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ORIGINAL RESEARCH

The Correlation Between the Expression Levels of Serum miR-19b and SOCS-1 mRNA and Clinical Symptoms in Patients with Allergic Rhinitis

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Objective: To investigate the correlation between the expression levels of microRNA-19b (miR-19b) and suppressor of cytokine signaling 1 messenger RNA (SOCS-1 mRNA) in the serum of patients with allergic rhinitis (AR) and clinical symptoms.

Methods: This prospective study included a total of 86 patients with allergic rhinitis who were admitted to the People's Hospital Affiliated to Hubei University of Medicine from January 2022 to January 2023. Seventy healthy individuals were included in the control group. The case group was further divided into a mild group (n=45) and a moderate to severe group (n=41) according to the severity of AR. The expression levels of miR-19b and SOCS-1 mRNA in serum samples of the two groups were detected and compared using real-time fluorescence quantitative polymerase chain reaction (qRT-PCR) technique. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were utilized to evaluate the predictive value of miR-19b and SOCS-1 levels for the severity of AR.

Results: The expression level of miR-19b in the serum of the case group was 1.52±0.36, significantly higher than that of the control group (1.02±0.24, $P<0.05$). Logistic regression analysis indicated that low levels of serum miR-19b and SOCS-1 mRNA were independent risk factors for moderate to severe AR, with an odds ratio (OR) of 3.575 (95% CI: 1.572–8.133, $P<0.001$) for miR-19b and 3.725 (95% CI: 1.637–8.473, $P<0.001$) for SOCS-1 mRNA. ROC curve analysis demonstrated that the levels of serum miR-19b and SOCS-1 mRNA had high accuracy in predicting moderate to severe AR, with AUC values of 0.879 (95% CI: 0.791–0.940) and 0.795 (95% CI: 0.694–0.875), respectively. When combined for prediction, the efficacy was significantly higher than that of individual detection, with an AUC value of 0.923 (95% CI: 0.856–0.967), $Z=3.261$, $P<0.01$.

Conclusion: The expression levels of serum miR-19b and SOCS-1 mRNA are closely related to the severity of clinical symptoms in patients with AR and may serve as new biomarkers for evaluating the condition of AR and guiding treatment.

Keywords: allergic rhinitis, microRNA-19b, SOCS-1 mRNA, logistic regression

Introduction

Allergic Rhinitis (AR), as a common chronic airway inflammatory disease, has witnessed a significant increase in its incidence worldwide in recent years. Especially against the backdrop of intensified climate change and environmental pollution, this problem has become increasingly severe.[1] AR is mainly caused by IgE-mediated type I hypersensitivity reaction, involving the complex interaction of various immune cells and cytokines. Among them, the Th1/Th2 immune imbalance is widely regarded as one of the key mechanisms of its pathogenesis.[2] In recent years, with the in-depth study

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of immunology, the role of the Suppressor of Cytokine Signaling (SOCS) family in immune regulation has gradually received attention. Especially SOCS1, it plays an important role in a variety of inflammatory diseases and autoimmune diseases.[3]

SOCS1, as a key negative feedback regulator of the JAK/STAT signaling pathway, can affect the differentiation and function of immune cells by inhibiting the activity of JAK kinase and blocking the conduction of cytokine signals.[4] Previous studies have shown that the expression of SOCS1 is abnormal in airway inflammatory diseases such as asthma and is closely related to the severity of the disease.[5] In addition, microRNAs, as a type of non-coding RNA, play an important role in immune regulation and the occurrence and development of diseases by regulating the expression of target genes.[6] In a research, miR-19b could suppress the inflammatory response by inhibiting SOCS3 to modulate chemokine production in intestinal epithelial cells (IECs) and thereby prevents the pathogenesis of Crohn's disease.[7] Among them, microRNA-19b (miR-19b) has been reported to be upregulated in various inflammatory diseases and may be involved in the pathological process of the disease by regulating target genes.[8] There was an review emphasized the importance of miRNA function in allergy and asthma to improve the knowledge of the molecular involved in the pathogenesis of this heterogeneous group of diseases.[9]

SOCS1 is highly likely to be another important target of miR-19b in regulating the differentiation of CD4+ T cells into Th1/Th2.[10] Although the roles of SOCS1 and miR-19b in immune regulation have been preliminarily recognized, their specific mechanisms of action in allergic rhinitis and their correlations with clinical symptoms are not fully clear. In particular, whether miR-19b affects the pathogenesis of AR by regulating the expression of SOCS1, this scientific question urgently needs in-depth study. Therefore, this study aims to detect the expression levels of miR-19b and SOCS-1 mRNA in the serum of patients with allergic rhinitis and explore their correlations with the clinical symptoms of AR, providing a theoretical basis for revealing the pathogenesis of AR and finding new therapeutic targets.

Materials and Methods

Case Collection

Eighty-six patients with allergic rhinitis at the People's Hospital Affiliated to Hubei University of Medicine from January 2022 to January 2023 were included in this prospective study as the AR group, along with 70 healthy individuals who underwent physical examinations during the same period as the control group. Inclusion criteria: (1) Meeting the diagnostic criteria of AR;[11,12] (2) The patients are aged between 18 and 65 years old, regardless of gender; (3) The clinical medical records are complete, and there is no history of concealment; (4) Have normal comprehension and communication abilities, and can clearly express their symptoms; (5) Voluntarily sign the informed consent form and are willing to participate in this study. Exclusion criteria include: (1) Presence of other severe nasal diseases, such as nasal polyps, sinusitis, etc.; (2) Suffering from mental illness, with impaired cognitive function and unable to cooperate to complete the study; (3) Having recent (within 3 months) acute respiratory tract infection or being under antibiotic treatment; (4) Suffering from systemic diseases that may affect immune function, such as autoimmune diseases, malignant tumors, endocrine disorders, etc.; (5) Currently using drugs that may affect immune system function, such as corticosteroids, immunosuppressants, etc.; (6) Pregnant or lactating women, because of their special physiological status, which may affect the interpretation of the study results; (7) Having severe liver and kidney dysfunction, which may affect drug metabolism and clearance; (8) Having received allergen-specific immunotherapy or biologic agent treatment recently (within 1 month), which may interfere with the objectivity of the study results.

Classification of Severity: Based on clinical condition, the case group was further divided into mild and moderate to severe groups. The classification criteria for allergic rhinitis severity were based on the total nasal symptom scores (TNSS) and the impact on quality of life:[12,13]

- Mild AR: Patients with a TNSS of 5 or less, with minimal impact on daily activities and quality of life.
- Moderate to Severe AR: Patients with a TNSS greater than 5, indicating significant symptoms that interfere with daily activities and quality of life.

This study has been approved by the hospital ethics committee and follows the principles of the Helsinki Declaration. All participants signed the informed consent form before the operation.

Detection of Serum miR-19b and SOCS-1 mRNA

4 mL of peripheral blood samples were collected from the control group and the AR group at the time of admission. The samples were centrifuged at 3000 r/min for 15 minutes. The upper serum was taken and added to Trizol. The total RNA of the serum was extracted using the miR kit. The RNA concentration was detected by spectrophotometry. The reaction system was configured according to the instructions of the PCR kit (1 μL of each upstream and downstream primer, 5 μL of buffer, 2 μL of cDNA, 10 μL of SYBR, and pure water was added to 20 μL). Using total RNA as the template, cDNA was obtained according to the instructions of the reverse transcription kit. Then, using cDNA as the template, amplification was performed by referring to the instructions of the fluorescence quantitative PCR kit. The reaction steps were set as follows: 95°C for 30 seconds, 95°C for 5 seconds, 56°C for 20 seconds, and 72°C for 30 seconds, with 40 amplification cycles. The levels of miR-19b and SOCS-1 mRNA were calculated using the 2 -ΔΔCT method. U6 and β-actin were used as internal references. The primer sequences are shown in Table 1.

Detection of Serum Specific IgE

This detection was performed using the A188 kit provided by Medivis Analysis Co., Ltd. It contains 18 main components of inhalation equipment: ① Detection plate: A nitrocellulose membrane with 29 allergen lines and 1 positive indicator band (rabbit anti-goat IgG antibody) marked, placed in a plastic reaction tank; ② Eluent: TRIS/NaCl, containing 0.099% NaN3, which can be diluted into 1×500 mL of cleaning solution, pH = 7.5; ③ Detection antibody: Anti-human IgE antibody labeled with biotin, polyclonal, containing 0.099% NaN3; ④ Conjugate: Streptavidin linked with alkaline phosphatase, 0.02% C4H5NOS and 0.02% C4H6BrNO4; ⑤ Substrate: BCIP/NBT (5-bromo-4-chloro-3-indolyl phosphate / nitroblue tetrazolium chloride).

Statistical Methods

All data were analyzed using SPSS 26.0 statistical software. Measurement data were expressed as mean ± standard deviation, and count data were expressed as the number of cases (n) and percentage (%). Data integrity was confirmed with no missing values. Outliers were identified using boxplots and scatter plots and manually verified against clinical context. No extreme values were excluded. First, the Shapiro–Wilk test was used to test the normal distribution of the data. For measurement data that conformed to a normal distribution, independent sample *t*-tests were used to compare the differences between the two groups; for data that did not conform to a normal distribution, the Mann–Whitney *U*-test was used. The chi-square test was used to compare categorical data. Spearman's rank correlation analysis was used to analyze the correlation between serum miR-19b and SOCS-1 mRNA levels and the severity of AR. To explore the factors influencing the severity of AR being moderate to severe, multivariate Logistic regression analysis was used. Finally, to evaluate the predictive value of serum miR-19b and SOCS-1 mRNA levels for moderate to severe AR, Receiver Operating Characteristic Curve (ROC) analysis was used to calculate the Area Under the Curve (AUC) and its 95% Confidence Interval (CI). All tests were two-sided tests, and $P < 0.05$ was considered statistically significant.

Table 1 qRT-PCR Primer Sequences

Gene	Upstream Primer	Downstream Primer	Fragment Length
miR-19b	5′-TAATAGTACCGATCTGACTAC	5′-GTATCATAGCCGAACAAGTAC	21bp
SOCS-1	5′-GCTCCTTCCCCTTCCAGATTT-3′	5′-AGAGGTAGGAGGTGCGAGTTCAG	304bp
IR	5′-GAAATCGTGCGTGACATTAAGGA-3′	5′-CGGATGTCCACGTCACACTTC-3′	105bp

Abbreviation: IR, internal reference.

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Results

General Situation of Patients

In the AR group, there were 47 males and 39 females, aged 18–65 (47.59 ± 0.56) years old. Among them, 51 cases were seasonal and 35 cases were perennial. In the control group, there were 36 males and 34 females, aged 18–60 (43.62 ± 0.48) years old. Among the 86 AR patients, 45 cases were mild and 41 cases were moderate to severe. There were statistically significant differences in gender, age, course of disease, age of onset, educational level, history of asthma, history of food allergy, history of allergic dermatitis, indoor decoration within 5 years, keeping small animals indoors, keeping flowers and plants indoors, family history of AR, exposure to dust, and sIgE/(IU/mL) levels between the two groups of AR patients ($P < 0.05$); The levels of serum miR-19b-3p and SOCS-1 mRNA in the moderate to severe group were higher than those in the mild group, and the differences were statistically significant ($P < 0.05$), as shown in Table 2.

Table 2 Comparison of Clinical Data of AR Patients with Different Disease Severity

Variables	Mild Group (n=45)	Moderate and Severe Group (n=41)	t/χ^2	*P*
Gender			0.047	0.829
Male	23(51.11)	20(48.78)		
Female	22(48.89)	21(51.22)		
Age			2.102	0.147
≥60 years	33(73.33)	24(58.54)		
<60 years	12(26.67)	17(41.46)		
Duration of Illness (years)	1.33±0.26	1.45±0.30	2.088	0.039
Age of Onset (years)	57.86±8.15	59.33±7.86	0.879	0.382
Education Level			1.006	0.605
College degree or above	17(37.78)	13(31.71)		
High school and junior high school	18(40.00)	16(39.02)		
Below junior high school	10(22.22)	12(29.27)		
History of Asthma			1.766	0.184
Yes	24(53.33)	16(39.02)		
No	21(46.47)	25(60.98)		
History of Food Allergy			0.031	0.860
Yes	20(44.44)	19(46.34)		
No	25(55.56)	22(53.66)		
History of Atopic Dermatitis			0.447	0.504
Yes	22(48.89)	23(56.10)		
No	23(51.11)	18(43.90)		
Indoor Renovation within 5 Years			1.021	0.312
Yes	8(17.78)	11(26.83)		
No	37(82.22)	30(73.17)		
Indoor Pet Ownership			4.620	0.032
Yes	17(37.78)	25(60.98)		
No	28(62.22)	16(39.02)		
Indoor Plant Ownership			0.240	0.624
Yes	9(20.00)	10(24.39)		
No	36(80.00)	31(75.61)		
Family History of AR				
Yes	2.36±0.68	2.61±0.81	1.639	0.105
No	1.33±0.37	1.35±0.41	0.243	0.808
sIgE/(IU/mL)	1.31±0.28	1.97±0.34	1.104	0.272
miR-19b	1.46±0.32	1.68±0.24	0.903	0.369
SOCS-1mRNA	1.35±0.38	1.62±0.26	7.416	<0.001

Notes: Univariate analysis identified age, gender, and IgE levels as borderline correlates of AR severity ($P < 0.1$), but they were not included in the multivariate model.
Abbreviation: AR, allergic rhinitis.

Comparison of Expression Levels of Serum miR-19b and SOCS-1 mRNA

The level of miR-19b in AR was higher than that in the control group, and the level of SOCS-1 mRNA was also higher than that in the control group, $P < 0.05$. See Table 3.

Expression Levels of miR-19b and SOCS-1 mRNA in Different Disease Severity Levels

The miR-19b level in moderate to severe patients was higher than that in mild patients, and the SOCS-1 mRNA level was also higher than that in mild patients, $P < 0.05$. See Table 4.

Multivariate Logistic Regression Analysis of Factors Influencing the Severity of the Disease

Logistic regression analysis showed that low levels of serum miR-19b and SOCS-1 mRNA were independent risk factors influencing the severity of AR ($P < 0.05$), as shown in Table 5.

Correlation Analysis of miR-19b, SOCS-1 and the Severity of Allergic Rhinitis

Spearman correlation analysis showed that the levels of serum miR-19b and SOCS-1 mRNA in AR patients were positively correlated with the severity of AR ($r = 0.610$, $P < 0.05$), (Figure 1).

The Predictive Value of Serum miR-19b and SOCS-1 mRNA Levels for the Severity of AR

The results of ROC analysis showed that the AUC values (95% CI) of serum miR-19b, SOCS-1 mRNA levels and the combination of the two for evaluating the severity of AR were 0.879 (95% CI: 0.791–0.940), 0.795 (95% CI: 0.694–0.875), and 0.92 (95% CI: 0.851–0.963), respectively. Optimal cutoff values were determined as 1.28 for miR-

Table 3 Comparison of the Expression Levels of miR-19b and SOCS-1 mRNA in the Two Groups

Variables	Control Group (n=70)	AR Group (n=86)	P value
miR-19b/U6	1.02 ± 0.24	1.52 ± 0.36	< 0.05
SOCS-1mRNA/β-actin	1.00 ± 0.22	1.42 ± 0.38	< 0.05

Abbreviation: AR, allergic rhinitis.

Table 4 Comparison of the Expression Levels of Serum miR-19b and SOCS-1 mRNA in Different Disease Severities

Variables	Mild Group (n=45)	Moderate and Severe Group (n=41)	P value
miR-19b/U6	1.46 ± 0.32	1.68 ± 0.24	< 0.05
SOCS-1mRNA/β-actin	1.35 ± 0.38	1.62 ± 0.26	< 0.05

Table 5 Multivariate Logistic Regression of the Disease Severity of AR Patients

Variables	OR	95% CI	*P*
Duration of Illness	0.951	0.549 ~ 1.629	0.059
Family History of AR	0.795	0.446 ~ 1.507	0.102
miR-19b	3.575	1.572 ~ 8.133	<0.001
SOCS-1mRNA	3.725	1.637 ~ 8.473	<0.001

Notes: Univariate analysis identified age, gender, and IgE levels as borderline correlates of AR severity ($P < 0.1$), but they were not included in the multivariate model.
Abbreviations: OR, odds ratio; CI, confidence interval.

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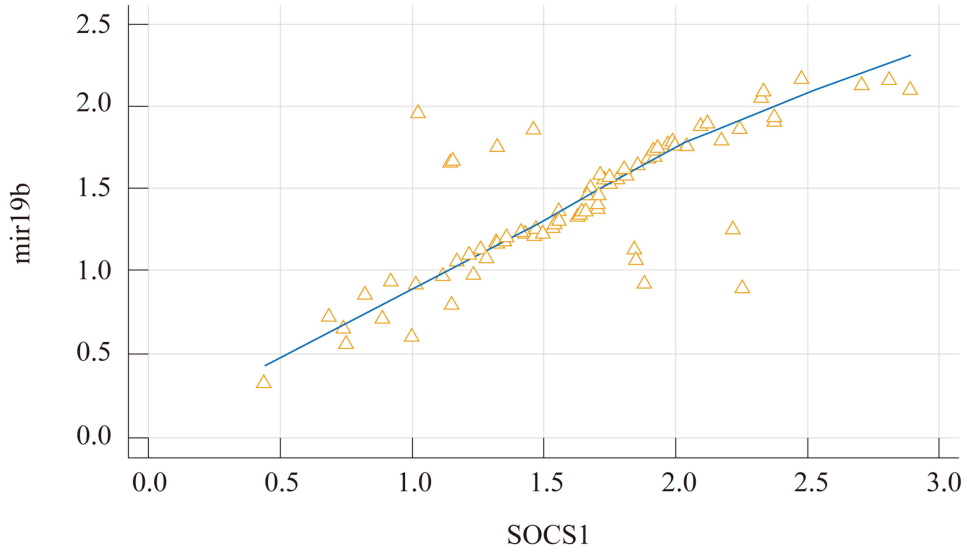

Figure 1 Correlation between serum miR-19b and SOCS-1 levels. Spearman correlation analysis showed that the levels of serum miR-19b and SOCS-1 mRNA in AR patients were positively correlated with the severity of AR.

19b (sensitivity: 81.5%, specificity: 82.2%) and 1.35 for SOCS-1 mRNA (sensitivity: 75.6%, specificity: 78.9%). The combined predictive efficacy was higher than that of each individual test ($Z = 3.261$, $P < 0.01$), as shown in Table 6 and Figure 2.

Discussion

In this study, by detecting the expression levels of serum miR-19b and SOCS-1 mRNA in AR patients, it was found that the expression levels of these biomarkers were positively correlated with the severity of AR. Spearman correlation analysis showed that the correlation coefficients of serum miR-19b and SOCS-1 mRNA levels with the severity of AR were 0.610 ($P < 0.05$), respectively, indicating that these biomarkers have potential application value in evaluating the severity of AR. ROC curve analysis further confirmed that the AUC values of serum miR-19b and SOCS-1 mRNA levels and their combined evaluation of the severity of AR were 0.879 (95% CI: 0.791–0.940), 0.795 (95% CI: 0.694–0.875), and 0.92 (95% CI: 0.851–0.963), suggesting that the combined application of the two has higher predictive efficacy.

The immune imbalance of Th1/Th2 is regarded as an important pathogenesis of AR.[14,15] Both Th1 and Th2 cells are differentiated from CD4+ T cells and are regulated by cytokines in the microenvironment.[16] When allergens enter the nasal cavity and trigger the IgE-mediated type I hypersensitivity reaction, a large number of immune cells are activated and release various cytokines, such as IL-4, IL-5 and IL-13.[17] These cytokines transmit signals through the JAK/STAT signaling pathway, inducing the proliferation, differentiation and functional activation of immune cells.[18,19] However, as the inflammatory reaction persists and intensifies, the expression level of SOCS-1, as a negative feedback regulator, will also be upregulated accordingly, attempting to inhibit the excessive immune response.[20] SOCS1 inhibits the

Table 6 The Predictive Value of Serum miR-19b and SOCS-1 mRNA Levels for the Severity of AR

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)	*P*	Cutoff Value
miR-19b	0.879	0.791–0.940	85.4	80.0	<0.001	1.28
SOCS-1	0.795	0.694–0.875	70.7	80.0	<0.001	1.35
miR-19b combined with SOCS-1	0.925	0.848–0.971	87.8	84.4	<0.001	

Abbreviation: AR, allergic rhinitis.

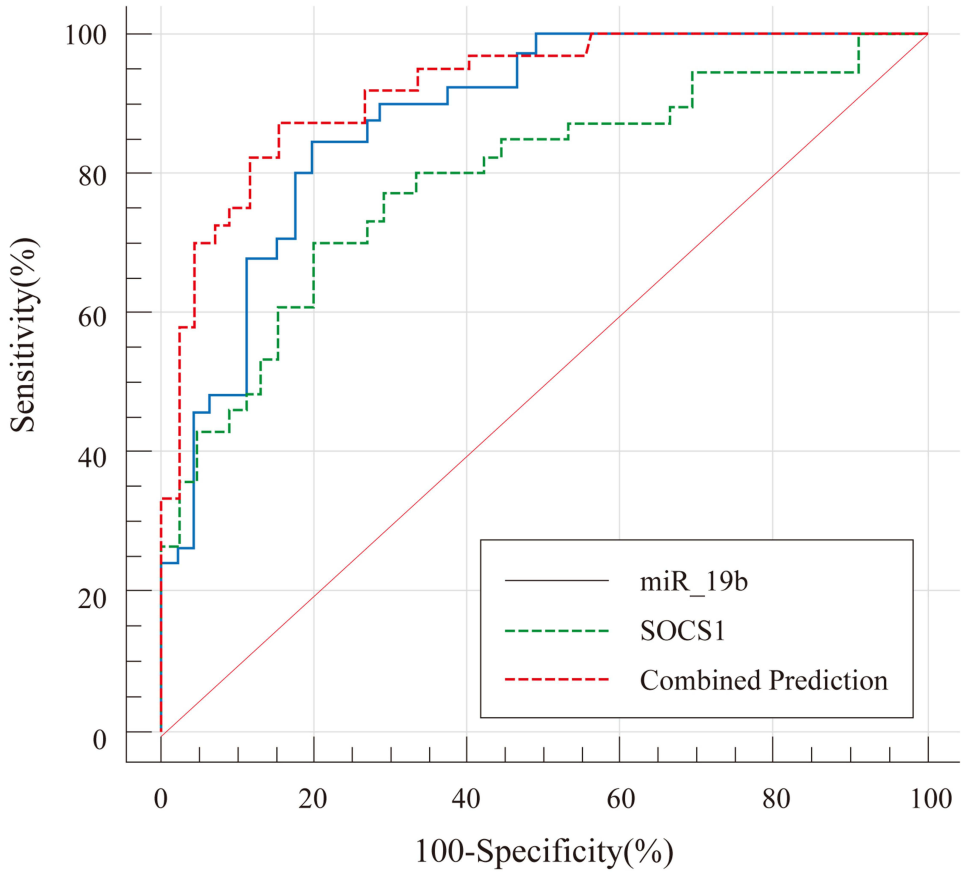

Figure 2 ROC curves of serum miR-19b and SOCS-1 levels for predicting moderate to severe AR. The results of ROC analysis showed that the AUC values (95% CI) of serum miR-19b, SOCS-1 mRNA levels and the combination of the two for evaluating the severity of AR were 0.879 (95% CI: 0.791–0.940), 0.795 (95% CI: 0.694–0.875), and 0.92 (95% CI: 0.851–0.963), respectively.

differentiation of Th2 cells under IL-4 induction by inhibiting the activation of STAT6. And T cells lacking SOCS1 can also promote the stable production of IFN-γ in the absence of specific stimulation. IFN-γ has the effect of promoting the differentiation of Th1 cells and inhibiting the response of Th2 cells.[21] The results of this study indicate that the high expression of serum miR-19b and SOCS-1 mRNA may affect the pathogenesis and development of AR by regulating the Th1/Th2 balance.

The miR-19b, as a kind of microRNA, plays an important role in immune regulation. Existing studies have shown that the expression level of miR-19b is significantly upregulated in patients with asthma and may play a role through the activation of 5-lipoxygenase (5-LO) and the subsequent inflammatory cytokine mechanism.[22] Furthermore, Karam and Abd Elrahman stated that miR-155 could help in asthma diagnosis, disease severity prediction, and the likelihood of response to therapy.[23] This study further confirmed the high expression of miR-19b in AR patients, suggesting that it may play a key role in the pathogenesis of AR. SOCS1, as a cytokine signal inhibitor, participates in regulating various immune responses by inhibiting the activation of the JAK/STAT signaling pathway.[24] The binding of SOCS to the corresponding receptor can activate the related signaling pathway, transfer the signal of cytokines from the cell membrane to the cytoplasm and finally into the nucleus, thereby causing the expression of the target gene.[25] This study found that the level of SOCS-1 mRNA in the serum of AR patients was significantly increased and positively correlated with the severity of the disease, indicating that SOCS1 plays an important role in the immune regulation of AR. Therefore, the study could benefit from more detailed speculation on therapeutic angles, such as whether targeting miR-19b or modulating SOCS-1 expression might be a future direction for AR interventions.

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Limitation

Although this study has achieved certain results, there are still some limitations. First of all, this study is a cross-sectional study, and it is impossible to determine the causal relationship between the expression levels of miR-19b and SOCS-1 mRNA and the severity of AR. In the future, longitudinal studies can be conducted to further verify the predictive value of these biomarkers. Secondly, the sample size is relatively small, which may affect the universality of the results. In the future, the sample size can be expanded and multi-center studies can be conducted to improve the external validity of the study. In addition, this study only detected the expression levels of serum miR-19b and SOCS-1 mRNA, and did not involve the detection of other related biomarkers. In the future, multiple biomarkers can be combined to construct a more comprehensive AR diagnosis and prognosis model. Finally, future studies should incorporate ELISA and Western blot to validate SOCS-1 protein expression and its correlation with mRNA levels.

Conclusion

This study found that the expression levels of serum miR-19b and SOCS-1 mRNA were closely related to the severity of clinical symptoms in AR patients, and they may become new biomarkers for evaluating the condition of AR and guiding treatment. Further studies are needed in the future to verify the clinical application value of these biomarkers and to deeply explore their role in the pathogenesis of AR.

Abbreviations

5-LO, 5-Lipoxygenase; AR, Allergic Rhinitis; AUC, Area Under the Curve; CI, Confidence Interval; miR-19b, MicroRNA-19b; OR, Odds Ratio; qRT-PCR, Real-Time Fluorescence Quantitative Polymerase Chain Reaction; ROC, Receiver Operating Characteristic; SOCS, Suppressor of Cytokine Signaling; SOCS-1 mRNA, Suppressor of Cytokine Signaling 1 Messenger RNA; TNSS, Total Nasal Symptom Scores.

Data Sharing Statement

The data and materials used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study protocol was in accordance with the Declaration of Helsinki of the World Medical Association. This study was approved by the Ethical Research Committee of Renmin Hospital, Hubei University of Medicine. All participants signed the informed consent form before the operation.

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Disclosure

The authors declare no competing interests.

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