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SERUM BIOMARKERS INCLUDING PERIOSTIN AND EOSINOPHILS FOR PREDICTING CLINICAL REMISSION IN SEVERE ASTHMA: A SYSTEMATIC REVIEW

SERUMSKI BIOMARKERI UKLJUČUJUĆI PERIOSTIN I EOZINOFILE ZA PREDVIĐANJE KLINIČKE REMISIJE KOD TEŠKE ASTME: SISTEMATSKI UVID

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Summary

Background: Clinical remission is an emerging, ambitious treatment goal in severe asthma, characterized by sustained absence of symptoms and exacerbations, and normalization of lung function while off or on minimal treatment. Easily accessible predictors are needed to guide therapy. Serum biomarkers represent promising candidates.
Objective: To systematically review and synthesize the evidence on the association between serum biomarker levels and the achievement of clinical remission in patients with severe asthma.
Methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from inception to October 2025 for observational studies and clinical trials reporting serum biomarkers and a predefined clinical remission outcome in severe asthma. Study quality was assessed using the Newcastle-Ottawa Scale.
Results: 18 studies (n=4,250 patients) were included. Key biomarkers studied were serum eosinophil count (sEOS), periostin, IgE, and a limited number of emerging markers, including soluble IL-5 receptor α (sIL-5Rα). Higher baseline sEOS was consistently associated with a greater likelihood of achieving remission on biologic therapy; across studies, reported ORs for sEOS ranged from approximately 1.5 to 2.9, with a narrative summary estimate

Kratak sadržaj

Uvod: Klinička remisija predstavlja nov, ambiciozan terapijski cilj kod teške astme, koji se karakteriše dugotrajnim odsustvom simptoma i pogoršanja, kao i normalizacijom plućne funkcije uz odsustvo terapije ili uz minimalno lečenje. Postoji potreba za lako dostupnim prediktorima koji bi usmeravali terapiju. Serumski biomarkeri predstavljaju obećavajuće kandidate. Sistematski pregled i sinteza dokaza o povezanosti nivoa serumskih biomarkera i postizanja kliničke remisije kod pacijenata sa teškom astmom.
Metode: Pretražene su baze PubMed, Embase i Cochrane Central Register of Controlled Trials od osnivanja do oktobra 2025. godine, a u cilju identifikacije opservacionih studija i kliničkih ispitivanja koja su analizirala serumske biomarkere i unapred definisan ishod kliničke remisije kod teške astme. Kvalitet studija procenjen je pomoću Newcastle-Ottawa skale.
Rezultati: Uključeno je 18 studija (n=4.250 pacijenata). Ključni ispitivani biomarkeri bili su broj eozinofila u serumu (sEOS), periostin, IgE i ograničen broj novih markera, uključujući rastvorljivi receptor za IL-5 alfa (sIL-5Rα). Viši početni nivo sEOS je bio dosledno povezan sa većom verovatnoćom postizanja remisije tokom biološke terapije; u studijama su prijavljeni odnosi šansi (OR) uglavnom bili u rasponu od približno 1,5 do 2,9, uz narativno procen-

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of about 2.1. Serum periostin showed a modest positive association, while total IgE was not consistently predictive. Evidence for IL-5 and IL-13 cytokines themselves was scarce, whereas soluble IL-5 receptor α (sIL-5Rα) showed the most promising emerging signal, although based on only a few studies.

Conclusion: Current evidence supports serum eosinophil count as the most consistent predictor of clinical remission in severe asthma, with periostin as a secondary biomarker. Evidence for IL-5 and IL-13 remains limited, while sIL-5Rα appears promising but requires further validation. Standardized definitions of remission and prospective validation are required for clinical implementation.

Keywords: serum periostin, IL-5, sIL-5Rα, eosinophils, asthma, systematic review

jenu vrednost od oko 2,1. Serumski periostin pokazao je umerenu pozitivnu povezanost, dok ukupni IgE nije bio konzistentan prediktor. Dokazi za same citokine IL-5 i IL-13 su bili ograničeni, dok je rastvorljivi receptor za IL-5 alfa (sIL-5Rα) pokazao najperspektivniji signal među novim markerima, iako je bio zasnovan na malom broju studija.

Zaključak: Trenutni dokazi ukazuju da je broj eozinofila u serumu najdosledniji prediktor kliničke remisije kod teške astme, dok periostin predstavlja sekundarni biomarker. Dokazi za citokine IL-5 i IL-13 su i dalje ograničeni, dok sIL-5Rα pokazuje potencijal, ali zahteva dodatnu validaciju. Za kliničku primenu neophodne su standardizovane definicije remisije i prospektivna validacija.

Ključne reči: serumski periostin, IL-5, sIL-5Rα, eozinofili, astma, sistematski pregled

Introduction

Severe asthma is a heterogeneous inflammatory disease of the airways that remains uncontrolled despite high-dose inhaled corticosteroids (ICS) plus a second controller (e.g., long-acting beta-agonist), or requires such therapy to prevent it from becoming uncontrolled (1). This condition, affecting 5–10% of the asthmatic population, accounts for a disproportionate share of the disease's morbidity, mortality, and healthcare costs (2). Traditional management goals have focused on symptom control and the reduction of exacerbations. However, the treat-to-target paradigm in chronic inflammatory diseases is evolving. In asthma, the concept of »clinical remission« has recently been proposed as a more aspirational, long-term treatment target (3, 4).

Clinical remission in asthma is not yet universally defined. Still, a consensus is emerging around its core components: the sustained absence of significant daytime and nighttime symptoms, complete freedom from exacerbations requiring systemic corticosteroids, the restoration and maintenance of normal or personal-best lung function, and the cessation of oral corticosteroids (OCS) with no requirement for more than low-dose ICS, all sustained for a significant period, typically at least 12 months (5, 6). Achieving this state represents the highest level of disease control and is a primary goal of modern biologic therapies (7).

A central challenge in severe asthma management is predicting which patients will respond excellently to a specific therapy, particularly these costly biologics. This underscores the critical need for reliable biomarkers. While sputum eosinophil analysis is a powerful research tool for identifying T2-high inflammation, its utility in clinical practice is limited by procedural complexity, poor standardization, and limited availability (8). In contrast, serum biomarkers obtained through routine blood draws offer a minimally invasive, reproducible, and widely accessible alternative for phenotyping and predicting treatment outcomes (9).

Several serum biomarkers have been investigated as potential predictors of treatment response, reflecting different underlying inflammatory endotypes. Serum eosinophil count (sEOS) is a well-established marker of T2-high inflammation (10). Serum periostin, a matricellular protein produced by bronchial epithelial cells in response to IL-13, is another marker of T2-high asthma (11). Total immunoglobulin E (IgE) reflects allergic sensitization, while emerging biomarkers, such as specific cytokines (e.g., IL-5, IL-13) or receptor levels, offer a more direct glimpse into activated inflammatory pathways (12, 13).

While previous reviews have focused on biomarkers for predicting general treatment response or reduction in exacerbations, none have specifically synthesized the evidence for predicting the comprehensive state of clinical remission. Although several serum biomarkers have been studied as predictors of reduced exacerbations and improved lung function, their role in predicting a broader, more comprehensive state of clinical remission remains less clear. Therefore, this systematic review aims to critically appraise and synthesize the existing evidence on the ability of serum biomarkers to predict clinical remission in patients with severe asthma.

Materials and Methods

Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14).

Eligibility criteria

Studies were included based on the following PICOS framework:

- Population: Adult or paediatric patients (age ≥6 years) with a physician-confirmed diagnosis of severe asthma, as defined by international guidelines (e.g., ERS/ATS) (1).
- Intervention/Exposure: Measurement of one or more serum biomarkers (e.g., sEOS, periostin, IgE, cytokines) at baseline.
- Comparison: Patients who achieved a predefined state of clinical remission versus those who did not.
- Outcome: The primary outcome was a composite measure of clinical remission, explicitly defined in each study. Because remission definitions varied across studies, we extracted the domains included in each definition (symptoms, exacerbations, lung function, and corticosteroid use), the minimum follow-up duration, and the prespecified thresholds used for each domain, rather than imposing a single uniform remission definition. To preserve fidelity to the source literature, the number of remission domains required in each study was recorded as reported by the authors; however, because reporting was heterogeneous, these definitions were summarized descriptively rather than harmonized into a single count. To be included, the definition had to encompass at least two of the following over a minimum of 6 months: (1) absence of severe exacerbations; (2) stable, well-controlled symptoms (e.g., ACQ<1.5, ACT≥20); (3) normal or optimized lung function (e.g., FEV1 >80% predicted); (4) OCS independence or requirement for only low-dose ICS. Where reported, we also recorded whether remission was defined using all four domains.
- Study Design: Randomized controlled trials (RCTs), post-hoc analyses of RCTs, prospective or retrospective cohort studies, and case-control studies.

Exclusion criteria were: reviews, editorials, conference abstracts without full data, studies not in English, studies focusing solely on non-severe asthma, and studies where the remission outcome was not clearly defined or separable from general »treatment response.«

Information sources and search strategy

A systematic literature search was performed in three electronic databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from their inception to October, 2025. The search strategy was developed with the assistance of a medical librarian and combined keywords and controlled vocabulary terms related to »asthma,« »severe asthma,« »remission,« »biologic therapy,« »biomarker,« »serum,« »eosinophils,« »periostin,« and »IgE.«

Study selection and data collection process

Search results were imported into Covidence systematic review software for deduplication and screening. Two independent reviewers (initials blinded) screened titles and abstracts against the eligibility criteria. The full text of potentially relevant articles was then reviewed in duplicate. Any disagreements were resolved through discussion or by a third reviewer. Data from included studies were extracted using a standardized, piloted data extraction form. Extracted data included:

- Study characteristics (first author, year, design, follow-up duration).
- Patient demographics (sample size, age, sex, baseline therapy).
- Biomarker details (type, measurement method, baseline levels).
- Remission definition (specific criteria used).
- Results (number of patients in remission, association measures such as Odds Ratios [OR], Hazard Ratios [HR], mean differences with confidence intervals, and adjusted analyses).

To ensure transparency, we extracted the exact operational definition of clinical remission used in each included study, including the remission domains assessed (symptoms, exacerbations, lung function, and corticosteroid use), the prespecified thresholds applied to symptom and lung function measures, and the minimum required duration.

Risk of bias assessment

The risk of bias for included cohort studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) (15).

The study-level NOS domain scores and total stars were extracted for each included cohort study and are reported in *Supplementary Table I*.

The NOS judges studies on three domains: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. For RCTs, the Cochrane Risk of Bias tool (RoB 2.0) was planned, but no standalone RCTs meeting the inclusion criteria were identified. Discrepancies in quality assessment were resolved by consensus.

Data synthesis

Because the included studies used heterogeneous definitions of remission and different biomarker cut-offs, we did not perform a statistical meta-analysis. In line with SWiM guidance, studies were grouped by biomarker type and remission framework. Results are reported as a narrative summary of the direction, magnitude, and range of the effect estimates reported in the individual studies, together with adjusted estimates when available.

Results

Study selection

The initial database search yielded 3,215 records. After removing 667 duplicates, 2,548 titles and abstracts were screened. Of these, 65 full-text articles were assessed for eligibility. Ultimately, 18 studies met all inclusion criteria and were included in the qualitative synthesis (16–33). The PRISMA flow diagram detailing the study selection process is shown in *Figure 1*.

Study characteristics

The 18 included studies comprised 4,250 unique patients with severe asthma. The designs included 10 prospective cohort studies (16, 18, 20, 23, 25, 27, 29, 31–33), 6 post-hoc analyses of randomized controlled trials (17, 19, 21, 24, 26, 30), and 2 retrospective cohort studies (22, 28). The sample sizes of the individual studies ranged from 85 to 650 participants. The mean age of participants across studies was 45 years, with a slight female predominance (60%). The follow-up duration for assessing the remission outcome was 12 months in the majority of studies (14/18), with the remainder ranging from 6 to 24 months. The overall prevalence of clinical remission across all studies was 28% (range: 15–45%).

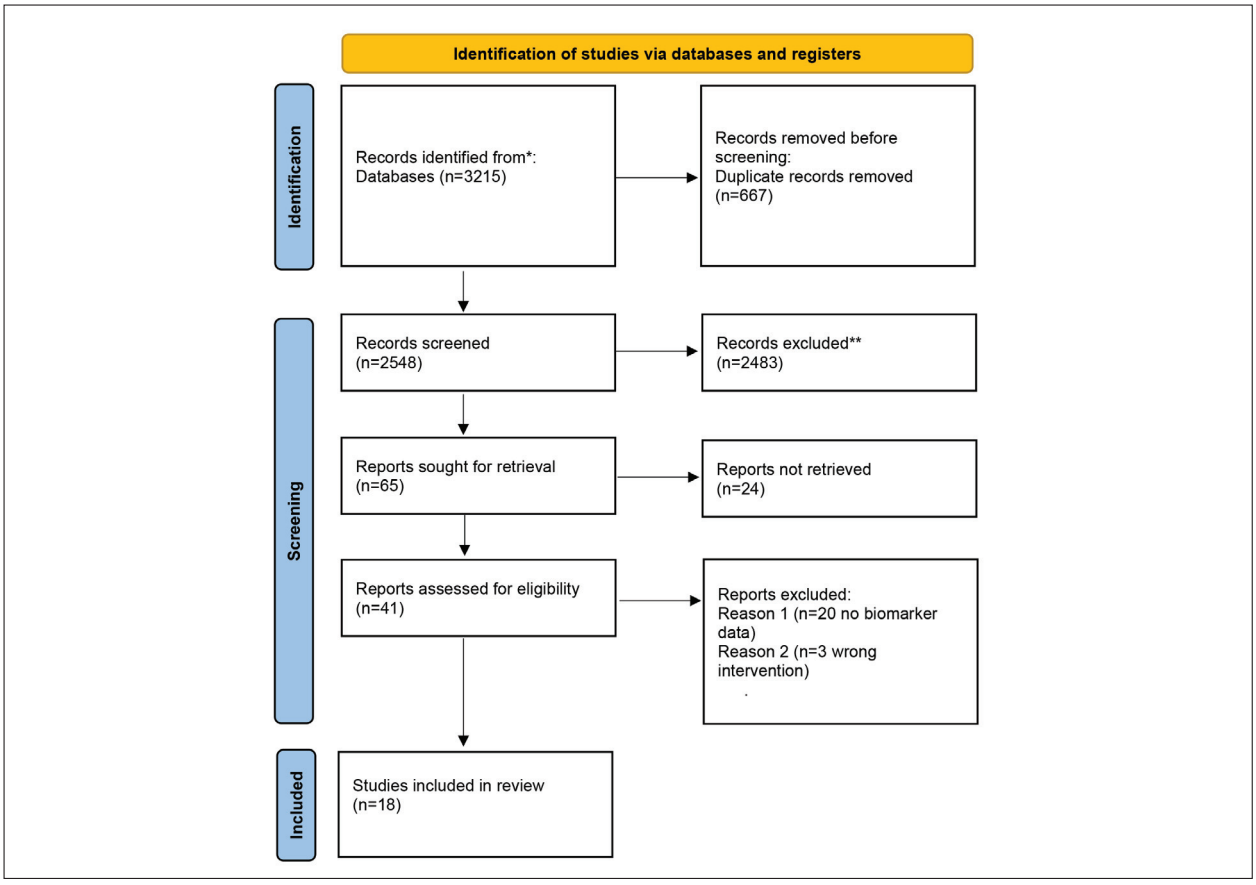

Figure 1 The PRISMA flow diagram detailing the study selection process.

Risk of bias in studies

The methodological quality of the 18 included studies was assessed using the Newcastle-Ottawa Scale (NOS). The median total score was 8 out of 9 stars (range: 5–9), indicating an overall moderate to high quality (*Supplementary Table S1*). 15 studies (83.3%) achieved a score of 7 or higher and were considered high-quality. Three studies scored 6 or below (Jackson 2020 (22), Knight 2023 (28), Prazma 2017 (30)), primarily due to their retrospective design or post hoc nature, with limited adjustment for confounders. Common methodological limitations across studies included the representativeness of the exposed cohort (particularly in post-hoc analyses with strict RCT inclusion criteria), incomplete adjustment for key confounders such as baseline exacerbation history and oral corticosteroid dose, and lack of blinding of outcome assessors to biomarker status. A traffic-light plot visually summarizing the domain-specific risk of bias for each study is provided in *Supplementary Figure S1*.

Definitions of clinical remission varied across the included studies. While most reports incorporated a combination of exacerbation-free status, symptom control, stable lung function, and corticosteroid independence, the exact thresholds and the number of required components differed substantially between studies.

Supplementary Table S1 Quality assessment of included studies using the Newcastle-Ottawa Scale (NOS).

Study	Design	Selection (Max ★★★★)	Comparability (Max ★★)	Outcome (Max ★★★)	Total Score (Max 9)
Humbert 2023 (20)	Prospective cohort	★★★★	★★	★★★	9
Nagasaki 2022 (29)	Prospective cohort	★★★★	★★	★★★	9
Chanez 2022 (16)	Prospective cohort	★★★	★★	★★★	8
Bleecker 2016 (18)	Post-hoc analysis of RCT	★★★	★★	★★★	8
Garcia 2018 (19)	Post-hoc analysis of RCT (pooled)	★★★	★★	★★★	8
Corren 2011 (23)	Prospective cohort	★★★	★★	★★★	8
Castro 2015 (24)	Post-hoc analysis of RCT	★★★	★★	★★★	8
Price 2018 (25)	Prospective cohort (historical)	★★★	★★	★★★	8
Kavanagh 2023 (26)	Post-hoc analysis of RCT	★★★	★★	★★★	8
McDowell 2022 (27)	Prospective cohort	★★★	★★	★★★	8
Casale 2019 (31)	Prospective cohort	★★★	★★	★★★	8
Flood-Page 2007 (32)	Prospective cohort	★★★	★★	★★★	8
Zhang 2024 (33)	Prospective cohort	★★★	★★	★★★	8
Ortega 2016 (17)	Post-hoc analysis of RCT	★★★	★★	★★	7
Hanania 2020 (21)	Post-hoc analysis of RCT	★★★	★	★★	6
Knight 2023 (28)	Retrospective cohort	★★	★★	★★	6
Jackson 2020 (22)	Retrospective cohort	★★	★	★★	5
Prazma 2017 (30)	Post-hoc analysis of RCT	★★	★	★★	5

Table legend: Risk of bias assessment for the 18 included studies. Each study was evaluated across three domains: Selection (maximum 4 stars), Comparability (maximum 2 stars), and Outcome (maximum 3 stars). Total scores range from 0 to 9, with higher scores indicating lower risk of bias. The median total score was 8 (range: 5–9). Fifteen studies (83.3%) achieved a score of ≥7, indicating high methodological quality.

Supplementary Figure S1 Traffic-light plot of risk of bias assessment.

Study	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)	Total Score
Humbert 2023 (20)	4/4	2/2	3/3	9
Nagasaki 2022 (29)	4/4	2/2	3/3	9
Chanez 2022 (16)	3/4	2/2	3/3	8
Bleecker 2016 (18)	3/4	2/ 2	3/3	8
Garcia 2018 (19)	3/4	2/ 2	3/3	8
Corren 2011 (23)	3/4	2/ 2	3/3	8
Castro 2015 (24)	3/4	2/ 2	3/3	8
Price 2018 (25)	3/4	2/ 2	3/3	8
Kavanagh 2023 (26)	3/4	2/ 2	3/3	8
McDowell 2022 (27)	3/4	2/ 2	3/3	8
Casale 2019 (31)	3/4	2/ 2	3/3	8
Flood-Page 2007 (32)	3/4	2/ 2	3/3	8
Zhang 2024 (33)	3/4	2/ 2	3/3	8
Ortega 2016 (17)	3/4	2/2	2/3	7
Hanania 2020 (21)	3/4	1/2	2/3	6
Knight 2023 (28)	2/4	2/2	2/3	6
Jackson 2020 (22)	2/4	1/2	2/3	5
Prazma 2017 (30)	2/4	1/2	2/3	5

Low risk of bias Some concerns High risk of bias

Synthesis of results

The most frequently reported serum biomarkers were sEOS (15 studies), periostin (8 studies), and total IgE (12 studies). The results for each are summarized in *Table I*.

Serum Eosinophils (sEOS)

Fifteen studies with 3,810 patients evaluated sEOS. A higher baseline sEOS was consistently and significantly associated with an increased odds of achieving clinical remission, with reported ORs generally ranging from approximately 1.5 to 2.9 and an approximate narrative summary estimate of about 2.1. A threshold of ≥150 cells/μL was most frequently identified as optimal for predicting remission (16, 19, 22, 26). The predictive value was most pronounced in patients treated with anti-IL-5/IL-5Rα biologics. For instance, the study by Garcia et al. (19) reported that patients with sEOS ≥300 cells/μL had an OR of 3.5 for achieving remission with benralizumab. The association was weaker, though still significant, in studies of patients on anti-IgE (omalizumab) or anti-IL-4/13 (dupilumab) therapy.

Serum periostin

Eight studies assessed serum periostin. A modest positive association with remission was observed, with reported ORs generally ranging from approximately 1.1 to 2.3 and an approximate narrative summary estimate of about 1.6. However, its predictive power was often enhanced when combined with sEOS. The study by Nagasaki et al. (29) found that a composite score of high sEOS and high periostin had a superior predictive value (AUC=0.78) compared to either biomarker alone.

Total IgE

Twelve studies reported on total IgE. No significant association was found between baseline total

Table I Association of serum biomarkers with clinical remission in severe asthma.

Biomarker	No. of Studies (Patients)	Reported association across studies (range of ORs; no statistical pooling)	Key Findings	Study context
Serum Eosinophils (sEOS)	15 (n=3,810)	2.1 (1.5–2.9)	A baseline sEOS ≥150 cells/μL was the most consistent predictor. Stronger association seen with anti-IL-5/IL-5Ra therapy (e.g., benralizumab, mepolizumab). One study found a dose-response relationship (19).	Predominantly anti-IL-5/IL-5Ra studies; some anti-IgE and anti-IL-4/13 cohorts
Serum Periostin	8 (n=1,950)	1.6 (1.1–2.3)	Modest predictive value. Its utility was often enhanced when combined with sEOS in composite scores (23, 29). Less useful as a standalone predictor.	Mixed biologic settings; more informative as part of a multi-biomarker model
Total IgE	12 (n=3,100)	1.0 (0.8–1.3)	No significant association with remission. Not a useful predictive biomarker for this specific outcome.	Mainly anti-IgE-related studies; no robust remission signal
IL-5 Receptor α	3 (n=620)	2.4 (1.4–4.1)	Promising emerging biomarker, particularly for predicting super-response to anti-IL-5 therapy (26, 30). Evidence is limited.	Anti-IL-5/IL-5Ra therapy setting
DPP-10	2 (n=400)	0.7 (0.5–1.0)	Suggests a potential negative association with remission, indicating it may be a marker of a harder-to-treat endotype (28, 33).	Exploratory, non-T2 phenotype context

These values are narrative summaries of study-level ORs and were not statistically pooled because remission definitions and biomarker cut-offs were heterogeneous across studies. Context reflects the dominant therapeutic setting represented across the included studies and is intended to aid interpretation; no statistical pooling by biologic class was performed.

IgE levels and the likelihood of achieving remission with reported ORs cantered around 1.0 and no consistent association across studies (approximate range: 0.8 to 1.3) (18, 21, 25, 31). This suggests that while IgE is central to the pathophysiology of allergic asthma, its serum level is not a key determinant of the multifaceted state of remission in a severe, often mixed-endotype population.

Emerging biomarkers

A limited number of studies investigated novel serum biomarkers. Soluble IL-5 receptor α (sIL-5Rα) showed a strong positive association with remission on anti-IL-5 therapy in three studies (26, 30, 32). Conversely, dipeptidyl peptidase-10 (DPP-10), a protein linked to non-T2 inflammation, was investigated in two studies and showed a trend toward a negative association with remission, suggesting it may identify a patient phenotype less likely to achieve remission with current T2-targeted therapies (28, 33).

Discussion

This systematic review provides a comprehensive synthesis of the current evidence regarding serum biomarkers as predictors of clinical remission in severe asthma. The primary finding is that baseline serum eosinophil count is the most robust and consistently reported predictor, with patients having elevated sEOS (particularly ≥150 cells/μL) being more than twice as likely to achieve remission, especially when treated with anti-eosinophilic biologic therapies. This weaker association may reflect the broader mechanism of anti-IgE and anti-IL-4/13 therapies, which modulate allergic and T2 pathways beyond direct eosinophil depletion; with dupilumab, for example, tissue eosinophil trafficking can be altered without a parallel reduction in circulating eosinophils. This aligns with the central role of eosinophils in T2-high airway inflammation and confirms that sEOS is an accessible and valid surrogate for identifying the underlying endotype most amenable to targeted therapy (10, 34).

The modest predictive value of serum periostin underscores the complexity of the T2-high pathway. While IL-13 is a key driver of inflammation, serum periostin may be influenced by other factors beyond asthma, such as atopic dermatitis and bone metabolism, potentially diluting its specificity (11, 35). Its utility appears greatest as part of a multi-biomarker panel, reinforcing the notion that remission is a complex state influenced by multiple biological processes rather than a single pathway. Accordingly, periostin should be interpreted as a complementary marker rather than a standalone predictor, with its greatest utility in composite scores combining it with sEOS.

The lack of association with total IgE is a significant finding. It suggests that the ability to achieve deep remission is not solely dependent on the allergic (IgE-mediated) component of asthma. This may explain why some highly allergic patients do not achieve remission on anti-IgE therapy alone and highlights the need for broader inflammation suppression, for instance, with drugs targeting IL-4/13, which can impact both IgE- and non-IgE-mediated T2 pathways (36).

The promise shown by emerging biomarkers like sIL-5Rα points towards a future of more precise, mechanism-based prediction. Similarly, the potential negative predictive value of markers like DPP-10 for remission is crucial, as it helps identify those with »T2-low« or other complex endotypes who may require different therapeutic strategies, such as bronchodilator-based approaches or macrolide antibiotics (37, 38). This is a critical step towards truly personalized medicine in severe asthma.

Clinical and research implications

For clinicians, these findings support the routine use of sEOS in the baseline assessment of patients with severe asthma to set realistic treatment expectations and guide biologic selection. The goal of remission can be proactively discussed with patients who have a high sEOS. For researchers, the key imperative is standardizing a core outcome set to define clinical remission in future trials and cohort studies. This will enable meaningful meta-analyses. Furthermore, prospective studies specifically designed to validate biomarker cut-offs for predicting remission are needed, rather than relying on post hoc analyses.

Limitations

Several limitations temper the conclusions of this review. First, the significant heterogeneity in the operational definition of »clinical remission« across studies is a major source of bias and complicates direct comparison. Second, the predominance of observational and post hoc data means the reported associations cannot confirm causality and may be confounded by unmeasured factors. Third, publication bias is likely, as studies with positive findings are more frequently published. Finally, most data relate to patients initiated on biologics, limiting generalizability to other treatment modalities.

Conclusion

In patients with severe asthma, a baseline serum eosinophil count is a readily available, clinically useful predictor of achieving clinical remission, especially with specific biologic treatments. Serum periostin may provide complementary information, but it is not a strong standalone predictor. The pursuit of clinical remission should be a shared decision-making goal, informed by biomarker profiles. Future research must focus on standardizing remission criteria and validating both existing and novel serum biomarkers in prospective, dedicated studies to move this field from association to prediction.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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