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Original Research Article

BEYOND SINGLE BIOMARKERS: THE CASE FOR COMPOSITE INDICES IN ASTHMA PHENOTYPING AND SEVERITY ASSESSMENT

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ABSTRACT

Background: Asthma is a heterogeneous disease characterized by diverse inflammatory pathways, clinical presentations, and treatment responses. Traditional approaches relying on single biomarkers have proven insufficient for capturing this complexity, often failing to adequately phenotype patients or predict disease severity and therapeutic outcomes.

Materials and Methods: This narrative review synthesizes current evidence on composite biomarker approaches in asthma phenotyping and severity assessment. We examined studies evaluating multi-biomarker panels, composite scoring systems, and integrated assessment tools that combine inflammatory, immunological, and clinical parameters.

Results: Composite biomarker indices demonstrate superior performance over single markers in distinguishing asthma phenotypes, predicting exacerbation risk, and guiding biologic therapy selection. Multi-parameter approaches incorporating Type 2 inflammatory markers show enhanced discriminatory capacity and improved correlation with disease severity. Emerging composite tools integrate blood eosinophils, fractional exhaled nitric oxide, serum periostin, and IgE levels to create multidimensional profiles that better reflect the underlying inflammatory complexity of asthma.

Conclusion: Composite biomarker indices represent a paradigm shift toward precision asthma management, offering more balanced patient stratification than single-marker approaches. Their integration into clinical algorithms holds promise for optimizing therapeutic decisions, particularly in the era of targeted biologics.

Keywords: Asthma, biomarkers, composite indices, phenotyping, precision medicine, Type 2 inflammation, disease severity, personalized medicine.

INTRODUCTION

Asthma represents a major public health challenge, affecting over 300 million individuals globally.[1] In India, asthma prevalence ranges from 2% to 4% in adults and up to 10% in children, with substantial regional variation.[2] Beyond its epidemiological impact, asthma is increasingly recognized as a heterogeneous syndrome encompassing multiple phenotypes and endotypes rather than a single disease entity.[3] This heterogeneity manifests in variable clinical presentations and diverse underlying inflammatory pathways that challenge traditional approaches to disease classification and management.

Conventional asthma severity classification has relied predominantly on symptom frequency, rescue medication use, and lung function impairment.[4] These symptom-based frameworks, while clinically practical, fail to capture the underlying biological mechanisms driving disease. The recognition that patients with similar symptom profiles may harbor fundamentally different inflammatory processes has driven efforts to identify biomarkers.

Type 2 (T2) inflammation represents the most extensively studied asthma endotype.[5] Biomarkers of T2 inflammation—including blood and sputum eosinophil counts, serum immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO)—have been proposed as tools for phenotyping and guiding targeted therapies. Elevated blood eosinophil counts predict response to anti-interleukin-5 therapy in severe asthma.[6] Similarly, FeNO levels above 25 parts per billion identify patients more likely to benefit from inhaled corticosteroid therapy.[7]

Despite their biological relevance, individual T2 biomarkers demonstrate significant limitations when used in isolation. Blood eosinophil counts show poor correlation with sputum eosinophilia, the gold-standard measure of airway inflammation.[8] FeNO levels are influenced by multiple factors including atopy, smoking, and recent corticosteroid use, limiting their specificity for active airway eosinophilia.[9] Total serum IgE correlates weakly with clinical severity and fails to distinguish allergic asthma from other atopic conditions.[10] This discordance between biomarker compartments—systemic blood measures versus airway-specific inflammation—results in phenotype misclassification and suboptimal treatment selection when clinicians rely on single markers.

The poor performance of single biomarkers reflects the multidimensional nature of asthma pathobiology, where T2 and non-T2 mechanisms often coexist within individual patients and vary over time.[11] A patient may exhibit elevated FeNO without blood eosinophilia, or vice versa, and these discordant profiles associate with different clinical outcomes and treatment responses. Single-biomarker thresholds, while useful for clinical trial enrollment, oversimplify the continuous and overlapping distributions of inflammatory markers across asthma populations.

Composite biomarker indices—mathematical combinations or algorithms integrating multiple inflammatory markers—have emerged as a potential solution to these limitations.[12] By capturing information from multiple biological compartments and weighting complementary markers, composite indices may more accurately reflect overall T2 inflammatory burden, reduce misclassification, and improve prediction of clinical outcomes and treatment response. The shift toward composite biomarker approaches aligns with the broader movement toward precision medicine in asthma, which seeks to match individual patients to optimal therapies based on their unique biological and clinical profiles.[13]

This review synthesizes current evidence on composite biomarker indices for asthma phenotyping and severity assessment. We examine the development and validation of existing composite scores, their performance relative to single biomarkers in predicting clinical outcomes and treatment response, and their potential role in guiding precision asthma management.

Single Biomarker Limitations

The inadequacy of individual biomarkers for asthma phenotyping stems from fundamental biological and technical constraints that limit their ability to capture disease heterogeneity. Each commonly used biomarker demonstrates specific weaknesses that compromise its utility when applied in isolation.

Serum IgE

Total serum IgE exhibits wide variability within asthma severity categories. In validation studies, total IgE levels showed no significant correlation with asthma control scores or lung function parameters.[10] Serum IgE reflects systemic atopic sensitization rather than active airway inflammation. Elevated IgE occurs in multiple atopic conditions including allergic rhinitis and atopic dermatitis. Among patients with severe asthma, IgE levels overlap substantially with those in mild disease, precluding reliable severity stratification based on this marker alone.

Blood Eosinophils

Blood eosinophil counts serve as a systemic marker that correlates only modestly with airway eosinophilia.[8] Corticosteroid therapy substantially influences blood eosinophil counts, complicating interpretation in patients receiving maintenance or intermittent corticosteroid therapy. Blood eosinophil thresholds demonstrate limited sensitivity and specificity for identifying sputum eosinophilia. A blood eosinophil threshold of 300 cells/μL identified sputum eosinophilia (≥3%) with sensitivity of 71% and specificity of 77% in one cohort, indicating substantial misclassification.[14]

Sputum Eosinophils

Sputum eosinophil percentage represents the gold standard for assessing airway eosinophilic inflammation.[15] However, sputum induction and processing require specialized training and equipment not widely available outside tertiary centers. Discordance between blood and sputum eosinophil counts occurs frequently in asthma patients. In a study of 508 patients with asthma, 28% demonstrated discordant blood-sputum eosinophil profiles, with elevated blood eosinophils but low sputum eosinophils or vice versa.[8] These discordant phenotypes associate with different clinical characteristics and treatment responses, yet reliance on blood eosinophils alone fails to identify them.

Fractional Exhaled Nitric Oxide

FeNO serves as a marker of T2 airway inflammation but demonstrates limited specificity due to multiple

confounding influences.[9] Atopy elevates FeNO independent of asthma presence. Current smoking reduces FeNO by approximately 50%, while smoking cessation leads to gradual increases over weeks to months. Inhaled corticosteroid therapy suppresses FeNO. In a meta-analysis of 3,206 patients, FeNO showed a pooled correlation coefficient of 0.28 with sputum eosinophil percentage, indicating weak concordance.[14]

Compartmentalization and Phenotype Misclassification

Systemic biomarkers measured in blood frequently diverge from airway-specific markers, reflecting compartmentalization of inflammatory processes. Patients with elevated FeNO but normal blood eosinophils demonstrate greater airway hyperresponsiveness than those with the reverse pattern. This compartmentalization implies that systemic blood markers may not accurately reflect the inflammatory state of the airways, the primary site of asthma pathology.

Reliance on single biomarkers leads to misclassification of asthma phenotypes, particularly in patients with mixed or overlapping inflammatory patterns. In cluster analyses using multiple biomarkers, single-biomarker classification misidentified the dominant inflammatory phenotype in a substantial proportion of patients.[12] This misclassification has clinical consequences, as patients with discordant biomarker profiles demonstrate different exacerbation rates and responses to anti-inflammatory therapy compared to those with concordant profiles.

Composite Biomarker Indices and Multi-Parameter Approaches

The limitations of single biomarkers have prompted development of composite indices that integrate multiple inflammatory markers to capture asthma heterogeneity more comprehensively. These multi-parameter approaches aim to improve phenotype discrimination, severity assessment, and treatment response prediction.

Rationale for Composite Approaches

Composite biomarker strategies rest on the premise that asthma pathobiology involves multiple overlapping inflammatory pathways that cannot be adequately characterized by any single marker. Integration of biomarkers from different biological compartments—systemic blood measures, exhaled breath markers, and serum proteins—may provide a more complete representation of the underlying inflammatory state.

T2 Signature Scores and Multi-Biomarker Panels

Several composite indices have been developed to quantify overall T2 inflammatory burden. A T2 signature score combining blood eosinophils, FeNO, and serum periostin demonstrated superior performance in predicting exacerbation risk compared to individual biomarkers.[16] Simplified T2 indices combining blood eosinophils and FeNO have been validated in patients with moderate-to-severe asthma, showing improved phenotype discrimination.

U-BIOPRED Molecular Phenotyping

The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) consortium applied unsupervised cluster analysis to transcriptomic, proteomic, and clinical data from adults with asthma.[17] This approach identified molecular phenotypes that could not be distinguished using conventional clinical or single-biomarker classification. A simplified clinical classifier derived from U-BIOPRED data combined blood eosinophils, FeNO, and serum IgE to stratify patients into clinically meaningful subgroups.

Machine Learning and Treatable Traits

Machine learning algorithms have been applied to integrate multiple biomarkers and clinical variables for asthma phenotyping. Random forest classifiers incorporating blood eosinophils, FeNO, IgE, lung function parameters, and clinical features achieved superior accuracy in distinguishing eosinophilic from non-eosinophilic asthma compared to single-biomarker thresholds.

The treatable traits approach, endorsed by the Global Initiative for Asthma (GINA) and the European Respiratory Society/American Thoracic Society (ERS/ATS), represents a paradigm shift toward multi-dimensional asthma assessment.[18] This framework identifies specific pulmonary, extrapulmonary, and behavioral traits that can be targeted with tailored interventions.

Comparative Performance Studies

Direct comparisons of composite versus single-biomarker approaches consistently demonstrate superior performance of multi-parameter strategies. In a meta-analysis of studies involving 3,847 patients, composite approaches demonstrated pooled area under the curve (AUC) of 0.79 for predicting exacerbations versus 0.64 for blood eosinophils alone and 0.66 for FeNO alone.[19] The improvement in predictive accuracy was most pronounced in patients with moderate asthma, where single biomarkers showed particularly poor discrimination.

Phenotype Discrimination and Treatment Response Prediction

Composite indices improve discrimination of eosinophilic, paucigranulocytic, and mixed-granulocytic phenotypes. Multi-biomarker panels classified patients into inflammatory clusters with distinct clinical characteristics that could not be distinguished using blood eosinophils or FeNO alone.[12] Specifically, mixed-granulocytic clusters with moderate elevations in both eosinophils and neutrophils were only identifiable through multi-biomarker assessment.

In post-hoc analyses of biologic therapy trials, composite scores incorporating baseline blood eosinophils, exacerbation history, and FeNO predicted treatment response more accurately than single markers.[20] Patients in the highest composite score quartiles achieved substantially greater

exacerbation reduction compared to those in the lowest quartiles.

Clinical Applications and Biologic Therapy Selection

The emergence of targeted biologic therapies for severe asthma has transformed treatment paradigms and underscored the clinical necessity of accurate phenotyping. Composite biomarker approaches have proven particularly valuable in guiding biologic selection, where matching patient inflammatory profiles to mechanism-specific therapies determines treatment success.

Anti-IgE Therapy

Omalizumab, a humanized anti-IgE monoclonal antibody, was the first biologic approved for severe allergic asthma. Initial prescribing criteria relied on total serum IgE levels and documented allergen sensitization. However, post-hoc analyses revealed that composite biomarker profiles predict response more accurately than IgE alone.[21] Patients with elevated IgE plus blood eosinophils ≥260 cells/μL demonstrated superior response rates compared to those with elevated IgE but lower eosinophil counts.

Anti-IL-5/5R Pathway Biologics

Biologics targeting the interleukin-5 pathway—mepolizumab, reslizumab, and benralizumab—have demonstrated efficacy in eosinophilic asthma. Blood eosinophil counts served as the primary biomarker in pivotal trials, yet composite indices incorporating additional T2 markers identify optimal responders more precisely.

In the DREAM and MENSA trials, mepolizumab reduced exacerbations in patients with severe eosinophilic asthma.[6,22] Post-hoc analyses stratifying by baseline eosinophil thresholds and FeNO levels revealed that patients with concordant elevation of multiple T2 markers achieved greater exacerbation reduction.[20]

Benralizumab, an anti-IL-5 receptor alpha monoclonal antibody, demonstrated efficacy in the SIROCCO and CALIMA trials.[23] Subgroup analyses examining efficacy by atopy status and serum IgE levels showed that patients with elevated eosinophils plus elevated IgE achieved superior outcomes compared to those with isolated eosinophilia.

Dupilumab and T2-High Composite Signatures

Dupilumab, a monoclonal antibody blocking the interleukin-4 receptor alpha subunit, inhibits signaling of both IL-4 and IL-13. The LIBERTY ASTHMA QUEST trial demonstrated that dupilumab reduced severe exacerbations by 46% in the overall population.[24] Pre-specified subgroup analyses revealed greater efficacy in patients with elevated baseline T2 biomarkers: among those with blood eosinophils ≥300 cells/μL, exacerbation reduction reached 65-67%.

Integration of FeNO with eosinophil counts identified patients achieving optimal outcomes. In the LIBERTY ASTHMA VENTURE trial, 80% of patients with eosinophils ≥300 cells/μL and FeNO ≥25 ppb achieved ≥50% oral corticosteroid reduction versus 59% with elevated eosinophils alone.[25]

GINA Recommendations

The Global Initiative for Asthma (GINA) 2023 and 2024 reports endorse biomarker-guided selection of biologic therapies for severe asthma.[26] GINA recommends measuring blood eosinophil counts, total IgE, and FeNO before initiating biologic therapy. For patients with blood eosinophils ≥300 cells/μL, GINA suggests anti-IL-5/5R agents or dupilumab as appropriate options. For patients with blood eosinophils 150–300 cells/μL, GINA recommends considering additional T2 markers such as FeNO to guide selection.

GINA emphasizes that biologic selection should integrate biomarker profiles with clinical phenotype, including presence of nasal polyposis, atopic comorbidities, and exacerbation history. The 2024 update reinforces that patients with concordant elevation of multiple T2 markers demonstrate higher response rates to targeted biologics than those with isolated biomarker elevation.

Real-World Implementation

Real-world effectiveness studies corroborate trial findings. In a prospective cohort of 318 patients initiating dupilumab for severe asthma, a composite T2 score incorporating blood eosinophils, FeNO, and serum IgE predicted 12-month treatment persistence and clinical response.[27] Patients in the highest T2 score tertile demonstrated 89% treatment persistence and 76% response rate compared to 68% persistence and 51% response in the lowest tertile.

A UK severe asthma registry analysis of 3,128 patients described real-world prescribing patterns.[28] Treatment persistence at 24 months was highest among patients selected using composite biomarker criteria (82%) versus single-biomarker criteria (68%).

Implementation Challenges and Future Directions

Despite robust evidence supporting composite biomarker approaches, translation into routine clinical practice faces substantial barriers, particularly in resource-limited settings.

Resource Constraints in Low- and Middle-Income Countries

Access to advanced biomarker testing remains severely limited in low- and middle-income countries (LMICs), including India. FeNO measurement requires specialized equipment with acquisition cost. Sputum induction and processing demand trained personnel and biosafety facilities rarely available outside tertiary centers. Multi-omics profiling remains confined to research laboratories, with high costs per patient.

The cost of biologic therapies compounds access barriers. Annual treatment costs for biologics range from $15,000 to $40,000 in high-income countries.[29] In India, where out-of-pocket health expenditure accounts for 62.6% of total health spending, biologic therapy remains unaffordable for the vast majority of patients with severe asthma.[2]

Standardization Challenges

Lack of standardization across laboratories and assay platforms undermines reproducibility. Blood eosinophil counts vary by up to 30% between automated hematology analyzers. FeNO measurements demonstrate inter-device variability of 5–15 ppb. Reference ranges for biomarkers differ across populations due to genetic and environmental factors. A study of healthy Asian adults found median FeNO values 20% lower than European reference populations, suggesting that universal cut-points may misclassify phenotypes in diverse populations.[30]

Point-of-Care Testing and Simplified Algorithms

Point-of-care biomarker devices offer potential solutions to resource constraints. Portable FeNO analyzers with electrochemical sensors have been developed, with device costs under $2,000. Simplified composite algorithms that rely on readily available biomarkers may improve feasibility in resource-limited settings. A two-biomarker index combining blood eosinophils and clinical exacerbation history predicted treatment response with accuracy comparable to more complex multi-biomarker panels.

Emerging Technologies

Integration of genomic, transcriptomic, proteomic, and metabolomic data promises to refine asthma phenotyping. Transcriptomic profiling identified molecular phenotypes with distinct inflammatory signatures and treatment responses in the U-BIOPRED cohort.[17] Machine learning algorithms offer potential to integrate complex biomarker data and predict clinically relevant outcomes. However, multi-omics approaches face barriers including high costs, lack of standardization, and limited bioinformatics expertise in clinical laboratories.

Research Gaps

Critical research gaps impede translation into global clinical practice. Most validation studies have been conducted in European and North American populations; performance in Asian, African, and Latin American cohorts remains poorly characterized. Pediatric asthma phenotyping lags behind adult research, with biomarker reference ranges differing between children and adults. Real-world effectiveness studies are needed to demonstrate that composite biomarker-guided care improves outcomes in routine practice, including primary care and resource-limited environments.

CONCLUSION

Asthma heterogeneity demands assessment strategies that extend beyond single biomarkers. The evidence demonstrates that composite biomarker indices capture the multidimensional nature of asthma inflammation more accurately than individual markers, reduce phenotype misclassification, and improve prediction of clinical outcomes and treatment responses. By integrating complementary markers from multiple biological compartments, composite approaches provide a more complete representation of underlying inflammatory pathways and enable precision matching of patients to mechanism-targeted therapies.

The clinical imperative for multi-parameter assessment has intensified with the expansion of biologic therapies for severe asthma. Composite biomarker indices consistently outperform single markers in predicting response to anti-IgE, anti-IL-5/5R, and anti-IL-4Rα biologics, translating into higher response rates and improved treatment persistence. Real-world implementation studies confirm that biomarker-guided algorithms incorporating multiple T2 markers achieve superior outcomes compared to single-marker selection strategies.

Despite this robust evidence base, translation into routine practice remains incomplete, particularly in resource-limited settings. Access barriers—including the cost of biomarker testing equipment and biologic therapies—restrict precision asthma care to tertiary centers in high-income countries. Standardization challenges and population-specific validation gaps further impede global implementation. Addressing these barriers requires coordinated investment in affordable diagnostic technologies, international quality assurance programs, and pragmatic effectiveness research in diverse healthcare systems.

The future of asthma phenotyping lies in the integration of composite biomarker strategies with emerging technologies. Multi-omics profiling promises to refine phenotype discrimination, while artificial intelligence and machine learning algorithms can synthesize complex biomarker data and enable dynamic phenotyping. As these technologies mature and costs decline, they will enhance the precision and accessibility of composite biomarker approaches.

For clinicians managing asthma today, the practical message is clear: shift from reliance on single biomarkers to multi-parameter assessment. Measure blood eosinophils, FeNO, and total IgE before initiating biologic therapy. Recognize that discordant biomarker profiles predict lower treatment response rates and may require alternative therapeutic strategies. Integrate biomarker data with clinical phenotype, exacerbation history, and comorbidities to guide individualized management decisions.

The transition from single-biomarker to composite-index approaches represents a fundamental shift in asthma care—from reductionist classification to integrative assessment that reflects disease complexity. By embracing composite biomarker approaches, investing in enabling infrastructure, and committing to equitable access, the asthma community can realize the promise of precision medicine and improve outcomes for patients worldwide.

Dataset Age Justification

This review integrates evidence spanning 1989–2024, reflecting the evolution of asthma biomarker science. Core pathophysiological studies (1989–2012) established foundational understanding of IgE biology, eosinophil function, and T2 inflammation mechanisms that remain valid today. Pivotal biologic therapy trials (2012–2021) provide the evidence base for current treatment guidelines and biomarker-guided selection strategies. Recent publications (2018–2024) include GINA guideline updates, real-world effectiveness studies, and emerging composite index validation data that reflect contemporary clinical practice.

Indian epidemiological data from the INSEARCH study (2012) represent the most comprehensive population-based asthma prevalence estimates available for the Indian subcontinent. More recent Indian publications (2020) provide context on severe asthma burden and biomarker utilization in tertiary care settings. The U-BIOPRED consortium data (2017) and subsequent cluster analyses (2021) represent state-of-the-art molecular phenotyping approaches that inform current composite biomarker strategies.

The temporal span of references reflects the maturation of asthma precision medicine from foundational biomarker discovery through clinical trial validation to real-world implementation. Older foundational studies are cited where they established concepts that remain current, while recent publications provide contemporary clinical context and guideline recommendations.

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