Role of IL-1RL1/ST2 in infantile asthma

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Abstract

Purpose

Wheezing is the dominant pathological characteristic of asthma. It is estimated that 50% of all children have experienced wheezing at least once in their first six years of life. This study aimed to investigate initial wheezing attacks in pediatric patients and to determine connection between transient wheezing (TW) attacks and persistent wheezing (PW).

Methods

The immune responses of children who initially presented with wheezing attacks were studied. A total of 231 children with wheezing attacks at the time of admission were enrolled in the study. The study population consisted of 68 children with wheezing episodes. Children with recurrent wheezing who were introduced to inhaled steroids after 12 months were further grouped into either PW or TW groups.

Results

At the initial onset, cytokine analysis of the children revealed a marked increase in serum soluble and transmembrane forms of interleukin receptor-2 (ST2) in PW. In contrast, there were no changes in serum levels of IL-4, IL-13, and IL-33. The serum ST2 levels of the PW group were higher compared to those of the TW group. Moreover, a significant increase in ST2 expression was observed in PW children with recurrent wheezing attacks.

Conclusion

The present study demonstrated that ST2 might be a useful index for predicting the prognosis of infantile asthma. Hence, elucidation of the mechanism of ST2 expression in childhood allergic diseases is essential.

Introduction

Asthma is a common chronic inflammatory disease of the lower respiratory tract that presents with recurrent exacerbations and narrowing of the airways [1, 2]. It is a significant health burden that causes swelling, wheezing, shortness of breath, coughing, and chest tightness [1, 2]. It is also associated with several otolaryngologic diseases, such as allergic rhinitis, chronic rhinosinusitis, and obstructive sleep apnea [3]. As a result of the severe increase in the prevalence of asthma globally, it is estimated that almost 2.5 million patients die annually [3–5]. Asthma is particularly prevalent in children and teenagers in urban areas of middle- and low-income countries. Nevertheless, the rise in asthma prevalence is now leveling off among children and adolescents in Australia and Northwest Europe [5]. Inhaled

corticosteroids are the most commonly recommended safe first-line therapy for persistent and mild asthma in both adults and children [6]. However, asthmatic patients often fail to receive maximum treatment benefits due to the proper technique required for optimal drug inhalation [4].

Asthma is characterized by reversible airway obstruction and hyperreactivity of the airways due to various stimuli [1, 2]. It is associated with bronchoconstriction, mucus hypersecretion, and mucosal edema, which leads to narrowed airways [1, 2]. Ultimately, these result in its dominant pathological characteristic, wheezing [1, 2]. It is estimated that 50% of all children have experienced wheezing at least once in their first six years of life [7]. In fact, wheezing is more frequent in infants and toddlers. Initial wheezing episodes are associated with respiratory infections, such as viral infections. Most cases do not lead to the development of asthma in the future and are often transient wheezing (TW). Such cases are more frequent in asymptomatic infants and toddlers [8]. The late development of recurrent wheezing and asthma is attributed to bacterial colonization of the newborn airway [7]. Persistent wheezing (PW) is classified as atopic, also known as immunoglobulin E (IgE)-associated, or non-atopic [7].

The development of wheezing and subsequent asthma is associated with interleukin-33 (IL33)-interleukin-1 receptor-like 1 (IL-1RL1) pathway polymorphisms. In particular, PW is affected by an IL-33 single-nucleotide polymorphism [9]. IL-33, a member of the IL-1 family, is a unique cytokine that plays multiple roles in tissue homeostasis, the prevention of parasitic infection, and the induction of allergic inflammation [10–13]. It is passively released from the cell nuclear region during cell necrosis or cell damage to function as an immune system alarm during infection, physical stress, or trauma [10–13]. IL-33 instigates type-2 innate immunity via the activation of group 2 innate lymphoid cells (ILC2s) through its receptor, ST2, which causes allergic inflammation [10–13]. Moreover, IL-33-ST2 receptor binding activates allergic inflammation-related eosinophils, basophils, mast cells, and macrophages [10–13]. The results of a genome-wide association study (GWAS) indicated that the polymorphisms of ST2 were strongly associated with allergic diseases and asthma [14].

The involvement of IL-33 and ST2 in pdiatric asthma has been examined by Savenije et al [9]. and Savenije et al [15]. However, the underlying mechanism of IL-33-ST2-mediated allergic inflammation-linked wheezing remains unclear. Thus, this study aimed to investigate initial wheezing attacks in children and determine the connection between transient or episodic wheezing attacks and PW. It also aimed to examine the immune responses of children who presented with initial wheezing attacks and determine which factors were present in children who developed recurrent wheezing.

Methods

Participants

This study was approved by the local ethics committee of Juntendo University (approval number 643-30.438) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed

consent for participation was obtained from all of the patients or their parents. A total of 231 children with a wheezing attack at the time of admission (male: female ratio: 1.13) were enrolled in the study from January 1, 2014, to December 31, 2018.

Study population

Children with one or more of the following conditions were excluded from this study: fever, atopic dermatitis, food allergy, premature birth or low birth weight, laryngomalacia, gastroesophageal reflux disease, tracheobronchomalacia, and vascular ring. Children who had not been previously diagnosed with bronchial asthma and whose expiratory wheezing was detected by a pediatrician during hospitalization were included in the study. The patients' age, sex, virus identified on admission, and number of days hospitalized were recorded (Fig. 1). The use of inhaled corticosteroids (ICS) was determined based on the diagnosis of infantile asthma in all participants who underwent a follow-up check-up within 12 months after discharge. Children with recurrent wheezing were further grouped into PW or TW groups.

Biochemical measures

Peripheral venous blood samples from all children were obtained for biochemical measurements on the first day of hospitalization. In the PW group, a 12-month follow-up check-up was conducted at the time of non-wheezing attacks during outpatient visits. Serum IgE and TARC (thymus and activation-regulated chemokine) were analyzed to determine atopic allergic inflammation-mediated wheezing. The serum levels of proinflammatory cytokines such as interleukins-4 (IL-4), IL-13, IL-33, IFN-γ, and ST2, were determined using ELISA (GenWay, Biotech Co. Ltd, San Diego, CA, USA).

Statistical analyses

Data were analyzed using Prism 8 (GraphPad Software Inc., La Jolla, CA, USA). Values for continuous variables were expressed as either mean ± standard deviation or median (interquartile range) based on the data's normality of distribution. Student's t-test was used to compare normally distributed variables. The Wilcoxon signed-rank sum test was used to examine the differences between continuous variables within the study groups. The Mann-Whitney U test was performed to analyze the relationship between the study groups. Statistical significance was set at $p < 0.05$.

Results

A total of 231 children who presented with a wheezing attack at the time of admission (male: female ratio: 1.13) between January 1, 2014, and December 31, 2018, were enrolled in the study. The study group consisted of 68 children (mean age: 10.8 ± 4.07 months; boy to girl ratio = 1.34). The administration of ICS in the 12 months after discharge was performed in 19 children with bronchial asthma in the PW group (27.9%) and in the rest of the children in the TW group. The backgrounds of the PW and TW groups are listed in Table 1. The mean age of the PW group was 11.9 ± 3.79 months. The male to female ratio was 1.38. Rapid antigen testing for respiratory syncytial virus (RSV), human metapneumovirus (hMPV),

and influenza was performed on 40% of the patients upon admission, and at least one of these viruses were confirmed to be present in the patients (Fig. 2).

The results of the therapeutic course analysis revealed that systemic steroidswere administered to 24 patients (35.3%). The average duration of hospitalization was 7.07 ± 1.70 days. The median of oxygen demand was 40 (58.8%). The mean administration duration was 2.35 ± 1.28 days. Among the 24 patients treated with steroids, 13 were in the PW group. There was no statistically significant difference between the PW and TW groups. The percentage of viral respiratory tract infections revealed that 24% had RSV, 13% had hMPV, and 3% had influenza virus infection (Fig. 2). There was no difference in the percentage of viral pathogens between the PW and TW groups.

Proinflammatory cytokine analysis revealed no statistically significant difference in the serum levels of IL-4, IL-13, IFN-γ, and IL-33 in the PW and TW groups. These proinflammatory cytokines during the initial wheezing attack (Fig. 3) are concerning. In addition, IgE and TARC analyses showed no statistically significant differences between the groups. In contrast, children who presented with an initial wheezing attack also had elevated serum levels of ST2. Interestingly, children with recurrent wheezing also had elevated ST2 from the initial onset in the PW group compared to the TW group. Especially in PW children, ST2 levels increased even higher after 12 months (Fig. 4). The Wilcoxon t-test revealed a statistically substantial increase in ST2 expression in children with recurrent wheezing attacks.

Discussion

In the present study, we evaluated the different proinflammatory cytokines and their receptors, which could help clinicians predict the prognosis of infantile asthma. We investigated the proinflammatory cytokines IL-4, IL-13, and IL33 and their association with the pathogenesis of childhood wheezing.

ST2 plays a role in the pathogenesis of inflammatory allergic diseases, and several studies have demonstrated that serum ST2 levels are higher in patients with bronchial asthma [16, 17]. In children, there have been several reports of elevated serum ST2 concentrations during acute exacerbations of bronchial asthma [18]. It is interesting to note that serum IL-33 did not increase despite ST2 elevations in the initial wheezing attack of participants without a diagnosis of bronchial asthma. Additionally, in the group that subsequently received a diagnosis of bronchial asthma (i.e., PW group), ST2 concentrations were high from the infancy stage. Overall, our findings provide clinical evidence that the expression of ST2 receptor levels is an appropriate predictor of infantile asthma.

IL-4 induces IgE production and Th2 cell differentiation. The IL-13 receptor is consistently expressed in the bronchial epithelial and smooth muscle cells [19]. A recent report provided evidence that the four-locus gene model, consisting of L13 rs20541, IL4 rs2243250, ADRB2 rs1042713, and FCER1B rs569108, can determine the risk of developing asthma and atopy in Chinese Han children [20]. Similarly, in African-American infants with a family history of atopy, the IL-4 C-589T polymorphism was associated with a 10-fold increased risk of wheezing without a cold [21]. Another clinical report indicated a significant correlation between serum IL-13 levels in infants and the number of wheezing episodes. Moreover, an

elevated serum IL-13 level and a positive history of allergy have functional significance in the recurrence of acute bronchiolitis [22]. Severe RSV disease is linked to an increased Th2 response resulting from the overexpression of IL-4, which leads to wheezing [23]. There was no change in IgE levels or the production of IL-4 and IL-13 in transient and recurrent wheezing. IL-4 produced by basophils activates NH cells in the lungs, and this interaction induces allergic diseases [24]. IL-4 and IL-13 are Th2-type inflammatory cytokines that increase in response to bronchial inflammation. Cysteine protease, when acting as an antigen that presents with wheezing attacks, strongly induces allergic inflammation.

In line with the above findings, IL-4 and IL-13 might be the key cytokines that prolong symptoms, but our results showed no statistical difference between the TW and PW groups. The wheezing attacks observed in infants may not be explained by Th2-type immune responses or innate immune responses alone They may also be related to cellular damage caused by substances called pathogen-associated molecular patterns (PAMPs), including allergens and viral infections.

We hereby discuss the immune responses associated with IL-33 and ST2. IL-33 is constitutively expressed in various cells, such as endothelial, epithelial, and mast cells, of barrier tissues. It contributes to the pathogenesis of inflammatory allergic diseases. Genetic variation of the IL-33 locus is strongly associated with increased susceptibility to allergic sensitization in childhood and the development of wheezing phenotypes [25]. A recent clinical report indicated that the interaction between IL-33 and CD4(+)CD25(+)Foxp3(+) regulatory T cells is implicated in the pathogenesis of asthma in children [26]. Moreover, single nucleotide polymorphisms of the IL-33-IL1RL1 pathway are linked to intermediate-onset wheezing and asthma through sensitization in early childhood [9]. ST2 is a well-replicated asthma gene associated with eosinophilia. Another clinical study indicated that ST2 has a predictive value for the development of eosinophilic airway inflammation in children with asthma [27]. Phylogenetic analysis showed co-circulation of hMPV, and the genotype ST2 was found [28].

Cysteine protease, an antigen that is associated with wheezing attacks, strongly induces allergic inflammation [29]. It damages epithelial cells, resulting in the release of IL-33 and the induction of asthmatic symptoms. IL-33 and ST2 levels were elevated during wheezing attacks, but children who developed PW did not present with differences in IL-33 levels at the initial admission. However, ST2 levels were notably elevated. It is conceivable that higher expression of ST2 in inflammatory cells is associated with increased inflammation and frequency of wheezing due to IL-33 released during acute exacerbations. The finding of elevated serum ST2 levels from infancy may be related to the phenomenon of increased susceptibility to repetitive wheezing, which may be due to epigenetic changes in ST2 expression genes and other factors that regulate these mechanisms.

IL-33 is localized in the nucleus and is upregulated in response to tissue damage [30]. In contrast, ST2 may be expressed due to atopic diathesis. Cases of infantile asthma that progress to PW have a high latent expression of ST2 and may suffer from wheezing through IgE.

This study has several limitations. Conducting ELISA to determine serum IL-33 levels is difficult. Moreover, it might not have necessarily measured *active* cytokines. Thus, we could not conclude that IL-

33 was not involved in children with PW and TW. It was also controversial whether serum ST2 levels measured soluble ST2 levels. In addition, it was unclear whether the ST2 measured in this study was associated with ST2 expression.

The function of ST2 has not been elucidated, although it may be important in allergic diseases, such as PW. The children who developed bronchial asthma (PW group) in our study had elevated serum ST2 when they presented with a wheezing attack for the first time compared with children with transient wheezing (TW group). Serum ST2 levels were further elevated in blood tests 12 months later. If soluble ST2 were detected, it would have bound to receptors and regulated their expression, which might have affected the prognosis of patients with infantile asthma.

ST2 levels were found to be elevated during PW attacks. However, ST2 was also notably increased in the initial measurements of children who eventually developed recurrent wheezing. Although there was no difference in the level of IL-33 in the serum between the transient and prolonged wheezing groups, the phenomenon of ST2 difference in its receptor might result in a potential predisposition to predict the future development of bronchial asthma. Patients who develop recurrent wheezing from infantile asthma have a high latent expression of ST2, which might be involved in the onset of wheezing through IgE.

Various factors should be considered in the management and prognosis of infantile asthma. For instance, biomarkers have a significant value in disease management. This study demonstrates that ST2 may be a useful index for predicting the prognosis of infantile asthma. Moreover, elucidation of the mechanism of ST2 expression in childhood allergic diseases is essential.

Declarations

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Conflicts of interest: The authors declare no conflicts of interest.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Author contributions: Conceived and designed research: Yosuke Baba. Performed experiments: Yosuke Baba, Hiromochi Yamada, Toshiyuki Yoneyama. Analyzed data: Yosuke Baba, Susumu Yamazaki. Interpreted results of experiments: Yosuke Baba, Eisuke Inage. Prepared figures: Akina Matsuda. Drafted manuscript: Yosuke Baba. Edited and revised manuscript: Yosuke Baba, Yoshikazu Ohtsuka, Masato Kantake, Toshiaki Shimizu. Approved final version of manuscript: All authors.

Ethics approval: This study was approved by the local ethics committee of Juntendo University (approval number 643-30.438) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate: Written informed consent for participation was obtained from all of the patients or their parents.

Consent for publication: Not applicable.

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Tables

Table 1 The backgrounds of patients

	TW group	PW group	p value
	n=49	n=19	
Age*	13 (2-31)	12 (4-23)	ns†
Sex (boy to girl ratio)	1.33	1.38	ns†
Virus identified on admission (n=56)	43	13	ns‡
Hospitalization* (day)	6 (3-11)	5.5 (4-14)	ns†

*Median (interquartile ranges)

†Mann-Whitney test

‡Fisher's exact test

TW, transient wheezing; PW, persistent wheezing; ns, no significant

Figures

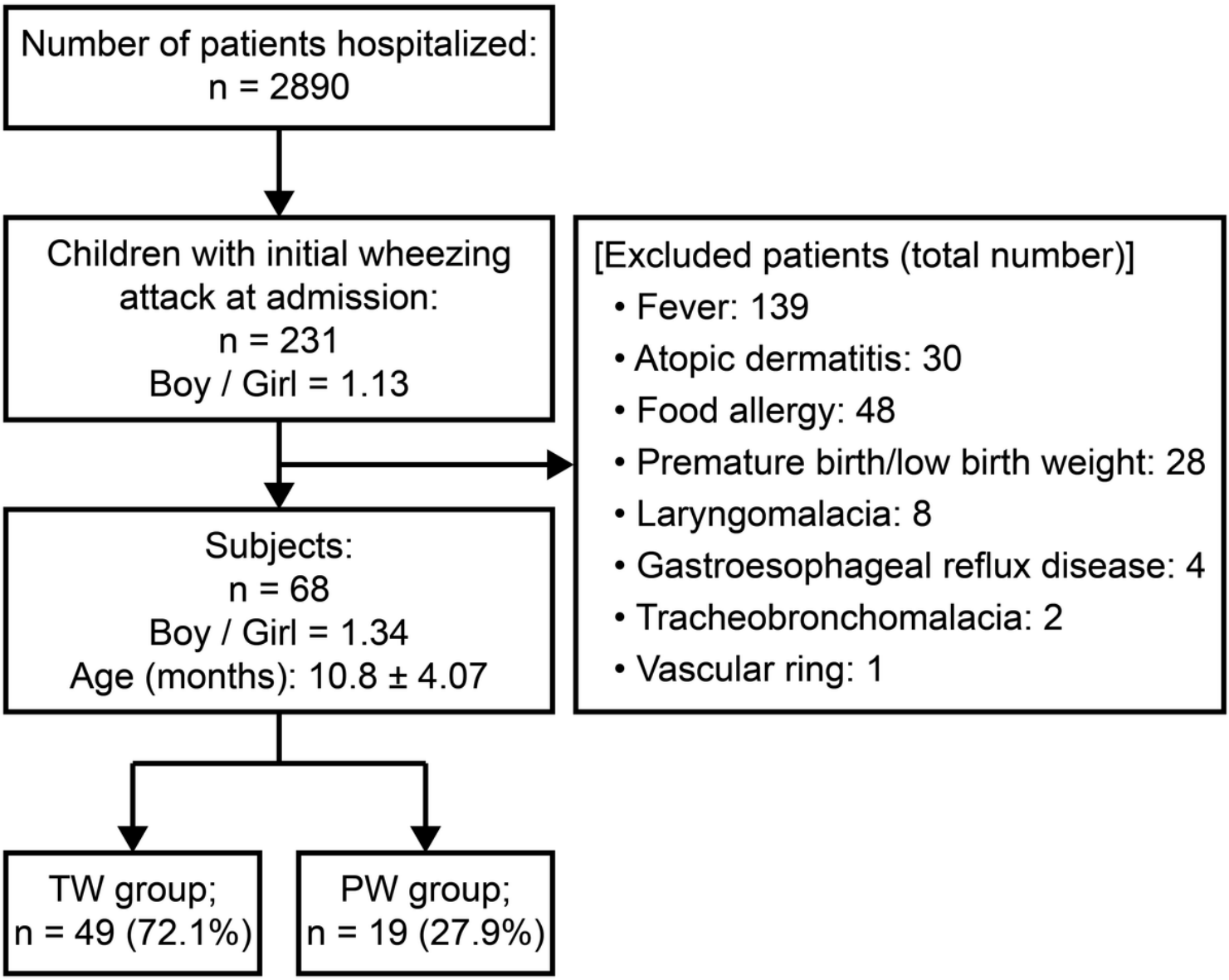

Figure 1

The patients' background, enrollment status, girl-to-boy ratio, and therapeutic courses

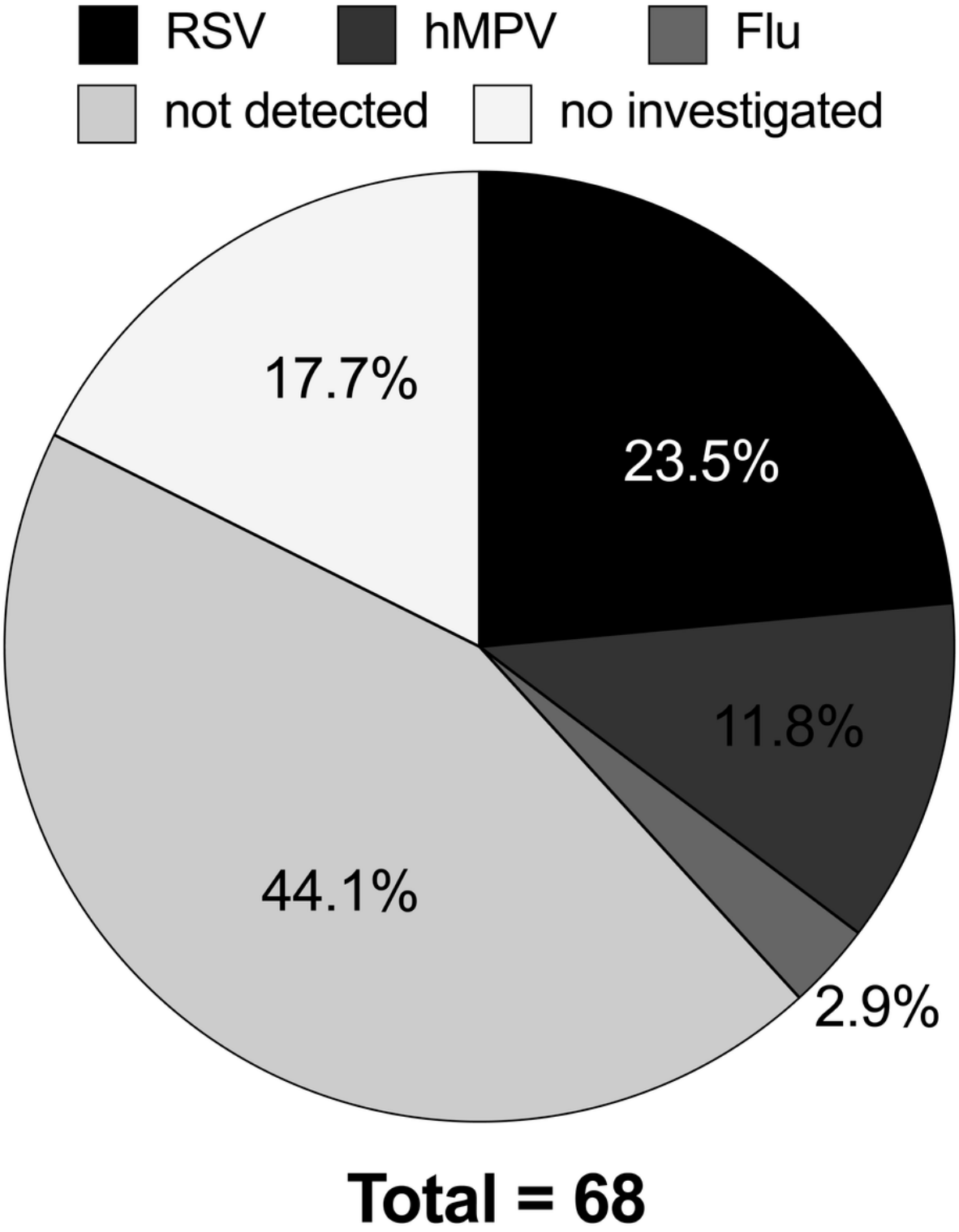

Figure 2

The percentage of viral respiratory tract infections. RSV, respiratory syncytial virus; hMPV, human metapneumovirus

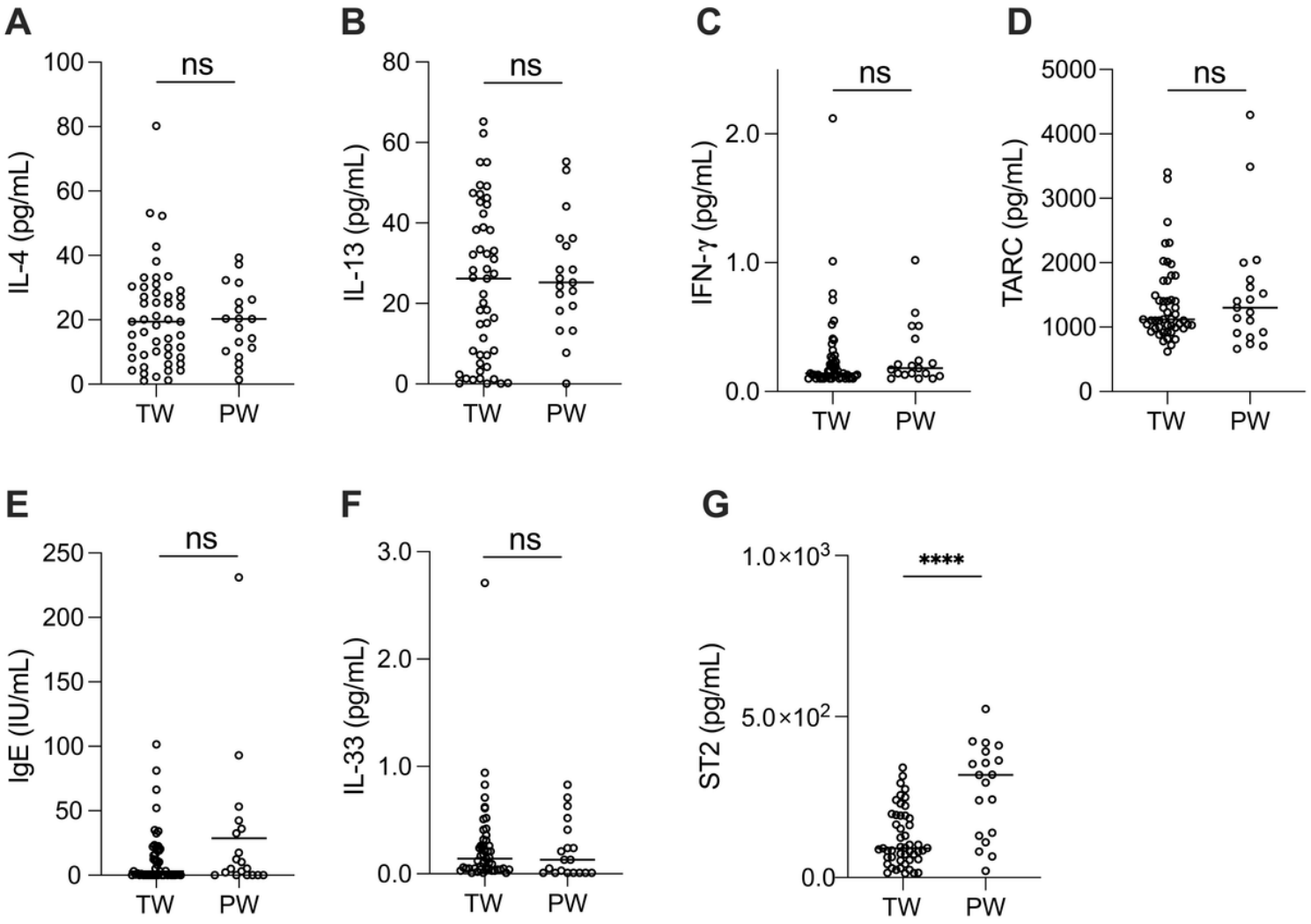

Figure 3

The serum levels of biomarkers in children with PW and TW There were no statistically significant differences in IL-4, IL-13, IFN-γ, TARC, IgE, and IL-33 levels between the two groups. (G) There was a statistically significant increase in ST2 in the PW group. TW, transient wheezing; PW, persistent wheezing; ns, not significant; ****P < 0.005

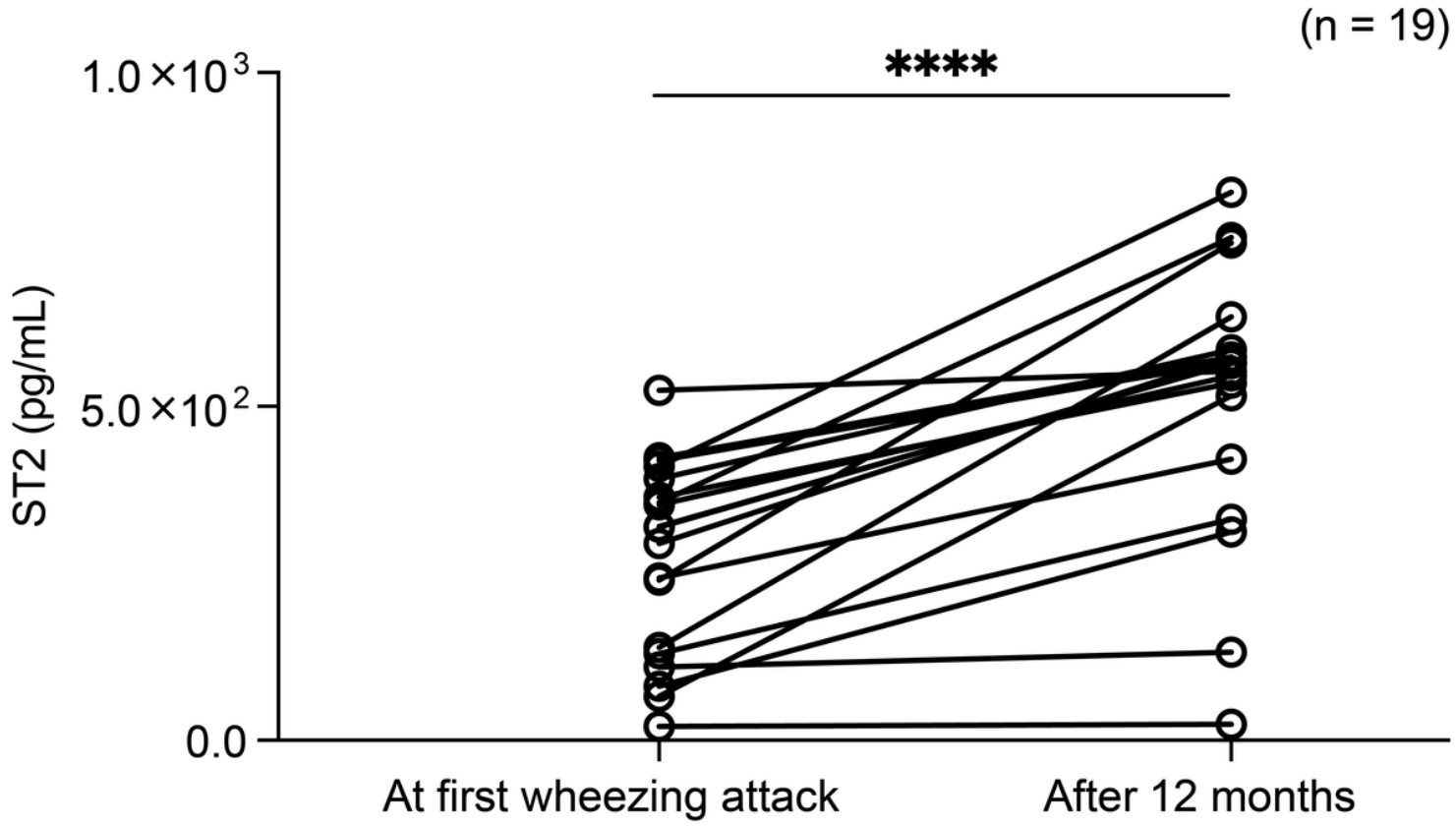

Figure 4

Change in the serum ST2 concentration in the PW group at the time of their first wheeze and 12 months thereafter, ****P < 0.005