Research Square

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Association of serum interleukin-6 with asthma control and subsequent exacerbations: a retrospective cohort study assessing incremental predictive value

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Research Article

Keywords: asthma, interleukin-6, asthma control, asthma exacerbation, risk prediction

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11198043/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Circulating interleukin-6 (IL-6) has been associated with adverse asthma outcomes, but its incremental value beyond routine clinical assessment remains uncertain. We evaluated the associations of serum IL-6 with asthma control and 12-month exacerbations and assessed its incremental value beyond the Asthma Control Test (ACT) and clinical variables.

Methods

This single-centre retrospective cohort included 984 adults with asthma. IL-6 was analysed as a continuous exposure using Pearson correlation, non-parametric receiver operating characteristic analysis and prespecified hierarchical multivariable logistic regression. Models were sequentially adjusted for basic clinical factors, ACT, forced expiratory volume in 1 s (FEV_1) % predicted and fractional exhaled nitric oxide (FeNO). Sensitivity analyses additionally included blood eosinophils and baseline leukotriene receptor antagonist use. Internal optimism in model discrimination was estimated using 1,000 bootstrap resamples.

Results

Overall, 347 participants (35.3%) experienced an exacerbation within 12 months. IL-6 correlated negatively with ACT ($r = -0.742$), FEV_1 % predicted ($r = -0.588$) and FEV_1/forced vital capacity ($r = -0.376$), and positively with exacerbation ($r = 0.413$; all $P < 0.001$). The area under the curve (AUC) for IL-6 alone was 0.752 (95% confidence interval [CI], 0.721–0.783). Each 1-standard-deviation increase in IL-6 was associated with higher odds of exacerbation after basic adjustment (odds ratio [OR], 2.337; 95% CI, 1.982–2.771; $P < 0.001$). The association was attenuated after adding ACT (OR, 1.247; 95% CI, 1.001–1.553; $P = 0.049$) and was not statistically significant after further adjustment for FEV_1 % predicted and FeNO (OR, 1.233; 95% CI, 0.988–1.539; $P = 0.063$). Adding IL-6 to the ACT-based clinical model increased the AUC from 0.817 to 0.819 (DeLong $P = 0.333$); the bootstrap-corrected AUC was 0.812. The exploratory IL-6 cut-off was 6.015 pg/mL (sensitivity, 81.0%; specificity, 59.7%).

Conclusions

Serum IL-6 was associated with poorer asthma control and higher odds of exacerbation, but showed no clear incremental discrimination beyond ACT and clinical variables. Its role as a clinical predictor requires external validation.

Background

Asthma is a heterogeneous chronic airway disease with diverse inflammatory phenotypes and clinical trajectories. Clinical assessment commonly integrates symptom control, lung function, exacerbation history and treatable traits. The Asthma Control Test (ACT) is a validated instrument for assessing asthma symptom control [1, 2]. Lung function is used to evaluate airflow limitation [3, 4], while fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophils can assist in assessing type 2 inflammation [3, 5]. The Global Initiative for Asthma (GINA) 2026 strategy further emphasises that symptom control and future exacerbation risk should be assessed separately [6]. A recent

cohort of adults with adult-onset asthma also suggested that exacerbation risk usually reflects multiple clinical factors [7]. Identifying systemic inflammatory biomarkers that complement current assessments may therefore be clinically relevant.

Interleukin-6 (IL-6) is an important cytokine linking innate immunity, adaptive immunity and tissue responses. It can activate downstream pathways, including JAK/STAT3, through classic and trans-signalling [8, 9]. IL-6 trans-signalling has been associated with airway epithelial inflammation and some type 2-low asthma phenotypes [10–12]. Experimental studies suggest that this pathway may also promote dendritic cell-mediated T-helper 17 polarisation and neutrophilic inflammation [13, 14]. IL-6 may additionally promote ferroptosis in bronchial epithelial cells through reactive oxygen species-dependent lipid peroxidation and disruption of iron homeostasis [15]. Viral-mimic stimulation can alter immune responses in asthmatic airway epithelium, while trained immunity of the epithelial IL6 gene may contribute to asthma exacerbations [16, 17]. These findings provide biological plausibility but do not replace verification of the associations in adult clinical cohorts.

Clinical studies in adults have associated elevated circulating IL-6 with metabolic dysfunction, impaired lung function and greater asthma severity [18]. A recent analysis of the CARDIA cohort further supported associations between high IL-6, lower lung function and metabolic dysfunction [19]. The longitudinal SARP-3 study suggested that baseline IL-6 was associated with subsequent exacerbation frequency [20]. Research in severe asthma found that combinations of IL-6 with FeNO or blood eosinophils could identify subgroups with different levels of severity and treatment response [21], while studies of epithelial trans-signalling suggested that it may characterise some type 2-low phenotypes [12]. Long-term follow-up of adult-onset asthma also showed that physical activity was associated with systemic inflammation, including IL-6, although its relationship with asthma outcomes was complex [22]. Population composition, specimen type, assay platform and outcome definitions differ among studies; thresholds reported previously cannot therefore be applied directly to this cohort.

Against this background, we evaluated the relationships of serum IL-6 with ACT-based control categories, lung function and 12-month exacerbations in a single-centre cohort of adults with asthma, with particular emphasis on the incremental value of IL-6 beyond ACT and clinical variables. The study was designed to assess associations and explore risk stratification rather than to develop a definitive prediction tool for direct clinical decision-making. This observational study is reported in accordance with the STROBE statement [23], and analyses and reporting involving risk models were informed by TRIPOD + AI principles [24].

Methods

Study design, setting and participants

This single-centre retrospective cohort study consecutively screened 1,285 adults with asthma who attended the Department of Respiratory and Critical Care Medicine at Hebei Yanda Hospital between January 2022 and June 2025. Asthma diagnoses were based on the clinical information available at presentation and were reviewed consistently using the applicable GINA diagnostic framework [3]. The inclusion criteria were: (1) a diagnosis of adult asthma, with typical variable respiratory symptoms and variable expiratory airflow limitation confirmed by lung-function testing, such as an increase in FEV_1 of ≥ 12% and ≥ 200 mL from baseline after bronchodilator administration; when variability in airflow limitation was not demonstrated at the initial assessment, the diagnosis was confirmed by subsequent repeat lung-function testing or improvement after standardised anti-inflammatory treatment; (2) age 18–70 years; (3) regular asthma-controller treatment containing an inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) for ≥ 3 months; (4) complete baseline clinical data, including ACT score, lung function,

FeNO, peripheral blood eosinophil count and serum IL-6; and (5) complete 12-month follow-up data sufficient to determine whether an asthma exacerbation occurred. The exclusion criteria were: (1) respiratory infection, asthma exacerbation or systemic corticosteroid use within 2 weeks before enrolment; (2) another structural respiratory disease, including chronic obstructive pulmonary disease, bronchiectasis or interstitial lung disease; (3) a systemic disease that could affect inflammatory-marker concentrations, including autoimmune disease, malignancy or severe hepatic or renal impairment; and (4) use of an IL-6 or IL-6 receptor antagonist or another targeted drug within the preceding 6 months.

Among the 1,285 patients initially screened, 68 were excluded because of respiratory infection, asthma exacerbation or systemic corticosteroid use within 2 weeks before enrolment; 52 had another structural respiratory disease; 56 had a systemic disease that could affect inflammatory-marker concentrations; 40 had used an IL-6 or IL-6 receptor antagonist or another targeted drug within the preceding 6 months; and 85 had incomplete baseline clinical data or missing 12-month outcome data. The final cohort comprised 984 patients. All included patients had complete baseline and 12-month outcome data and were included in the correlation, logistic regression and receiver operating characteristic (ROC) analyses.

Classification of asthma control

Baseline symptom control was assessed using the ACT [1, 2]. According to the prespecified analytical stratification used in this study, patients were categorised as well controlled (20–25 points), partly controlled (16–19 points) or uncontrolled (5–15 points). This stratification was used to describe and compare the clinical characteristics of patients with different levels of symptom control. ACT score was included as a continuous variable in multivariable regression analyses.

Ethics statement

The study was reviewed and approved by the Medical Ethics Committee of Hebei Yanda Hospital (approval No. Ethics Review [Research] 2026-07-005). Because this retrospective study used previously collected clinical data that had been anonymised before analysis, the ethics committee waived the requirement for informed consent. The study was conducted in accordance with the Declaration of Helsinki.Clinical trial number: not applicable.

Variables, data sources and outcome definition

Clinical data collection

General clinical data, including age, sex, body mass index (BMI), asthma duration, smoking history and comorbidities, were obtained from the hospital electronic medical-record system and follow-up records. Baseline symptom control was assessed using the ACT. We also collected the history and number of asthma exacerbations during the 12 months before baseline and extracted FEV_1 % predicted, FEV_1/FVC, FeNO, peripheral blood eosinophil count and serum IL-6 using a standardised procedure [3–5]. Information on asthma-controller medication, prescribed dose and concomitant treatments at baseline was collected, including leukotriene receptor antagonist (LTRA) and biologic use.

Follow-up and outcome definition

The primary outcome was the occurrence of at least one asthma exacerbation during the 12 months after baseline. An exacerbation was defined as an acute or subacute worsening of wheeze, dyspnoea, chest tightness or cough that required at least one of the following: initiation or escalation of systemic corticosteroid treatment, an emergency department visit, hospitalisation or intensive care, or substantial intensification of bronchodilator treatment under a physician's direction [3]. Exacerbations separated by ≥ 14 days were counted as independent events; events occurring less than 14 days apart with a continuous clinical course were counted as a single event. Exacerbations were identified from specialist diagnoses in medical records or follow-up documentation and verified against emergency department, hospitalisation and systemic corticosteroid treatment records.

Measurements and quality control

Peripheral venous blood was collected from all patients in the morning after fasting and while at rest. After clotting at room temperature, serum was separated by centrifugation at 3,000 × g and 4°C for 10 min and analysed within 2 h. Serum IL-6 was measured using the Elecsys IL-6 electrochemiluminescence immunoassay (Roche Diagnostics; catalogue No. 07027532500) on a Roche cobas e602 automated electrochemiluminescence analyser. Peripheral blood eosinophil counts were obtained from contemporaneous complete blood counts. The IL-6 assay had a measuring range of 1.5–5,000 pg/mL and a limit of detection of 1.5 pg/mL; laboratory-verified within-run and between-run coefficients of variation were < 3% and < 5%, respectively. Before FeNO measurement, patients avoided smoking, caffeinated or alcoholic drinks, nitrate-rich foods and strenuous exercise for 1 h. After 10 min of seated rest, FeNO was measured online at an expiratory flow rate of 50 mL/s using an instrument that was calibrated regularly. Short-acting β_2-agonists (SABAs) were withheld for ≥ 12 h, and procedures and interpretation followed ATS guidance [5]. FEV_1 and forced vital capacity (FVC) were measured by standard spirometry. Patients were seated, wore a nose clip and completed at least three acceptable forced vital capacity manoeuvres; the difference between the two best FEV_1 measurements was ≤ 150 mL. Before testing, SABAs were withheld for ≥ 12 h, LABAs for ≥ 24 h and long-acting muscarinic antagonists for ≥ 24–48 h. Spirometry was performed in accordance with ATS/ERS technical standards [4]. FeNO measurement and spirometry were performed by trained specialist technicians.

Statistical analysis, bias control and internal validation

Primary analyses were performed in R version 4.4.2 with a random seed of 20260920. Continuous variables are summarised as mean ± standard deviation and categorical variables as n (%). Overall comparisons across the three groups used one-way analysis of variance, Pearson's χ^2 test or Fisher's exact test. Pearson correlation was used to describe linear relationships among continuous variables. For the association between IL-6 and ACT score, sensitivity analyses used Spearman rank correlation and Pearson correlation after natural-log transformation of IL-6; a natural cubic spline was used to assess non-linearity. To assess the adequacy of modelling IL-6 as a linear term in logistic regression, the fit of linear and natural cubic spline terms was compared in the fully adjusted model. Binary logistic regression was performed with the occurrence of at least one exacerbation within 12 months as the dependent variable. IL-6 was analysed primarily as a continuous exposure and odds ratios (ORs) were reported per 1-standard-deviation increase. For interpretability, continuous covariates were rescaled before modelling: ACT per 5-point increase, age per 10-year increase, FEV_1 % predicted and FeNO per 10-unit increase, eosinophils per 0.1 × 10^9/L increase, and ICS dose per 320 μg/day increase. Regression variables were prespecified on clinical grounds rather than selected according to univariable P values. Three hierarchical main models were fitted. Model 1 included IL-6, age, sex, BMI, smoking history, exacerbation during the preceding 12 months and ICS dose. Model 2 added ACT, and model 3 additionally included FEV_1 % predicted and FeNO. Eosinophils were first added to model 3, followed by

baseline LTRA use, in additional sensitivity analyses. Incremental discrimination was assessed using an ACT-based clinical model comprising ACT and the basic clinical covariates and a complete model that additionally included IL-6. Discrimination was assessed using the AUC, and correlated ROC curves were compared using the DeLong method [25]. Internal optimism in the complete-model AUC was estimated using 1,000 bootstrap resamples [24, 26]. The Youden-index cut-off was examined only as an exploratory analysis. All tests were two-sided, and $P < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was made in exploratory analyses.

A total of 1,285 patients were screened, 301 were excluded and 984 were included. All included patients had complete 12-month outcome data.

Results

Baseline and clinical characteristics

The study flow is shown in Fig. 1. Of the 1,285 patients screened, 301 were excluded and 984 were included: 330 in the well-controlled group, 291 in the partly controlled group and 363 in the uncontrolled group. Overall, 347 patients (35.3%) experienced at least one exacerbation within 12 months. Sex, smoking history, comorbidities and FeNO did not differ significantly among the groups; age, BMI, asthma duration, eosinophil count, ICS dose, exacerbation during the preceding 12 months, LTRA use and biologic use differed among groups. Mean IL-6 concentrations were 3.27 ± 1.17, 6.99 ± 1.98 and 9.49 ± 2.30 pg/mL in the well-controlled, partly controlled and uncontrolled groups, respectively ($F = 943.449$; $P < 0.001$). Corresponding 12-month exacerbation rates were 9.1%, 28.5% and 64.5% ($\chi^2 = 240.387$; $P < 0.001$).

Table 1
Baseline characteristics and clinical measures by ACT control group

Variable	Well controlled (n = 330)	Partly controlled (n = 291)	Uncontrolled (n = 363)	F/χ²	P value
Age, years	41.8 ± 10.6	44.4 ± 10.8	45.2 ± 11.9	8.744	< 0.001
Male sex, n (%)	186 (56.4)	157 (54.0)	185 (51.0)	2.041	0.360
BMI, kg/m²	24.2 ± 2.4	25.3 ± 3.7	25.2 ± 3.1	12.101	< 0.001
Asthma duration, years	6.0 ± 3.0	8.1 ± 4.1	8.1 ± 5.0	28.296	< 0.001
Smoking history, n (%)	77 (23.3)	53 (18.2)	87 (24.0)	3.584	0.167
Comorbidity, n (%)	92 (27.9)	79 (27.1)	106 (29.2)	0.355	0.837
ACT score	20.88 ± 0.81	17.39 ± 1.02	12.10 ± 1.52		
FEV_1, % predicted	91.3 ± 7.3	78.8 ± 9.5	71.5 ± 9.2	453.431	< 0.001
FEV_1/FVC, %	80.4 ± 4.6	75.4 ± 5.4	74.8 ± 5.3	120.663	< 0.001
FeNO, ppb	25.9 ± 9.0	25.4 ± 8.2	25.7 ± 8.5	0.262	0.770
Eosinophils, ×10⁹/L	0.14 ± 0.07	0.13 ± 0.06	0.12 ± 0.07	4.270	0.014
IL-6, pg/mL	3.27 ± 1.17	6.99 ± 1.98	9.49 ± 2.30	943.449	< 0.001
Exacerbation within 12 months, n (%)	30 (9.1)	83 (28.5)	234 (64.5)	240.387	< 0.001
Exacerbation in preceding 12 months, n (%)	85 (25.8)	146 (50.2)	204 (56.2)	70.902	< 0.001
Budesonide 640 μg/day, n (%)	244 (73.9)	283 (97.3)	358 (98.6)	140.799	< 0.001
Concomitant LTRA, n (%)	58 (17.6)	106 (36.4)	111 (30.6)	29.265	< 0.001
Biologic therapy, n (%)	0 (0)	0 (0)	29 (8.0)	51.118	< 0.001

Data are mean ± standard deviation or n (%). Overall comparisons across the three groups used one-way analysis of variance, Pearson's χ² test or Fisher's exact test. ACT was used to define the groups and is presented descriptively only; no between-group significance test was performed.

Correlation analysis

Pearson correlation analysis (Table 2) showed a strong negative correlation between IL-6 and ACT ($r = -0.742$; $P < 0.001$). Sensitivity analyses showed a Spearman correlation coefficient of −0.763 ($P < 0.001$) and, after natural-log transformation of IL-6, a Pearson correlation coefficient with ACT of −0.728 (95% CI −0.756 to −0.697; $P < 0.001$),

indicating consistency across analytical methods. Restricted cubic spline analysis indicated a non-linear association between IL-6 and ACT (P for non-linearity < 0.001; Additional file 1: Fig. S1). In contrast, the fully adjusted logistic regression model for 12-month exacerbation showed no statistical evidence of non-linearity in the association between IL-6 and exacerbation risk (P for non-linearity = 0.917), supporting the use of a continuous linear term in the primary analysis. IL-6 also correlated negatively with FEV_1 % predicted and FEV_1/FVC (r = − 0.588 and − 0.376, respectively; both P < 0.001) and positively with 12-month exacerbation (r = 0.413; P < 0.001). IL-6 was not significantly correlated with FeNO (r = − 0.020; P = 0.526). Its correlations with eosinophils and BMI were weak (r = − 0.066, P = 0.038; and r = 0.107, P < 0.001, respectively), and their clinical relevance is uncertain.

Table 2
Pearson correlations among study variables

Variable	ACT	FEV_1 % predicted	FEV_1/FVC	FeNO	Eosinophils	IL-6	Exacerbation	BMI
ACT	1							
FEV_1 % predicted	0.703**	1						
FEV_1/FVC	0.389**	0.311**	1					
FeNO	−0.001	0.010	0.009	1				
Eosinophils	0.088**	0.047	0.007	0.286**	1			
IL-6	−0.742**	−0.588**	−0.376**	−0.020	−0.066*	1		
Exacerbation	−0.504**	−0.380**	−0.221**	0.031	−0.049	0.413**	1	
BMI	−0.122**	−0.111**	−0.054	0.003	−0.007	0.107**	0.080*	1

**P < 0.01; *P < 0.05 (two-sided).

Multivariable logistic regression for asthma exacerbation

For continuous IL-6 alone, the AUC for 12-month exacerbation was 0.752 (95% CI, 0.721–0.783). The exploratory cut-off that maximised the Youden index was 6.015 pg/mL, with sensitivity of 81.0%, specificity of 59.7%, positive predictive value of 52.2% and negative predictive value of 85.2%. Because this cut-off was derived and evaluated in the same dataset, it was not used for the primary inference.

Hierarchical regression results are shown in Table 3 and summarised in Fig. 2. In model 1, each 1-standard-deviation increase in IL-6 was associated with higher odds of exacerbation (OR, 2.337; 95% CI, 1.982–2.771; P < 0.001). After adding ACT in model 2, the IL-6 estimate was attenuated but remained statistically significant (OR, 1.247; 95% CI, 1.001–1.553; P = 0.049), whereas each 5-point increase in ACT was associated with lower odds of exacerbation (OR, 0.281; 95% CI, 0.210–0.373; P < 0.001). After further adjustment for FEV_1 % predicted and FeNO in model 3, the IL-6 estimate was not statistically significant (OR, 1.233; 95% CI, 0.988–1.539; P = 0.063), while the ACT estimate was largely unchanged (OR, 0.309; 95% CI, 0.222–0.425; P < 0.001). Adding eosinophils yielded an IL-6 OR of 1.234 (95% CI, 0.989–1.540; P = 0.062) and an ACT OR of 0.313 (95% CI, 0.225–0.432; P < 0.001). Further adjustment for baseline LTRA use gave an IL-6 OR of 1.235 (95% CI, 0.990–1.541; P = 0.061) and an ACT OR of 0.315 (95% CI, 0.226–0.434; P < 0.001).

Table 3
Hierarchical logistic regression of IL-6 and 12-month exacerbation

Model	IL-6 OR (95% CI)	P value	ACT OR (95% CI)	P value
Model 1	2.337 (1.982–2.771)	< 0.001	—	—
Model 2	1.247 (1.001–1.553)	0.049	0.281 (0.210–0.373)	< 0.001
Model 3	1.233 (0.988–1.539)	0.063	0.309 (0.222–0.425)	< 0.001
Sensitivity 1	1.234 (0.989–1.540)	0.062	0.313 (0.225–0.432)	< 0.001
Sensitivity 2	1.235 (0.990–1.541)	0.061	0.315 (0.226–0.434)	< 0.001

Basic covariates were age, sex, BMI, smoking history, exacerbation during the preceding 12 months and ICS dose. Model 1 included IL-6 and the basic covariates; model 2 additionally included ACT; model 3 additionally included FEV_1 % predicted and FeNO. Sensitivity analysis 1 additionally included eosinophils; sensitivity analysis 2 additionally included baseline LTRA use. ORs are reported per 1-standard-deviation increase in IL-6, 5-point increase in ACT, 10-unit increase in FEV_1 % predicted and FeNO, 0.1 × 10^9/L increase in eosinophils and 320 μg/day increase in ICS dose.

filled circles indicate P < 0.05 and open circles indicate P ≥ 0.05. Points represent ORs, horizontal lines represent 95% CIs and the vertical dashed line indicates OR = 1. Model 1 adjusted for basic clinical covariates; model 2 added ACT; model 3 additionally included FEV_1 % predicted and FeNO.

Predictive performance by ROC analysis

ROC results are shown in Fig. 3 and Table 4. The AUC for IL-6 alone was 0.752 (95% CI, 0.721–0.783). The exploratory Youden-index cut-off for IL-6 was 6.015 pg/mL, with sensitivity of 81.0%, specificity of 59.7%, positive predictive value of 52.2% and negative predictive value of 85.2%. This cut-off was derived in the present cohort and is intended for exploratory risk stratification only. The ACT-based clinical reference model (model A) had an AUC of 0.817. Adding IL-6 (model B) increased the AUC to 0.819, a difference of 0.002 (DeLong P = 0.333). The bootstrap-corrected AUC for model B was 0.812, suggesting mild optimism in apparent performance.

Table 4
ROC analysis of IL-6 and its incremental value

Analysis	AUC (95% CI)	AUC difference	*P*	Bootstrap-corrected AUC
IL-6 alone	0.752 (0.721–0.783)	—	—	—
Model A	0.817 (0.790–0.844)	—	—	—
Model B	0.819 (0.792–0.846)	0.002	0.333	0.812

Model A included ACT, age, sex, BMI, smoking history, exacerbation during the preceding 12 months and ICS dose. Model B added continuous IL-6 to model A. The AUC difference and P value are from the paired DeLong comparison of model B with model A. The IL-6 cut-off was derived using the Youden index and is descriptive only; its reproducibility and clinical applicability require validation in an independent cohort.

The blue line represents IL-6 alone, the orange line represents the reference model comprising ACT and prespecified clinical variables, and the green line represents the combined model with IL-6 added to the reference model. The diagonal dashed line represents no discrimination.

Discussion

In this single-centre cohort of 984 adults with asthma, serum IL-6 was associated with poorer asthma control, lower lung function and higher odds of exacerbation during the subsequent 12 months. IL-6 alone showed moderate discrimination. After basic clinical adjustment, IL-6 remained associated with exacerbation; the estimate was attenuated after ACT was included and was not statistically significant after further adjustment for FEV_1 % predicted and FeNO. Sensitivity analyses including eosinophils and baseline LTRA use were similar. Adding IL-6 to the model containing ACT and clinical variables increased the AUC only from 0.817 to 0.819 and did not show significant incremental discrimination. These findings suggest that IL-6 may reflect inflammatory burden associated with adverse outcomes while sharing substantial information with symptom control, previous disease activity and lung function.

Peters et al. found that elevated IL-6 was associated with metabolic dysfunction, lower lung function and more severe asthma in two adult cohorts [18], and a recent CARDIA analysis reported similar findings [19]. Subsequent SARP-3 data linked IL-6 with future exacerbation frequency [20]. Severe-asthma studies suggest that IL-6, FeNO and blood eosinophils may provide partly complementary phenotypic information [21], and that epithelial trans-signalling signatures are enriched in some type 2-low asthma [12]. In our cohort, IL-6 was not significantly correlated with FeNO and had a statistically significant but very weak negative correlation with eosinophils ($r = -0.066$; $P = 0.038$). Given the large sample size, this finding is more likely to reflect a minimal linear relationship of limited clinical relevance. Adding eosinophils to the multivariable model left the IL-6 estimate essentially unchanged, while eosinophils were not independently associated with exacerbation. These findings do not establish that IL-6 and type 2 inflammatory pathways are independent, nor do they justify using serum IL-6 alone to classify patients as having non-type 2 or neutrophilic asthma [14]. Recent adult data further show that systemic inflammation may be influenced by physical activity and metabolic status [22], while hospitalised exacerbations can have distinct and potentially reproducible infectious and inflammatory phenotypes [28]. Circulating IL-6 may therefore represent an integrated signal spanning airway inflammation, systemic metabolism and disease activity rather than a specific marker of a single asthma endotype.

The strong negative correlation between IL-6 and ACT provides an important clue for interpreting the multivariable models. ACT integrates symptom frequency during the preceding 4 weeks, nocturnal symptoms, activity limitation, reliever use and patients' overall assessment of control, and therefore represents a clinical summary of multiple pathophysiological processes. Attenuation of the IL-6 estimate after ACT adjustment could reflect overlapping information and control of confounding, but statistical adjustment along a mediating pathway is also possible. The observational design cannot distinguish among these explanations and does not imply that ACT eliminates the biological effect of IL-6. For an aetiological association question, model 1 describes the overall relationship between IL-6 and the outcome. For a clinical prediction question, models A and B more directly assess whether IL-6 improves discrimination once ACT is known. Strength of association must be distinguished from incremental prediction: a marker can be significantly associated with an outcome without materially improving individual risk discrimination beyond an existing model.

In additional sensitivity analyses, further adjustment for eosinophils and baseline LTRA use did not materially alter the estimates for IL-6 or ACT. This consistency concerns direction and magnitude rather than repeated statistical significance, because the 95% CIs for IL-6 crossed 1 in the extended and sensitivity models. IL-6 may therefore retain a residual risk signal, but the available data do not confirm a stable independent predictive role.

Using continuous IL-6 as the primary exposure avoided the information loss caused by artificial dichotomisation and reduced the optimism arising from selecting a best cut-off in the same dataset. Prespecified hierarchical models demonstrated how the IL-6 estimate changed with increasing adjustment and helped clarify overlapping information. The 347 outcome events improved the stability of multivariable estimation and enabled bootstrap internal validation. Nevertheless, internal validation can estimate optimism only in similar samples and cannot replace temporal, geographical or assay-platform external validation.

IL-6 trans-signalling may contribute to airway epithelial dysfunction, T-helper 17 polarisation and inflammatory amplification [8–12, 14]. Oxidative stress-related ferroptosis and virus-induced trained immunity of the IL6 gene provide additional mechanistic clues [15, 17]. Combined blockade in animal models and Mendelian randomisation studies suggest therapeutic potential for the IL-6 pathway [30, 31]. However, these lines of evidence arise from animal experiments or genetic proxies and do not show that tailoring treatment to the serum IL-6 concentrations measured in this study would improve outcomes in adults.

This study has several limitations. First, its single-centre retrospective design may have introduced selection bias, residual confounding and outcome misclassification; mild exacerbations managed outside our hospital may have been under-recorded. Second, IL-6 was measured only once at baseline, preventing distinction between a stable inflammatory phenotype and short-term biological variability and precluding assessment of whether changes in IL-6 preceded deterioration in ACT score or exacerbation. Third, IL-6 may be influenced by obesity, incipient infection, metabolic dysfunction and other comorbidities. Despite exclusions and partial adjustment, asthma-specific inflammation could not be isolated fully. Fourth, although the enlarged cohort included 347 outcome events, the absence of independent external validation, calibration assessment and decision-curve analysis prevents assessment of clinical net benefit across risk thresholds. Fifth, the cut-off of 6.015 pg/mL was derived in the same cohort, and its reproducibility may depend on the assay platform, specimen-handling procedures and exacerbation definition. Finally, because ACT and IL-6 were highly correlated, attenuation of the IL-6 estimate in the complete model cannot be interpreted causally. Future multicentre prospective studies should include repeated IL-6 measurements and independently validate discrimination, calibration and clinical net benefit.

Conclusions

Higher serum IL-6 was associated with poorer asthma control, impaired lung function and higher odds of exacerbation during the subsequent 12 months, with moderate discrimination when considered alone. The IL-6 estimate was weaker after ACT was included and was not statistically significant after additional adjustment for lung function, FeNO, eosinophils and baseline LTRA use. Adding IL-6 to a model containing ACT and other clinical variables did not show clear incremental discrimination. Serum IL-6 should currently be considered a complementary inflammatory and risk marker requiring further validation rather than an independent clinical prediction or decision-making marker.

Abbreviations

ACT
Asthma Control Test
ATS
American Thoracic Society
AUC
area under the receiver operating characteristic curve

BMI
body mass index
CI
confidence interval
EOS
eosinophils
ERS
European Respiratory Society
FeNO
fractional exhaled nitric oxide
FEV_1
forced expiratory volume in 1 s
FVC
forced vital capacity
GINA
Global Initiative for Asthma
ICS
inhaled corticosteroid
IL-6
interleukin-6
LABA
long-acting β_2-agonist
LAMA
long-acting muscarinic antagonist
LTRA
leukotriene receptor antagonist
OR
odds ratio
ROC
receiver operating characteristic
SABA
short-acting β_2-agonist.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Medical Ethics Committee of Hebei Yanda Hospital (approval No. Ethics Review [Research] 2026-07-005). Because this retrospective study used previously collected clinical data that had been anonymised before analysis, the ethics committee waived the requirement for informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. The manuscript contains no identifiable individual participant data.

Availability of data and materials

Due to patient confidentiality and institutional regulations, the raw dataset is not publicly available. De-identified data may be available from the corresponding author upon reasonable request, subject to applicable ethical and institutional requirements.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no external specific funding.

Authors' contributions

JYL conceived and designed the study, collected and curated the data, performed the statistical analyses, drafted the manuscript, critically revised it and approved the final version. JYL had full access to the data, takes final responsibility for the integrity of the data and accuracy of the analyses, and serves as guarantor. JJL contributed to study conception and design, data collection and curation, assisted with statistical analysis, critically revised the manuscript and approved the final version. QMS, YPW and DH contributed to data collection and curation, assisted with interpretation of the results, critically revised the manuscript and approved the final version. DDZ contributed to study conception and design, supervised the statistical analyses, critically revised the manuscript and approved the final version. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the staff of the Department of Respiratory and Critical Care Medicine at Hebei Yanda Hospital for their assistance with data collection and all patients whose clinical data contributed to this study.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study.

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32. Additional. file 1.

Figures

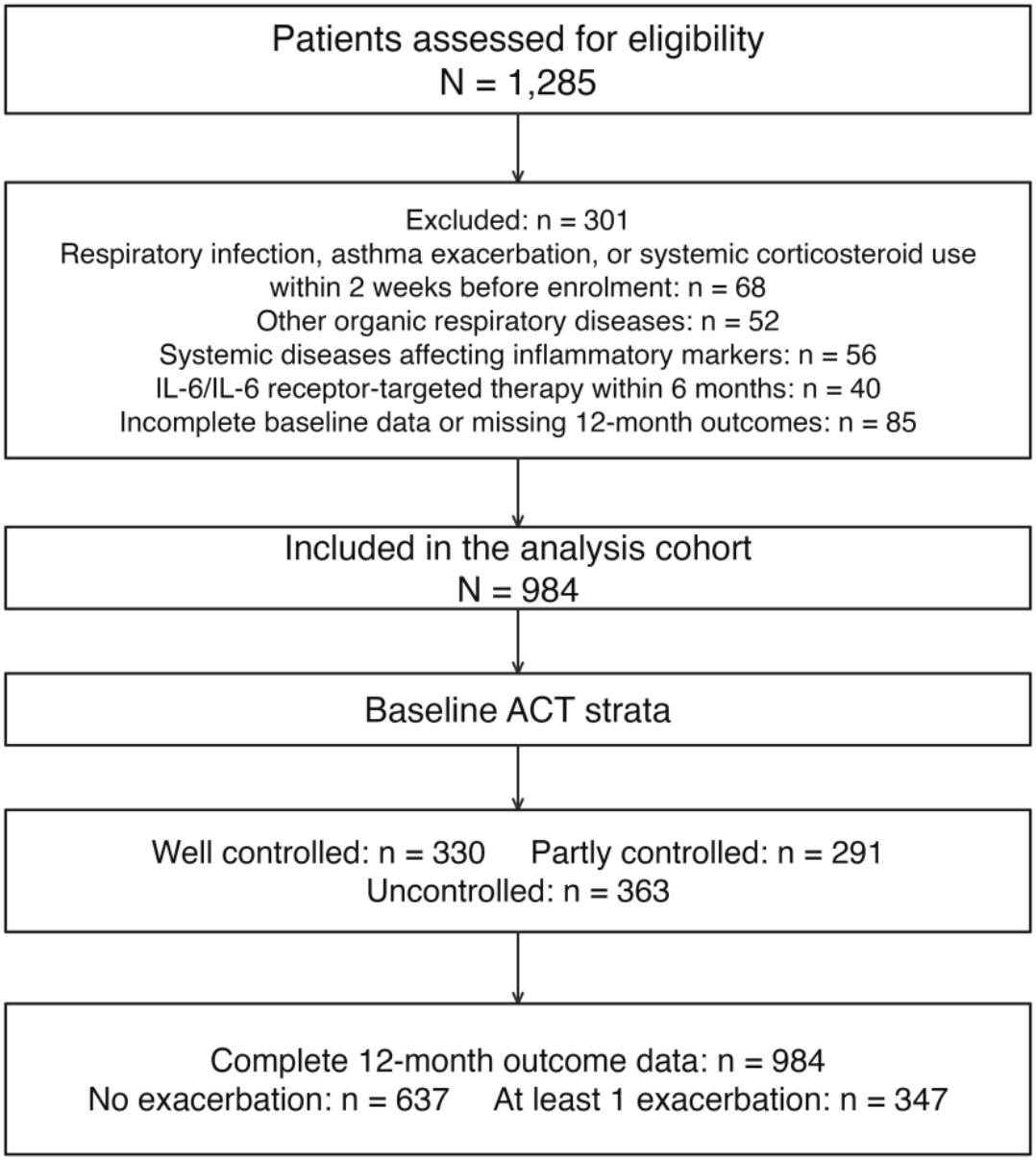


Figure 1

Participant selection and 12-month follow-up

A total of 1,285 patients were screened, 301 were excluded and 984 were included. All included patients had complete 12-month outcome data.

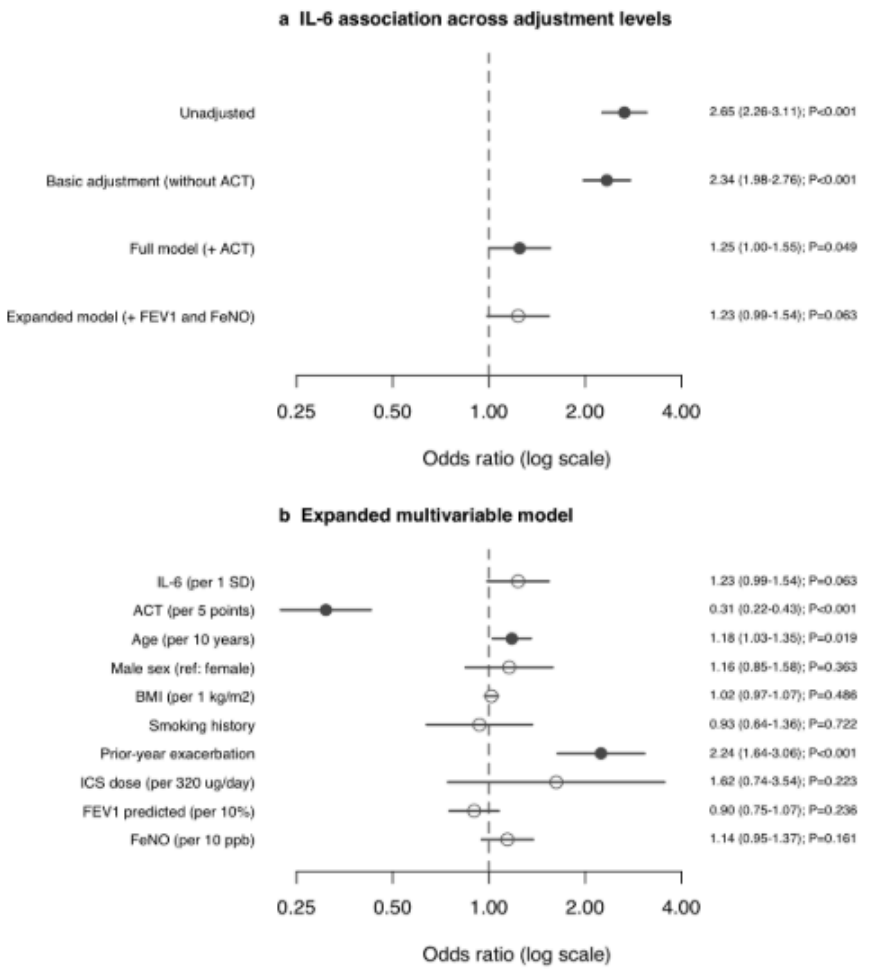


Figure 2

Associations of serum IL-6 and ACT with 12-month exacerbation filled circles indicate P < 0.05 and open circles indicate P ≥ 0.05. Points represent ORs, horizontal lines represent 95% CIs and the vertical dashed line indicates OR = 1. Model 1 adjusted for basic clinical covariates; model 2 added ACT; model 3 additionally included FEV_1 % predicted and FeNO.

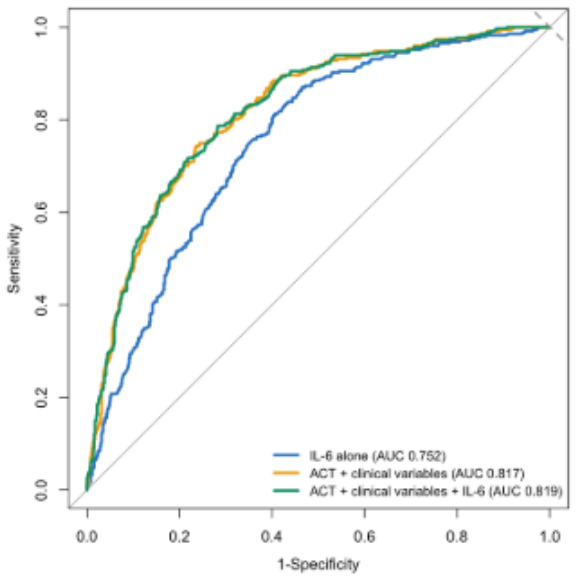


Figure 3

ROC curves for predicting 12-month exacerbation

The blue line represents IL-6 alone, the orange line represents the reference model comprising ACT and prespecified clinical variables, and the green line represents the combined model with IL-6 added to the reference model. The diagonal dashed line represents no discrimination.

Supplementary Files

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