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Systemic Inflammatory Biomarkers Associated with More Severe Disease Status in Bronchial Asthma

Jiayan Qian, Guanglin Shi, and Xinxin Mao

Department of Respiratory and Critical Care Medicine, Nantong No.1 Geriatric Hospital, Nantong, China

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ABSTRACT

This systematic review and meta-analysis evaluated associations between peripheral blood systemic inflammatory biomarkers and clinically worse asthma-related status. PubMed and China National Knowledge Infrastructure were searched through December 2025. Two reviewers independently screened studies, extracted data, and assessed methodological quality using the Newcastle–Ottawa Scale or an adapted framework.

Eighteen studies were included in the systematic review; 7 provided data suitable for quantitative pooling, yielding 16 comparisons. Random-effects meta-analyses evaluated high-sensitivity C-reactive protein (hs-CRP; 7 comparisons), interleukin-6 (IL-6; 5), neutrophil-to-lymphocyte ratio (NLR; 2), and platelet-to-lymphocyte ratio (PLR; 2) using standardized mean differences (SMDs).

hs-CRP was positively associated with worse asthma-related status (SMD=0.95; 95% CI, 0.69–1.21; I^2=63.13%). NLR (SMD=1.30; 95% CI, 1.11–1.49; I^2=0.00%) and PLR (SMD=1.22; 95% CI, 1.03–1.41; I^2=0.00%) also showed positive associations, although only 2 comparisons were available for each. IL-6 showed an upward trend that was not statistically significant (SMD=1.90; 95% CI, −0.09 to 3.89; I^2=98.50%).

Peripheral blood systemic inflammatory biomarkers may provide complementary information for asthma assessment. hs-CRP had the most consistent evidence, whereas findings for NLR and PLR remain preliminary and IL-6 requires cautious interpretation because of substantial heterogeneity. These biomarkers should not replace established clinical evaluation, lung function testing, or type 2 inflammatory biomarkers.

Keywords: Asthma; Biomarkers; C-reactive protein; Inflammation; Interleukin-6

INTRODUCTION

Bronchial asthma is a common respiratory disease characterized primarily by chronic airway inflammation, variable airflow limitation, and airway hyperresponsiveness. It is marked by a prolonged course, recurrent attacks, and substantial heterogeneity. Although the use of inhaled corticosteroids (ICS), long-acting bronchodilators, and various biologic agents has markedly improved clinical outcomes in some patients in recent years, asthma remains a major global chronic disease burden, especially among patients with poor

Corresponding Author: Xinxin Mao, BM;
Department of Respiratory and Critical Care Medicine, Nantong No.1 Geriatric Hospital, Nantong, China. Tel: (+86 513) 8088 6121, Email: 15162816527@163.com

*The first and second authors contributed equally to this study

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disease control, frequent exacerbations, and severe disease. In these groups, asthma continues to place a heavy burden on patients and healthcare systems.[1] Current management guidelines indicate that asthma severity cannot be defined by a single symptom or laboratory index alone, but should instead be judged comprehensively on the basis of symptom control, prior exacerbation history, lung function, and the treatment intensity required to maintain control.[1] This highlights the clinical need for simpler, more objective, and reproducible auxiliary markers to improve disease stratification and risk identification.

For a long time, asthma has mainly been understood as an inflammatory disease confined to the airways, with core pathological processes including airway mucosal inflammation, inflammatory cell infiltration, smooth-muscle contraction, and airway remodeling. However, increasing evidence suggests that patients with more severe disease, recurrent acute exacerbations, obesity-related asthma, and refractory asthma often exhibit not only local airway inflammation but also varying degrees of low-grade systemic inflammation.[2–4] This systemic inflammation may be more than a mere accompanying phenomenon; through mechanisms such as immune dysregulation, metabolic disturbance, endothelial dysfunction, and inflammation-coagulation interaction, it may further increase disease burden and influence lung function, disease control, and the risk of acute exacerbations. Therefore, expanding the conceptual framework from "local airway inflammation" to the coexistence of local and systemic inflammation may help us better understand the complex phenotypes of asthma and differences in disease severity.

In current clinical practice, the more established inflammation-related biomarkers of asthma include blood eosinophils, fraction of exhaled nitric oxide (FeNO), total immunoglobulin E (IgE), and sputum cytology indices. These markers are valuable for identifying type 2 inflammation, guiding targeted therapy, and predicting treatment response.[1] However, they also have limitations. Most of them are more closely related to specific inflammatory pathways and may not comprehensively reflect the complex background of systemic inflammation. Some are greatly influenced by medications, sampling time, and assay platforms, and some tests cannot always be obtained conveniently and consistently in primary care settings. By contrast, systemic inflammatory markers derived from peripheral blood counts or serum inflammatory responses, such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII), have gradually become a research focus in the assessment of asthma severity because they are simple to measure, relatively inexpensive, and reasonably reproducible.

Among these candidate markers, hs-CRP is one of the earliest indicators used to reflect the systemic inflammatory burden of asthma. Previous studies have shown that hs-CRP levels may be higher in patients with asthma than in healthy individuals and, in some studies, have been associated with decreased lung function, poor control, and more severe disease.[5–8] Takemura et al[5] reported that hs-CRP was associated with airflow limitation and airway inflammation, Qian et al[6] suggested that higher hs-CRP levels were independently associated with severe asthma, and Monadi et al[7] found higher hs-CRP levels in patients with poor control. However, Sigari and Ghasri[8] did not observe significant associations between hs-CRP and forced expiratory volume in 1 second (FEV_1), FeNO, or control scores, suggesting that although hs-CRP may have potential value, its actual effect is still influenced by disease stage, phenotype composition, and confounding factors.

IL-6 represents a more upstream inflammatory mediator. As an important inflammatory mediator secreted by a variety of immune cells, epithelial cells, and endothelial cells, IL-6 not only participates in amplification of acute inflammation but is also closely related to metabolic dysfunction, obesity, T_H17-related responses, and chronic tissue remodeling. Peters et al[3] showed that elevated plasma IL-6 was associated with severe asthma, poorer lung function, and metabolic abnormalities, and Jackson et al[9] in a pediatric asthma study, further found that higher IL-6 was associated with increased risk of future exacerbations.

Meanwhile, blood count-derived indices such as NLR and PLR have received increasing attention in recent years. Increased neutrophils may reflect heightened innate immunity and inflammatory activation, whereas relative lymphopenia suggests stress status and impaired immune regulation. Platelet activation is also closely related to inflammation, vascular responses, and tissue injury. Therefore, in theory, NLR and PLR may be more sensitive than single cell counts in reflecting systemic inflammatory burden. Previous systematic reviews and meta-analyses have

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suggested that NLR is generally elevated in patients with asthma and is associated with severity stratification and acute exacerbations, and that PLR may also have auxiliary value in pediatric populations.[10–12] However, existing studies have mostly focused on individual markers, and their endpoint definitions are not uniform, often mixing mild/moderate/severe stratification, control status, acute exacerbations, and hospitalization risk. This creates some fragmentation in the clinical interpretation of the evidence.

On this basis, the present study focused on the association between systemic inflammatory biomarkers and clinically worse asthma-related status in patients with bronchial asthma. The term "more severe disease status" in this study refers to a composite adverse asthma-related status, including severe asthma stratification, poor or uncontrolled asthma, acute exacerbation, hospitalization, and asthma-versus-control comparisons. These outcomes are clinically related but not biologically identical. Therefore, the present meta-analysis was designed to evaluate the overall direction and strength of association between systemic inflammatory biomarkers and worse asthma-related status, rather than to establish a single biomarker-based model for direct severity prediction. Among the available biomarkers, hs-CRP, IL-6, NLR, and PLR were selected for quantitative synthesis because they were the most frequently reported indicators with extractable continuous data and were closely related to systemic inflammatory burden, cytokine activation, and routine blood-cell-derived inflammatory responses.

MATERIALS AND METHODS

Literature Sources and Search Strategy

This systematic review and meta-analysis were reported in accordance with the PRISMA 2020 statement. Studies indexed in PubMed and China National Knowledge Infrastructure (CNKI), together with full-text articles that had already been obtained, were used as the main data sources. The final literature search was conducted in December 2025, and no subsequent search update was performed after this date.

The PubMed search strategy was based on a combination of subject-related and biomarker-related terms. The main search string was as follows: ("asthma" OR "bronchial asthma") AND ("severity" OR "control" OR "exacerbation" OR "hospitalization" OR "severe asthma" OR "uncontrolled asthma") AND ("high-sensitivity C-reactive protein" OR "hs-CRP" OR "C-reactive protein" OR "interleukin-6" OR "IL-6" OR "neutrophil-to-lymphocyte ratio" OR "NLR" OR "platelet-to-lymphocyte ratio" OR "PLR" OR "systemic immune-inflammation index" OR "SII" OR "MMP-9" OR "IL-16" OR "MCP-1" OR "TNF-α" OR "IL-33" OR "TGF-β1" OR "miR-30"). Similar Chinese search terms were used in CNKI, including bronchial asthma, asthma severity, asthma control, acute exacerbation, hospitalization, hs-CRP, IL-6, NLR, PLR, and systemic inflammatory markers. No restrictions were imposed on publication date or language during the search process.

Two reviewers independently screened titles, abstracts, and full texts. Disagreements were resolved through discussion, and when necessary, by consultation with a third reviewer. Two reviewers independently extracted the relevant data. The review protocol was not registered in the International Prospective Register of Systematic Reviews (PROSPERO), which is acknowledged as a study limitation.

Outcome Definition

The primary outcome of this study was the association between peripheral blood systemic inflammatory biomarkers and clinically worse asthma-related status. In this study, "more severe disease status" was defined as a composite adverse asthma-related condition, including severe asthma stratification, poor or uncontrolled asthma, acute exacerbation, hospitalization, or asthma-versus-healthy-control comparisons. These categories were not considered biologically identical. They were pooled because all reflected clinically worse asthma-related conditions or greater disease burden. Therefore, the pooled estimates should be interpreted as exploratory evidence of association rather than as direct evidence of linear severity prediction.

For further interpretation, comparisons were classified into 4 outcome domains according to clinical meaning: asthma versus healthy controls, severity stratification, control status, and acute phase or exacerbation-related status.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) the study population consisted of patients with a clear diagnosis of bronchial asthma based on physician diagnosis, guideline-based criteria, or clearly stated clinical diagnostic criteria; (2) pediatric and adult populations

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were both eligible if asthma-related data could be interpreted separately; (3) the study reported at least 1 peripheral blood systemic inflammatory biomarker, including but not limited to hs-CRP, IL-6, NLR, PLR, SII, MMP-9, IL-16, MCP-1, TNF-α, IL-33, TGF-β1, or microRNA-30 (miR-30); (4) the study included comparisons reflecting asthma-related disease burden, such as asthma versus healthy controls, mild/moderate/severe stratification, well-controlled versus poorly controlled disease, acute exacerbation versus stable phase, or hospitalized versus non-hospitalized status; (5) sample size and mean±standard deviation could be extracted for quantitative pooling, or effect sizes such as OR, RR, AUC, correlation coefficients, or descriptive results could be obtained for qualitative synthesis; and (6) the full text was available and the data were interpretable.

The exclusion criteria were as follows: (1) reviews, systematic reviews, meta-analyses, case reports, conference abstracts without sufficient data, and animal experiments; (2) studies focusing only on local airway markers without peripheral blood systemic inflammatory biomarkers; (3) studies lacking extractable or interpretable data; (4) studies with seriously mixed populations in which asthma data could not be separately isolated; and (5) duplicate publications or studies with clearly overlapping populations in which the independent dataset could not be determined.

Laboratory assay methods were accepted if the biomarker measurement was clearly described or interpretable from the original article. Corticosteroid exposure, including inhaled or systemic corticosteroid use, was extracted when reported. However, because adjustment for corticosteroid exposure was inconsistent across studies, medication exposure could not be quantitatively controlled in the pooled analysis and was considered in the interpretation of heterogeneity. The methodological quality of the included observational studies was assessed using the Newcastle–Ottawa Scale or an adapted Newcastle–Ottawa Scale framework according to study design. The results are summarized in Supplementary Table 1.[15,16,19–21]

Statistical Analysis

For studies reporting continuous variables with means, standard deviations, and sample sizes, standardized mean differences (SMDs) and their 95% CIs were used as pooled effect sizes. SMDs were calculated as Hedges' g to reduce small-sample bias. Given the differences across studies in population characteristics, disease stage, comparison methods, and detection platforms, the primary analyses were conducted using random-effects models with restricted maximum likelihood estimation.

Between-study heterogeneity was evaluated using the I^2 statistic. I^2 values of approximately 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Subgroup analysis was performed for hs-CRP by outcome domain because sufficient comparisons were available. Additional subgroup analyses according to age group, study design, disease phase, asthma phenotype, and geographic region were planned but were not formally performed because the number of comparisons for IL-6, NLR, and PLR was too small for reliable subgroup analysis or meta-regression.

Leave-one-out sensitivity analysis was performed for IL-6 to evaluate the stability of the pooled result. Because some studies contributed multiple comparisons from overlapping populations, the potential non-independence of comparisons was considered during interpretation. Where possible, sensitivity analysis retaining only 1 clinically representative comparison per study was considered. However, because the number of available studies for each marker was limited, formal multilevel meta-analysis was not statistically robust, and the pooled results were interpreted mainly as exploratory associations.

Studies reporting only ORs, RRs, AUCs, correlation coefficients, medians/IQRs, or descriptive results were not included in the primary continuous-variable meta-analysis. Effect conversion was not attempted because the required distributional assumptions, baseline risks, and auxiliary statistics were not consistently available across studies. Converting these effect measures could have introduced additional uncertainty and reduced interpretability. These studies were therefore integrated descriptively as supplementary evidence.

Publication bias was considered but was not formally tested using Egger's test because fewer than 10 comparisons were available for each marker, making funnel plot asymmetry and regression-based tests unreliable. Potential publication bias and small-study effects were therefore discussed qualitatively as limitations. Figures and major pooled analyses were completed in Stata 16.0.

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RESULTS

Included Studies and Basic Characteristics

A total of 18 studies were included in the systematic review and data extraction. The study-selection process is summarized in Supplementary Figure 1.

The included studies were conducted in regions including China, Japan, the United States, Iran, India, Israel, and Saudi Arabia, and the designs were mainly case-control, cross-sectional, retrospective, and cohort observational studies (Tables 1 and 2).[3,5,7–9,13–25]

Studies included in the systematic review but not incorporated into the primary continuous-variable meta-analysis, together with reasons for non-pooling, are summarized in Supplementary Table 2.[3,8,9,13,14,18–21,24,25]

Baseline differences across studies, including study design, age group, disease phase, comparison domain, and biomarker type, are summarized in Supplementary Table 3.[3,5,7–9,13–25]

Table 1. Characteristics of studies included in the systematic review of systemic inflammatory biomarkers in asthma.

First author	Year, country	Design and sample size	Age, y	Sex, male/female	Main grouping	Main indicators
Takemura[5]	2006, Japan	Cross-sectional/ case-control; asthma 45, control 14	NR	NR	Steroid-naive 22; ICS treatment 23; healthy 14	hs-CRP
Ramirez[13]	2010, United States	Cross-sectional; asthma 54	27.6±16.1	NR	Well controlled 27; partly/uncontrolled 27	hs-CRP
Sigari and Ghasri[8]	2013, Iran	Prospective case-control; asthma 100	NR	43/57	GINA: well controlled 59, partly controlled 30, uncontrolled 11; ACT ≥20: 61, 16–19: 26, ≤15: 13	hs-CRP
Bai and Chen[14]	2015, China	Grouped clinical study; acute 30, remission 30, control 32	Acute 39±3; remission 41±4; control 40±3	Acute 16/14; remission 18/12; control 17/15	Acute exacerbation, remission, healthy controls; within the acute phase: mild 12, moderate-to-severe 18	IL-16, MCP-1
Naik et al[15]	2015, India	Case-control; asthma 50, control 30	39.94±11.75	Matched	Moderate persistent 25; severe persistent 25; healthy 30	IL-6, MMP-9
Liu et al[16]	2016, China	Retrospective; asthma 162	43±12	85/77	Intermittent 28; mild persistent 42; moderate persistent 76; severe persistent 16	hs-CRP
Monadi et al[7]	2016, Iran	Case-control; asthma 120, control 115	48±10	NR	Well controlled 80; poorly controlled 40	hs-CRP
Peters et al[3]	2016, United States	Pooled cross-sectional analysis; asthma 695	NR	NR	High IL-6 expression group vs low-expression group	IL-6

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Table 1. Continued...

First author	Year, country	Design and sample size	Age, y	Sex, male/female	Main grouping	Main indicators
Shi et al[17]	2017, China	Case-control/ cross-sectional; acute exacerbation 262, control 130	NR	NR	Critical 87; non-critical 175; healthy 130	NLR, PLR
Ren et al[18]	2018, China	Case-control + follow-up; asthma 199, control 174	Asthma 47.4±4.5; control 46.6±5.3	112/87; 88/86	Acute 65; chronic persistent 46; remission 88; within the acute phase: mild 18, moderate 22, severe 25	TNF-α, IL-8, ECP
Jackson et al[9]	2020, United States	Post-hoc cohort analysis; asthma 702	6–17 y	NR	IL-6 quartiles; follow-up risk of exacerbation	IL-6
Esmaeilzadeh et al[19]	2021, Iran	Cross-sectional; asthma 211	NR	124/87	Hospitalized 91; non-hospitalized 120	NLR, EOS
Yu et al[20]	2021, China	Retrospective; asthma 92	Mild 52.63±11.89; moderate 51.57±13.32; severe 53.38±12.69	Mild 9/18; moderate 11/17; severe 16/21	Mild 27; moderate 28; severe 37	SII,CRP,Neu, Plt,Lym
Arwas et al[21]	2023, Israel	Emergency database cross-sectional study; 831 visits	NR	NR	NLR quartiles	NLR
Asseri[22]	2024, Saudi Arabia	Case-control; acute 128, stable 131	Acute 5.32±2.5; stable 5.12±1.2	Boys 37% vs 64%	Acute exacerbation group vs stable-phase group	NLR, PLR,WBC, ANC,ALC, Platelets
Xiao et al[23]	2024, China	Case-control; asthma 80, control 80	Asthma 60.85±5.93; control 59.93±5.96	49/31; 50/30	Mild 28; moderate 34; severe 18; healthy 80	miR-30, TGF-β1, IL-6, IL-33, TNF-α, EOS
Zhang and Ren[24]	2025, China	Cross-sectional; asthma 50	58.73±5.20	28/22	Mild 15; moderate 18; severe 17	FeNO, TNF-α, IL-8, blood EOS

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Table 1. Continued...

First author	Year, country	Design and sample size	Age, y	Sex, male/female	Main grouping	Main indicators
Feng et al[25]	2026, China	Case-control; asthma 115, control 42	Asthma 45.12±12.21; control 43.31±10.24	66/49; 25/17	Mild 57; moderate 47; severe 11; healthy 42	GRP78, IL-4, IL-13, IL-17, IFN-γ

NR: not reported; ICS: inhaled corticosteroids. hs-CRP was generally reported in mg/L, IL-6 in pg/mL, whereas NLR and PLR are unitless blood-cell-derived ratios. Because reference ranges vary across laboratories, populations, age groups, and assay platforms, normal reference values were not used for quantitative pooling. ACT: Asthma Control Test; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; CRP: C-reactive protein; ECP: eosinophil cationic protein; EOS: eosinophils; FeNO: fraction of exhaled nitric oxide; GINA: Global Initiative for Asthma; GRP78: glucose-regulated protein 78; hs-CRP: high-sensitivity C-reactive protein; ICS: inhaled corticosteroids; IFN-γ: interferon-γ; IL-4: interleukin-4; IL-6: interleukin-6; IL-8: interleukin-8; IL-13: interleukin-13; IL-16: interleukin-16; IL-17: interleukin-17; IL-33: interleukin-33; Lym: lymphocytes; MCP-1: monocyte chemoattractant protein-1; miR-30: microRNA-30; MMP-9: matrix metalloproteinase-9; Neu: neutrophils; NLR: neutrophil-to-lymphocyte ratio; NR: not reported; PLR: platelet-to-lymphocyte ratio; Plt: platelets; SII: systemic immune-inflammation index; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor-α; WBC: white blood cell.

Table 2. Studies included in the primary meta-analysis and comparison methods

Indicator	First author	Year	Comparison	Outcome domain	Experimental group, n	Control group, n
hs-CRP	Takemura[5]	2006	Steroid-naive asthma vs healthy controls	asthma vs control	22	14
hs-CRP	Liu et al[16]	2016	Moderate-to-severe persistent vs intermittent + mild persistent	severity	92	70
hs-CRP	Liu et al[16]	2016	Severe persistent vs non-severe	severity	16	146
hs-CRP	Liu et al[16]	2016	Uncontrolled vs fully controlled	control status	25	65
hs-CRP	Liu et al[16]	2016	Uncontrolled vs non-uncontrolled	control status	25	137
hs-CRP	Monadi et al[7]	2016	Asthma vs healthy controls	asthma vs control	120	115
hs-CRP	Monadi et al[7]	2016	Poorly controlled vs well controlled	control status	40	80
IL-6	Naik et al[15]	2015	Asthma vs healthy controls	asthma vs control	50	30
IL-6	Naik et al[15]	2015	Severe persistent vs moderate persistent	severity	25	25
IL-6	Xiao et al[23]	2024	Asthma vs healthy controls	asthma vs control	80	80
IL-6	Xiao et al[23]	2024	Moderate-to-severe vs mild	severity	52	28
IL-6	Xiao et al[23]	2024	Severe vs non-severe	severity	18	62
NLR	Shi et al[17]	2017	Critical acute exacerbation vs non-critical acute exacerbation	severity	87	175
NLR	Asseri[22]	2024	Acute exacerbation phase vs stable phase	acute phase	128	131
PLR	Shi et al[17]	2017	Critical acute exacerbation vs non-critical acute exacerbation	severity	87	175
PLR	Asseri[22]	2024	Acute exacerbation phase vs stable phase	acute phase	128	131

The primary meta-analysis included 7 studies and 16 combinable comparisons, including 7 comparisons for hs-CRP, 5 for IL-6, 2 for NLR, and 2 for PLR. Some studies contributed more than one comparison derived from related or partially overlapping populations; therefore, the pooled estimates should be interpreted as exploratory associations rather than fully independent effect estimates. hs-CRP was generally reported in mg/L, IL-6 in pg/mL, whereas NLR and PLR are unitless ratios.
hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

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RESULTS

Meta-analysis Results for hs-CRP and More Severe Asthma-related Status

A total of 7 comparisons were included in the primary meta-analysis of hs-CRP. Because the included comparisons simultaneously covered different outcome domains-such as asthma versus healthy controls, control-status stratification, and severity stratification-these findings are better interpreted as showing an overall association between hs-CRP and more severe asthma status, rather than a strictly linear severity-stratification effect in a single sense. The random-effects model showed that hs-CRP levels were overall higher in the group with more severe disease status or in the asthma group than in the group with less severe disease status or healthy controls, with a pooled effect size of SMD=0.95 (95% CI: 0.69–1.21; I^2=63.13%). Further subgroup analysis showed that in the asthma-versus-control comparison, the pooled effect size was 0.65 (95% CI: 0.41–0.90); in the control-status domain, it was 0.89 (95% CI: 0.52–1.26); and in the severity domain, it was 1.31 (95% CI: 1.02–1.60). In terms of effect size, hs-CRP appeared to show a stronger association in the severity-stratification domain than in the asthma-versus-control and control-status domains. However, this finding should be interpreted as subgroup-level exploratory evidence rather than as definitive proof of severity prediction (Figure 1).

Meta-analysis Results for IL-6 and More Severe Asthma-related Status

A total of 5 comparisons from 2 studies were included in the primary meta-analysis of IL-6. The random-effects model showed that IL-6 levels in the group with more severe disease status or in the asthma group had an overall upward trend, with a pooled effect size of SMD=1.90 (95% CI: −0.09 to 3.89; I^2=98.50%). Because the 95% CI crossed 0 and the overall test yielded p=0.06, this pooled result did not reach statistical significance. Therefore, the IL-6 result should be interpreted as an unstable upward trend rather than definitive pooled evidence of association (Figure 2).

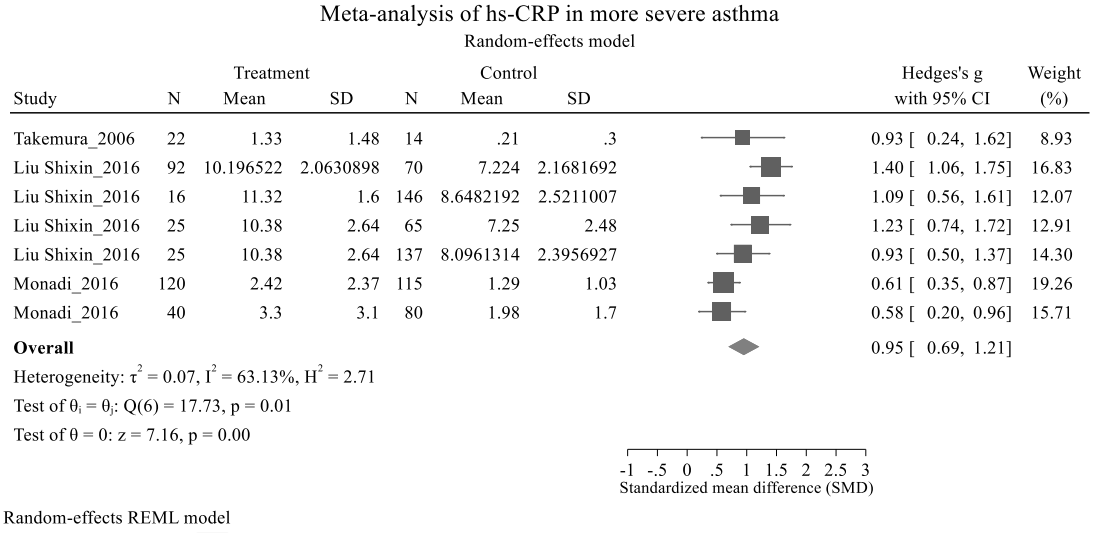

Figure 1. Forest plot of the meta-analysis of hs-CRP and more severe asthma-related status. Effect sizes are presented as Hedges' g standardized mean differences with 95% confidence intervals. Pooled estimates were calculated using a random-effects restricted maximum likelihood model. Positive values indicate higher hs-CRP levels in the more severe disease-status group or asthma group.

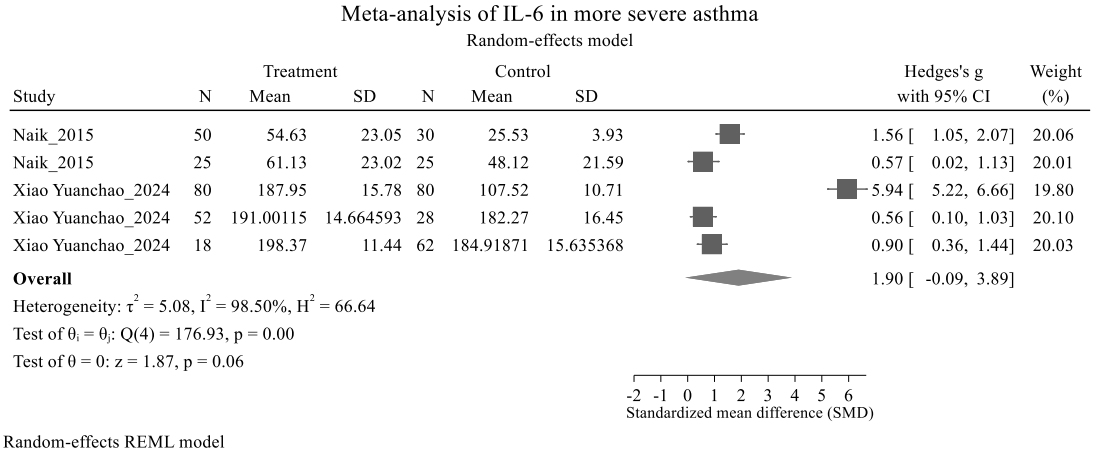

Figure 2. Forest plot of the meta-analysis of IL-6 and more severe asthma-related status. Effect sizes are presented as Hedges' g standardized mean differences with 95% confidence intervals. Pooled estimates were calculated using a random-effects restricted maximum likelihood model. Positive values indicate higher IL-6 levels in the more severe disease-status group or asthma group. Because the 95% confidence interval of the pooled estimate crossed zero and heterogeneity was very high, the pooled IL-6 result should be interpreted cautiously.

The very high heterogeneity indicates that the IL-6 findings were strongly influenced by differences in study population, age structure, disease phase, comparison framework, assay platform, and potential confounding factors such as obesity, metabolic dysfunction, infection, smoking, and corticosteroid exposure. Leave-one-out sensitivity analysis showed that the overall direction of effect did not reverse after sequential omission of individual comparisons; however, the pooled effect estimates fluctuated substantially across the leave-one-out models, as shown in Figure 3.

Meta-analysis Results for NLR and More Severe Asthma-related Status

Two studies were included in the primary meta-analysis of NLR. The relevant comparisons came from stratification of severe acute exacerbation and from comparisons between the acute exacerbation phase and the stable phase; therefore, the results mainly reflect the association between NLR and more severe asthma-related status, particularly exacerbation-related status. The random-effects model showed that NLR was higher in the group with more severe disease status than in the group with less severe disease status, with a pooled effect size of SMD=1.30 (95% CI: 1.11–1.49; I^2=0.00%). This result suggests a positive association between NLR and more severe asthma-related status. However, because only 2 comparisons were available, the apparent consistency and low heterogeneity should be interpreted cautiously, and further studies are needed to confirm its stability and generalizability (Figure 4).

Meta-analysis Results for PLR and More Severe Asthma-related Status

Two studies were included in the primary meta-analysis of PLR. Because the included comparisons mainly involved acute exacerbation and other more severe asthma-related scenarios, the results should be regarded as evidence of association between PLR and worse asthma-related status rather than as direct evidence for all severity-stratification settings. The random-effects model showed that PLR levels were higher in the group with more severe disease status than in the group with less severe disease status, with a pooled effect size of SMD=1.22 (95% CI: 1.03–1.41; I^2=0.00%). This result suggests a positive association between PLR and more severe asthma-related status. However, because only 2 comparisons were included, the conclusion regarding consistency remains preliminary and should be generalized with caution (Figure 5).

Summary of Main Findings

Taken together, the primary meta-analysis showed that hs-CRP, NLR, and PLR were positively associated with clinically worse asthma-related status. hs-CRP had the largest number of comparisons and showed a moderate degree of heterogeneity, while subgroup

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analysis suggested that its association may be stronger in the severity-stratification domain (Figure 6).

IL-6 showed an upward trend, but the pooled result did not reach statistical significance and heterogeneity was extremely high. NLR and PLR showed positive associations with low statistical heterogeneity, but these results were based on only 2 comparisons for each marker. Therefore, the current evidence supports the potential auxiliary value of these biomarkers in identifying worse asthma-related status, but does not support their use as stand-alone markers for strict linear severity prediction (Figures 6 and 3).

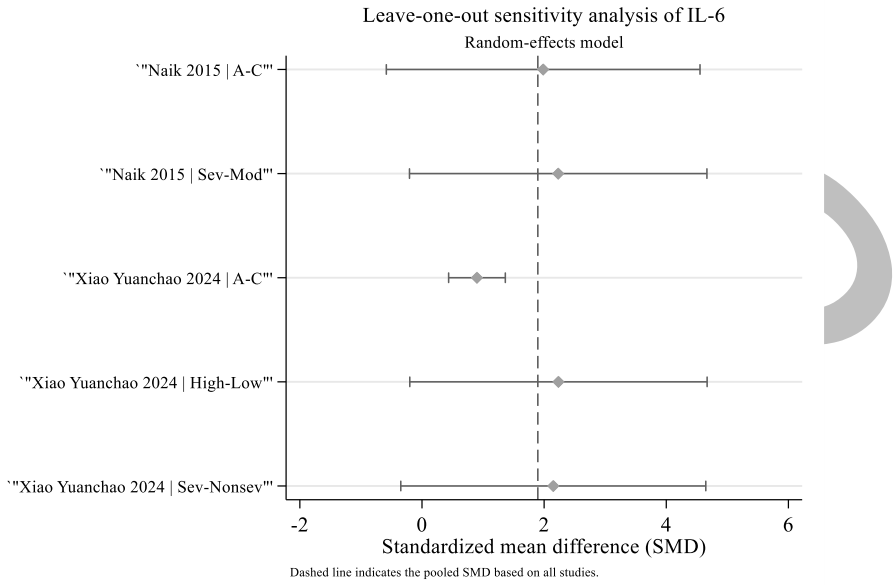

Figure 3. Leave-one-out sensitivity analysis for IL-6. Each estimate represents the pooled standardized mean difference after sequential omission of one individual comparison. The dashed line indicates the overall pooled estimate based on all included comparisons. The direction of effect did not reverse after omission of individual comparisons, but the magnitude of the pooled estimate fluctuated substantially, indicating instability of the IL-6 result.

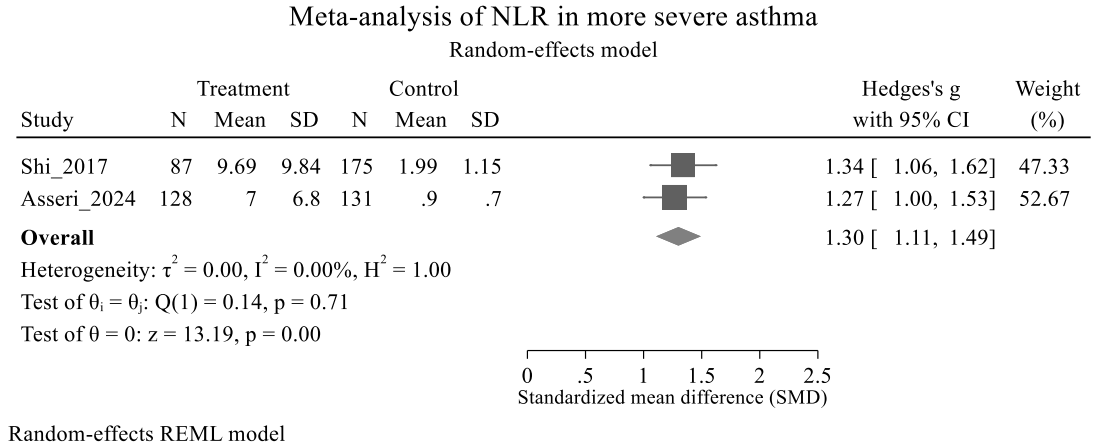

Figure 4. Forest plot of the meta-analysis of NLR and more severe asthma-related status. Effect sizes are presented as Hedges' g standardized mean differences with 95% confidence intervals. Pooled estimates were calculated using a random-effects restricted maximum likelihood model. Positive values indicate higher NLR in the more severe disease-status group. Because only two comparisons were available, the result should be interpreted as preliminary.

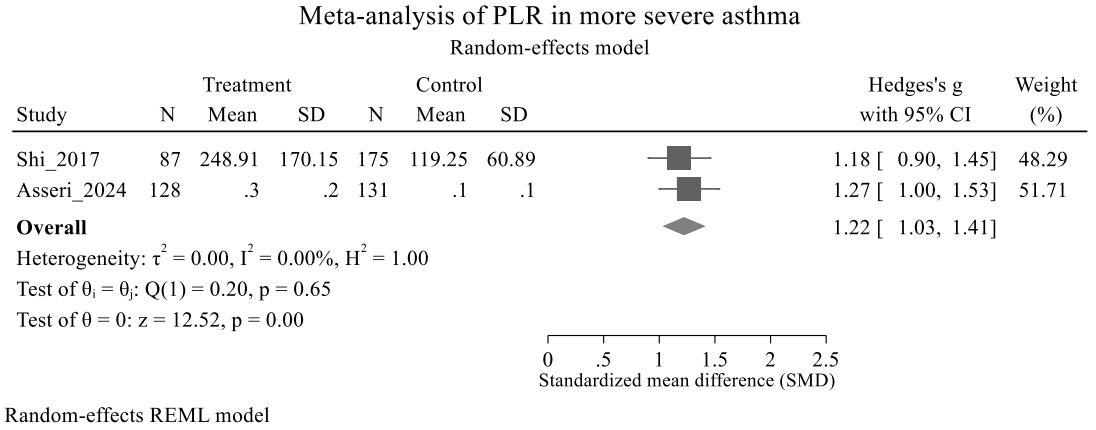

Figure 5. Forest plot of the meta-analysis of PLR and more severe asthma-related status. Effect sizes are presented as Hedges' g standardized mean differences with 95% confidence intervals. Pooled estimates were calculated using a random-effects restricted maximum likelihood model. Positive values indicate higher PLR in the more severe disease-status group. Because only two comparisons were available, the result should be interpreted as preliminary.

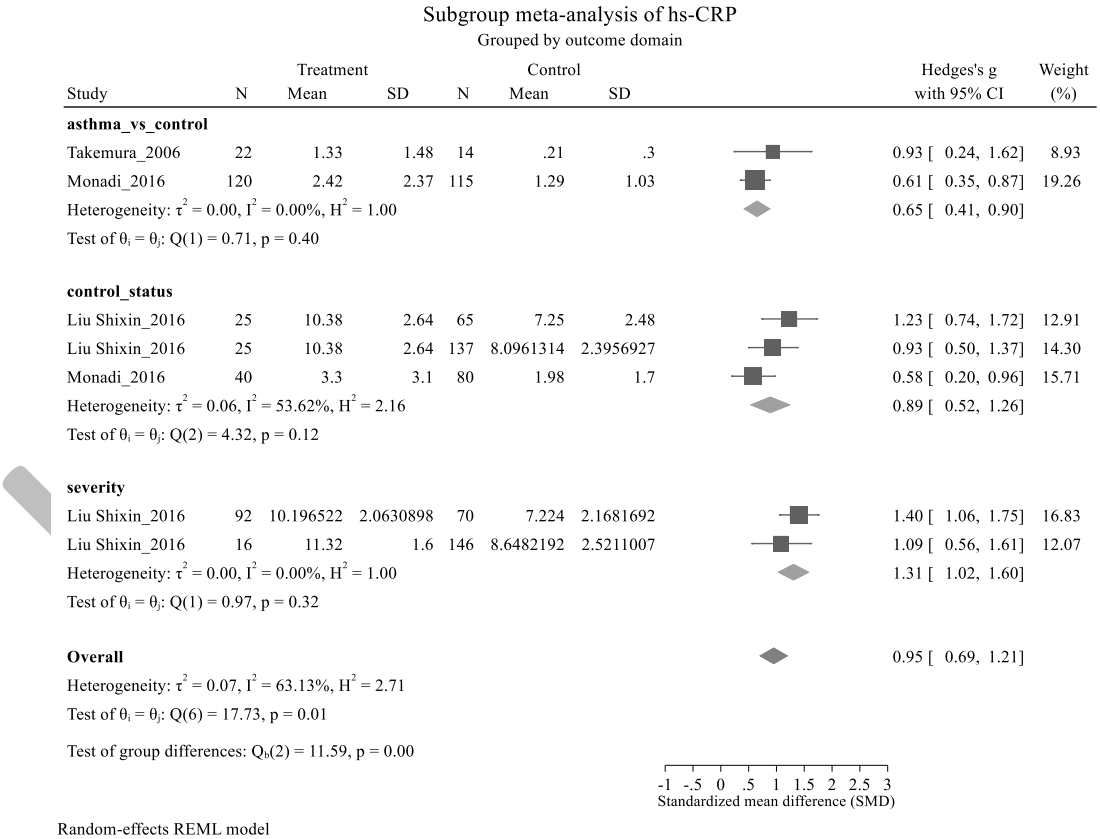

Figure 6. Subgroup forest plot of the meta-analysis of hs-CRP stratified by outcome domain. "Asthma vs control" refers to comparisons between patients with asthma and healthy controls; "control status" refers to poorly controlled or uncontrolled asthma versus well-controlled asthma; and "severity" refers to comparisons between more severe and less severe asthma categories. Effect sizes are presented as Hedges' g standardized mean differences with 95% confidence intervals. Pooled estimates were calculated using a random-effects restricted maximum likelihood model.

DISCUSSION

This study systematically reviewed the association between peripheral blood systemic inflammatory biomarkers and clinically worse asthma-related status in patients with bronchial asthma. Based on the included studies, quantitative pooling was performed for 4 indicators with relatively complete continuous-variable data: hs-CRP, IL-6, NLR, and PLR. The results showed positive associations for hs-CRP, NLR, and PLR. IL-6 showed an upward trend, but the pooled result did not reach statistical significance and heterogeneity was extremely high. Overall, these findings suggest that systemic inflammatory biomarkers may provide complementary information for identifying worse asthma-related status, but they should not be interpreted as independent or stand-alone tools for direct asthma severity prediction.

From the perspective of disease understanding, the findings of this study are consistent with current concepts of asthma management. Existing management concepts and consensus studies generally hold that asthma severity should be judged comprehensively according to the treatment intensity required to achieve control, symptom control, lung function, and prior exacerbation history, rather than being directly defined by a single marker.[1] This means that no inflammatory biomarker can replace the current assessment system. However, if some markers can stably indicate "more severe disease" or "greater inflammatory burden," they may play a role in risk identification or auxiliary stratification in routine management. This is particularly meaningful in clinical settings where lung-function testing has not yet been completed, specialized inflammatory pathway markers have not been measured, or resources are limited.

Among the 4 main indicators, the result for hs-CRP has relatively strong clinical interpretability. CRP is not an asthma-specific molecule; rather, it is a typical acute-phase reactant synthesized mainly by the liver in response to stimulation by upstream inflammatory cytokines such as IL-6 and TNF-α. Therefore, it is closer to a downstream amplification signal of overall inflammatory burden. In this study, the overall pooled effect size for hs-CRP was 0.95, and subgroup analysis showed that the effect size in the severity domain was larger than that in the control-status domain and the asthma-versus-control comparison, suggesting that hs-CRP may be more suitable for identifying patients whose disease burden has already increased substantially, rather than for simple asthma screening. This is generally consistent with the direction of previous original studies: Takemura et al[5] reported that hs-CRP was associated with airflow limitation and increased sputum eosinophils, Qian et al[6] suggested an association with severe asthma, and Monadi et al[7] found higher levels in patients with poor control.

However, the moderate heterogeneity of hs-CRP also reminds us that it should not be regarded as a universally stable marker. CRP is clearly influenced by obesity, infection, smoking, metabolic abnormalities, cardiovascular comorbidities, and recent steroid exposure. Ramirez et al[13] in relatively well-controlled outpatients with asthma, did not observe a significant association between hs-CRP and FEV_1 or control scores. This indicates that the discriminatory ability of hs-CRP depends to a large extent on the disease stage and inflammatory burden of the study population. When the overall inflammatory activity of the study population is low, the effect of hs-CRP may be weakened; when disease burden is already clearly separated, its discriminatory capacity becomes more apparent. Therefore, in clinical application, hs-CRP is better interpreted together with symptoms, lung function, and prior exacerbation history rather than being used in isolation.

IL-6 was the indicator with the largest pooled point estimate but also the strongest heterogeneity in this study. Unlike downstream acute-phase proteins such as hs-CRP, IL-6 lies at a more upstream regulatory level of inflammation and may be influenced by asthma-related inflammation, obesity, insulin resistance, T_H17-related responses, infection, smoking, corticosteroid exposure, and metabolic dysfunction.[3,9] Therefore, IL-6 may reflect a complex systemic inflammatory and metabolic phenotype rather than asthma severity alone.

In the present pooled analysis, IL-6 tended to be elevated overall, but the 95% CI of the pooled effect size ranged from −0.09 to 3.89, and the overall test yielded p=0.06, which did not reach statistical significance. Between-study heterogeneity reached 98.50%, indicating substantial differences in age structure, comparison method, disease phase, endpoint definition, detection platform, and background metabolic factors. Therefore, the IL-6 result should not be described as a statistically significant increase. It is more appropriate to interpret IL-6 as a hypothesis-generating biomarker that may be related to complex high-risk asthma phenotypes, rather than as a stable marker for direct severity stratification.

The leave-one-out sensitivity analysis further supports

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this cautious interpretation. After sequential exclusion of individual comparisons, the direction of effect did not fundamentally reverse, but the magnitude of the pooled effect fluctuated markedly. This indicates that the IL-6 result was easily influenced by individual comparisons. Given the limited number of included studies, the very high heterogeneity, and possible confounding by obesity or metabolic syndrome, IL-6 should be interpreted with greater caution than hs-CRP, NLR, or PLR.

Compared with hs-CRP and IL-6, NLR and PLR have practical advantages because they are derived from routine blood counts and are inexpensive, convenient, and widely available. NLR integrates information on neutrophil elevation and relative lymphopenia, whereas PLR incorporates platelet-related inflammatory and vascular responses. In this study, NLR and PLR showed positive associations with more severe asthma-related status. However, these findings were based on only 2 comparisons for each marker. Therefore, although the direction of the results was consistent and statistical heterogeneity was low, the conclusion regarding their stability should remain cautious. At present, NLR and PLR may be considered potential auxiliary indicators for risk stratification or monitoring, particularly in exacerbation-related settings, but they should not be regarded as validated stand-alone severity markers.

Another point worth emphasizing is that different inflammatory markers do not lie at the same biological level, and their clinical roles should not be simply treated as equivalent. hs-CRP is more of a downstream acute-phase response marker and is suitable for reflecting overall inflammatory burden. IL-6 is more of an upstream cytokine marker and is suitable for indicating complex high-risk phenotypes. NLR and PLR, by contrast, are routine hemogram-derived indices that combine simplicity with relatively good stability. This means that when comparing these markers, one should not focus only on which value is higher or which SMD is larger; more attention should be paid to which marker is more stable, which is more suitable for routine clinical settings, and which can better complement the existing assessment system. Based on the current evidence, NLR and PLR may be more suitable as auxiliary stratification indicators in outpatient or inpatient settings, hs-CRP as an amplification signal of inflammatory burden, and IL-6 as a marker of complex phenotype and higher-risk status.

It is also important to position these systemic inflammatory biomarkers within the current asthma management framework. Established type 2 inflammatory biomarkers, such as blood eosinophils, FeNO, total IgE, and sputum eosinophils, are more closely related to type 2 airway inflammation and are useful for guiding targeted therapy and predicting treatment response.[1] By contrast, hs-CRP, IL-6, NLR, and PLR are less pathway-specific and may reflect broader systemic inflammation, metabolic comorbidity, infection, smoking-related inflammation, or medication effects. Therefore, their clinical role is not to replace type 2 biomarkers or lung function testing. Instead, they may provide complementary information about systemic inflammatory burden, especially in patients with poor control, frequent exacerbations, obesity-related asthma, or suspected non-type 2 inflammatory features.

From a clinical implementation perspective, these biomarkers are more suitable for auxiliary risk stratification and monitoring than for population screening, definitive phenotype classification, or stand-alone prediction of asthma severity. Their interpretation should be integrated with symptoms, lung function, exacerbation history, medication exposure, FeNO, eosinophil counts, and comorbid conditions.

In addition to the 4 main indicators, this study also reviewed supplementary markers including matrix metalloproteinase-9 (MMP-9), interleukin-16 (IL-16), monocyte chemoattractant protein-1 (MCP-1), systemic immune-inflammation index (SII), GRP78, tumor necrosis factor-α (TNF-α), interleukin-33 (IL-33), transforming growth factor-β1 (TGF-β1), and microRNA-30 (miR-30). Although these markers were not all included in the primary meta-analysis because of the limited number of studies, non-uniform data distributions, or complex data sources, their direction was generally consistent with the main findings. For example, Naik et al[15] reported that MMP-9 was markedly higher in patients with asthma than in controls and was higher in severe persistent asthma than in moderate persistent asthma, and it was negatively correlated with FEV_1% and PEF%. Yu et al[20] found that SII was positively correlated with asthma severity, CRP, and neutrophil count, and negatively correlated with FEV_1%. Bai and Chen[14] found that IL-16 and MCP-1 were elevated during acute exacerbation and were higher in patients with moderate-to-severe disease than in those with mild disease. These findings indirectly suggest that more severe disease status is unlikely to reflect a single-pathway abnormality, but rather coordinated activation of multiple inflammatory networks.

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Strengths and Limitations

This study has several limitations. First, the number of studies available for quantitative synthesis was small, particularly for IL-6, NLR, and PLR. Second, most included studies were observational, so the present findings reflect associations rather than causal relationships. Third, the definition of "more severe disease status" was not standardized across studies and included severity stratification, asthma control status, acute exacerbation, hospitalization, and asthma-versus-control comparisons. These outcomes are clinically related but not fully equivalent, which may contribute to heterogeneity and limits direct interpretation as strict severity prediction. Fourth, systemic inflammatory biomarkers may be influenced by obesity, metabolic abnormalities, infection, smoking, cardiovascular comorbidities, and corticosteroid exposure, while control of these confounders was inconsistent across the included studies. Fifth, some studies contributed multiple comparisons from related or overlapping populations, which may introduce non-independence and affect pooled weights. Finally, publication bias and small-study effects cannot be excluded. Because fewer than 10 comparisons were available for each marker, formal funnel plot analysis or Egger's test would be underpowered and potentially misleading.

Based on these limitations, future studies should include prospective multicenter cohorts with standardized asthma severity criteria, predefined biomarker collection protocols, and consistent adjustment for corticosteroid exposure, obesity, metabolic comorbidities, infection status, and smoking. Future research should also distinguish severity stratification, asthma control, acute exacerbation, and hospitalization as separate endpoints rather than combining them indiscriminately. In addition, joint evaluation models integrating hs-CRP, IL-6, NLR, PLR, SII, lung function, FeNO, blood eosinophils, prior exacerbation history, and treatment intensity may provide a more clinically realistic framework for risk assessment.

In conclusion, this systematic review and meta-analysis suggests that hs-CRP is positively associated with clinically worse asthma-related status. NLR and PLR also showed positive associations, but the evidence remains preliminary because only 2 comparisons were available for each marker. IL-6 showed an overall upward trend, but the pooled result did not reach statistical significance and heterogeneity was extremely high; therefore, its interpretation should remain cautious. Overall, peripheral blood systemic inflammatory biomarkers may provide complementary information for asthma assessment, particularly for auxiliary risk stratification and monitoring. However, they should be interpreted together with clinical characteristics, lung function, exacerbation history, medication exposure, and established type 2 inflammatory biomarkers, rather than being used as stand-alone substitutes for current asthma assessment systems.

STATEMENT OF ETHICS

This study is a systematic review and meta-analysis of previously published studies; therefore, direct institutional review board or ethics committee approval was not required.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data supporting this systematic review and meta-analysis were obtained from published studies cited in the manuscript. The extracted data used in the analyses are available from the corresponding author upon reasonable request via the email address provided in the manuscript.

AI ASSISTANCE DISCLOSURE

Not applicable.

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