

Expression and diagnostic value of miR-142-5p and miR-155-5p in the serum of children with allergic rhinitis

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ABSTRACT

Background: Recent studies have demonstrated that microRNAs (miRNAs) play an essential role in the regulation of allergic rhinitis (AR), but the underlying mechanism is still unclear.

Objective: This case-control study aimed to measure the expression levels of serum miRNAs in children with AR, to evaluate their potential as diagnostic markers, and investigate the association between miRNAs and IL-4, total nasal symptom score (TNSS), and specific IgE (Artemisia).

Methods: Twenty allergic rhinitis patients and 20 healthy controls were included. The expression levels of serum miR-18a-5p, miR-142-5p, miR-155-5p, and miR-3687 were measured using quantitative real-time polymerase chain reaction. Serum cytokine levels were measured using IL-4 enzyme-linked immunosorbent assay kits. Nasal symptoms were assessed using the TNSS. A receiver operating characteristic (ROC) curve was used to test the diagnostic ability of the study parameters.

Results: The AR case group had a higher serum expression of miR-142-5p, miR-155-5p, and IL-4 than did the control group. However, there were no significant differences in the serum miR-18a-5p and miR-3687 expression levels between the two groups. We found that serum miR-142-5p and miR-155-5p levels were positively correlated with the expression of specific IgE (Artemisia). TNSS did not correlate with miR-142-5p or miR-155-5p levels. In addition, no significant correlation was identified between miR-142-5p and IL-4 expression, whereas miR-155-5p was positively correlated with IL-4 expression. The receiver operating characteristic curve did not look promising. The AUC was around 0.7 and it was not high enough for diagnostic tool.

Conclusion: The expression levels of serum miR-142-5p and miR-155-5p were upregulated in children with AR; however, they were insufficient as diagnostic tools for AR. MiR-155-5p may be involved in T helper type 2 cell-mediated immune response.

1. Introduction

Allergic rhinitis (AR) is one of the most common inflammatory upper respiratory disorders worldwide, and is characterized by IgE-mediated allergic inflammation. This disease seriously affects patients' productivity and quality of life, given that it relapses easily and is difficult to cure [1]. It is currently believed that the hyperfunction of T helper type 2 (Th2) cells and an imbalance of Th1/Th2 are important immunological bases for the pathogenesis of AR. Th2 cells release large amounts of Th2 cytokines, such as IL-4, IL-5 and IL-13, while decreasing the production of Th1 cytokines. At the same time, these immune cytokines induce plasma cells to produce immunoglobulin E (IgE), followed by a cascade

of reactions, including nasal itching, sneezing, rhinorrhea, and nasal congestion [2]. However, the application of specific immunotherapies for AR has been limited. Therefore, it is of great significance to study the pathogenesis of AR so that suitable drugs for the treatment of AR can be developed.

MicroRNA (miRNAs) are a class of non-coding RNAs. Through mRNA degradation or translational repression, miRNAs inhibit gene expression and ultimately promote cell response to stimulation. They may also regulate the pathogenesis of various diseases [3–5]. Many studies have shown that miR-155-5p is involved in the pathogenesis of AR [6,7]. MiRNAs, including miR-18a-5p, miR-3687, and miR-142-5p, were also found to be differentially expressed in the nasal mucosa specimens of the

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AR and non-AR groups using high-throughput sequencing technology; however, whether these miRNAs are also involved in the pathogenesis of AR has not been verified yet [8].

In this study, we measured the expression levels of miR-18a-5p, miR-142-5p, miR-155-5p, and miR-3687 in the serum of patients with AR. The associations of miRNA levels with age, serum IL-4, specific IgE, and TNSS were analyzed, aiming to provide a reference for the clinical diagnosis and treatment of AR.

2. Materials and methods

2.1. Participants

Twenty children with AR who were treated as outpatients at the Department of Otorhinolaryngology, Affiliated Hospital of Chengde Medical University from July 2021 to October 2021 were included in the case group (AR group). The participants were aged between 3 and 18 years, and included 13 boys and 7 girls. We included patients who were confirmed to have AR based on medical history, symptoms, physical examination, and a specific IgE test (Artemisia-this is the most common allergen in the region). Twenty age- and sex-matched healthy children were enrolled as the control group. Patients with other allergic diseases, other types of rhinitis or respiratory diseases, active infectious diseases, and on medications in the last 4 weeks were excluded. The study was approved by the ethics committee boards, Affiliated Hospital of Chengde Medical University (the approval number: CYFYLL2022158) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the guardian of each participant.

2.2. Collection and preservation of serum samples

Under aseptic conditions, 5 mL peripheral blood samples were taken from each participant by venipuncture and centrifuged at 3000 rpm for 10 min. A portion of the separated serum was stored at -80°C for specific IgE and IL-4 detection, while the other portion was centrifuged at 12000 rpm for 10 min, with the supernatant being stored in liquid nitrogen for miRNA extraction. The experiments were conducted at the Central Laboratory of the Affiliated Hospital of Chengde Medical University.

2.3. TNSS

The TNSS was calculated as the sum of scores for four symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing). Each symptom was assessed on a 4-point scale (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms); the total score ranged from 0 to 12 [9].

2.4. Measurement of IL-4 and specific IgE levels in serum

Serum IL-4 levels were measured using a Human High Sensitivity IL-4 ELISA kit (Neobioscience, Shenzhen, China). The experiment was conducted in strict accordance with the manufacturer's instructions. Specific IgE levels were detected using the AllergyScreen® assay (Mediawiss Analytic GmbH, Germany). The concentration of specific IgE was measured using a Western blot assay, in strict accordance with the manufacturer's instructions. A positive test was defined as IgE concentration >0.35 IU/mL.

2.5. miRNA extraction and reverse transcription

Serum miRNA was treated using the miRcute miRNA Isolation Kit DP501 (Tiangen, Beijing, China), according to the manufacturer's instructions. Total RNA from serum samples was reverse-transcribed into cDNA using the miRcute Plus miRNA First-Strand cDNA Kit KR211

(Tiangen, Beijing, China), performed according to the manufacturer's instructions. Total RNA 8 μL , miRNA RT Enzyme Mix 2 μL , and $2 \times$ miRNA RT Reaction Buffer 10 μL were used to prepare a 20 μL reverse transcription system. Reverse transcription was performed using PCR at 42°C for 60 min and 95°C for 3 min.

2.6. Determination of serum miRNA levels using quantitative real-time PCR (qRT-PCR)

For real-time PCR, the miRcute Plus miRNA qPCR Kit (SYBR Green) FP411 (Tiangen, Beijing, China) was used for relative quantification of miRNAs, done according to the manufacturer's instructions. An external control (CR100-01; Tiangen, Beijing, China) was added to the serum before miRNA extraction. The following PCR conditions were adopted: 0.4 μL reverse primer (10 μM), 0.4 μL forward primer, 10 μL $2 \times$ miRcute Plus miRNA PreMix, 2.5 μL of 10-fold diluted DNA sample, and 6.7 μL ddH₂O, brought to 20 μL . Quantitative real-time PCR was performed using the Cobas z480 real-time PCR instrument (Roche, Basel, Switzerland) under the following conditions: initial denaturation at 95°C for 15 min, followed by 45 cycles at 94°C for 20 s and 62°C for 34 s. A melting curve was obtained by heating the sample from 55°C to 95°C . The expression levels of miRNAs were calculated using the $2^{-\Delta\Delta\text{Ct}}$ method [$\Delta\text{Ct} = \text{Ct}(\text{sample}) - \text{Ct}(\text{CR100})$; $\Delta\Delta\text{Ct} = \Delta\text{Ct}(\text{AR case group}) - \text{mean } \Delta\text{Ct}(\text{control group})$].

2.7. Statistical analysis

Statistical analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Data from each group were subjected to the normality test, and the measurement data that accorded to a non-normal distribution were expressed as the medians (25th-75th quartiles). The independent-samples t-tests were used for parametric group comparisons, while the Mann-Whitney test was used for non-parametric group comparisons. Categorical were expressed as frequencies, and the chi-square test was used to compare data between the two groups. Correlations between variables were analyzed using Spearman's correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of serum miR-142-5p and miR-155-5p levels for AR. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic characteristics

Data from 20 AR cases and 20 healthy age- and sex-matched controls were analyzed. The demographic and clinical data of the participants are summarized in Table 1. The participants were aged between 3 and 18 years. There were 13 boys (65%) and 7 girls (35%) with an average age of 6.0(5, 10) years in the AR group, and 11 boys (55%) and 9 girls (45%) with an average age of 5.0(4, 10) years in the control group. The average TNSS was 7.0(5, 8), while the average IgE level in AR patients was 22.6

Table 1
Demographic characteristics of children with allergic rhinitis and controls.

		AR group(n = 20)	Control (n = 20)	Test Statistic	P
Sex	Male	13(65%)	11(55%)	0.417	0.519
	Female	7(35%)	9(45%)		
Age (year)	3–18	6.0(5, 10)	5.0(4, 10)	−1.69	0.09
TNSS		7.0(5, 8)			
Specific IgE (IU/mL)		22.60 (10.3, 33.4)			

Data ARE presented as medians (25th-75th quartiles). AR, allergic rhinitis; TNSS, total nasal symptom score.

(10.3, 33.4)IU/mL.

3.2. Comparison of serum IL-4 and miRNA levels between the two groups

The serum IL-4 level of the AR group was significantly higher than that of the control group ($P = 0.025$) (Fig. 1). Furthermore, the expression levels of serum miR-142-5p and miR-155-5p in the AR group were significantly higher than those in the control group (miR-142-5p $P = 0.021$; miR-155-5p $P = 0.033$) (Fig. 1). However, there was no statistical difference in the expression levels of serum miR-18a-5p and miR-3687 between the two groups (miR-18a-5p, $P = 0.93$; miR-3687, $P = 0.07$) (Fig. 1).

3.3. ROC curve analysis

ROC curves were constructed to evaluate the diagnostic value of serum miR-142-5p and miR-155-5p levels for AR (Fig. 2). The area under the miR-142-5p curve (AUC) was 0.713 (0.552, 0.873) and the optimal cutoff value was 1.09, with a sensitivity of 80% and specificity of 55%. The area under the miR-155-5p curve was 0.700 (0.534, 0.862) and the sensitivity and specificity were 80% and 50%, respectively, with the optimal cutoff value of 0.65.

3.4. Correlation of serum miR-142-5p and miR-155-5p with age, IL-4 levels, TNSS, and specific IgE levels in children with AR

In the AR group, serum miR-142-5p was positively associated with specific IgE to artemisia ($r = 0.659$, $P = 0.002$), but not with age, IL-4 levels, and TNSS (Fig. 3). However, serum miR-155-5p levels were negatively correlated with age ($r = -0.463$, $P = 0.04$) positively correlated with IL-4 ($r = 0.580$, $P = 0.007$) and specific IgE levels ($r = 0.480$, $P = 0.032$), and not significantly correlated with TNSS (Fig. 3).

4. Discussion

MiR-142 may be involved in the regulation of immune cell proliferation and activation, inflammatory reaction, autoimmune diseases, immune rejection, tumor immunity, and viral replication [10]. miR-142

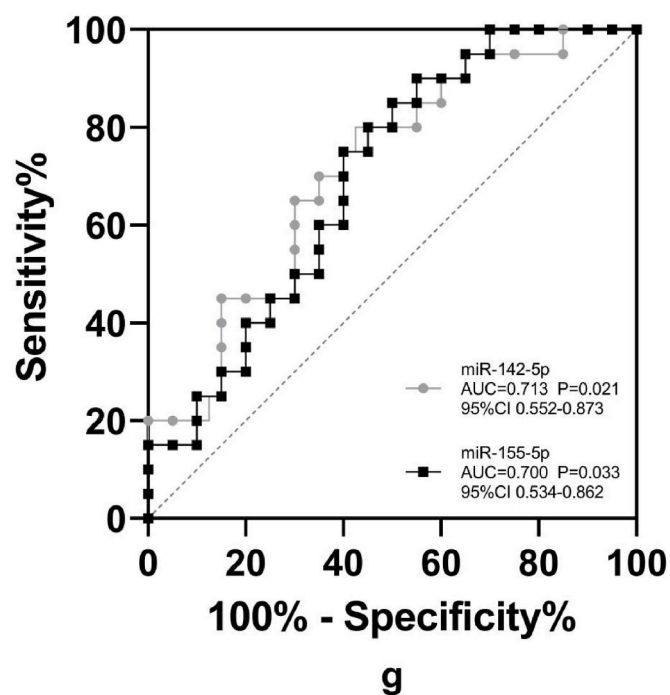


Fig. 2. (g) ROC curve of miR-142-5p and miRNA-155-5p for allergic rhinitis diagnosis.

has also been shown to be involved in various allergic diseases. Venegaard et al. first described the differential expression of miRNA in cases of allergic contact dermatitis (ACD), and found that four miRNAs, including miR-142-3p and miR142-5p, were significantly upregulated [11]. Sabine et al. found that miR-142 might be associated with the regulation of the balance between cell proliferation and differentiation of airway smooth muscle in patients with asthma, by controlling the Wnt signaling pathway. Therefore, miR-142-3p may be a therapeutic target for preventing airway smooth muscle proliferation in asthma [12].

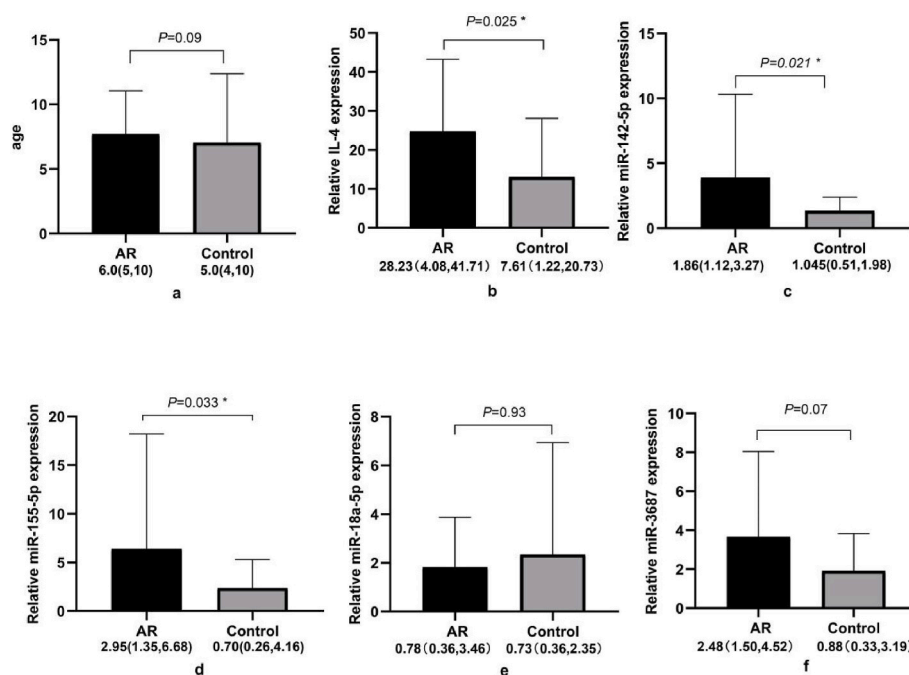


Fig. 1. Comparisons between the allergic rhinitis and control groups: (a) age, (b) serum IL-4 levels, (c) serum miR-142-5p levels, (d) serum miR-155-5p levels, (e) serum miR-18a-5p levels, (f) serum miR-3687 levels. Data ARE presented as medians (25th-75th quartiles) * $P < 0.05$.

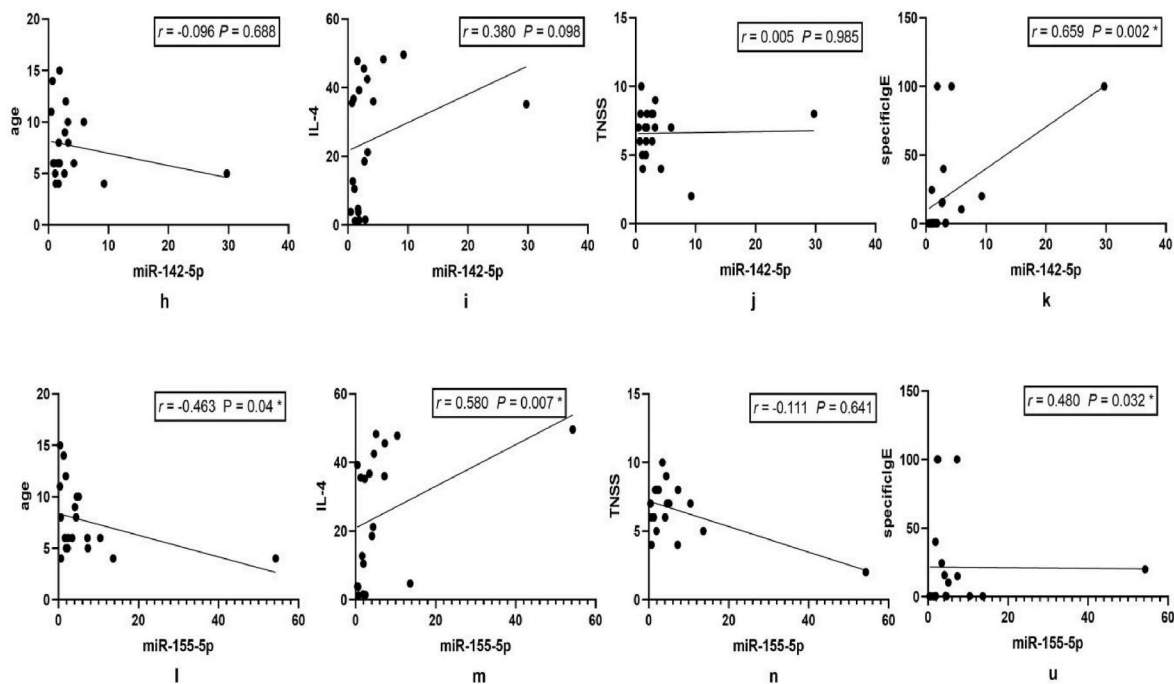


Fig. 3. Correlation between miR-142-5p, miR-155-5p and (h, l) age, (i, m) IL-4 levels, (j, n) TNSS, and (k, u) Specific IgE. * $P < 0.05$ ** $P < 0.01$.

Yamada et al. showed that the overexpression of miR-142-3p could enhance mast cell degranulation mediated by the high-affinity IgE Fc receptor. The result highlighted the important role of miR-142-3p in the pathogenesis of allergic diseases [13]. Maes et al. identified miR-142-3p expression to be upregulated in the supernatant of sputum samples from patients with severe neutrophilic asthma. They also reported that miR-142-3p expression was significantly associated with airway obstruction (FEV1/FVC ratio). Importantly, miR-142-3p was correlated with proinflammatory mediator IL-1b levels, but not with the type 2 cytokine IL-5 [14]. In other study, He et al. found that nasal mucosa miR-142-3p expression was elevated in AR patients compared to that in controls; moreover, the area under curve (AUC) of individual miR-221 and miR-142-3p for AR were 0.622 and 0.762, respectively, but the expression of miR-142-3p was not related to TNSS [15].

In the present study, we showed that serum miR-142-3p levels were increased in patients with AR compared to healthy controls, though elevated miR-142-3p levels were not correlated with TNSS. This is consistent with the results of He et al., who studied the levels of miR-142-3p in AR nasal mucosa, while we studied its levels in the serum. Our results showed that serum miR-142-5p levels were not correlated with Th2 cytokine IL-4 levels, while a study by Maes et al. showed that upregulated miR-142-3p expression in the sputum supernatant samples of patients with severe asthma was not correlated with Th2 cytokine IL-5 — the two conclusions seem to be consistent. Furthermore, high miR-142-5p expression in the serum was positively associated with specific IgE levels in AR in this study, which shows that the levels of specific IgE might be regulated by miR-142-5p. As we did not locate any literature on the correlation between serum miR-142-5p of AR and specific IgE, its mechanism still needs further experimental study.

MiR-155 has been suggested to play a crucial modulatory role in the pathogenesis of various diseases, and is mainly involved in immune cell development and immune responses [16–18]. It is primarily responsible for the induction of inflammatory reactions and Th2 immune responses [19]. This study demonstrated that the expression of serum miR-155-5p was upregulated in children with AR, in accordance with the findings of previous studies. Zhu et al. demonstrated that miR-155 expression was upregulated in the nasal mucosa of patients with AR [20]. Similarly, Hammad et al. suggested that miR-155 was upregulated in children with

AR and was positively associated with TNSS, suggesting that miR-155 could be used as a biomarker for the diagnosis of AR [21]. The present study confirmed a negative correlation between miR-155-5p levels and age of children with AR. The literature on the relationship between serum miR-155-5p levels and age in patients with AR is scarce. It has been speculated that the immune system gradually matures with age in children; therefore, the expression levels of miR-155-5p, which may affect the pathogenesis of the disease, decreases. Our hypothesis needs to be verified through further experiments.

This study also showed that the expression level of miR-155-5p was positively correlated with that of IL-4, suggesting that the overexpression of miR-155-5p significantly promoted the level of IL-4 and might play an important role in activating the immune response mediated by Th2 cells that mainly secrete IL-4, thereby participating in the pathogenesis of AR. This is similar to the results of Zhu et al., who showed that upregulation of miR-155 could facilitate Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) in the nasal mucosa of AR mice [20]. There was also no correlation between serum miR-155 and IL-4 expression levels in AR patients in Hammad's study [21]. Our research shows a positive correlation between serum miR-155-5p and serum specific IgE (Artemisia) levels in children with AR, in concurrence with Suojalehto et al. who observed a weak positive correlation between miR-155 and IgE [22]. In the pathogenesis of AR, there exists a certain latent period after the allergen first contacts the nasal mucosa, during which the allergen impairs the barrier function of the nasal mucosa and promotes the synthesis of inflammatory factors through activation of proteases. At the same time, dendritic cells in the nasal mucosa ingest allergens, expose the effective antigenic determinants, and present them to naive helper T cells (Th0 cells) together with stimulation signals, which promote the differentiation of Th0 cells into Th2 cells. Th2 cells produce cytokines that play critical roles in subsequent inflammatory processes. For example, IL-4 and IL-13 can promote B cells to differentiate into plasma cells, which secrete immunoglobulins and promote the production of specific IgE. Accordingly, IL-4 is an important Th2 cytokine for IgE production [23]. Therefore, in this study, miR-155-5p might have promoted the expression of specific IgE by upregulating IL-4. In addition, it is possible that miR-155-5p affects the expression level of specific IgE through other Th2 cytokines or by acting on B cells. This conjecture must

be verified through further experiments in the future.

There were no significant differences in the serum miR-18a-5p and miR-3687 expression levels between the two groups in this study. Geng et al. found that there was no significant difference in the levels of miR-18a in peripheral B cells from AR patients and that from healthy participants [24]. This should be the first article to study the expression of miR-3687 in allergic rhinitis. The shortcoming of this paper is that the sample size is small, and Th1 cytokines have not been studied for some reasons. In order to further explore the mechanism of miRNAs, our subsequent studies will involve the experiment of miRNA expression in nasal mucosa.

5. Conclusions

In conclusion, we found that the expression of miR-142-5p and miR-155-5p was upregulated in the serum of children with AR, and propose that miR-155-5p may be involved in the regulation of Th2; however, the mechanisms underlying the high expression of miR-142-5p in AR remain unclear. The expression levels of serum miR-142-5p and miR-155-5p were insufficient as diagnostic tools for AR.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Previous meetings/presentations

None.

Declaration of conflicts of interest

The authors declare that there is no conflict of interest.

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