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Surfactant proteins levels in asthmatic patients and their correlation with severity of asthma: a systematic review

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Abstract

Background Surfactant decreases surface tension in the peripheral airways and plays a role in regulating the lung's immune responses. Several reports have documented changes in surfactant proteins levels, especially surfactant protein D (SP-D) and surfactant protein A (SP-A), suggesting their potential as biomarkers for asthma. However, the results of these studies are controversial. This systematic review was done to assess the levels of surfactant proteins in asthmatic patients compared to healthy individuals.

Methods A systematic review was conducted according to PRISMA guidelines. Searches were performed in the Medline/PubMed, Web of Science, Embase, and ScienceDirect databases to identify studies that assessed surfactants proteins levels in asthmatic patients. Pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using R version 4.4.3 meta package.

Results A total of 16 studies met the inclusion criteria and were thus considered for this systematic review. Among these, SP-D was the most frequently studied protein in relation to asthma, asthma severity, and lung function parameters in asthmatic patients. Serum and sputum levels of SP-D in asthmatic patients were slightly elevated compared to non-asthmatic individuals. However, these differences were not statistically significant; the pooled SMDs were 0.27 (95% CI: -0.034 to 0.574, $P=0.082$) for serum levels and 1.47 (95% CI, -0.197 to 3.103, $P=0.084$) for sputum levels. Similarly, no significant difference was detected for the analysis of serum SP-A levels, with SMD = 0.18 (95% CI, -0.505 to 0.866, $P=0.606$). Though, some of the reviewed studies showed an association between SP-D levels and disease severity in asthmatic patients.

Conclusion Although alterations have been observed in asthma and proposed as biomarkers, this systematic review did not find significant differences in the levels between asthmatics and healthy individuals. However, some studies have suggested an association between SP-D levels and asthma severity. Given the limited number of studies investigating this association, further research is needed to validate the clinical relevance of correlation between SP-D levels and asthma severity.

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Keywords Asthma, Surfactant, Surfactant proteins, SP-D, SP-A, Systematic review

Background

Asthma is a respiratory disease with a high global health burden, affecting millions worldwide. In 2019, the incidence rate was 477.92 per 100,000 people, accompanied by a mortality rate of 5.96 per 100,000 [1]. This is a condition characterized by chronic inflammation of the lower airways, manifested by symptoms like wheezing, shortness of breath, and cough. Asthma is classified into different degrees of severity, basically according to clinical findings and lung function tests, which are important for guiding effective management [2]. The development of asthma is influenced by multiple factors, asthma is influenced by many factors, including genetic predisposition, exposure to irritants or allergens, respiratory tract infections during early childhood. Nevertheless, immunological factors play a crucial role. Various biomarkers targeting specific immune pathways have been identified, contributing to the pathogenesis of asthma and offering insights into its progression to more severe forms [3].

Evidence indicates that pulmonary surfactant proteins are involved in development, progression, and severity of various pulmonary diseases, including asthma [4]. These lipoproteins, secreted by type II pneumocytes, function to reduce surface tension in the lungs peripheral airways at the air-liquid interface and modulates the immunological responses of the lung. The primary surfactant proteins include surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, and SP-D), with SP-A and SP-D being particularly important in the innate immune response [5–7]. Both SP-A and SP-D act as pattern recognition molecules that bind to various pathogens, including viruses, bacteria, and fungi [4, 7]. Their functions in immune defense include enhancing phagocytosis through opsonization, aggregating pathogens, and regulating inflammatory mediators [4, 7].

Because of the established link between surfactant proteins and airway inflammation and remodeling, which are key features of asthma, several studies suggested that levels of surfactant proteins, especially SP-A and SP-D, may be associated with asthma and could potentially serve as biomarkers [8]. In asthma, alterations in surfactant proteins have been reported by several studies, though with variations and inconsistencies across findings [1, 3, 9].

Surfactant proteins, especially SP-A and SP-D, have emerged as potential biomarkers in individuals with several pulmonary diseases, including chronic obstructive pulmonary disease (COPD), connective tissue disease-associated interstitial lung diseases, and acute respiratory distress syndrome [10–13]. A previous meta-analysis showed that serum SP-A and SP-D can be useful for differential diagnosis and prediction of survival in patients with idiopathic pulmonary fibrosis [14]. These findings suggested that SP-D can be used clinically as a feasible, noninvasive marker of the permeability or integrity of the blood-air barrier in these pulmonary disorders.

Likewise, it has been hypothesized that the levels of surfactant proteins are significantly altered in asthmatics compared to the healthy populations, and these changes can be associated with the severity of asthma. Hence, it has been suggested that these proteins could serve as lung specific biomarkers of small airway damage, potentially predicting progression to severe forms of asthma. Surfactant proteins levels have been studied in relation to asthma, revealing mixed findings regarding their correlation with asthma. This systematic review gives an overview of available data and a more precise estimate of the association between surfactant protein levels and asthma. The findings of this systematic review could contribute to a better evidence base for the use of surfactant proteins as prognostic markers in asthma, ultimately informing clinical decision making and improving patient care.

Methods

Search approach and studies inclusion criteria

This review followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Additional file 1) [15]. The systematic review was previously registered on the Open Science Framework platform (https://osf.io/r8fhd). In order to identify relevant literature, an electronic literature search was conducted via the databases of PubMed, Web of Science, Embase, and ScienceDirect. No limitations regarding sex, race, geographical area, and publication date were applied during the search. The electronic search used the following key words: (surfactant protein OR surfactant-related protein OR SP-A OR SP-A1 OR SP-A2 OR SP-B OR SP-C OR SP-D) AND (asthma*). The details of the search strategy used for this review were presented in (Additional file 2). In addition, the references in the included articles were screened to make sure that no relevant studies have been missed. All the publications were uploaded to Endnote software for initial screening of titles and abstracts as well as to remove duplicates.

We sought to determine whether there is a significant difference in the levels of surfactant proteins between asthmatic patients and healthy subjects, or between patients with mild asthma and asthmatic patients who had severe forms of the illness. The PICO framework was used to formulate the primary research query of this systematic review. The "population" consisted of those with and without asthma. The "intervention/exposure"

was the presence of asthma. Healthy individuals were subjects of "comparison". The "outcomes" measured were mean levels of surfactant proteins. The secondary research question explored whether surfactant protein levels varied based on asthma severity within the asthmatic population.

Inclusion and exclusion criteria

The selection process involved a two-step approach. Initially, the titles and abstracts of all identified articles were screened by four independent reviewers to identify potentially relevant studies. Then, we did a full-text review of the selected studies in detail to assess their eligibility according to our set inclusion criteria. The inclusion criteria for the articles in this review were cross-sectional, case-control, and cohort studies that supplied data on surfactant protein levels in asthmatic patients. Case reports, editorials, reviews, abstracts, and studies with incomplete data for the variables of interest were excluded.

Quality assessment and data extraction

To evaluate the methodological rigor of the studies included for potential biases, critical appraisal checklists from the Joanna Briggs Institute were utilized (https://jbi.global/critical-appraisal-tools). These checklists facilitate assessment of the possibility of bias in study design, conduct, and data analysis. Data retrieved from every study

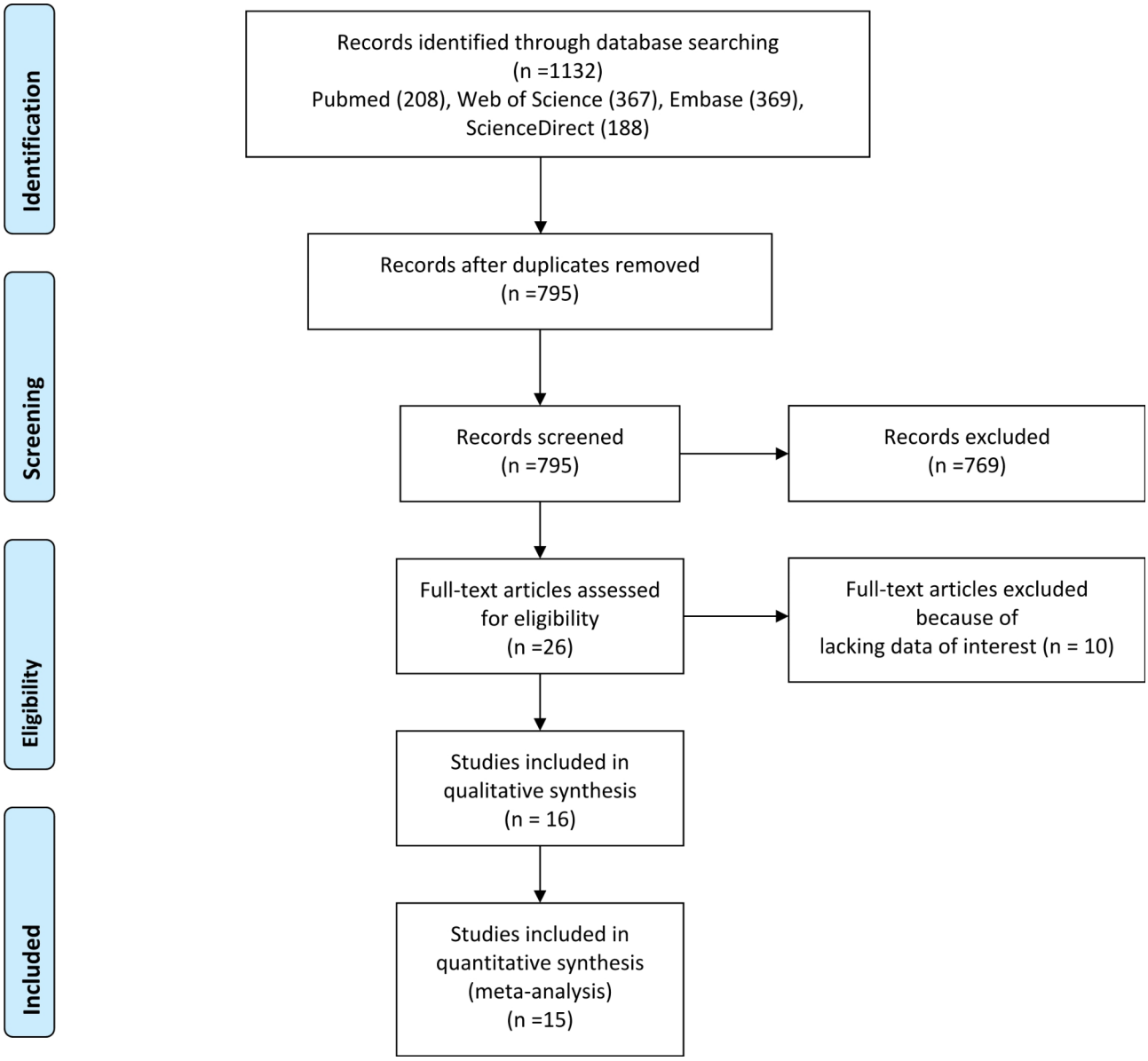


Fig. 1 Flow chart for studies selection process

Table 1 Baseline characteristics of the studies included in the review:

Study	Year	Country	Sample size	No. of asthma patients	Study group	Age	Quality assessment
Akiki et al.	2016	Lebanon	349	124	Adults	46 (32–61)	9/10
Campo et al.	2022	US	144	46	Adults	46.2 (13.5)	7/10
Cheng et al.	2000	Japan	21	10	Adults	42 (21–64)	8/10
Emmanouil et al.	2015	Greece	96	84	Not available	Not available	6/10
Erpenbeck et al.	2006	Germany	33	23	Adults	25.3 (0.7)	7/10
Fakih et al.	2017	Lebanon	436	123	Adults	46 (32–61)	8/8
Hoffmann-Petersen et al.	2021	Denmark	763	196	Children and young adults	18.7 (4.1)	9/11
Iwamoto et al.	2013	Finland	134	32	Adults	58.3 (1.5)	7/8
Koopmans et al.	2004	Netherlands	75	25	Adults	27 (6)	6/11
Mackay et al.	2016	UK	60	50	Adults	18 to 65	7/10
Mutti et al.	2006	Italy	110	30	Adults	44.6 (2.7)	8/8
Okazaki et al.	2017	Japan	40	21	Children	8 (5–11)	8/10
Principe et al.	2021	Italy	28	19	Adults	44 (12.5)	6/8
Samarasinghe et al.	2020	US	142	95	Children	9.86 (4.09)	6/10
Wright et al.	2000	UK	48	36	Adults	18–61	5\10
Yousif et al.	2023	Egypt	60	30	Children	2–5	8\10

included author, year, region, number of patients, age group of participants, and levels of surfactant protein for all groups. In cases where a study reported medians and interquartile ranges, mean and SD were estimated using the method described by Wan et al. [16]. In cases where a study provided means and SDs for multiple groups of asthmatic patients, we combined them into a single set of values using the Meta-Analysis Accelerator platform [17].

Statistical analysis

The statistical analyses were carried out by using R version 4.4.3 meta package to calculate the pooled standardized mean difference (SMD) with the 95% confidence intervals (CI). Random-effects model, using DerSimonian–Laird method, was used to compensate for the heterogeneity of studies. Heterogeneity among studies was assessed using the I^2 statistic. Publication bias, a potential source of bias due to the tendency for studies with statistically significant results to be published more often, was tested with Begg's and Egger's tests. For analyses involving more than 10 studies, funnel plots were visually checked to evaluate publication bias [18–20]. When publication bias was detected, the Duval and Tweedie trim-and-fill method was applied to account for potentially missing studies [21].

Results

Studies characteristics

The schematic flow of the study identification and selection process is presented in Fig. 1. Initially, the search yielded a total of 1,137 records. After removing duplicates, 795 studies were included for title and abstract screening, of which 769 were excluded due to irrelevance. Full texts of the remaining 26 records were screened, leading to the exclusion of 10 records, as shown in Fig. 1. Lastly, a total of 16 studies met the eligibility criteria and were included in the evidence synthesis [22–37]. The main features of the included studies, including risk of bias assessment, are presented in Table 1.

Most of the included studies assessed adult asthmatic populations, while four studies included pediatric populations. The most common types of surfactant proteins assessed were SP-D and SP-A. For SP-D, serum level quantification was the most commonly used assessment method, while two studies performed bronchoscopy to acquire bronchoalveolar lavage (BAL) fluid, and four studies measured SP-D levels in sputum. For SP-A, serum levels were assessed by four studies, while three and two studies measured BAL fluid and sputum levels of SP-A, respectively (Table 2). One study conducted by Erpenbeck et al. measured levels of SP-B and SP-C related to phospholipids in BAL fluid from healthy control and asthmatic subjects. A summary of the main results is presented in Table 2.

SP-D levels

We conducted meta-analyses to assess the difference in the mean serum and sputum levels of SP-D between asthma patients and healthy people. Although the pooled effect size showed that serum, BAL, and sputum SP-D levels tend to be higher among asthmatic patients compared to the non-asthmatic individuals, no statistically significant difference was detected between the two groups. The pooled SMD of serum SP-D levels, based on nine studies, was 0.27 (95% CI: -0.034 to 0.574,; I^2 = 84.10%, P = 0.082) (Fig. 2). There was no evidence of

Table 2 Summary of findings related to surfactant proteins levels in asthmatic patients

Study	Main findings
Akiki et al.	There were no significant differences in SPD serum levels between asthma patients and healthy controls. Significantly elevated SP-D serum levels was present in COPD patients compared to asthmatic patients and healthy controls.
Campo et al.	There were no significant differences in serum and BAL levels of SP-A and SP-D between asthma patients and healthy controls. Higher serum and BAL levels of SP-A and SP-D was present in aPAP patients and COPD patients compared to asthmatic patients and healthy controls.
Cheng et al.	Increased levels of SP-A and SP-D in asthmatic patients compared to healthy controls. The concentration of SP-A or SP-D did not correlate with pulmonary functions in asthmatics patients.
Emmanouil et al.	Increased sputum levels of SP-D in asthmatic patients compared to healthy controls. Both sputum and BAL levels of SP-D were higher in severe asthma group compared to mild-moderate asthma and healthy people groups. SP-D levels correlate with bronchial remodeling indices in bronchial biopsies (smooth muscle area and reticular basement membrane thickness).
Erpenbeck et al.	No significant difference in baseline levels before allergen challenge. Increased BAL fluid levels of SP-B, SP-C, and SP-D after allergen challenge in asthmatic patients compared to healthy controls. Both SP-C and SP-D were related to the degree of the allergic inflammation after allergen challenge (SP-C levels correlated with eosinophil numbers, IL-5, and IL-13, while SP-D levels correlated with eosinophil numbers).
Fakih et al.	There were no significant differences in SPD serum levels between asthma patients and healthy controls. Significantly elevated SP-D serum levels was present in COPD patients compared to asthmatic patients and healthy controls.
Hoffmann-Petersen et al.	No differences were found in mean levels of SP-D or three SNPs in SFTPD among subjects with current asthma, no current asthma, and controls. They were not associated with clinical parameters of asthma (lung function tests).
Iwamoto et al.	There were no significant differences in SPA serum levels between asthma patients and healthy controls. Higher SP-A serum levels was present in COPD patients compared to asthmatic patients and healthy controls.
Koopmans et al.	There was no significant difference in serum SP-D levels between asthmatics and non-asthmatic people. Serum SP-D was related to levels of inflammatory parameters after allergen challenge. Higher baseline SP-D levels predicted a stronger late asthmatic response following allergen exposure.
Mackay et al.	Serum SP-D was significantly increased in patients severe asthma compared with mild asthma group.
Mutti et al.	There were no significant differences in SPD serum levels between asthma patients and healthy controls. Significantly elevated SP-D serum levels was present in COPD patients compared to asthmatic patients and healthy controls.
Okazaki et al.	Salivary SP-D levels were higher in asthmatic children than in healthy controls. SP-D levels correlated with parameters of peripheral airways resistance and with the severity of asthma exacerbation.
Principe et al.	Serum SP-D was significantly higher in asthmatic patients compared to healthy controls. In the asthmatic group, serum SP-D was significantly correlated to alveolar nitric oxide concentration. Both serum SP-D and SP-A concentrations did not significantly correlate with spirometry parameters.
Samarasinghe et al.	Asthmatic patients had higher levels of serum SP-D compared to non-asthmatic people.
Wright et al.	There was no difference in the SP-A concentration between asthmatic and control groups for either BAL or sputum samples.
Yousif et al.	Salivary SP-D levels were higher in asthmatic children than in healthy controls. SP-D levels were correlated with poor pulmonary functions in asthmatic children.

SP-D: surfactant protein D, **SP-A: surfactant protein A**, **BAL: bronchoalveolar lavage**, **IL: interleukin**, **aPAP: autoimmune pulmonary alveolar proteinosis**, **SFTPD: surfactant protein D-encoding gene**, **SNP: single nucleotide polymorphisms**

publication bias from the results of Begg's test ($p = 0.358$) and Egger's test ($p = 0.072$).

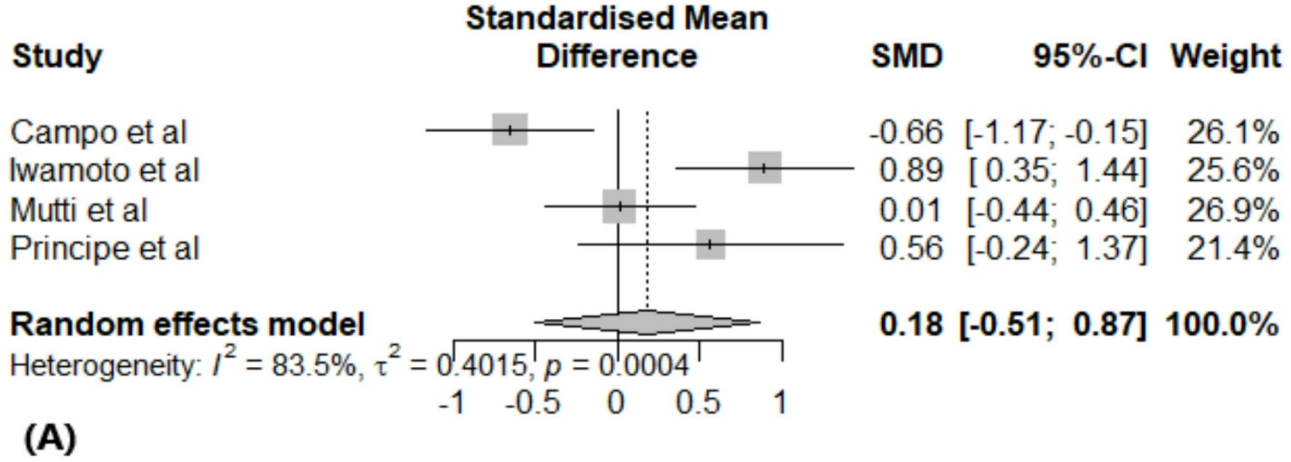
Meta-analysis of BAL data from two studies showed a pooled SMD of 1.45 (95% CI: -3.222 to 6.122, $P = 0.541$). For sputum SP-D levels, four studies provided sufficient data to calculate the pooled SMD, which was 1.47 (95% CI: -0.196 to 3.146, I^2 = 96.05%, $P = 0.083$) (Fig. 2) (Table 3). The publication bias test was significant for Egger's test ($p < 0.001$) but not for Begg's test ($p = 0.333$). However, the Duval and Tweedie trim and fill method indicated that no potential studies are missing.

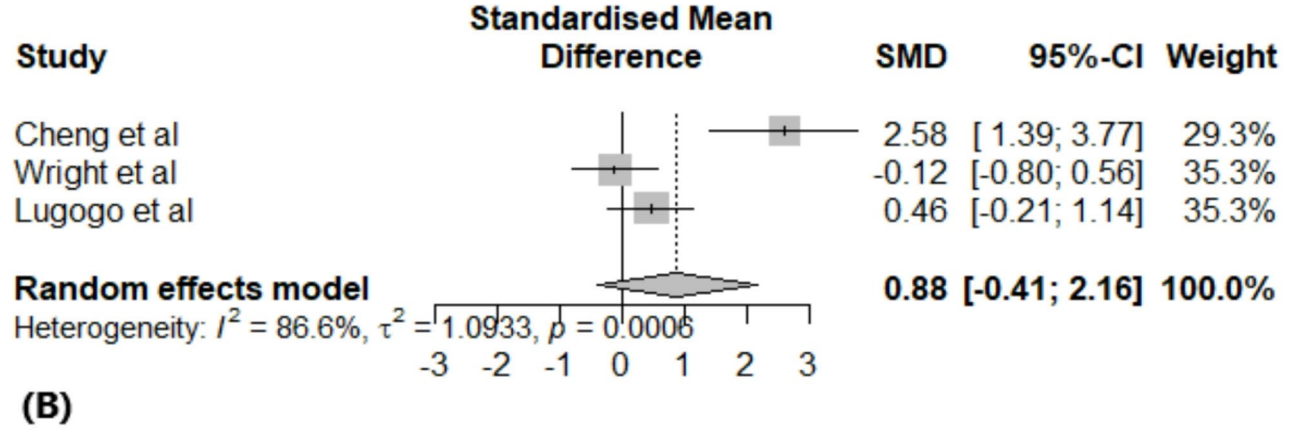
SP-A levels

There were four studies with sufficient data to calculate the SMD of serum SP-A estimates. Although the pooled effect size showed that serum and BAL SP-A levels were slightly higher in asthmatic patients, the difference was not statistically significant. The pooled SMD of serum SP-A levels, based on four studies, was 0.18 (95% CI: -0.505 to 0.866; I^2 = 83.08%, $P = 0.606$), with no evidence of publication bias from the results of Begg's test ($p = 0.750$) and Egger's test ($p = 0.494$) (Fig. 3). Sputum SP-A levels, analyzed in two studies, showed a pooled SMD of -1.09 (95% CI: -2.802 to 0.624; I^2 = 93.3%, $P = 0.212$), BAL samples from three studies yielded a pooled SMD of 0.88 (95% CI: -0.405 to 2.162, $P = 0.179$), with no evidence of publication bias from the results of Begg's test ($p = 0.601$) and Egger's test ($p = 0.202$) (Table 3).

Meta-regression and sensitivity analyses and

Due to the limited number of studies available for other outcomes, meta-regression and sensitivity analysis were conducted only for serum SP-D levels. Meta-regression





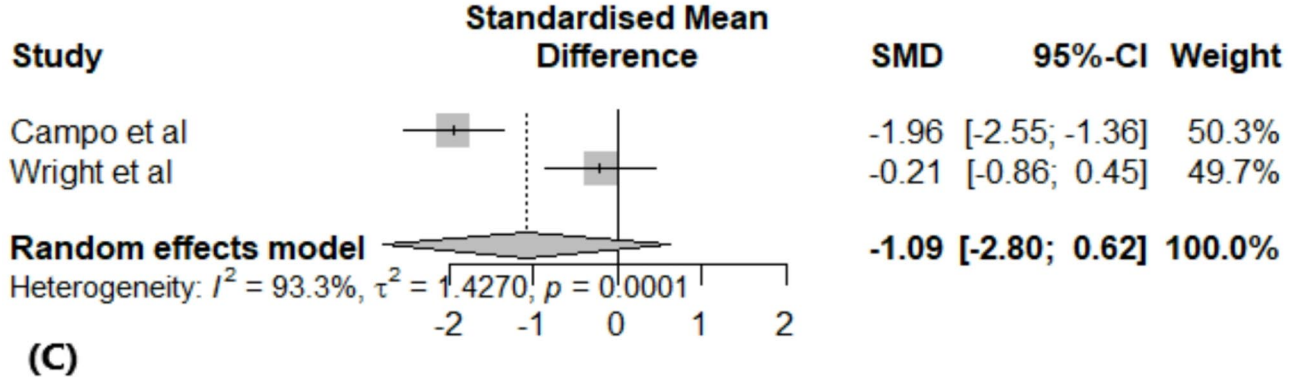


Fig. 2 Pooled SMD of SP-D estimates in asthmatic patients compared to healthy controls (**A**; serum, **B**; BAL, **C**; sputum)

was performed to investigate potential sources of heterogeneity, including study year, study size, number of asthmatic patients, and age groups. The analysis revealed no statistically significant associations between any of the included covariates and the effect size: year (coefficient = 0.0111, P = 0.686), study size (coefficient = -0.0009,

Table 3 Pooled SMDs with 95% CIs for surfactant protein levels in asthmatic patients compared to healthy controls

Surfactant protein	Measurement	No. of studies	Pooled SMD	*P* value
SP-D	Serum	9	0.27 (-0.034 to 0.574)	0.082
	BAL	2	1.45 (-3.222 to 6.122)	0.541
	Sputum	4	1.47 (-0.196 to 3.146)	0.083
SP-A	Serum	4	0.18 (-0.505 to 0.866)	0.606
	BAL	3	0.88 (-0.405 to 2.162)	0.179
	Sputum	2	-1.09 (-2.802 to 0.624)	0.212

$P = 0.223$), number of patients (coefficient = -0.0019, $P = 0.511$), and age group (coefficient = 0.3108, $P = 0.442$).

A leave-one-out sensitivity analysis was conducted to assess the robustness of the pooled estimate. Although some variation in the SMD was observed, no single study, except for Campo et al. and Mutti et al., substantially altered the statistical significance of the result (Fig. 4).

Association between surfactant proteins and asthma severity among asthmatic patients

A few of the included studies assessed the association between surfactant proteins levels and asthma severity or parameters of lungs function. Okazaki et al. found that salivary SP-D levels increase during acute asthma exacerbation in asthmatic children. Emmanouil et al. and Mackay et al. found that SP-D levels were higher in individuals with severe asthma compared to those with mild asthma. Principe et al. showed a significant correlation between serum SP-D and alveolar nitric oxide concentration, a parameter of poor asthma control (Table 2).

Regarding lung function parameters, two pediatric studies by Okazaki et al. and Yousif et al. assessed respiratory functions and peripheral small airways resistance using the oscillation technique, a sensitive and non-invasive approach for measuring respiratory function in young children [31, 35]. Both studies showed significant correlations between sputum SP-D levels and poor pulmonary function in asthmatic children. In contrast, three studies that used spirometry measures, including FEV1% (forced expiratory volume in the first second) and FVC% (forced vital capacity), found no significant associations between SP-D levels in serum or BAL fluid and lung function in patients with asthma. However, all of these three studies focused specifically on patients classified as having mild or mild-moderate asthma [32, 36, 37] (Table 2).

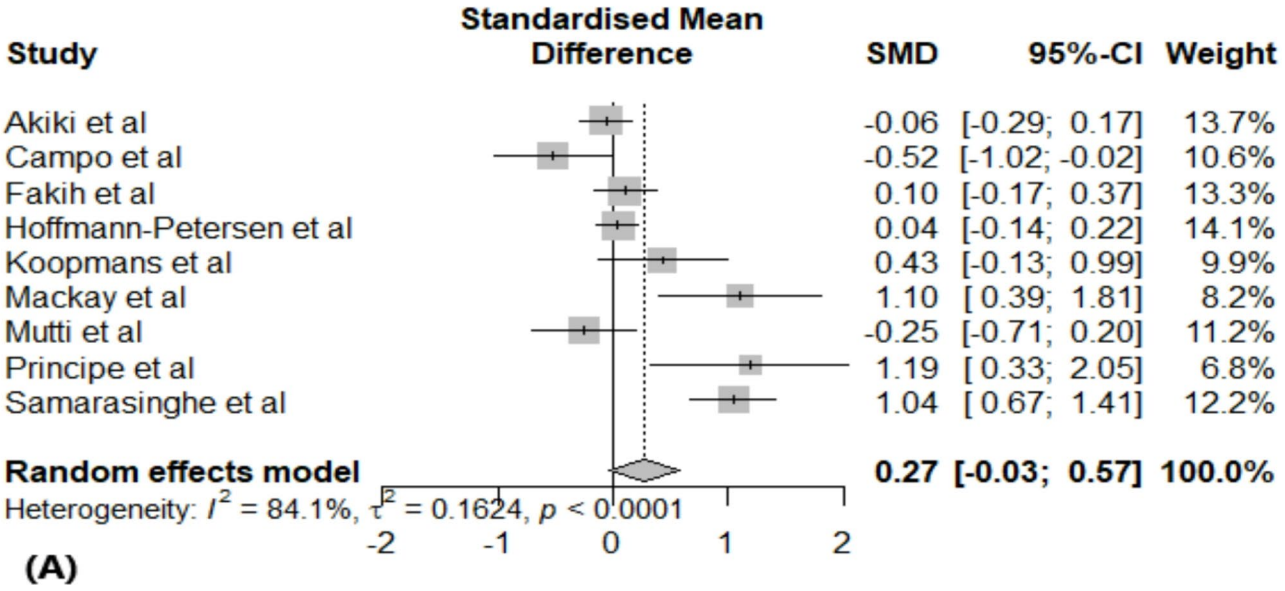
Discussion

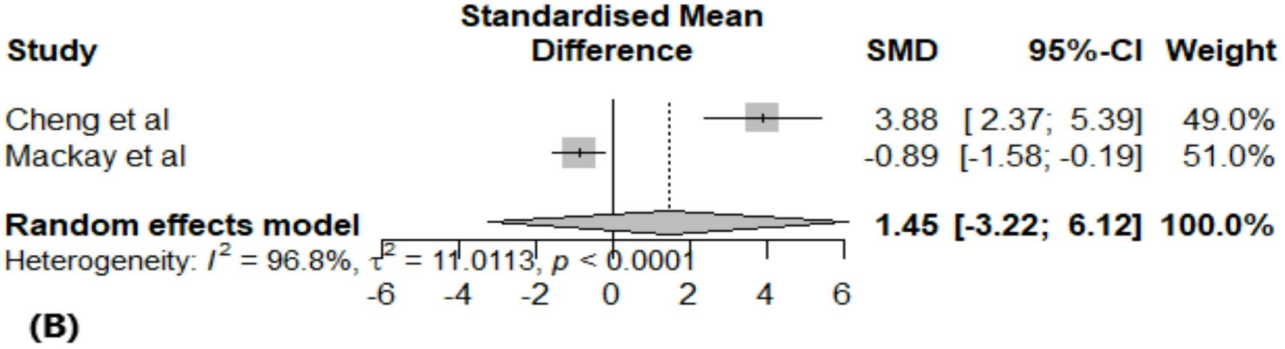
This systematic review assessed differences in surfactant protein levels between asthma patients and controls. While some studies suggest that surfactant proteins, particularly SP-D and SP-A, are altered in asthma, other findings do not support a significant relationship between these proteins and asthma.

Our review found that the evidence for altered surfactant protein levels in asthma is not as strong as that reported in systematic reviews of other respiratory conditions, such as COPD, pulmonary fibrosis, and interstitial lung disease [11, 14, 38, 39]. Moreover, all of the reviewed studies that included COPD patients showed that COPD patients had higher serum surfactant protein levels, especially SP-D, compared to asthmatic patients and healthy controls. A possible reason for this is that conditions like COPD and interstitial lung disease involve significant structural lung damage, making surfactant proteins alterations more likely. In those patients, loss of air–blood barrier integrity lead to the outward intravascular leakage of secreted lung proteins [4]. Since asthma typically does not result in significant structural alveolar damage, especially in early stages or milder forms, surfactant proteins changes may be less prominent in mild and well-controlled asthma.

Although not statistically significant, the trend towards higher SP-D levels in asthmatics was consistently observed across most of the included studies. The discrepancies in findings across studies can be attributed to various factors related to the baseline characteristics of the study populations, such as sex, obesity, and age distribution [4]. In addition, asthma is a very heterogeneous disease with various phenotypes. This variability makes it challenging to identify consistent patterns in surfactant protein levels across all asthma phenotypes and disease severity levels. Moreover, discrepancies may arise from differences in treatment regimens. While none of the included studies in this review assessed the impact of treatment on SP-D levels among asthmatic patients, some studies in chronic obstructive pulmonary disease (COPD) populations have found a significant correlation between inhaled corticosteroid (ICS) treatment and SP-D levels [10, 40]. Therefore, further research is needed to understand how common asthma controller medications impact surfactant protein levels in asthmatic patients.

Regarding the relationship between surfactant proteins and disease severity in asthmatic patients, several of the included studies reported findings indicating that SP-D levels correlate with asthma severity. Although we did not find a significant overall difference in surfactant protein levels between asthmatic and non-asthmatic individuals in the main analysis, SP-D levels appear to be associated with asthma severity, suggesting a potential link to more severe or uncontrolled disease. Specifically, research has shown that serum SP-D levels correlate with inflammatory parameters and are elevated in allergic patients who exhibit a dual asthmatic response after allergen exposure, along with more pronounced eosinophilic airway inflammation [24, 25, 28, 29, 41].





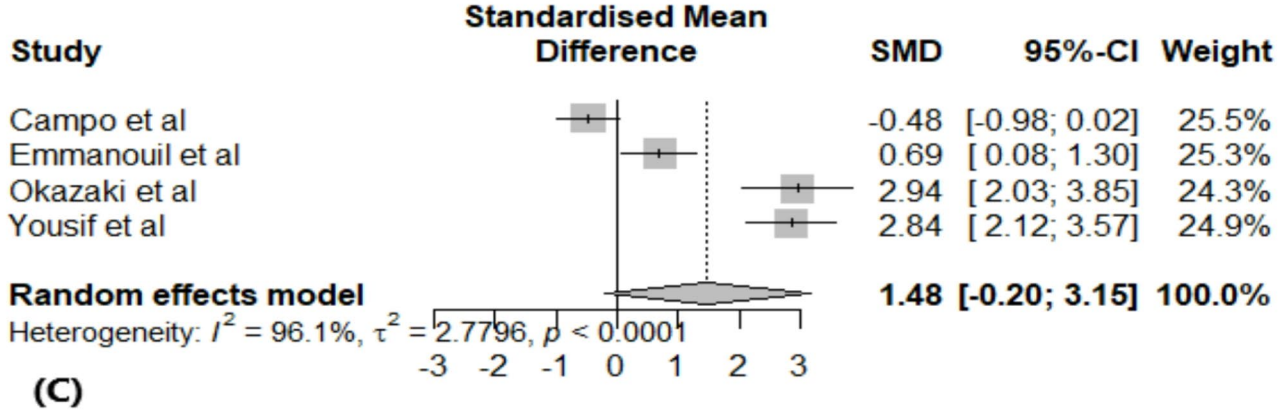


Fig. 3 Pooled SMD of SP-A estimates in asthmatic patients compared to healthy controls (**A**; serum, **B**; BAL, **C**; sputum)

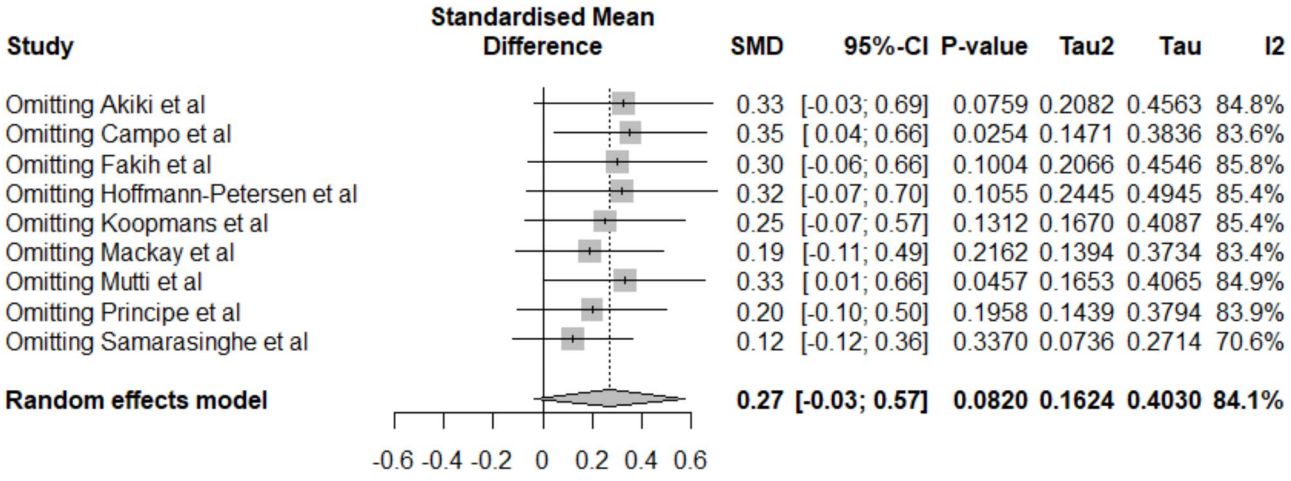


Fig. 4 Leave-one-out sensitivity analysis of serum SP-D levels

This suggests that while baseline surfactant protein levels are not markers for the presence of asthma, elevated levels within asthmatics could reflect disease progression, highlighting their role in modulating disease activity. Therefore, surfactant proteins levels may be more clinically relevant in patients severe asthma. Despite reported evidence supporting elevated SP-D as a marker of asthma severity among asthmatic patients, the limited number of studies and the variability in data highlight the need for additional research to better understand its role in asthma diagnostics and management.

This review acknowledges that while some studies show differences in surfactant protein levels between asthmatic and non-asthmatic individuals, inconsistencies in the literature persist, with some studies finding no significant differences. These inconsistencies highlight the need for further research to clarify the association between surfactant protein levels and asthma and their potential as prognostic biomarkers, particularly in regard to salivary SP-D, which could offer a quick and non-invasive assessment method. Given its non-invasive nature, salivary SP-D warrants further investigations to evaluate its utility in monitoring treatment response and predicting exacerbations.

The key limitations of this review are limited number of eligible studies and limitations in the available data. Significant heterogeneity existed across the included studies with regards to patient populations and disease characteristics such as severity, phenotypes, and treatment regimens. There were limited data regarding influence of different severity degrees of asthma on surfactant proteins levels. These limitations restricted our ability to conduct additional meta-analyses to explore relationships between surfactant protein levels and asthma severity. The relatively small number of eligible studies may limit statistical power of our analyses In addition, most of the studies that assessed surfactant proteins and asthma have relatively small sample sizes, which can limit the generalizability of their findings and make it difficult to draw definitive conclusions.

Conclusion

Though some research addresses this topic, the findings are not yet definitive or consistent enough to draw firm conclusions about potential value of using surfactant proteins as biomarkers in asthma. While elevated SP-D levels may correlate with severity of asthma and indicate airway damage, their utility as a consistent biomarker across different populations remains uncertain. More large-scale studies are needed to fully understand this association and its clinical implications. The review's limitations necessitate further studies to establish association and clinical utility of measuring surfactant proteins in asthmatic patients.

Abbreviations

BAL	Bronchoalveolar lavage
COPD	Chronic obstructive pulmonary disease
SMD	Standardized mean difference
SP	Surfactant protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03654-5.

Additional file 1: PRISMA checklist.

Additional file 2: Search strategy.

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Author contributions

SM conceptualized the research idea. SM, AM, TM, and EG undertook database searches and articles screening. AA, HF, and NY undertook quality assessment. SA, HM, SS, and FS extracted and summarized data. SM analyzed data. SM, AM,

MS, ANA and AHM drafted the manuscript. All authors read and approved the final manuscript.

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Data availability
The dataset generated during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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