Patients with sickle cell disease and asthma have a higher risk for acute chest syndrome: A systematic review and meta-analysis of observational studies

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Abstract. Sickle cell disease (SCD) is a hereditary hematologic disorder characterized by abnormal hemoglobin polymerization, leading to vaso-occlusion, hemolysis and multi-organ complications. Acute chest syndrome (ACS) is a severe pulmonary complication and a leading cause of morbidity and mortality in patients with SCD. Asthma, a prevalent comorbidity in SCD, has been implicated in worsening disease outcomes, including increased ACS risk. This systematic review and meta-analysis aimed to evaluate the association between asthma and ACS in patients with SCD by synthesizing data from observational studies. A comprehensive search of the PubMed, Cochrane Library and Scopus databases, as well as gray literature, identified 13 eligible studies, 12 of which were included in the quantitative synthesis. The meta-analysis demonstrated that patients with SCD and asthma had a significantly higher risk of ACS (risk ratio=2.27, 95% confidence interval: 1.61-3.20, P=0.0003) compared to patients with SCD without asthma, with substantial heterogeneity observed (I^2=74%). The underlying mechanisms linking asthma and ACS may include chronic airway inflammation, increased susceptibility to infections, oxidative stress and endothelial dysfunction. Despite variations in study design and population characteristics, the findings underscore the need for vigilant asthma management in patients with SCD to mitigate ACS risk. Further research is required to elucidate the pathophysiological interactions and develop targeted interventions to improve patient outcomes.

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Introduction

Sickle cell disease (SCD) is an autosomal recessive hematologic disorder caused by a single nucleotide mutation, leading to the production of abnormal hemoglobin S (HbS). First described by Dr Herrick in 1910, this mutation replaces glutamic acid with valine in the β-globin chain, altering red blood cell shape and function. Under hypoxic or acidic conditions, these cells sickle, triggering vaso-occlusive crises, hemolysis and multi-organ dysfunction (1).

SCD comprises several genotypes, with sickle cell anemia (HbSS) being the most prevalent (70%), followed by hemoglobin SC disease (HbSC) and sickle β-thalassemia (HbS/β-thalassemia). The severity of symptoms varies, with HbSS being the most severe. HbSC results from inheriting an HbS allele from one parent and hemoglobin C from the other, typically causing a milder course. In HbS/β-thalassemia, severity depends on the degree of β-globin production (1).

Globally, SCD remains a major health challenge, particularly in malaria-endemic regions, where the sickle cell trait provides a survival advantage against malaria. Each year, >500,000 infants are born with SCD, with the highest prevalence in Sub-Saharan Africa, India, the Mediterranean and the Middle East (2,3).

The disease's pathophysiology is driven by HbS polymerization, which stiffens red blood cells, reducing flexibility and increasing their tendency to block small vessels. This leads to ischemia, inflammation and endothelial dysfunction. Chronic hemolysis releases free hemoglobin into the circulation, depleting nitric oxide (NO), which worsens vasoconstriction and vascular injury. Adhesion molecules such as selectins further contribute to vaso-occlusion and disease progression (4).

SCD manifests through acute and chronic complications. The hallmark is vaso-occlusive crises, characterized by severe pain, anemia, fatigue, jaundice and increased susceptibility

to infections, particularly from encapsulated bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae*. Long-term complications include pulmonary hypertension, left-sided heart disease, stroke, renal impairment, avascular necrosis and growth delays (1). Among the most severe complications is acute chest syndrome (ACS), an acute lung injury presenting with respiratory distress, fever and hypoxia. It is a leading cause of morbidity and mortality in SCD and can be triggered by infections, pulmonary vasoconstriction and fat embolism. Management includes oxygen therapy, hydration, analgesics, broad-spectrum antibiotics and, in severe cases, blood transfusions (1,5).

Diagnosing asthma in patients with SCD presents a unique clinical challenge due to overlapping respiratory manifestations. Symptoms such as wheezing, cough and dyspnea-typical of asthma-are also common during vaso-occlusive crises and episodes of ACS, both of which are prevalent in SCD. These overlapping features can lead to misclassification or delayed diagnosis. Furthermore, pulmonary function testing may reveal restrictive or obstructive patterns in SCD that do not clearly align with classic asthma profiles, further complicating differentiation (6). Additionally, chronic airway inflammation due to SCD itself may mimic or mask asthma, and standard biomarkers such as elevated IgE or eosinophilia may be variably expressed (6), necessitating a multifaceted diagnostic approach incorporating spirometry, detailed history and longitudinal symptom monitoring (6).

Asthma is a common comorbidity in SCD, further complicating disease management. It exacerbates airway inflammation, increasing the risk of hypoxia, vaso-occlusive events and ACS. Patients with SCD and asthma or recurrent wheezing have higher rates of painful crises, stroke and mortality (7). The mechanisms linking asthma and ACS include chronic airway inflammation, heightened vulnerability to respiratory infections and exacerbation of pulmonary complications (6).

Cohort studies and biomarker research have emphasized the immunological and pulmonary complexity in patients with both SCD and asthma. It has been demonstrated that increased eosinophilic airway inflammation, as evidenced by elevated fractional exhaled NO (FeNO) and sputum eosinophils, is significantly associated with higher rates of ACS in children with SCD (8). Furthermore, convergence points within key inflammatory signaling pathways have been identified. For instance, the activation of signal transducer and activator of transcription 6 by interleukin-4 (IL-4) and IL-13, a well-established mechanism in asthma, was highlighted. Additionally, the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway, which plays a central role in regulating immune responses, was found to be active in both SCD and asthma. These shared molecular pathways suggest potential overlapping mechanisms of inflammation between the two conditions (9).

Recognizing ACS as a significant complication of SCD highlights the need for further research into its risk factors and optimal management. The link between asthma and ACS is particularly critical. Thus, to the best of our knowledge, in the present study, the first meta-analysis was conducted to quantify ACS risk in patients with SCD and asthma.

Materials and methods

General. This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (10) and the Meta-analysis Of Observational Studies in Epidemiology guidelines (11). This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/) with ID no. CRD420251012367.

Search strategy. Articles were searched in the electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane library (https://www.cochrane.org/) and Scopus (https://www.scopus.com/home.uri?zone=header&origin=sbrowse), as well as gray literature, including conference proceedings, from inception until the 4th of March, 2025. No restriction regarding sample size, study setting or publication language was imposed. MeSH terms were used for both intervention (asthma) and outcome (ACS), along with free-text words. The Boolean operators 'OR' and 'AND' were also used. The detailed search strategy applied in PubMed is presented in Table SI. Equivalent search terms and Boolean logic were adapted and applied appropriately to the Cochrane Library, Scopus and gray literature sources to ensure consistency across databases.

Eligibility criteria. Studies enrolling patients with SCD and asthma of any age with asthma, compared with patients with SCD without asthma, assessing ACS episodes, were searched for. Case reports, case series, previous meta-analyses (if any), editorials, opinion papers and narrative reviews were excluded.

PRISMA screening process. A total of 501 records were identified from electronic databases: PubMed (n=133), Cochrane Library (n=1), Scopus (n=367) and grey literature (n=1). After removing duplicates, 178 records remained for screening.

During the screening process, 178 records were reviewed based on titles and abstracts and 154 were excluded. This left 24 full-text articles for eligibility assessment. Of these 24 full-text articles, 11 were excluded for the following reasons: 1 lacked a control group; 2 included a different intervention (i.e., they evaluated asthma treatment efficacy without specifically assessing its association with ACS); 2 included populations without confirmed SCD; 4 examined outcomes other than ACS (e.g., general hospitalization rates or pulmonary function indices); and 2 were narrative review articles rather than original research. Ultimately, 13 studies were included in the systematic review and 12 were included in the quantitative synthesis (meta-analysis).

The flowchart of the study selection process is illustrated in Fig. 1.

Quality assessment. The Newcastle-Ottawa Scale (NOS) (12) was used by two independent reviewers (T-VK, KD) to assess the quality of the included observational studies. The included studies were evaluated based on the following broad perspectives: Study groups, group comparability and ascertainment of either the exposure or outcomes of interest. According to the NOS, studies are evaluated across three domains: Selection (maximum 4 stars), comparability (maximum 2 stars) and

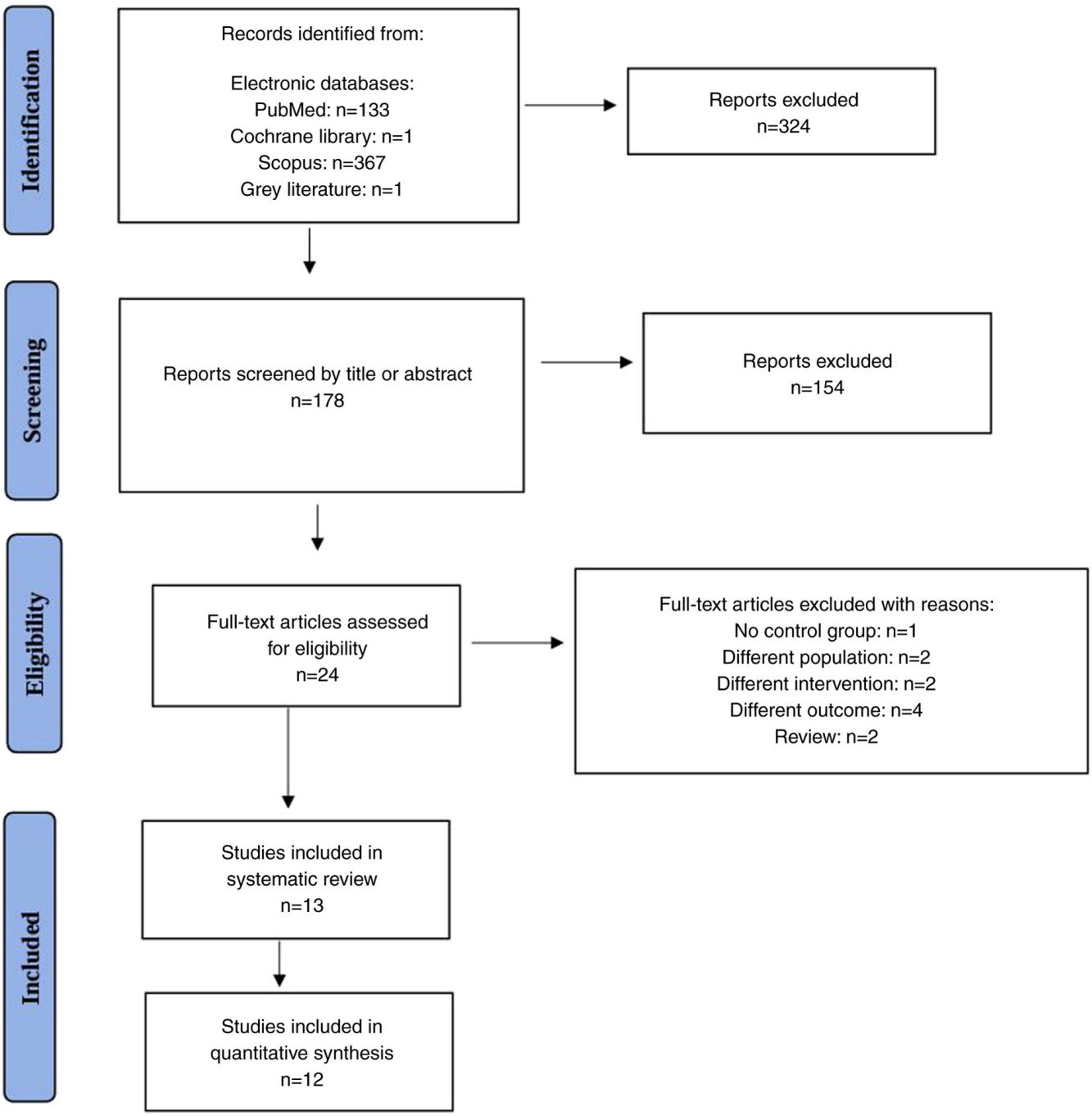

Figure 1. Flowchart of the study selection process.

outcome/exposure (maximum 3 stars), for a total of up to 9 stars. A higher number of stars indicates higher methodological quality and lower risk of bias. Studies scoring 7-9 stars were considered high quality, 4-6 stars moderate quality and <4 stars low quality. The individual scores for each study are presented in Tables SII and SIII. Divergent views among reviewers were settled through debate, consensus or arbitration by a third senior reviewer (VEG).

Data extraction. A total of three independent reviewers (TVK, KD, VEG) extracted the data from the eligible reports. Relevant information was extracted and recorded in a data collection form developed in Excel© (Microsoft Corp.). Extracted information included the following: First author, year of study conduction, country of origin, study sample size, key clinical outcome (ACS), diagnostic method of asthma and ACS.

Data synthesis and analysis. The study aimed to assess the major clinical endpoint (ACS) representing a dichotomous variable; thus, the risk ratio (RR) with 95% confidence intervals (CI) was estimated. To generate the pooled estimates of the outcome, the Mantel-Haenszel random-effects formula was implemented. The I^2 statistic was used for the evaluation of the extent to which statistical heterogeneity in a meta-analysis is due to differences among studies. Low heterogeneity was present if I^2 was between 0 and 25%, moderate if I^2 was

between 25 and 50%, or high if I^2 was >75%. Forest plots were created for a visual representation of the presence and nature of statistical heterogeneity (13). All analyses were performed with the Meta-Mar software (version 3.5.1) (14) and P<0.05 was considered to indicate statistical significance.

Results

Characteristics of the included studies. A detailed description of characteristics of the included studies (8,15-26) is provided in Table I. In cases where the number of episodes of ACS per patient per year was available, appropriate calculations were made in order to determine the number of events in the asthma group and in the non-asthma group. The inclusion of the study by Strunk *et al* (22) in the meta-analysis was not possible, as the number of ACS episodes per group was unknown. However, it should be noted that the result of this study (patients with SCD and asthma had a higher risk of ACS) was similar to that of the present meta-analysis. Regarding the outcome ACS, data were combined from 12 studies with a total of 2,269 enrolled subjects, of which 497 (21.9%) had asthma. Overall, 725 episodes of ACS were recorded. Among patients with SCD and asthma, 270 out of 497 (54.3%) experienced at least one episode of ACS. By contrast, the proportion of ACS among patients with SCD without asthma was significantly lower, at 25.7%.

Meta-analysis. As presented in Fig. 2, it was demonstrated that asthma is associated with a significantly higher risk for ACS in patients with SCD [RR=2.27, 95% CI (1.61, 3.20)], with the test for the overall effect confirming statistical significance (P=0.0003). The heterogeneity of the included studies was substantial (I^2=74%). The funnel plot is provided in Fig. S1.

Subgroup and sensitivity analysis. Subgroup analysis revealed that studies with a prospective design exhibited no heterogeneity (I^2=0%), indicating that the overall heterogeneity observed in the meta-analysis originated primarily from retrospective studies. To further explore this, a sensitivity analysis was performed by excluding the studies by Knight-Madden *et al* (16) and Intzes *et al* (21), which contributed substantially to heterogeneity in the retrospective group. This exclusion reduced the I^2 of the retrospective subgroup from 85.5 to 68%, confirming their disproportionate influence on variability. Following these exclusions, 10 studies remained, comprising 401 participants in the asthma (experimental) group and 1,669 in the non-asthma (control) group. Using a Mantel-Haenszel random-effects model, the pooled RR for ACS was 1.88 (95% CI: 1.59-2.24), demonstrating a significantly increased risk in the asthma group (P<0.05). Moderate heterogeneity was detected (I^2=52%, P=0.03), indicating that just over half of the observed variation among studies was due to real differences rather than chance (Figs. S2 and S3).

Discussion

To our knowledge, this is the first systematic evaluation and meta-analysis of the association between asthma and ACS episodes. A notable systematic review and qualitative analysis of the existing evidence was presented in 2016 by DeBaun and Strunk (6), who performed a literature search in PubMed investigating the association between asthma and ACS in children with SCD. The authors concluded that asthma is common in children with SCD, leading to higher rates of severe vaso-occlusive pain and ACS and indicating that there is strong justification for routinely assessing asthma risk factors and symptoms at each clinic visit and that spirometry should complement respiratory histories to detect and monitor lower airway obstruction and treatment responses. Three years later, Willen *et al* (27) reported on the relationship between asthma and ACS in their review article, focusing on three important studies (17,19,22). More specifically, the study by Willen *et al* (27) found that a physician's diagnosis of asthma in children with SCD is significantly associated with increased incidence of both vaso-occlusive pain episodes and ACS. The analysis of three major cohorts including 1,685 children demonstrated a 1.89-fold increased risk of ACS [incidence rate ratio=1.89; 95% CI: 1.61-2.22; P<0.001] among those with asthma. The authors emphasized that pulmonary symptoms-whether due to asthma or asthma-like features-substantially contribute to SCD morbidity and warrant routine respiratory screening and specialist referral (27).

The present study demonstrates a statistically significant association between asthma and an increased risk of ACS in patients with SCD, with a pooled RR of 2.27 (95% CI: 1.31-3.20; P=0.0003). By synthesizing all available observational data, this meta-analysis provides the first quantitative estimate of ACS risk in patients with asthma and SCD, contributing valuable evidence to the existing literature.

This finding is particularly important given the complex interplay between asthma and the pulmonary complications associated with SCD. The underlying mechanisms for this association warrant further exploration. Understanding the potential pathogenetic relationship between these two conditions is crucial for improving clinical outcomes and guiding management strategies.

Asthma and SCD exhibit several similarities regarding the immunological factors linked to their disease states. Both conditions lead to inflammation and airway hyperreactivity, affect vulnerability to respiratory infections and necessitate targeted interventions to alleviate their associated complications (7,28). The link between asthma and ACS in patients with SCD can be possibly unraveled through several interrelated mechanisms, including inflammation, hypoxemia, oxidative stress and vascular complications (7).

Asthma is a chronic respiratory condition characterized by persistent inflammation that activates a range of immune cell types, including eosinophils, mast cells and T lymphocytes. This inflammatory reaction produces cytokines and chemokines, which enhance bronchial hyperreactivity and airway obstruction, imitating or intensifying ACS symptoms, including dyspnea and chest pain. SCD also has higher levels of endothelial activation markers, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. Shared inflammatory pathways between SCD and asthma may result in an asthma-like phenotype in patients with SCD, potentially increasing the likelihood of developing asthma. Exacerbation of airway inflammation caused by asthma may significantly increase the possibility of developing ACS in patients with

Table I. Characteristics of the included studies.

First author, year	Design	Country	SCD type	Age	A/NA subjects	Follow-up	ACS episodes	(Refs.)
De, 2023	Retrospective	USA	HbSS 85.5%, HbSC 9.1%, HbSB 3.6%, HbS/HPFH 1.8%,	3-18 y	16/39	2 y	A: 13 NA: 27	(8)
Boyd, 2004	Retrospective case-control	USA	HbSS HbSβ HbSC	2-21 y	31/108	-	A: 22 NA: 41	(15)
Knight-Madden, 2005	Retrospective	Jamaica	HbSS	5-10 y	38/42	-	A: 38 NA: 3	(16)
Boyd, 2006	Prospective	USA	HbSS	<6 m at entry	49/242	11.7 y	A: 19 NA: 48	(17)
Sylvester, 2007	Retrospective	UK	HbSS	<18 y	12/153	-	A: 6 NA: 27	(18)
Bartram, 2008	Retrospective	UK	HbSS HbSC	1-15 y	16/47	-	A: 10 NA: 12	(24)
Bernaudin, 2008	Retrospective	France	HbSS	0-18 y	25/272	6-7 y	A: 18 NA: 118	(25)
An, 2011	Cross-sectional	North America, Europe	HbSS 94%, HbSβo 6%	5-14 y	140/381	-	A: 27 NA: 46	(19)
Glassberg, 2012	Retrospective	USA	HbSS 68.4%, HbSβo 10.5%, HbSβ+ 7.9%, HbSC 13.2%	6 m-67.5 y	48/214	-	A: 16 NA: 37	(20)
Intzes, 2013	Retrospective	USA	HbSS 79.6%, HbSβo 3.2%, HbSβ+ 14.1%, HbSC 30.2% HbSα 1.1%	5-18 y	58/61	-	A: 45 NA: 9	(21)
Strunk, 2014	Prospective	USA, UK	HbSS HbSβ	4-18 y	53/134	4.61±1.16 y	IRR=2.21 (CI 95% 1.31-3.76)	(22)
Pahl, 2016	Retrospective	USA	HbSS HbSβo HbSβ+ HbSC	2-21 y	29/73	-	A: 23 NA: 17	(26)
Bafunyembaka, 2024	Retrospective nested case control	French Guiana	HbSS HbSβ+ HbSC	6 m-18 y	35/140	-	A: 33 NA: 70	(23)

SCD, sickle cell disease; HbSS, homozygous SCD (two copies of the sickle cell gene); HbSβ, sickle β thalassemia (unspecified subtype); $HbS\beta^0$, sickle β-zero thalassemia (severe form with no normal β-globin production); $HbS\beta^+$, sickle β-plus thalassemia (milder form with some normal β-globin production); HbSC, sickle cell hemoglobin C disease (heterozygous for hemoglobin S and hemoglobin C); HbSα, sickle cell α thalassemia (coexistence of sickle cell trait with α thalassemia); HbS/HPFH, SCD with hereditary persistence of fetal hemoglobin; IRR, incidence rate ratio; CI, confidence interval; ACS, acute chest syndrome; A, asthmatic; NA, non-asthmatic; y, years; m, months.

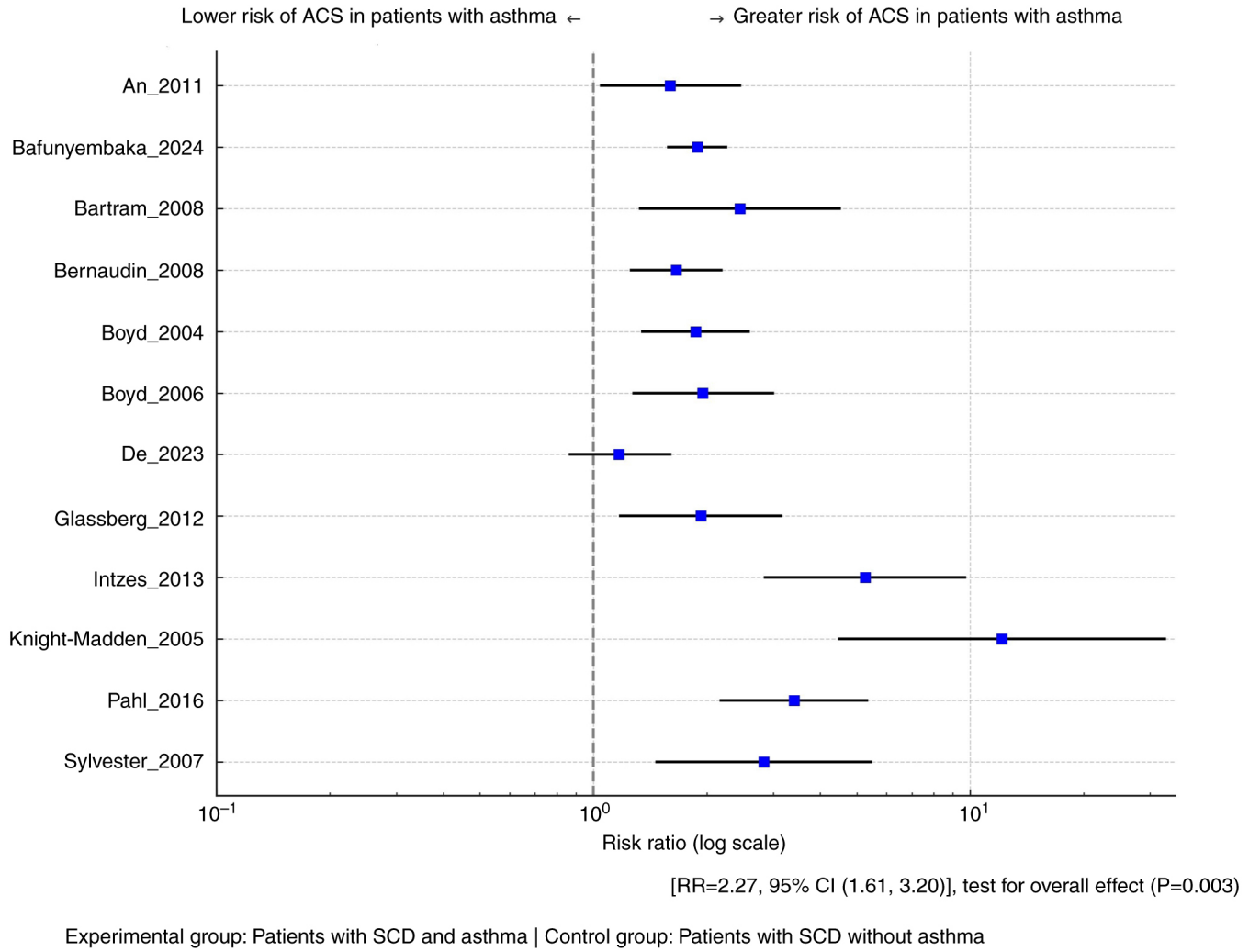

Figure 2. Forest plot for the association between asthma and acute chest syndrome in patients with sickle cell disease. CI, confidence interval; RR, risk ratio; SCD, sickle cell disease; ACS, acute chest syndrome.

SCD who are already at risk of pulmonary complications due to vaso-occlusive crises and impaired gas exchange (8,29).

Endothelial activation and oxidative stress are critical processes that connect sickled red blood cells with vaso-occlusion. Sickle cells bind to endothelium integrins, inducing damage via reactive oxygen species and sustaining additional endothelial activation. This mechanism causes the influx of monocytes and neutrophils, which contributes to increased cell adhesion in patients with SCD. The combination of sickling and inflammation can worsen vascular integrity, increasing the risk of an ACS. SCD is characterized by elevated levels of pro-inflammatory cytokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as steady-state levels of tumor necrosis factor α (TNF-α) and other cytokines. Increased neutrophil counts contribute to acute lung injury by forming neutrophil extracellular traps, which worsens pulmonary functioning and infection susceptibility (9).

Asthma may exacerbate SCD-related vascular issues. Inflammation and oxidative stress may cause endothelial dysfunction, which is a precursor to atherosclerosis and acute coronary events. In patients with SCD, the combination of sickling and inflammation can worsen vascular integrity, increasing the risk of ACS. Furthermore, asthma can cause hemodynamic changes such as increased heart rate and blood pressure fluctuations, which can contribute to cardiovascular stress. Asthma can increase acute coronary events in patients with SCD, whose cardiovascular systems are already stressed by chronic hemolysis and vaso-occlusive crises (30).

Although the present discussion outlines inflammation, hypoxemia, oxidative stress and vascular complications as potential mechanisms linking asthma to ACS in patients with SCD, a deeper exploration of molecular pathways can provide clearer targets for intervention. Inflammatory mediators play a central role in both asthma and SCD-related pulmonary events. In asthma, allergen-induced activation of type 2 T-helper (Th2) cells leads to the release of interleukins such as IL-4, IL-5 and IL-13, promoting eosinophilic inflammation, mucus production and airway hyperresponsiveness (9,28). In patients with SCD, a parallel increase in pro-inflammatory cytokines such as IL-3, TNF-α and GM-CSF is observed (9,30), which contributes to neutrophil activation and adhesion to the endothelium, further exacerbating vascular occlusion. These cytokines converge on NF-κB, a key transcription factor regulating inflammatory gene expression. Activation of NF-κB in both airway epithelial cells and endothelial cells promotes

a pro-inflammatory milieu conducive to ACS onset (9). Furthermore, oxidative stress from repeated hemolysis in SCD diminishes NO bioavailability, impairing vasodilation and amplifying endothelial injury, while concurrently asthma-associated hypoxemia further aggravates pulmonary vasoconstriction (30). Collectively, these overlapping pathways-particularly those involving IL-5 and GM-CSF signaling in eosinophils and neutrophils-highlight actionable targets such as anti-IL-5 or NF-κB inhibitors.

It is important to consider how age influences the risk of ACS among patients with both asthma and SCD. The majority of included studies focused on pediatric populations, with most participants being children or adolescents. Evidence suggests that the risk of ACS is highest in early childhood and tends to decline with age (6). This may be due to developmental changes in lung structure, immune response maturation and a reduced frequency of upper respiratory infections, which are common triggers for both asthma exacerbations and ACS in younger children. Boyd *et al* (17) conducted a prospective study with a median follow-up of 11.7 years, while Bernaudin *et al* (25) reported follow-up durations of 6-7 years in a large pediatric cohort. These extended observation periods enabled the identification of asthma-related complications well into adolescence and early adulthood. The findings from these cohorts support the hypothesis that younger children with SCD and coexisting asthma are particularly susceptible to ACS. This increased vulnerability likely stems from age-related physiological factors, including heightened airway hyperresponsiveness, underdeveloped immune regulation and narrower airway calibers, which interact with the pro-inflammatory and vaso-occlusive state characteristic of SCD.

Incorporating recent molecular evidence also broadens the implications of the present findings. The work by Habib *et al* (28) and De *et al* (8) supports a precision medicine approach, where monitoring Th2 cytokines and airway eosinophilic activity may guide tailored interventions in patients with SCD with asthma. This is crucial in light of the emerging evidence that biologics such as anti-IL-5 or anti-IL-13 agents (e.g., mepolizumab, dupilumab) not only reduce asthma exacerbations but may also minimize inflammatory triggers of ACS (28). Similarly, Pahl and Mullen (26) reported differential ACS risk based on genotype (HbSS vs. HbSC), suggesting that genetic stratification should be combined with the asthma phenotype for effective risk assessment and personalized treatment planning.

The present results underscore the importance of comprehensive management of asthma in patients with SCD. While the study demonstrates a significant association between asthma and ACS, it is important to acknowledge potential limitations. Substantial heterogeneity of the studies included in the present meta-analysis was noted. Variations in study design should be highlighted, as some of the studies were cohort studies, either prospective or retrospective, and others were case-control and cross-sectional studies. The retrospective design frequently lacks complete access to risk factor data and comorbidities. Population variability was also present, as the studies enrolled participants with different characteristics, such as age (ranging from infancy to elderly) and geographic contexts. Furthermore, the duration of asthma diagnosis was different among studies, which can also lead to varied outcomes. Of course, random variation should be acknowledged, as some heterogeneity may be due to random chance, particularly in the present study, where the number of the pooled studies is relatively small. Nonetheless, the present findings should be highlighted, even if they need to be verified in future large-scale prospective, well-designed studies.

One of the primary strengths of the present meta-analysis is its comprehensive approach to synthesizing existing research. By systematically reviewing numerous studies in the SCD field, the precision of the estimates was increased, which enhances the reliability of the conclusions drawn in the present study. This large sample size allows for more robust generalizations. In addition, the inclusion of diverse study designs and populations strengthens the external validity of the present findings. By aggregating data from various settings, it is possible to better understand the broader implications of the results and their applicability across different demographic groups. Another significant advantage of this meta-analysis is the rigorous methodology employed throughout the research process. A comprehensive literature search was conducted, adhering to established guidelines for meta-analyses. This careful selection process helped ensure that the studies included were of high quality and relevant to the research question. Furthermore, the use of advanced statistical techniques allowed for the assessment of heterogeneity and publication bias, providing a more nuanced understanding of the data. By aggregating results from various studies, a more unified perspective on the topic was offered, which is beneficial for both researchers and practitioners. This synthesis not only reinforces existing evidence but also highlights areas where further research is needed, guiding future investigations in the fields. While this meta-analysis provides strong evidence of a significant association between asthma and increased risk of ACS in patients with SCD, the generalizability of these findings may be influenced by variations in demographic and geographic factors. Most of the included studies were conducted in specific populations, often in high-income countries with predominantly African or African-American cohorts. Future research should aim to validate these findings across diverse ethnic and geographic groups to ensure broader applicability. A well-designed, multicenter, prospective cohort study encompassing diverse clinical settings and populations would offer a more comprehensive understanding of how asthma modifies ACS risk in the global SCD population. Such an approach would also allow the evaluation of potential interactions between genetic, environmental and socio-economic determinants that may influence disease severity and comorbidity burden.

Furthermore, although this review suggests a biological interplay between asthma and ACS, the causal mechanisms remain inadequately understood. The overlap in clinical presentation between asthma exacerbations and early ACS episodes adds to the diagnostic complexity and may contribute to under-recognition or misclassification. To explore the underlying pathophysiology in greater depth, future studies should incorporate translational approaches, including animal models and *in vitro* experiments. These models can help delineate the specific roles of airway inflammation, eosinophilic activity, oxidative stress and endothelial dysfunction in the pathogenesis of ACS among

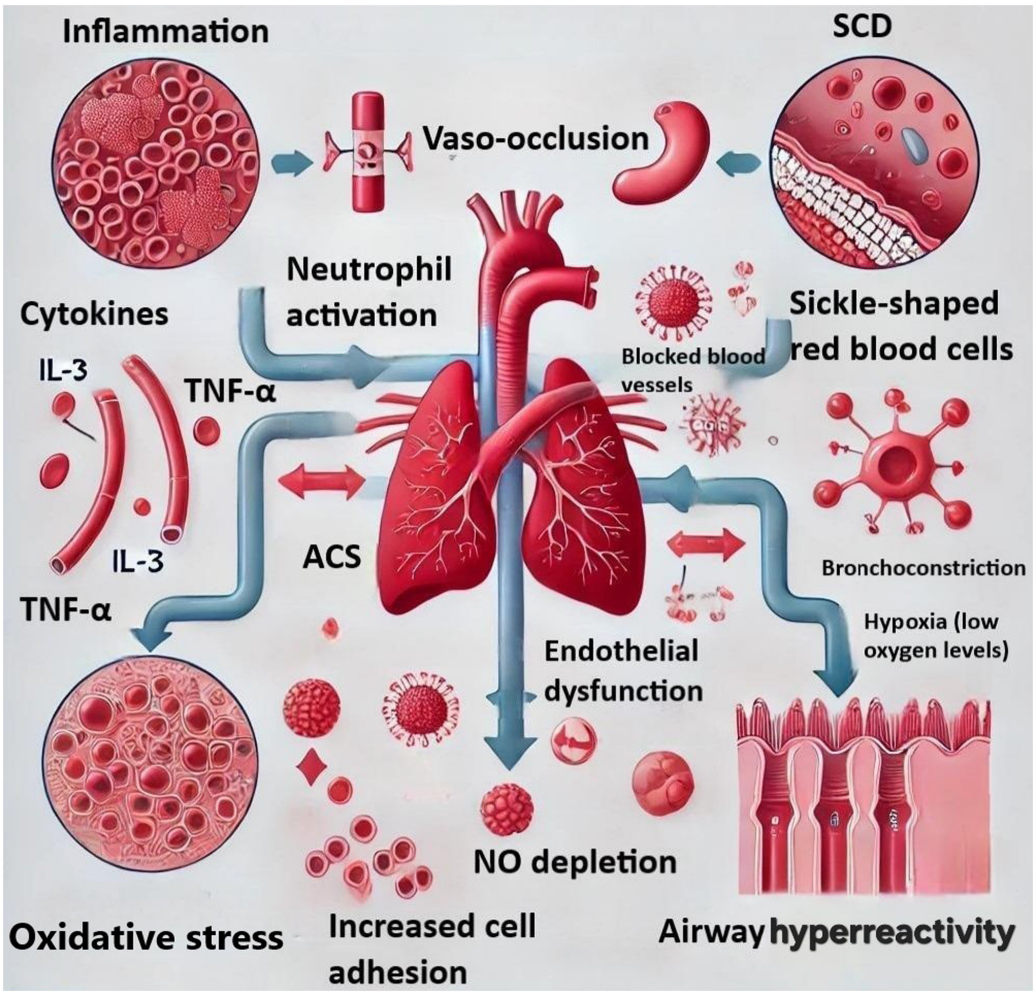

Figure 3. Mechanisms linking asthma in patients with SCD with ACS. ACS, acute chest syndrome; SCD, sickle cell disease; IL-3, interleukin-3; TNF-α, tumor necrosis factor α; NO, nitric oxide.

individuals with coexisting asthma and SCD. Additionally, population-based interventional studies, such as randomized controlled trials evaluating asthma-specific therapies (e.g., inhaled corticosteroids or leukotriene inhibitors) in patients with SCD, would be valuable in determining whether asthma management can effectively reduce the incidence or severity of ACS episodes.

Another important consideration to be addressed in future studies is the possible inconsistency of the asthma diagnostic criteria, ranging from self-reported asthma history to physician-diagnosed cases without standardized pulmonary function testing, which can lead to misclassification and impact the strength of the observed association between asthma and ACS. To enhance the validity and reproducibility of future findings, it is essential that unified and clearly defined asthma diagnostic and evaluation criteria are employed. Ideally, studies should incorporate objective measures such as spirometry, bronchodilator responsiveness and biomarkers of airway inflammation to ensure accurate asthma classification. Standardizing asthma diagnosis will not only reduce methodological bias but also facilitate more robust cross-study comparisons and meta-analyses, ultimately contributing to a clearer understanding of the interplay between asthma and ACS in SCD.

Although subgroup or meta-regression analyses could potentially help identify sources of heterogeneity, the current meta-analysis was limited by the small number of included studies and the incomplete reporting of relevant stratifying variables, such as age, region, gender and genotype. These limitations restricted the feasibility and statistical power of conducting such additional analyses. However, the significant heterogeneity observed highlights the need for future research that incorporates more detailed and standardized demographic and clinical data, enabling more granular subgroup analyses. Large-scale, multicenter cohort studies with harmonized reporting standards would be particularly valuable for disentangling the influence of various factors on the relationship between asthma and ACS in patients with SCD. The convergence of inflammatory mediators, endothelial dysfunction and oxidative stress represents a mechanistic continuum linking asthma and ACS in SCD. By visually consolidating these interactions, Fig. 3 serves as a conceptual tool for clinicians and researchers evaluating therapeutic targets such as IL-5 inhibition or NF-κB pathway modulation.

Although the association between asthma and increased risk of ACS in SCD is well established, future research should focus on elucidating the underlying pathophysiological

mechanisms and developing targeted interventions. Chronic hemolysis and NO depletion in SCD contribute to endothelial dysfunction, while Th2-driven airway inflammation in asthma-characterized by elevated IL-4, IL-5 and IL-13-promotes eosinophilic infiltration, mucus overproduction and airway hyperreactivity (6,17,25). These converging pathways exacerbate pulmonary vascular occlusion, leading to ACS. Furthermore, asthma-related hypoxemia may amplify sickling and microvascular adhesion, further increasing pulmonary complications (8,9).

To improve outcomes, future clinical studies should evaluate whether biomarker-guided asthma management (e.g., FeNO or eosinophil counts) reduces ACS incidence in SCD. Investigations into leukotriene receptor antagonists and biological therapies targeting IL-5 or IL-4/IL-13 signaling are also warranted, as these may modulate the shared inflammatory environment. Additionally, integrated treatment strategies combining disease-modifying therapies such as hydroxyurea with optimized asthma control should be explored to determine their synergistic potential in preventing ACS.

A key limitation of this meta-analysis is the presence of substantial heterogeneity (I^2=74%) across the included studies. Although subgroup and sensitivity analyses were performed, more advanced statistical approaches such as meta-regression were not conducted. Such analyses could have provided deeper insights into potential sources of heterogeneity, including age distribution, sickle cell genotypes, asthma diagnostic methods and regional or ethnic differences among study populations (13,15,17). Future meta-analyses incorporating these variables could help clarify their individual contributions and improve the precision of pooled estimates.

Another important limitation is the inconsistency in asthma diagnostic criteria across the included studies. While certain studies relied on self-reported asthma history, others used physicians' diagnosis, and only a minority incorporated objective assessments such as spirometry, bronchodilator responsiveness or airway inflammatory biomarkers (16,18,21). This variability increases the likelihood of diagnostic misclassification, which could have influenced the observed association between asthma and acute chest syndrome. Standardizing diagnostic approaches in future research-ideally using objective pulmonary function tests and validated biomarkers-will be essential to improve the reliability and reproducibility of results.

A further limitation of this meta-analysis is that it focused exclusively on the risk of ACS occurrence without evaluating how asthma may influence the severity of ACS episodes. Clinically relevant outcomes such as the duration of hospitalization, need for intensive care unit admission, requirement for mechanical ventilation or mortality were not consistently reported across studies and, therefore, could not be included in the pooled analysis (17,20,25). Incorporating these severity-related endpoints in future research would provide a more comprehensive understanding of the clinical impact of asthma in patients with sickle cell disease and better inform risk stratification and management strategies.

Another methodological limitation concerns the assessment of publication bias. Although a funnel plot was presented, no quantitative statistical tests, such as Egger's regression test or Begg's rank correlation test, were performed to evaluate the potential presence of small-study effects (13,14). The absence of these tests limits the objectivity of the publication bias assessment and may leave residual uncertainty regarding the robustness of the pooled estimates. Future meta-analyses should incorporate both graphical and statistical methods for publication bias evaluation to strengthen the validity of their conclusions.

Finally, although subgroup analyses based on study design were performed, the statistical power of these analyses was not assessed or reported. This omission raises concerns that some non-significant findings may reflect insufficient power rather than a true absence of association (12,15,19). Future studies should predefine subgroup analyses and ensure adequate sample sizes to detect clinically meaningful differences, thereby minimizing the risk of false-negative results and enhancing the interpretability of subgroup findings.

In conclusion, the association between asthma and ACS in patients with SCD highlights the need for heightened awareness and targeted management of asthma in this population. By addressing asthma as a significant comorbidity, healthcare providers can potentially mitigate the risk of ACS and improve the overall health and quality of life for individuals with SCD. The present results have clinical implications, as careful evaluation by a respiratory medicine specialist should be included in patient monitoring and assessment, so that asthma is diagnosed early and is appropriately treated. The significant association between asthma and increased risk for ACS in patients with SCD highlights a critical area for clinical attention and further research.

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Authors' contributions

KD and VEG conceptualized the study. KD, VEG, TVK, AC and DAS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. KD and VEG analyzed the data and provided critical revisions. KD, TVK, DAS, AC and VEG confirmed the authenticity of all the raw data. All authors contributed to manuscript revision, and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the AI tool ChatGPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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