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Original Article

Screening and analysis for potential clinical diagnostic and prognostic markers in allergic rhinitis

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Abstract: Purpose: To identify potential clinical diagnostic and prognostic markers for allergic rhinitis (AR) by analyzing a range of inflammatory and clinical markers in a cohort of patients. Methods: We conducted a retrospective analysis of clinical data from 493 AR patients treated at Qianjiang Central Hospital from January to March 2023. Patients were categorized based on their outcome. Inclusion and exclusion criteria were strictly applied to select the study population. Various clinical and inflammatory markers were assessed, and statistical analyses were performed to evaluate their diagnostic and prognostic utility. Results: No significant differences in traditional demographic factors were found between the good and poor prognosis groups (all $P > 0.05$). However, significant differences were observed in several inflammatory and clinical markers: Interleukin-4 (IL-4) levels were 17.32 ± 4.21 pg/mL in the good prognosis group versus 18.56 ± 5.89 pg/mL in the poor prognosis group ($t=2.562$, $P=0.011$). Interleukin-5 (IL-5) levels were 15.65 ± 3.78 pg/mL versus 16.52 ± 4.56 pg/mL, respectively ($t=2.221$, $P=0.027$). Transforming growth factor-β1 (TGF-β1) levels were 39.16 ± 8.92 pg/mL versus 41.32 ± 9.67 pg/mL ($t=2.513$, $P=0.012$), and histamine levels were 11.87 ± 3.21 ng/mL versus 12.56 ± 4.03 ng/mL ($t=1.991$, $P=0.047$). Interleukin-13 (IL-13) levels were 16.32 ± 3.56 pg/mL versus 17.09 ± 4.21 pg/mL ($t=2.108$, $P=0.036$). Serum immunoglobulin E (IgE) levels were significantly different, with 164.87 ± 45.32 IU/mL in the good prognosis group compared to 198.56 ± 58.21 IU/mL in the poor prognosis group ($t=6.866$, $P < 0.001$). The composite biomarker model demonstrated high predictive value for AR prognosis with an Area Under Curve of 0.906. Individual markers such as TGF-β1, IL-13, and serum IgE levels showed strong diagnostic potential. Conclusion: Our findings underscore the clinical utility of various inflammatory and clinical markers as diagnostic and prognostic indicators for AR. TGF-β1, IL-13, and serum IgE levels, in particular, demonstrated significant diagnostic and prognostic value. An integrated approach combining multiple biomarkers could enhance the accuracy of AR diagnosis and prognosis. Further validation through prospective clinical studies and consideration of treatment interventions are recommended to clarify the clinical implications of these markers.

Keywords: Screening, analysis, clinical diagnostics, prognostic progress markers, allergic rhinitis

Introduction

Allergic rhinitis (AR) is a prevalent chronic respiratory disorder characterized by nasal inflammation upon exposure to allergens [1-3]. It affects a significant portion of the global population and imposes a substantial burden on healthcare systems and patient quality of life [4-6]. Traditionally, the clinical diagnosis of AR has relied on symptom assessment and allergen-specific testing. However, there is increasing interest in identifying reliable clinical diagnostic and prognostic markers to enhance the accuracy of AR diagnosis and prognosis.

The pathophysiology of AR involves a complex interplay of inflammatory mediators, immune responses, and clinical manifestations. This complexity underscores the importance of exploring a broad range of candidate biomarkers for their diagnostic and prognostic value [7, 8]. With advancements in biomarker detection methods and analytical techniques, there is now an opportunity to identify biomarkers that

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could serve as valuable indicators of AR diagnosis and prognosis.

This study aimed to elucidate potential clinical diagnostic and prognostic markers for AR through comprehensive analysis of inflammatory and clinical markers in a cohort of AR patients. By retrospectively analyzing clinical data from a substantial cohort and integrating various biomarkers, this research seeks to provide insight into the relevance of these specific markers in AR.

Materials and methods

Subjects

This study involved a retrospective analysis of clinical data from 493 patients with AR admitted to Qianjiang Central Hospital between January 2023 and March 2023. Patients were categorized into good prognosis (n=295) and poor prognosis (n=198) groups based on their outcome. To assess the predictive role of biomarkers in AR, the study also included 493 health examination records from the same period at the medical examination center, matched in a 1:1 ratio as a control group.

The Qianjiang Central Hospital Institutional Review Board and Ethics Committee approved this study. Informed consent was waived due to the exclusive use of de-identified patient data, which posed no potential harm or impact on patient care.

Inclusion and exclusion criteria

AR patients: Inclusion criteria: Patients diagnosed with rhinitis according to the "Diagnosis and Treatment Guidelines for AR" [9]. Patients with positive results on skin prick tests and serum-specific immunoglobulin E (IgE) tests. Patients with normal mental and cognitive function. Patients with complete clinical data.

Exclusion criteria: Individuals with concurrent bronchial asthma or other respiratory diseases. Those with a history of nasal surgery or nasal anatomical abnormalities. Individuals with a history of long-term use of analgesic drugs. Those with insufficient white blood cell counts or coagulation disorders.

Healthy individuals: Inclusion criteria: Individuals with unobstructed nasal breathing and moist, smooth nasal mucosa. Those with normal olfactory function and unobstructed airflow in the olfactory area.

Exclusion criteria: Individuals with nasal swelling, congestion, bleeding, or other abnormal nasal conditions. Those with noticeable nasal cartilage deformities or significant deviation of the nasal septum. Individuals experiencing symptoms such as loss of appetite, easy fatigue, or decreased memory function.

Grouping methods

Patients were categorized into the good prognosis group (n=295) and the poor prognosis group (n=198) based on differing outcomes of AR. A favorable prognosis indicates patient recovery or successful treatment, while an unfavorable prognosis suggests treatment inefficacy. Clinical efficacy was assessed based on changes in patient symptoms post-treatment. A "cure" was defined as the disappearance of clinical symptoms such as nasal congestion, runny nose, and sneezing, along with a reduction in nasal turbinate swelling. "Effective" denoted an improvement in clinical symptoms following treatment, while "ineffective" indicated no improvement in clinical symptoms. Patients were further divided into effective and ineffective groups based on their nasal symptom scores during a one-month follow-up visit. The symptom score was calculated using the following formula: Symptom Score = (pre-treatment symptom score - post-treatment symptom score)/pre-treatment symptom score × 100%. Patients with a symptom score > 66% were included in the effective group, while those with a symptom score < 25% were classified into the ineffective group [10].

To assess the predictive role of biomarkers for the clinical diagnosis of AR, the study included 493 health examination records from the same period at the medical examination center, matched in a 1:1 ratio as a control group.

Treatment method

Patients were treated with the following regimen: symptomatic medication included loratadine (Hebei Yuansen Pharmaceutical Co., Ltd.) - for patients weighing > 30 kg, 10 mg per dose, orally, once daily; for patients weighing ≤ 30 kg, 5 mg per dose, orally, once daily.

Budesonide nasal spray (McNeil Sweden ABH) was administered as 64 μg per nostril, twice daily. Additionally, standardized house dust mites sublingual immunotherapy (SLIT) was conducted using Changdi (Zhejiang Wumei Biotechnology Co., Ltd.). This involved sublingual administration of Changdi No. 1 (1 μg/ml, 1-7 drops for the first 1-4 weeks), No. 2 (10 μg/ml, same as No. 1), No. 3 (100 μg/ml, same as No. 1), and No. 4 (333 μg/ml, 3 drops per dose) once daily, typically in the morning. Patients were instructed to refrain from eating for 30 minutes after medication administration, with the treatment duration set at one month.

Outcome measures

Serum inflammatory factor detection: Five milliliters of fasting venous blood were collected from patients early in the morning and allowed to stand at room temperature for 30 minutes. The serum was then separated by centrifugation at 3000 rpm for 10 minutes using a high-speed, low-temperature centrifuge, and stored at -80°C until analysis. The levels of several cytokines and mediators were determined using enzyme-linked immunosorbent assay kits: Interleukin-13 (IL-13) (ab288591, Abcam, USA), Interleukin-4 (IL-4) (ab215089, Abcam, USA), Interleukin-5 (IL-5) (ab216795, Abcam, USA), Interferon-γ (IFN-γ) (ab174443, Abcam, USA), transforming growth factor-β1 (TGF-β1) (ab100647, Abcam, USA), histamine (ab213-975, Abcam, USA), Leukotriene C4 (1234-00-00, eBioscience, USA), and Prostaglandin D2 (D751029, Sangon Biotech, China) [11, 12].

Clinical marker detection: IgE: Five milliliters of antebrachium venous blood were collected from all patients and left at 37°C for 2 hours, then centrifuged at 3500 rpm for 30 minutes (radius r=30 cm) to obtain the supernatant. The concentration of serum immunoglobulin E (IgE) was measured using an enzyme-linked immunosorbent assay kit (Model EV 3840-9601, Shenzhen Xinbosheng Biotechnology Co., Ltd., registration number 20163404546).

Immunoglobulin: A 3 mL sample of fasting venous blood was collected from the patients, allowed to stand, and then centrifuged at 3000 rpm for 20 minutes (radius r=3 cm). The serum was stored at -70°C. Immunoglobulin levels were determined using the AU5800 fully automated biochemical analyzer (Beckman Coulter, USA) [13].

Serum Albumin and Total Protein: A 3 mL sample of fasting venous blood was collected and centrifuged at 2000 rpm for 15 minutes (radius r=3 cm). The supernatant was transferred to an Eppendrf tube, and the levels of serum albumin and total protein were measured using a fully automatic analyzer (SEAC, Italy).

Erythrocyte sedimentation rate (ESR): The ESR was measured using whole blood anticoagulated with ethylenediaminetetraacetic acid and assessed with a fully automatic erythrocyte sedimentation rate analyzer (TEST-1, ALIFAX, Italy).

Nasal symptom scoring: Patients underwent an evaluation of nasal symptoms using the Otolaryngology examination scoring system. This system employs a graded scale from 0 to 10, where 0 indicates no abnormalities and 10 indicates severe abnormalities. The nasal examination assessed the nasal cavity, nasal septum, nasal sinuses, and related areas, focusing on symptoms such as nasal congestion, increased secretion, and nasopharyngeal congestion. Physicians assigned scores to each item based on the patient's symptoms and examination results according to the criteria on the scoring sheet. These individual scores were then aggregated to derive an overall nasal health score. The reliability of this scoring system is documented at 0.870 [14].

Pulmonary function testing: Pulmonary function testing was conducted using the Sensormedics 2200 pulmonary function instrument (USA). Patients were advised to avoid vigorous exercise for two hours and to sit calmly for 15 minutes prior to the test to stabilize their breathing. The assessment included measurements of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, peak expiratory flow rate, and peak expiratory flow level. This preparation ensured the accuracy and reliability of the pulmonary function readings.

Data collection

Patient data were extracted from the medical record system, encompassing general charac-

Table 1. Demographic and clinical characteristics of the study population

Data	Good prognosis (n=295)	Poor prognosis (n=198)	t	*P* value
Age (years)	37.76 ± 7.89	38.21 ± 8.56	0.587	0.557
Gender (M/F)	142/153	92/106	0.074	0.785
Duration of symptoms (months)	31.14 ± 9.67	32.05 ± 10.22	0.992	0.322
Smoking history	85 (28.81%)	53 (26.77%)	0.155	0.694
Drinking history	103 (34.92%)	65 (32.83%)	0.146	0.702
Hypertension [n (%)]	56 (18.98%)	32 (16.16%)	0.465	0.495
Diabetes [n (%)]	52 (17.63%)	36 (18.18%)	0.001	0.970
Hyperlipidemia [n (%)]	38 (12.88%)	24 (12.12%)	0.012	0.912
Family history of allergic rhinitis	127 (43.05%)	81 (40.91%)	0.144	0.705
Comorbidities				
Asthma	78 (26.44%)	65 (32.83%)	2.048	0.152
Atopic dermatitis	39 (13.22%)	31 (15.66%)	0.395	0.530
Chronic sinusitis	52 (17.63%)	45 (22.73%)	1.641	0.200
Previous nasal surgery	35 (11.86%)	29 (14.65%)	0.584	0.445

teristics at initial hospital admission, such as age, gender, duration of symptoms, smoking history, alcohol consumption history, hypertension, diabetes, hyperlipidemia, family history of allergic rhinitis (AR), and comorbidities. Additionally, inflammatory markers specific to AR (IL-4, IL-5, IFN-γ, TGF-β1, histamine, leukotriene C4, prostaglandin D2, IL-13) and clinical markers (serum IgE, serum albumin, total protein, ESR, nasal symptom score, FEV1, FVC, FEV1/FVC ratio, peak expiratory flow rate, peak nasal inspiratory flow, forced expiratory flow 25-75%) were collected. These same values were also assessed one month post-treatment to predict patient outcomes. All data were consistently collected by an experienced physician.

Statistical analysis

Data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). For categorical data, representation was by [n (%)] format. The chi-square test was employed when the sample size was ≥ 40 and the expected frequency was ≥ 5, denoted by χ^2. For sample sizes ≥ 40 with expected frequencies between 1 and 5, the chi-square test was adjusted using a correction formula. In cases where the sample size was < 40 or the expected frequency was < 1, Fisher's exact probability method was used. Continuous data that followed a normal distribution were presented as (mean ± SD). Non-normally distributed data were analyzed using the Wilcoxon rank-sum test, and Spearman correlation analysis was used for correlational studies. A Gradient Boosting Machine model was constructed to predict the prognosis of AR using the assembled biomarkers. A *P*-value < 0.05 was considered significant. Receiver operating characteristic (ROC) curves were generated using the pROC package in R software (version 4.1.2).

Results

Demographic and clinical characteristics

The analysis of demographic and clinical characteristics revealed no significant differences between the good prognosis and poor prognosis groups across various measures (**Table 1**). These included age (37.76 ± 7.89 years vs. 38.21 ± 8.56 years; t=0.587, P=0.557), gender distribution (M/F: 142/153 vs. 92/106; t=0.074, P=0.785), duration of symptoms (31.14 ± 9.67 months vs. 32.05 ± 10.22 months; t=0.992, P=0.322), smoking history (28.81% vs. 26.77%; t=0.155, P=0.694), alcohol consumption history (34.92% vs. 32.83%; t=0.146, P=0.702), hypertension (18.98% vs. 16.16%; t=0.465, P=0.495), diabetes (17.63% vs. 18.18%; t=0.001, P=0.970), hyperlipidemia (12.88% vs. 12.12%; t=0.012, P=0.912), family history of AR (43.05% vs. 40.91%; t=0.144, P=0.705), and comorbidities such as asthma (26.44% vs. 32.83%; t=2.048, P=0.152), atopic dermatitis (13.22% vs. 15.66%; t=0.395, P=0.530), chronic sinusitis (17.63% vs. 22.73%; t=1.641, P=0.200), and previous

Table 2. Total nasal symptom score (baseline)

	Good prognosis (n=295)	Poor prognosis (n=198)	t	P
Total nasal symptom score				
2	15 (5.08%)	10 (5.05%)	5.551	0.352
3	49 (16.61%)	41 (20.71%)		
4	168 (56.95%)	120 (60.61%)		
5	36 (12.2%)	16 (8.08%)		
6	24 (8.14%)	9 (4.55%)		
7	3 (1.02%)	2 (1.01%)		

Table 3. Comparison of inflammatory mediators in AR between the two groups

Value	Good prognosis (n=295)	Poor prognosis (n=198)	t	*P* value
IL-4 level (pg/mL)	17.32 ± 4.21	18.56 ± 5.89	2.562	0.011
IL-5 level (pg/mL)	15.65 ± 3.78	16.52 ± 4.56	2.221	0.027
IFN-γ level (pg/mL)	24.17 ± 5.32	25.43 ± 7.01	2.154	0.032
TGF-β1 level (pg/mL)	39.16 ± 8.92	41.32 ± 9.67	2.513	0.012
Histamine level (ng/mL)	11.87 ± 3.21	12.56 ± 4.03	1.991	0.047
Leukotriene C4 (pg/mL)	20.76 ± 6.32	22.45 ± 7.89	2.514	0.012
Prostaglandin D2 (ng/mL)	7.53 ± 1.89	7.98 ± 2.21	2.315	0.021
IL-13 level (pg/mL)	16.32 ± 3.56	17.09 ± 4.21	2.108	0.036

IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; AR, allergic rhinitis.

nasal surgery (11.86% vs. 14.65%; t=0.584, P=0.445).

Total nasal symptom score (baseline)

Analysis of the total nasal symptom scores at baseline between the good prognosis and poor prognosis groups showed no significant differences (**Table 2**). The distribution of nasal symptom scores was similar across both groups, with scores of 2, 3, 4, 5, 6, and 7 occurring in 5.08% vs. 5.05%, 16.61% vs. 20.71%, 56.95% vs. 60.61%, 12.2% vs. 8.08%, 8.14% vs. 4.55%, and 1.02% vs. 1.01% of patients respectively (t=5.551, P=0.352).

Inflammatory mediators in AR

Significant differences were observed in the levels of inflammatory mediators between the good prognosis and poor prognosis groups, suggesting their association with the prognosis of AR. Specifically, the levels of IL-4 were 17.32 ± 4.21 pg/mL in the good prognosis group compared to 18.56 ± 5.89 pg/mL in the poor prognosis group (t=2.562, P=0.011). IL-5 levels were 15.65 ± 3.78 pg/mL versus 16.52 ± 4.56 pg/mL (t=2.221, P=0.027), IFN-γ levels were 24.17 ± 5.32 pg/mL versus 25.43 ± 7.01 pg/mL (t=2.154, P=0.032), and TGF-β1 levels were 39.16 ± 8.92 pg/mL versus 41.32 ± 9.67 pg/mL (t=2.513, P=0.012). Histamine levels were 11.87 ± 3.21 ng/mL versus 12.56 ± 4.03 ng/mL (t=1.991, P=0.047), leukotriene C4 levels were 20.76 ± 6.32 pg/mL versus 22.45 ± 7.89 pg/mL (t=2.514, P=0.012), prostaglandin D2 levels were 7.53 ± 1.89 ng/mL versus 7.98 ± 2.21 ng/mL (t=2.315, P=0.021), and IL-13 levels were 16.32 ± 3.56 pg/mL versus 17.09 ± 4.21 pg/mL (t=2.108, P=0.036) (**Table 3**).

Clinical markers for AR

The analysis of clinical markers also revealed significant differences between the good prognosis and poor prognosis groups, highlighting their relevance in predicting the prognosis of AR. Significant differences were noted in serum IgE levels (164.87 ± 45.32 IU/mL vs. 198.56 ± 58.21 IU/mL; t=6.866, P < 0.001), serum albumin (4.43 ± 0.35 g/dL vs. 4.31 ± 0.25 g/dL; t=4.289, P < 0.001), total protein (7.54 ± 0.58 g/dL vs. 7.35 ± 0.47 g/dL; t=4.016, P < 0.001), ESR (17.55 ± 2.14 mm/hour vs. 18.26 ± 3.46 mm/hour; t=2.568, P=0.011), eosinophil count (290.35 ± 68.92

Table 4. Comparison of clinical markers for AR between the two groups

Values	Good prognosis (n=295)	Poor prognosis (n=198)	t	*P* value
Serum IgE level (IU/mL)	164.87 ± 45.32	198.56 ± 58.21	6.866	P < 0.001
Serum Albumin (g/dL)	4.43 ± 0.35	4.31 ± 0.25	4.289	P < 0.001
Total Protein (g/dL)	7.54 ± 0.58	7.35 ± 0.47	4.016	P < 0.001
ESR (mm/hour)	17.55 ± 2.14	18.26 ± 3.46	2.568	0.011
Eosinophil count (cells/μL)	290.35 ± 68.92	320.76 ± 75.21	4.55	P < 0.001
Nasal cytology score	2.98 ± 0.67	3.22 ± 0.81	3.49	P < 0.001
Total nasal symptom score	7.16 ± 1.32	7.89 ± 1.67	5.125	P < 0.001
FEV1 (L)	2.95 ± 0.45	2.88 ± 0.51	1.428	0.154
FVC (L)	3.25 ± 0.55	3.21 ± 0.62	0.604	0.546
FEV1/FVC (%)	85.14 ± 3.29	84.64 ± 4.17	1.412	0.159
Peak Expiratory Flow Rate (L/min)	420.36 ± 35.46	418.11 ± 40.23	0.636	0.525
Peak nasal inspiratory flow (L/min)	68.32 ± 7.98	63.87 ± 8.54	5.828	P < 0.001
Forced Expiratory Flow 25-75% (L/s)	3.57 ± 0.42	3.53 ± 0.52	0.801	0.424

AR, Allergic rhinitis; IgE, immunoglobulin E; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 5. Correlation analysis between various indicators and prognosis of AR

Values	rho	P
IL-4 level (pg/mL)	0.122	0.007
IL-5 level (pg/mL)	0.103	0.022
IFN-γ level (pg/mL)	0.102	0.024
TGF-β1 level (pg/mL)	0.114	0.011
Histamine level (ng/mL)	0.094	0.038
Leukotriene C4 (pg/mL)	0.118	0.009
Prostaglandin D2 (ng/mL)	0.107	0.017
IL-13 level (pg/mL)	0.098	0.03
Serum IgE level (IU/mL)	0.309	P < 0.001
Serum Albumin (g/dL)	-0.179	P < 0.001
Total Protein (g/dL)	-0.172	P < 0.001
ESR (mm/hour)	0.126	0.005
Eosinophil count (cells/μL)	0.204	P < 0.001
Nasal cytology score	0.161	P < 0.001
Total nasal symptom score	0.235	P < 0.001
Peak nasal inspiratory flow (L/min)	-0.258	P < 0.001

IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; AR, allergic rhinitis; IgE, immunoglobulin E; ESR, erythrocyte sedimentation rate.

cells/μL vs. 320.76 ± 75.21 cells/μL; t=4.55, P < 0.001), nasal cytology score (2.98 ± 0.67 vs. 3.22 ± 0.81; t=3.49, P < 0.001), total nasal symptom score (7.16 ± 1.32 vs. 7.89 ± 1.67; t=5.125, P < 0.001), and peak nasal inspiratory flow (68.32 ± 7.98 L/min vs. 63.87 ± 8.54 L/min; t=5.828, P < 0.001). However, no significant differences were observed in FEV1 (L), FVC (L), FEV1/FVC ratio, peak expiratory flow rate, and forced expiratory flow 25-75% between the two groups (**Table 4**).

Correlation analysis of prognosis

Correlation analysis between various indicators and the prognosis of AR identified significant associations. Positive correlations were found for IL-4, IL-5, IFN-γ, TGF-β1, histamine, leukotriene C4, prostaglandin D2, IL-13, serum IgE levels, ESR, eosinophil count, nasal cytology score, and total nasal symptom score. Conversely, negative correlations were observed for serum albumin, total protein, and peak nasal inspiratory flow (**Table 5**). These findings suggest that these indicators could serve as prognostic markers for AR, meriting further exploration in clinical settings.

ROC of prognosis

The predictive value of various indicators for the prognosis of AR was assessed using receiver operating characteristic (ROC) analysis (**Table 6**). The area under the curve (AUC) values for IL-4 (0.569), IL-5 (0.554), IFN-γ (0.566), TGF-β1 (0.567), histamine (0.548), leukotriene C4 (0.566), prostaglandin D2 (0.556), IL-13 (0.551), serum IgE (0.673), serum albumin (0.612), total protein (0.607), ESR (0.574), and eosinophil count (0.612) were calculated. These results indicate that while individual bio-

Table 6. The predictive value of various indicators for the prognosis of AR (ROC)

Value	Sensitivities	Specificities	AUC
IL-4 level (pg/mL)	0.298	0.895	0.569
IL-5 level (pg/mL)	0.298	0.854	0.554
IFN-γ level (pg/mL)	0.434	0.749	0.566
TGF-β1 level (pg/mL)	0.495	0.644	0.567
Histamine level (ng/mL)	0.162	0.956	0.548
Leukotriene C4 (pg/mL)	0.414	0.742	0.566
Prostaglandin D2 (ng/mL)	0.652	0.471	0.556
IL-13 level (pg/mL)	0.313	0.831	0.551
Serum IgE level (IU/mL)	0.434	0.875	0.673
Serum Albumin (g/dL)	0.869	0.336	0.612
Total Protein (g/dL)	0.818	0.4	0.607
ESR (mm/hour)	0.343	0.841	0.574
Eosinophil count (cells/μL)	0.48	0.719	0.612

IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; AR, allergic rhinitis; IgE, immunoglobulin E; ROC, Receiver operating characteristic; AUC, area under the curve.

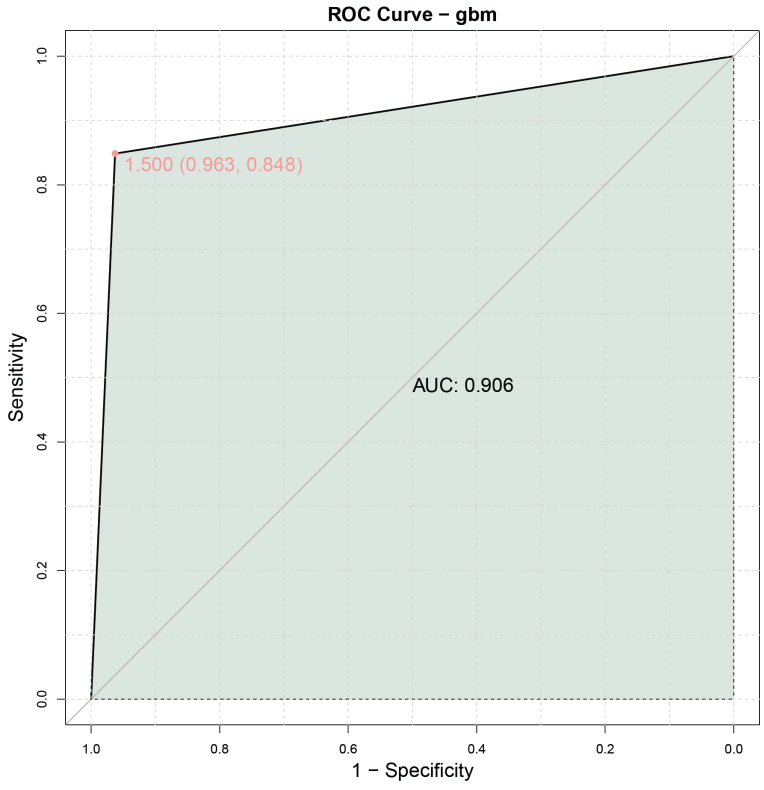

Figure 1. Composite model for predicting the prognosis of AR. ROC, Receiver operating characteristic; AR, allergic rhinitis.

markers provided some insight, none demonstrated significant predictive value for the prognosis of AR independently.

Composite model

The aforementioned biomarkers were integrated to construct a composite model for predicting the prognosis of AR. The model demonstrated an area under the curve (AUC) value of 0.906, indicating significant predictive value for the prognosis of AR (**Figure 1**).

General information on patients with AR and healthy individuals

To evaluate the predictive role of biomarkers in the clinical diagnosis of AR, this study included 493 health examination records from the same period as a control group in a 1:1 ratio. Comparison between healthy individuals and AR patients showed no significant differences in age (37.64 ± 7.35 vs. 37.76 ± 7.89, t=0.235, P=0.814) or gender distribution (M/F: 254/239 vs. 249/244, t=0.065, P=0.799) (**Table 7**). There were also no significant differences in the prevalence of smoking (36.11% vs. 34.28%, χ^2=0.285, P=0.594) or alcohol consumption (31.03% vs. 35.09%, χ^2=1.654, P=0.198), as well as hypertension, diabetes, family history of AR, or hyperlipidemia.

Markers

Significant differences in biomarkers between healthy individuals and AR patients were noted (**Table 8**). AR patients exhibited elevated levels of IL-4 (17.32 ± 4.21 vs. 13.32 ± 4.21, t=14.897, P < 0.001), IL-5 (15.65 ± 3.78 vs. 14.65 ± 3.78, t=4.151, P < 0.001), TGF-β1 (39.16 ± 8.92 vs. 20.76 ± 8.92, t=32.415, P < 0.001), histamine (11.87 ± 3.21 vs. 9.87 ± 3.21,

Table 7. General information on patients with AR and healthy individuals

Data	Healthy individuals (n=493)	Allergic Rhinitis (n=493)	t	*P* value
Age (years)	37.64 ± 7.35	37.76 ± 7.89	0.235	0.814
Gender (M/F)	254/239	249/244	0.065	0.799
Smoking history	178 (36.11%)	169 (34.28%)	0.285	0.594
Drinking history	153 (31.03%)	173 (35.09%)	1.654	0.198
Hypertension [n (%)]	82 (16.63%)	94 (19.07%)	0.837	0.36
Diabetes [n (%)]	37.64 ± 7.35	37.76 ± 7.89	0.235	0.814
Family history of allergic rhinitis	205 (41.58%)	212 (43%)	0.15	0.699
Hyperlipidemia [n (%)]	79 (16.02%)	64 (12.98%)	1.603	0.205

AR, Allergic rhinitis.

Table 8. Analysis of biomarkers for the progression of AR

Values	Healthy individuals (n=493)	Allergic Rhinitis (n=493)	t	*P* value
IL-4 level (pg/mL)	13.32 ± 4.21	17.32 ± 4.21	14.897	P < 0.001
IL-5 level (pg/mL)	14.65 ± 3.78	15.65 ± 3.78	4.151	P < 0.001
IFN-γ level (pg/mL)	24.13 ± 5.32	24.17 ± 5.32	0.122	0.903
TGF-β1 level (pg/mL)	20.76 ± 8.92	39.16 ± 8.92	32.415	P < 0.001
Histamine level (ng/mL)	9.87 ± 3.21	11.87 ± 3.21	9.759	P < 0.001
Leukotriene C4 (pg/mL)	20.36 ± 5.12	20.76 ± 6.32	1.094	0.274
Prostaglandin D2 (ng/mL)	7.51 ± 1.14	7.53 ± 1.89	0.125	0.9
IL-13 level (pg/mL)	9.32 ± 3.29	16.32 ± 3.56	32.012	P < 0.001
Serum IgE level (IU/mL)	97.14 ± 15.24	164.87 ± 45.32	31.453	P < 0.001
Serum Albumin (g/dL)	3.96 ± 0.33	4.43 ± 0.35	21.628	P < 0.001
Total Protein (g/dL)	7.25 ± 0.58	7.54 ± 0.58	8.01	P < 0.001
ESR (mm/hour)	17.52 ± 2.14	17.55 ± 2.14	0.213	0.832
Eosinophil count (cells/μL)	250.35 ± 68.92	290.35 ± 68.92	9.114	P < 0.001
Nasal cytology score	2.34 ± 0.63	2.98 ± 0.67	15.528	P < 0.001
Total nasal symptom score	4.18 ± 1.35	7.16 ± 1.32	35.038	P < 0.001
FEV1 (L)	2.98 ± 0.44	2.95 ± 0.45	0.841	0.401
FVC (L)	3.31 ± 0.56	3.25 ± 0.55	1.901	0.058
FEV1/FVC (%)	85.04 ± 3.21	85.14 ± 3.29	0.496	0.62
Peak Expiratory Flow Rate (L/min)	422.33 ± 41.25	420.36 ± 35.46	0.803	0.422
Peak nasal inspiratory flow (L/min)	161.48 ± 37.58	68.32 ± 7.98	53.84	P < 0.001
Forced Expiratory Flow 25-75% (L/s)	3.61 ± 0.34	3.57 ± 0.42	1.848	0.065

IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; AR, allergic rhinitis; IgE, immunoglobulin E; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

t=9.759, P < 0.001), and IL-13 (16.32 ± 3.56 vs. 9.32 ± 3.29, t=32.012, P < 0.001). Serum IgE (164.87 ± 45.32 vs. 97.14 ± 15.24, t=31.453, P < 0.001), serum albumin (4.43 ± 0.35 vs. 3.96 ± 0.33, t=21.628, P < 0.001), total protein (7.54 ± 0.58 vs. 7.25 ± 0.58, t=8.01, P < 0.001), eosinophil count (290.35 ± 68.92 vs. 250.35 ± 68.92, t=9.114, P < 0.001), nasal cytology score (2.98 ± 0.67 vs. 2.34 ± 0.63, t=15.528, P < 0.001), and total nasal symptom score (7.16 ± 1.32 vs. 4.18 ± 1.35, t=35.038, P < 0.001) were also significantly higher, indicating their potential as diagnostic and prognostic markers for AR progression. No significant differences were observed in IFN-γ, leukotriene C4, prostaglandin D2, ESR, FEV1, FVC, FEV1/FVC, peak expiratory flow rate, peak nasal inspiratory flow (or forced expiratory flow) 25-75% between the two groups.

Table 9. Correlation analysis between various indicators and the diagnosis of AR

Values	rho	P
IL-4 level (pg/mL)	0.429	P < 0.001
IL-5 level (pg/mL)	0.131	P < 0.001
TGF-β1 level (pg/mL)	0.719	P < 0.001
Histamine level (ng/mL)	0.297	P < 0.001
IL-13 level (pg/mL)	0.714	P < 0.001
Serum IgE level (IU/mL)	0.708	P < 0.001
Serum Albumin (g/dL)	0.568	P < 0.001
Total Protein (g/dL)	0.247	P < 0.001
Eosinophil count (cells/μL)	0.279	P < 0.001
Nasal cytology score	0.444	P < 0.001
Total nasal symptom score	0.745	P < 0.001
Peak nasal inspiratory flow (L/min)	-0.864	P < 0.001

IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; AR, allergic rhinitis; IgE, immunoglobulin E.

Correlation analysis of diagnosis

Correlation analysis identified significant associations between various biomarkers and the diagnosis of AR (**Table 9**). Positive correlations were evident for IL-4 level (rho=0.429, P < 0.001), IL-5 level (rho=0.131, P < 0.001), TGF-β1 level (rho=0.719, P < 0.001), histamine level (rho=0.297, P < 0.001), IL-13 level (rho=0.714, P < 0.001), serum IgE level (rho=0.708, P < 0.001), serum albumin (rho=0.568, P < 0.001), total protein (rho=0.247, P < 0.001), eosinophil count (rho=0.279, P < 0.001), nasal cytology score (rho=0.444, P < 0.001), and total nasal symptom score (rho=0.745, P < 0.001). Conversely, peak nasal inspiratory flow showed a strong negative correlation (rho=-0.864, P < 0.001).

ROC analysis of diagnosis

The predictive value of various biomarkers for diagnosing AR was assessed using receiver operating characteristic (ROC) analysis (**Table 10**). TGF-β1 level displayed a high AUC value (0.928) with sensitivities and specificities of 0.836 and 0.86, respectively, resulting in a Youden index of 0.696. IL-13 level and serum IgE level also showed substantial AUC values (0.922), with sensitivities of 0.803 and 0.852 and specificities of 0.901 and 0.939, respectively, leading to Youden indices of 0.704 and 0.791. Conversely, IL-5 level, with a lower AUC value (0.578) and sensitivities and specificities of 0.726 and 0.414 respectively, resulted in a Youden index of 0.14. Additional measurements such as IL-4, histamine, serum albumin, total protein, and eosinophil count demonstrated modest to moderate AUC values, varying sensitivities, specificities, and Youden indices, further validating their diagnostic utility in AR.

Discussion

Allergic rhinitis (AR) is a prevalent chronic respiratory condition significantly affectingpatients' quality of life [15-17]. This study aimed to identify potential clinical diagnostic and prognostic markers for AR by analyzing a range of inflammatory and clinical markers. Our findings provide valuable insights into the roles of various biomarkers in predicting the prognosis and diagnosis of AR, highlighting the complex interplay of inflammatory mediators, clinical markers, and patient outcomes.

Significant differences in inflammatory markers such as IL-4, IL-5, IFN-γ, TGF-β1, histamine, leukotriene C4, prostaglandin D2, and IL-13 were observed between the good and poor prognosis groups. These differences align with existing literature, confirming the value of these inflammatory biomarkers for AR diagnosis and prognosis [18-22].

Furthermore, the analysis of clinical markers revealed significant differences in serum IgE levels, serum albumin, total protein, ESR, eosinophil count, nasal cytology score, total nasal symptom score, and peak nasal inspiratory flow between the prognosis groups. Correlation analysis supported the association of these markers with AR prognosis, indicating their value as prognostic indicators in clinical settings. These findings suggest avenues for improving diagnosis and treatment of AR, leading to more targeted and effective treatment strategies.

The identified biomarkers, specifically TGF-β1, IL-13, and serum IgE levels, demonstrate significant potential as robust diagnostic and prognostic indicators for AR. These biomarkers reflect the underlying pathophysiological processes and disease progression characteristic of AR.

TGF-β1, a multifunctional cytokine, plays a crucial role in regulating immune responses,

Table 10. The predictive value of various indicators for the diagnosis of AR (ROC)

Values	Sensitivities	Specificities	AUC	Youden index
IL-4 level (pg/mL)	0.736	0.677	0.752	0.413
IL-5 level (pg/mL)	0.726	0.414	0.578	0.14
TGF-β1 level (pg/mL)	0.836	0.86	0.928	0.696
Histamine level (ng/mL)	0.669	0.606	0.671	0.275
IL-13 level (pg/mL)	0.803	0.901	0.922	0.704
Serum IgE level (IU/mL)	0.852	0.939	0.922	0.791
Serum Albumin (g/dL)	0.7	0.807	0.835	0.507
Total Protein (g/dL)	0.716	0.511	0.642	0.227
Eosinophil count (cells/μL)	0.529	0.726	0.662	0.255

ROC, Receiver operating characteristic; AR, allergic rhinitis; IL-4, Interleukin-4; IL-5, Interleukin-5; IFN-γ, Interferon-γ; TGF-β1, Transforming growth factor-β1; IL-13, Interleukin-13; IgE, immunoglobulin E.

inflammation, and tissue remodeling. In the context of AR, TGF-β1 is pivotal in modulating immune cell differentiation and function, promoting airway inflammation, and contributing to nasal mucosa tissue remodeling. Elevated levels of TGF-β1 are associated with airway remodeling features, such as subepithelial fibrosis and increased deposition of extracellular matrix components, which are typical of chronic inflammatory conditions like AR. Thus, TGF-β1 serves as an indicator of chronic inflammation and structural changes, making it a valuable biomarker for the diagnosis and prognosis of AR.

IL-13 is central to the allergic inflammation that typifies AR, driving the type 2 immune response. It facilitates IgE production, eosinophil recruitment, mucus hypersecretion, and airway hyperresponsiveness, which are key aspects of AR. High IL-13 levels correlate with disease severity, exacerbations, and poor prognosis, highlighting its role as a critical biomarker that reflects ongoing allergic inflammation, disease activity, and potential progression in AR.

Serum IgE is fundamentally associated with allergic diseases, including AR, where it plays a critical role in allergic sensitization and the immediate allergic response. Elevated serum IgE levels are indicative of the presence and severity of allergic sensitization, as well as the likelihood of allergen-induced symptoms and exacerbations in AR. This makes serum IgE a valuable biomarker for assessing the extent of allergic sensitization and predicting the clinical course of AR.

These biomarkers are significant because they reflect the pathophysiologic processes, immune dysregulation, and inflammatory responses that underpin the development and progression of AR. Their value as diagnostic and prognostic indicators is derived from their close relationship with the immune and inflammatory mechanisms central to AR, making them crucial for assessing disease severity, predicting outcomes, and guiding personalized management strategies.

Our study also assessed the diagnostic value of these biomarkers by comparing data from healthy individuals with those from AR patients. The results showed significant differences in various biomarkers between the healthy and AR groups, underscoring the diagnostic relevance of IL-4, IL-5, TGF-β1, histamine, IL-13, serum IgE, serum albumin, total protein, eosinophil count, nasal cytology score, and total nasal symptom score. The ROC analysis particularly highlighted the robust diagnostic value of TGF-β1, IL-13, and serum IgE levels, with high AUC values and strong discriminative abilities. These findings suggest the diagnostic value of these markers and ability to and distinguishing AR from other respiratory conditions.

Notably, the composite biomarker model constructed in this study exhibited a high AUC value, indicating significant predictive value for the prognosis of AR. This emphasizes the potential of a multimodal approach that integrates multiple biomarkers to enhance prognostic accuracy in AR. However, the limited predictive value of individual biomarkers underscores the necessity for a comprehensive

approach that considers the cumulative effects of multiple markers in predicting the prognosis of AR.

The identified biomarkers, including TGF-β1, IL-13, and serum IgE levels, demonstrate potential as robust diagnostic and prognostic indicators for AR. These markers effectively reflect the underlying pathophysiologic mechanisms and disease progression in AR. Research by Hassannia, et al. corroborates the close relationship of TGF-β1 with AR [23]. TGF-β1, a multifunctional cytokine, plays a critical role in regulating immune responses, inflammation, and tissue remodeling [24]. In AR, TGF-β1 is instrumental in modulating immune cell differentiation and function, promoting airway inflammation, and contributing to nasal mucosa tissue remodeling [25]. Elevated levels of TGF-β1 are associated with airway remodeling, including subepithelial fibrosis and increased extracellular matrix component deposition, hallmarks of chronic inflammatory conditions like AR [26]. Therefore, TGF-β1 serves as an indicator of chronic inflammatory processes and structural changes in AR, making it a valuable biomarker for both diagnosis and prognosis [27].

IL-13, a principal mediator of allergic inflammation, orchestrates the type 2 immune response characteristic of AR [28]. It enhances IgE production, eosinophil recruitment, mucus hypersecretion, and airway hyperresponsiveness, which are critical aspects of AR [29]. Elevated IL-13 levels have been linked to increased disease severity, exacerbations, and poor prognosis, positioning it as a significant biomarker that reflects ongoing allergic inflammation and disease progression in AR [30].

Serum IgE is a fundamental marker of allergic diseases, including AR [31, 32]. IgE plays a crucial role in allergic sensitization and the immediate phase of allergic responses, connecting environmental allergen exposure to symptom development in AR [33]. Consequently, serum IgE levels are invaluable for determining the presence and severity of allergic sensitization, as well as predicting the likelihood of allergen-induced symptoms and exacerbations in AR [34].

Collectively, these biomarkers are significant as they mirror the pathophysiological processes, immune dysregulation, and inflammatory responses that underlie the development and progression of AR. Their efficacy as diagnostic and prognostic tools is derived from their deep association with the immune and inflammatory mechanisms essential to AR, making them crucial for assessing disease severity, predicting outcomes, and guiding personalized management strategies.

The limitations of our study should be acknowledged. First, its retrospective nature may introduce biases and limit the ability to establish causal relationships. Additionally, the study focused on a specific patient population, and further work is needed to validate the generalizability of the findings across broader populations. Moreover, the study did not evaluate the impact of treatment interventions on the identified biomarkers, which could provide further insights into their dynamic changes and prognostic implications.

In conclusion, our study provides comprehensive insight into and prognostic markers for AR. The findings highlight the complex interplay of inflammatory and clinical markers in predicting prognosis and diagnosing AR, emphasizing the need for a holistic approach to biomarker assessment in clinical practice. The identified biomarkers, particularly TGF-β1, IL-13, and serum IgE levels, demonstrate promise as robust diagnostic and prognostic indicators for AR. These results warrant further validation and exploration in prospective clinical studies. Overall, our study contributes to the growing body of evidence aimed at enhancing the evaluation of AR, with implications for personalized management.

Disclosure of conflict of interest

None.

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