Narrative Review:
Role of Cytokines and Chemokines in the Outcome of Children With Severe Asthma

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ABSTRACT

Context: Asthma, characterized by airway inflammation, is a common chronic disease of childhood. Cytokines and chemokines could be used in the diagnosis, treatment, and management of asthma severity in children. In this review, we have explained the application of cytokines and chemokines as biomarkers in pediatric asthma.

Evidence Acquisition: All related articles were separately searched by two researchers using the following keywords in PubMed, Scopus, and Embase databases: Cytokine biomarkers, chemokines biomarkers, and children asthma. Articles published from 2000 to 2017 were investigated in the research, and 28 articles were included in the final analysis for this review.

Results: About cytokines, serum Interleukin 4 (IL-4) level is a marker of the presence of asthma, and IL-13 is a key cytokine involved in the manifestation of asthma symptoms. High IL-13 concentration and number of IL-13+ cells in the bronchial submucosa specimens are characteristic of severe asthma. Serum IL-5 concentration 3.1 times in children with severe asthma. IL-17 is involved in airway obstruction. IFN-γ gene polymorphism (+874A/T) in children elevates susceptibility to asthma. TGFB1 polymorphisms are considered as indicators of asthma severity. IL-26 plays an important role in asthma severity. IP-10 may be a useful inflammatory marker of asthma severity. High periostin level has been identified in pediatric asthma. PDGF level, which is high in asthma patients, plays an important role in bronchial fibrosis. About chemokines, plasma TARC concentration may be a useful biomarker of airway inflammation and asthma severity in children. Studies have supported the association between high serum RANTES levels and severe airway obstruction in children. CXCR4 levels are high in pediatric asthma and are associated with disease severity.

Conclusions: A wide range of cytokines and chemokines may play important roles in asthma severity in pediatric patients. Therefore, several studies have recommended the use of multiple molecular biomarkers, such as cytokines, for determining asthma severity in children.

Keywords:
Severe asthma,
Cytokines, Chemotactic

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1. Context

Asthma is a complex disorder and one of the most common chronic diseases of childhood; it is characterized by reversible airflow obstruction, bronchial hyperresponsiveness, mucus hypersecretion, inflammatory cell migration into the airways, and structural airway remodeling (1). Over the last decade, the worldwide incidence of asthma in children has been increasing (2).

Although the clinical features of asthma in children have been well described, the pathophysiological characteristics of asthma are less understood, and therapeutic strategies have mostly focused on asthma control. Inflammatory responses in asthma are driven by immune mechanisms involving cytokines, which are novel mediators that integrate signals between various immune cells (3) and thus play important roles in the pathogenesis of asthma. The National Institutes of Health defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (4). Therefore, knowledge about the actions of cytokines will provide a novel clinical context to develop novel biomarkers and therapies for various asthma subgroups in pediatric patients. The molecular phenotypes and endotypes of asthma differ between children and adult (5, 6). Unlike adults, mild to moderate asthma in most children is characterized by eosinophilic and neutrophilic airway inflammation (7). Based on pathogenesis, the degree of airway obstruction, and responses to medications, pediatric asthma can be divided into intermittent, mild, moderate, and severe stages (8, 9).

Clinically, asthma severity is associated with lung function and airway responsiveness, but underlying pathogenesis of asthma are not clear exactly (10). Thus, the characterization of cytokines might play an important role in the development of diagnostic markers for and treatment and management of pediatric asthma severity (8). This study further supports the use of cytokines as biomarkers, with particular emphasis on noninvasive sampling and cytokine assessment, to evaluate pediatric asthma severity. Tissue-specific diagnostic methods, such as bronchoalveolar lavage (BAL) and bronchoscopy, are also useful to detect airway inflammation and airway remodeling in asthma patients (11, 12). However, the invasiveness of these methods decreases their clinical utility in children. Therefore, the availability of noninvasive sampling procedures to examine and manage asthma in pediatric patients is particularly essential. Many noninvasive methods, such as peripheral blood/serum collection, Exhaled Breath Condensate (EBC) collection, and sputum induction, are available for assessing pediatric asthma (13). This review aims to develop knowledge in the field of pediatric asthma biomarkers, with a focus on cytokines and chemokines in blood/serum, EBC, and induced sputum.

2. Evidence Acquisition

All related articles were separately searched by two researchers. PubMed, Scopus, and Embase databases were searched using the following keywords: cytokine biomarkers, chemokines biomarkers, and children asthma. Articles published during 2000–2017 were included in the search. The primary search rendered 128 related articles, which were narrowed down to 28 suitable articles for inclusion in the final analysis for this review.

3. Results

Cytokines are small glycoproteins that coordinate an effective immune response among various immune cells (14). A wide range of cytokines and chemokines play important roles in asthma severity in pediatric patients. These include interleukin (IL)-4, IL-5, IL-13, IL-17, IL-26, transforming growth factor beta (TGF-β), interferon gamma (IFN-γ), and novel mediators such as IFN-γ-inducible protein 10 (IP-10; CXCL10), periostin, and proangiogenic factors.

3.1. IL-4

IL-4 is a key cytokine produced by $CD4^{+}$Th2 cells (15), mast cells, and basophils. It induces the production of IgE and expression of major histocompatibility complex class-II molecules, B7, CD40, and surface IgM on B cells, thereby enhancing their antigen-presenting capacity (14). It is the key cytokine involved in the pathogenesis of allergic diseases (16) and is implicated in airway remodeling and stimulation of mucus-producing cells (17). Its overexpression in the lungs induces eosinophilic inflammation without airway hyperreactivity (18); Therefore, demonstrating its involvement in asthma had been difficult. An increased IL-4/IFN-γ ratio in the EBC, predominantly accompanied by an increased number of Th2 cells in the airway, is associated with pediatric asthma severity (19). IL-4 is a useful biomarker for detecting severe asthma along with other inflammatory markers, such as INF-γ, IL-5, and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) (20, 21). IL-4 levels are low in BAL Fluids (BALF) of children using inhaled corticosteroids (11) but do not differ between intermittent, mild, moderate, and severe persistent asthma (22).

3.2. IL-13

The functional and structural characterization of IL-13 are similar to that of IL-4 (14). Their receptors (IL-4Rα/

IL-13Rα1) are present on activated B and T cells, macrophages, mast cells, fibroblasts, epithelial cells, muscle cells, and hematopoietic progenitor cells (23). IL-13 signaling influences the Th1/Th2 balance via the STAT6 pathway and is involved in asthma. High levels of IL-13 are secreted by Th2 cells in asthma patients (24). IL-13 induces eosinophil infiltration, goblet cell hyperplasia, mucus secretion, contractility of airway smooth muscle cells, and IgE production from B cells. Serum IL-13 levels increase in pediatric asthma, supporting the positive correlation between severe asthma and high IgE levels (18).

Another study has demonstrated that the percentage of CD4+/IL-13+ T cells is higher than that of CD4+/IL-4+ T cells in the peripheral blood of children with severe asthma, suggesting that IL-13 is an important cytokine associated with asthma symptoms and is the key inflammatory cytokine in the Th2-driven immunopathology involved in asthma (3). In addition, IL-13 expression in bronchial submucosa specimens, BALF, induced sputum, and serum increases in adult asthma patients (21). IL-13 overexpression in BALF is reportedly the best marker of pediatric asthma (25). High sputum IL-13 concentration and number of IL-13+ cells in the bronchial submucosa specimens are characteristic of severe asthma (26).

3.3. IL-5

IL-5 is produced by eosinophils, mast cells, Natural Killer (NK) cells, epithelial cells, CD4+ and CD8+ T cells, and non-hematopoietic cells, such as epithelial cells. IL-5 Receptor (IL-5R) is expressed on eosinophils, basophils, and B lymphocytes. IL-5 plays a key role in the development, survival, and chemoattraction of eosinophils (14). It is secreted by T lymphocytes in asthmatic airways and increases the sputum eosinophil count in asthma patients. Blocking of IL-5 with anti-IL-5 (mepolizumab) in asthma significantly reduces eosinophilic inflammation and airway hyperresponsiveness (27-29). Plasma IL-5 levels decrease during steroid therapy in severe pediatric asthma (30). High serum IL-5 and IgE levels have been documented in children with severe asthma (16).

3.4. IL-17

IL-17 is a CD4+ T cell (Th17)-derived cytokine; its release is induced by IL-23 (31). IL-17A is the main cytokine produced by Th17 cells. It stimulates epithelial, endothelial, and fibroblastic cells to secrete proinflammatory cytokines, such as IL-8, IL-6, GM-CSF, IL-1β, TGF-β, and tumor necrosis factor α (14). Various samples (sputum, BALF, bronchial biopsies, and plasma) from children with asthma have shown the involvement of high IL-17 levels in airway obstruction. Blocking of IL-17 in asthma leads to a significant reduction in airway inflammation (3, 32). The IL-17 expression is significantly elevated in the serum of children with severe asthma; therefore, serum IL-17 concentration has been described as an independent marker of inflammation in severe asthma and its measurement provides a noninvasive method for evaluating asthma severity (19). Il-17 may also be involved in steroid hyperresponsiveness (33). Moreover, another study has reported that IL-17 expression decreases in patients using corticosteroids (34).

3.5. IFN-γ

IFN-γ is a Th1 cytokine that inhibits the production of Th2 cytokines, such as IL-4, IL-5, and IL-13, and decreases the production of IgE (14, 20, 35). Children with asthma exhibit significantly low IFN-γ levels. High serum IFN-γ levels are correlated with reduced blood eosinophil counts and total IgE levels in such children (20). IFN-γ gene polymorphism (+874) increases the susceptibility to asthma in children (18). Elevated serum IFN-γ levels in BALF and during Respiratory Syncytial Virus (RSV) infection have been reported in pediatric asthma (11, 32). Thus, the hypothesis that only increased Th2 cytokine levels are involved in asthma is not correct, and Th1 cytokines may also have inflammatory responses in pediatric asthma (21, 28).

3.6. IL-6 and IL-8

In our previous study, serum IL-6 and IL-8 levels did not differ between patients with mild and severe asthma (36), indicating that these cytokines could not predict asthma severity.

3.7. TGF-β

TGF-β is a cytokine produced by many cells, including eosinophils,neutrophils, mast cells, structural cells such as epithelial and endothelial cells, airway smooth muscle cells and fibroblasts (35, 37). It plays a key role in pediatric asthma severity and the degree of subepithelial fibrosis (38). TGF-β, together with Platelet-Derived Growth Factor (PDGF), is considered as a marker of airway remodeling in asthma. It modulates the action of T cells during inflammation. One study that evaluated the key role of Treg cells in asthma suppression has found that blood Treg cell counts and the level of its transcription factor FOXP3 are low and TGF-β gene expression is high in pediatric asthma (34). Alternatively, it is speculated that high TGF-β levels can control a feedback mechanism to maintain immune response, but the source of this feedback loop is unclear (39). TGF-β levels increase in Bronchoalveolar Lavage Fluid (BALF) in pediatric asthma. Another study has found that TGF-β levels are positively correlated with IL-13 levels in severe

pediatric asthma (40). Increased serum TGF-β levels in children with severe asthma reportedly cause significant reductions in inflammatory responses despite steroid inhalation therapy (41). Another study involving bronchial biopsy specimens obtained from children with severe asthma has demonstrated significantly high TGF-β expression (34). TGFB1 polymorphisms are considered as useful indicators of asthma severity (airway responsiveness and disease exacerbations) in children (42) (Table 1).

3.8. IL-26

IL-26 is a member of the IL-10 cytokine family and is expressed by Th17 cells and other leukocytes. It has both pro- and anti-inflammatory properties and contributes to neutrophil mobilization in the airways. High sputum IL-26 levels are found in pediatric asthma, indicating that IL-26 plays an important role in asthma severity. Thus, IL-26 has been suggested as a novel biomarker of asthma severity in children (43).

3.9. IP-10

IP-10, known as CXCL-10, is a CXC chemokine produced by activated T cells. Through its interaction with CXCR3+, a ligand highly expressed on activated Th1 cells, IP-10 attracts inflammatory cells to the inflammation site. Viral infections in children promote Th1 inflammation. Type I and II IFNs stimulate IP-10 expression by T cells in the bronchial epithelia as a chemoattractant leading to severe acute asthma. Studies have shown elevated serum IP-10 levels in virus-induced pediatric asthma (44). IP-10 levels are significantly elevated in acute pediatric asthma compared with that in stable pediatric asthma, especially in the BALF of children with asthma. In addition, their levels are positively correlated with the severity of airway obstruction in pediatric asthma. Thus, IP-10 may be a useful inflammatory marker of asthma severity (45).

3.10. Periostin

Periostin is the extracellular matrix protein secreted by osteoblasts and mesenchymal cells. POSTN gene expression increases in the airway epithelium of children with asthma. The Th2 cytokines IL-4 and IL-13 induce periostin production in bronchial epithelial cells in asthma (46), which is secreted directly into the blood vessels. Increased periostin levels in the blood of children with asthma stimulate collagen synthesis, fibrillogenesis, and TGF-β activation. POSTN gene expression decreases in pediatric asthma after treatment with corticosteroids (8). Serum periostin level is a more useful biomarker of pediatric asthma than blood eosinophil count and IgE level. Therefore, a useful systemic biomarker of eosinophilia in the airway lumen and tissue (46). In growing children, periostin is released from the bones, but higher periostin levels have been identified in asthmatic children than in healthy children (1, 8). More studies are needed on the use of periostin level as a biomarker in clinical practice. Nonetheless, serum periostin level is considered as an independent predictor of increased asthma severity (1).

3.11. Angiogenic factors

Asthma severity has been highly correlated with airway remodeling in the airway tract; these changes include extracellular matrix enhancement, smooth muscle cell hyperplasia, and neovascularization (47). Proangiogenic factors play important roles in asthma progression. Several angiogenesis regulators, including thrombospondin-1, matrix metalloproteinase-9 and its inhibitor TIMP-1, dipeptidyl peptidase IV, and PDGF-AA, are involved in the regulation of airway remodeling and angiogenesis in pediatric asthma. Elevated PDGF-AA levels are observed in the EBC of asthmatic children with severe airflow limitation. PDGF plays an important role in bronchial fibrosis (47, 48).

3.12. Chemokines

Chemokines are a group of chemotactic cytokines that regulate cell trafficking. They can be classified into four subclasses, namely CXC, CC, C, and CX3C, depending on the spacing of conserved cysteine residues (49). Certain regulatory factors, such as CXCR4, CCR3, RANTES, and Thymus and Activation-Regulated Chemokine (TARC), that are categorized as chemokines play key roles in pediatric asthma severity.

3.13. TARC

TARC is a novel chemokine. The TARC-encoding gene is located on chromosome 16 (16q13) and expresses a 71-amino-acid-long basic protein with a molecular weight of 8 kDa (50). It acts on the chemokine receptor CCR4, which is expressed on peripheral blood mononuclear cells and human T lymphocytes (49). High serum and sputum levels of CCR4+ CD4+ cells and TARC accompanied by high total IgE concentration in the plasma of children with asthma have been documented (50). Another study utilizing BALF specimens obtained from children with severe asthma has demonstrated high TARC levels. However, because BALF analysis is an invasive method, a noninvasive method, such as sputum analysis, should be considered in children (51). Plasma TARC concentration may be a useful biomarker for airway inflammation and asthma severity in children before the clinical presentation (50).

3.14. RANTES

RANTES (regulated upon activation, normal T-cell expressed and secreted), also known as chemokine ligand 5 (CCL5), is a CC chemokine produced by T lymphocytes, fibroblasts, eosinophils, endothelial cells, platelets, and other cells and has been suggested as the key mediator in asthma (52). CCL5 attracts several types of inflammatory cells, including eosinophils, monocytes, and Th cells, to inflammation site, and exhaled RANTES levels are associated with asthma severity and serum IgE levels (19). In one study, exhaled RANTES levels were found to be higher in children with mild to severe asthma than in healthy controls (19). RANTES has also been implicated in airway inflammation responses because of its ability to attract and stimulate several types of inflammatory cells (19, 45). A study that evaluated the important role of RANTES in asthma development has found that increased serum RANTES levels in pediatric asthma may enhance Th2 lymphocyte migration into the airway (45). Serum RANTES level may be a useful noninvasive marker of airway inflammation and may play a significant role in monitoring asthma severity (52). Notably, RANTES has also been introduced as an important marker for differentiating between moderate and severe pediatric asthma. Studies showing increased RANTES levels in the BALF of asthma patients have implicated RANTES in eosinophil chemoattractant activity, which is blocked in the presence of anti-RANTES antibody. In one study, among the cytokines and chemokines, namely growth-related oncogene (CXCL1), RANTES, IL-12, IL-6, IFN-γ, and IL-10, that were examined in the BALF and Alveolar Macrophage (AM) lysate of children with asthma, RANTES was found to be a potential factor for distinguishing between severe and moderate pediatric asthma. However, analyses of BALF and AM lysate are invasiveness methods and therefore unsuitable for children (25).

A significant correlation has been found between the CCL5 −28C/G polymorphism and pediatric asthma severity (53). Reportedly, the RANTES 403G/A polymorphism enhances RANTES transcriptional activity and gene expression, supporting the association between high serum RANTES levels and severe airway obstruction in children (32).

3.15. CXCR4

The Th2 cell subset expresses CCR3, CCR4, CCR8, and CXCR4 receptors. Among these, CXCR4 has been associated with marked attenuation of asthma. CXCR4 and its ligand SDF-1 have been considered as more effective markers of migratory response in asthma than the CCR3/eotaxin system. In children with bronchial asthma, lymphocytes tend to overexpress CXCR4, which is associated with asthma severity (54). CXCR4 plays a crucial role in airway inflammation and promotes the differentiation of B cells into IgE-secretory plasma cells as well as Th2 cell infiltration, leading to asthma (51, 54). The MCP-4/CCR3 interaction acts as a chemoattractant for eosinophils in asthma and has been related to asthma exacerbation (55); consequently, eosinophil counts in the sputum and serum of children with asthma are significantly high. A recent trial of inhaled corticosteroids therapy in pediatric asthma has

Table 1. Association of selected molecular polymorphisms with asthma severity in children

Marker	SNP	Alleles	Function	Asthmatic Population	References
RANTES	-28 (rs2280788)	C>G	Higher CCL5 expression	Children(meta-analysis)	[53]
INF-$_{\gamma}$	+874	T>A	Decrease INF-$_{\gamma}$ expression	Children from Saudi Arabia	[18]
IL4	-589 (rs 2243250)	C>T	Increased IL-4	German children (age 9 to 11 years)	[15]
IL13	-1112 (rs 1800925)	C>T	Elevated serum IgE levels		
IL4Rα	148 (rs 1805010)	A>G	Higher IgE,IL-4 and stat6 expression		
STAT6	2829 (rs 324011)	C>T	Elevated serum IgE levels		
TGFβ1	-509 (rs1800469)	C>T	Higher TGFβ1 expression	Children 6 to 14 years of age in Costa Rica cohort	[42]
TLR2	-16934	T>A	Modify interaction with microbial molecules	Children from rural communities in Austria and Germany	[57]

shown that corticosteroids decrease Th2 cell activation and MCP-4 expression (56).

The mechanisms of airway inflammation in children are unknown. The mechanisms underlying asthma may differ between children and adults (6, 7, 12, 57, 58). Cytokines play an important role in coordinating mechanisms involved in asthma and are directly associated with asthma phenotypes. The genetic polymorphisms and profiles of cytokines and chemokines are key factors affecting the airway inflammatory processes. No relationship has yet been established between inflammatory markers (serum eosinophil count, exhaled nitric oxide, and serum eosinophil cationic protein) and pediatric asthma severity (10, 59-61). Therefore, further studies are required on the use of multiple molecular biomarkers, such as cytokines, for differentiating between asthma severities in children (25).

Eosinophil and mast cell cytokines (IL-4, IL-5 and eotaxin) involved in allergic sensitization in children are important for the pathogenesis of severe pediatric asthma in most cases and play key roles in airway remodeling (62). Airway remodeling is characterized by the thickening of reticular basement membrane, subepithelial fibrosis, and airway smooth muscle hyperplasia (34, 62).

Table 2. Description of multiple cytokine biomarkers, which increase in noninvasive samples (sputum, exhaled breath condensate, and blood), for assessing pediatric asthma severity

Biomarker	Sample	Function	Asthmatic Children Age	References
TARC	Serum	Increase the trafficking of Th2 lymphocytes into sites of airway inflammation and total IgE level	6-15 Years old	[50]
TGF- β	Peripheral blood	Remodeling process and modulate the action of T cells	2-6 Years old	[39]
RANTES	Serum	Enhancement of Th2 lymphocyte migration into the airway	4.5-16 Years old	[45]
	EBC	Increase the eosinophils migration and IgE level	6-18 Years old	[19]
PERIOSTIN	Serum	Stimulates collagen synthesis and TGF-β activation	6-15 Years old	[8]
IL-26	Sputum	Mobilization of neutrophils in the airways	13.7 Years median age	[43]
IL-13	Serum	Enhance contractility of airway smooth muscle cells and IgE level	10.12 Years median age	[18]
	Peripheral blood	Inducing IgE expression	9.02 Years median age	[22]
IL-5	Serum	Survival and chemoattraction of eosinophils	13.5 Years median age 12.2 Years median age	[21] [16]
IL-4	EBC	Promote eosinophilic inflammation and Th2 response	6-18 Years of age 2-18 Years of age	[19] [17]
	Serum	Increase the eosinophils inflammation and IgE level	12.2 Years median age	[16]
CXCR-4	Peripheral blood	Enhancement of Th2 lymphocyte migration into the airway and Inducing IgE expression	5-12 Years old	[54]
CCR3	Sputum	Eosinophil chemotactic effects	10.72 Years median age	[56]
IL-17	Serum	Induce expression of pro-inflammatory cytokines and neutrophils recruitment	Under the age of 5 year	[33]
IP-10	Serum	Attract inflammatory cells (Th-1) into site of inflammation	Significantly under the age of 3 year	[44]
INF-$_{\gamma}$	Serum	Inflammatory effects and Th1/Th2 imbalance	13.5 Years median age 10.12 Years median age 2–18 Years of age	[21] [18] [17]
Angiogenic factors	EBC	Functional and structural changes in respiratory tract (remodeling)	14 Years median age 12.7 Years median age	[47] [48]

Several studies have shown the usefulness of some cytokines, such as IL-4, in only identifying asthma and that they are not helpful in distinguishing between mild and severe asthma phenotypes (18, 22). IL-26 has been described as a biomarker of pediatric asthma severity without Th2-mediated eosinophilic airway inflammation. However, the relationship between IL-26 and low sensitivity to inhaled steroids is unknown (43). TGF-β contributes to the development of severe airway inflammation in children and increased collagen (types I and III) synthesis compared with IL-11 and IL-17 (34). High TGF-β expression leads to airway remodeling, whereas decreased TGF-β expression leads to anti-fibrotic effects (42).

Several other biomarkers, such as vitamin D, are involved in the severity, pathogenesis, and immunopathology of pediatric asthma (63, 64). Vitamin D plays an important role in pediatric asthma severity and airway remodeling by inducing the expression of CD23/21 (low-affinity IgE receptor on B lymphocytes) and FoxP3 factor (key translation factor in Treg lymphocytes) (39, 65). Another study has shown that individuals with FOXP3 gene polymorphism could be susceptibility to allergic diseases, such as allergic rhinitis (66).

Stimulation of the highly sensitive receptors of innate cells known as toll-like receptors (TLRs) promotes cytokine expression and inflammatory processes (67, 68). TLR stimulation is known to promote the involvement of innate immune cells (eosinophils, basophils, and NK cells) in severe Th2-associated responses involved in pediatric asthma (57). Therefore, further investigations are required to obtain new insights into the role of innate immune responses in cytokine expression involved in pediatric asthma.

Cytokines synthesis in response to viral infection (RSV infection) in children is associated with asthma severity. Reportedly, RSV infection stimulates the secretion of several cytokines, including IL-4, IL-5, IL-13, IL-17, IL-6, IL-8, IFN-γ, CCL5, CCL11, and CXCL10, which are involved in severe asthma responses (32, 44). One study has suggested the involvement of Th1 proinflammatory cytokines, such as IFN-γ and IL-12, in the pathogenesis of pediatric asthma, indicating that in some cases, pediatric asthma is not simply a Th2-driven response (11).

Invasive methods requiring repeated sampling are not suitable for asthma monitoring (69). BAL and endobronchial biopsy are the reference standards for distinguishing the extent of eosinophilic airway inflammation (70). These approaches have been used to measure airway inflammatory molecules, such as cytokines, in many studies but are invasive and expensive. Therefore, noninvasive techniques are needed for evaluating biomarkers of airway inflammation in pediatric asthma patients (Table 2).

Noninvasive methods, such as analyses of induced sputum and EBC samples, are clinically useful in evaluating asthma (13, 69, 71, 72) and can be performed repeatedly. However, EBC and sputum samples require appropriate standardization (1, 73). Currently, the measurement of fractional exhaled nitric oxide is the only validated minimally invasive method for assessing asthma-related eosinophilic inflammation in clinical practice (13, 74). However, its accuracy to distinguish asthma severity between children with different phenotypes and endotypes remains unclear, and it has various shortcomings; therefore, its results should be confirmed using other useful biomarkers, such as cytokines, in sputum, EBC, and blood/serum, which have been described for assessing asthma severity in children (75).

4. Conclusions

A wide range of cytokines and Chemokines may be important in disease severity in pediatric. However, Studies recommend the use of multiple molecular biomarkers such as cytokines for differentiation of asthma severity in children.

Ethical Considerations

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Conflict of interest

All authors certify that this manuscript has neither been published in whole nor in part nor being considered for publication elsewhere. The authors declare no conflict of interest.

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