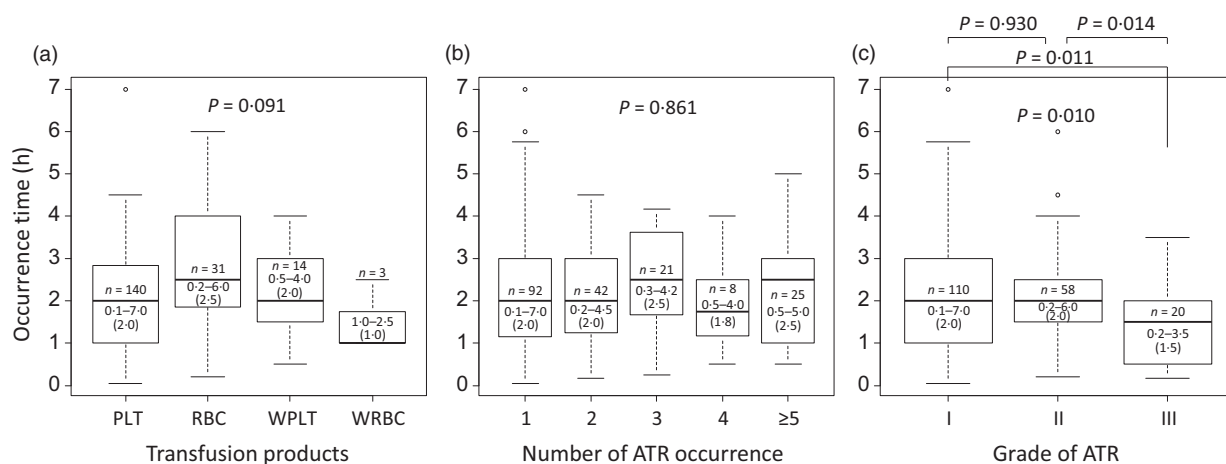


Fig. 2 Analysis of the occurrence time of ATR symptoms after the initiation of transfusion. (a) Comparison according to the type of blood product. (b) Comparison based on the frequency of ATRs. (c) Comparison according to the ATR severity (grade). *n*, number of ATRs confirmed in each analysed group; the range (median) is indicated. PLT, platelet concentrate; RBC, red blood cell concentrate; WPLT, washed platelet concentrate; WRBC, washed red blood cell concentrate.

paediatric studies on ATRs and their occurrence time after beginning a transfusion. In one report, adult reactions occurred approximately 100 min after the initiation of blood transfusion, regardless of the type of blood product [23]. However, severe side effects occurred sooner (approximately 20 min) when the analysis included severity [23]. In the latter study, the method of blood transfusion differed in adults and children, and the report analysed several transfusion side effects other than ATRs. Therefore, these findings cannot be directly compared with those of our study. However, as in our paediatric results, the median time of ATR occurrence was approximately 2 h after transfusion. Furthermore, similar results were observed in terms of severe symptoms, such as anaphylaxis occurring

in a short time after transfusion compared with minor ATRs. Therefore, the pattern of ATR onset was similar in adults and children. Generally, the onset of anaphylaxis caused by various triggers occurs over a wide range of times, reported as minutes to hours after exposure to a trigger [24]. Future data could clarify the features of transfusion-related allergic reactions and anaphylaxis. Through these investigations, medical staff might acquire more useful information for observing ATRs.

In studying the frequency of FNHTR, no difference in its incidence was found in children with or without a history of such reactions [25]. Nonetheless, FNHTRs caused by RBC were likely to appear after the first transfusion [26]. Another report indicated that the incidence of

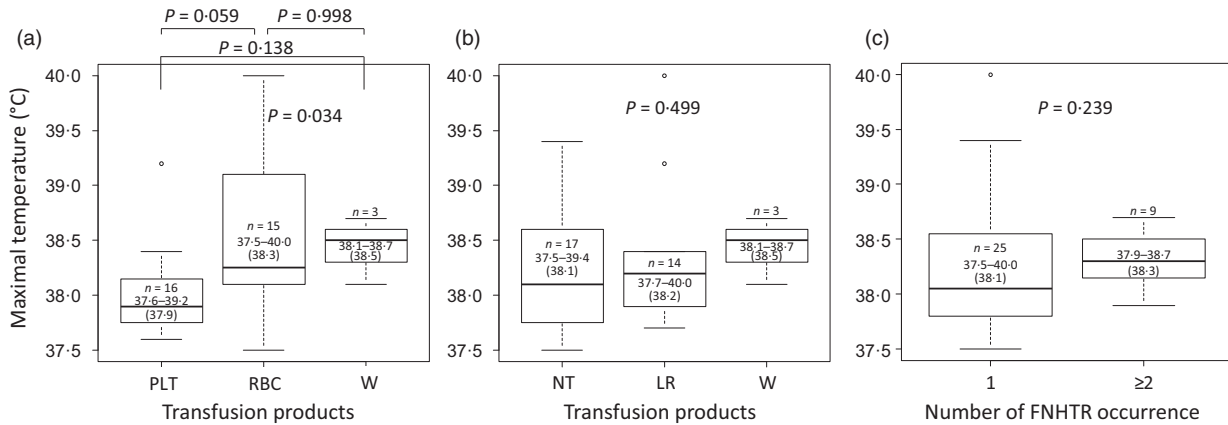


Fig. 3 Analysis of the maximum body temperature for each FNHTR. (a) Comparison based on the type of blood transfusion product. (b) Comparison based on whether LR procedures (washing or not) were performed. (c) Comparison according to the frequency of FNHTRs. *n*, number of FNHTRs confirmed in each analysed group; the range (median) is indicated. LR, prestorage leucocyte reduction; NT, non-treated; PLT, platelet concentrate; RBC, red blood cell concentrate; W, washed products.

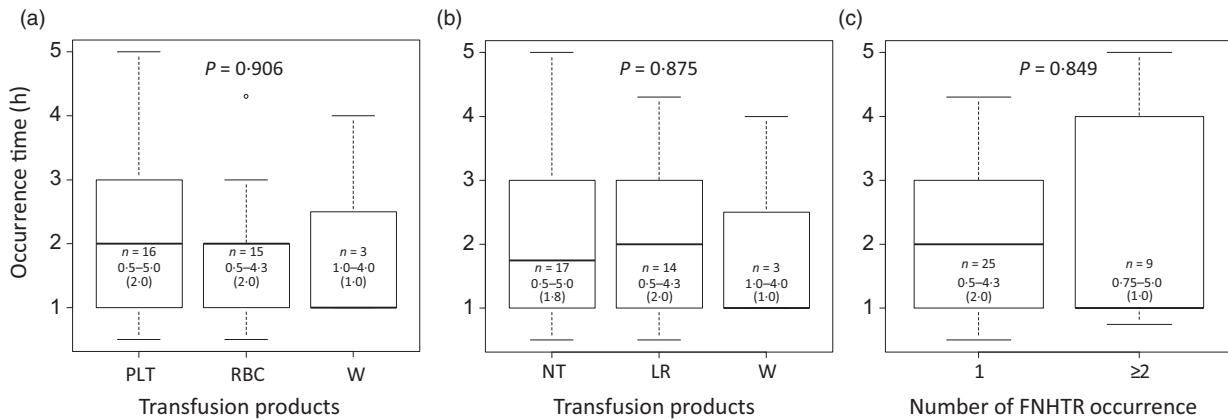


Fig. 4 Analysis of the occurrence time of FNHTRs after the initiation of transfusion. (a) Comparison based on the type of blood product. (b) Comparison based on whether LR procedures (washing or not) were performed. (c) Comparison according to the frequency of FNHTRs. *n*, number of FNHTRs confirmed in each analysed group; the range (median) is indicated. LR, prestorage leucocyte reduction; NT, non-treated; PLT, platelet concentrate; RBC, red blood cell concentrate; W, washed products.

FNHTRs increased as the frequency of transfusions increased [27]. Therefore, controversy regarding FNHTRs still exists. However, detailed data on the pattern of onset of FNHTRs, including data for the adult population, are not available. Our results showed that the severity of fever and its occurrence time in children did not change regardless of the type of blood product or the number of FNHTRs. Furthermore, ATRs and FNHTRs tended to occur at the same time after starting a transfusion. In patients with haematologic or malignant disease receiving transfusions, comprising the majority of patients in this study, it is usually important to distinguish FNHTRs from other causes of fever, such as neoplastic fever and febrile neutropenia [28,29]. In comparison with neoplastic fever in adults and febrile neutropenia in children, the peak

temperature in febrile patients was similar among FNHTRs and other causes of fever. Therefore, determining the cause of fever in the actual clinical setting may be difficult. However, neoplastic fever is associated with a once daily spike pattern [28], while febrile neutropenia is sometimes characterized by persistent fever for several days [29]. Previous guidelines have also outlined that bacterial contamination and haemolytic reactions should be suspected if a patient develops a sustained fever or a moderately severe fever (temperature $\geq 39^\circ\text{C}$ or an increase of $\geq 2^\circ\text{C}$ from baseline and/or systemic symptoms, such as chills, rigour, myalgia, nausea or vomiting) [30]. Although our study included a limited analysis, several features of paediatric FNHTRs, such as development in a relatively short period of time (median, 2.0 h) after

the initiation of transfusion and a moderately severe fever (38–39°C), may provide useful information associated with blood transfusion for medical staff.

Some interesting information similar to the results of our study is in the open-access haemovigilance number, for example, the SHOT-report of the UK Haemovigilance group [31]. Although the classification of FNHTR/ATR severity was different from that in our study, many ATR cases were severe, whereas a number of FNHTRs were moderate. Mixed types of reactions were also collected in a given number of cases. Furthermore, approximately half of the reactions occurred within standard hours in the classification of the timing of transfusion. Although the information obtained from haemovigilance systems have revealed useful knowledge regarding TRARs, evidence related to paediatric transfusion therapy remains insufficient. Furthermore, there is little information regarding

the detailed patterns of occurrence of individual TRARs in both adults and children. This study revealed certain features of the onset patterns of ATRs and FNHTRs, and similar features might exist in adults as well. In the future, it may be possible to further clarify the features of each TRAR. By evaluating such patterns, medical staff may be able to share information about the actual detailed features of TRARs and ultimately provide safer blood transfusion to patients. Since this study was conducted as a retrospective evaluation of a small number of cases in a single facility, future verification in prospective studies is necessary.

Conflict of interest

The authors have no potential conflicts of interest to declare.

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