

Beyond joints: pulmonary hypertension in spondyloarthropathies (Literature review)

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Spondyloarthritis (SpA) represents a complex and dynamic spectrum of inflammatory rheumatic diseases. A nuanced understanding of its clinical, genetic, and immunologic aspects is imperative for accurate diagnosis and effective management. The comprehensive literature review reveals a nuanced connection between spondyloarthropathies and pulmonary hypertension (PH), expanding our understanding of these conditions beyond joint pathology. The synthesis of data from various studies provides valuable insights into the complex interplay of factors contributing to the development of PH in individuals with SpA. The reviewed studies consistently indicate a heightened prevalence of elevated arterial blood pressure in the pulmonary artery among patients with ankylosing spondylitis and psoriatic arthritis. However, the limited research on reactive arthritis and other subtypes necessitates further exploration to determine the prevalence and characteristics of pulmonary hypertension across the entire spectrum of SpA.

The identified gaps in research emphasize the importance of future studies that encompass the entire SpA spectrum, to provide a more complete understanding of the association with PH. It is crucial to consider all pathogenetic mechanisms, including the impact of chronic persistent inflammation, endothelial dysfunction, and other relevant factors. Recognizing the significance of these mechanisms is vital for comprehensive insights into the complex interplay between both pathologies, guiding the development of targeted interventions and enhancing patient care strategies. This discussion serves as a foundation for future research directions and clinical considerations in the evolving landscape of spondyloarthropathies. This comprehensive overview sets the stage for a deeper exploration of the intricate facets of SpA, including its systemic implications and emerging therapeutic strategies.

Keywords: spondyloarthritis, psoriatic arthritis, ankylosing spondyloarthritis, reactive arthritis, spondyloarthropathies, pulmonary hypertension.

Поза суглобами: легенева гіпертензія при спондилоартропатіях (Огляд літератури)

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Спондилоартрит (SpA) є складним і динамічним спектром запальних ревматичних захворювань. Детальне розуміння його клінічних, генетичних та імунологічних аспектів є необхідним для вчасної діагностики та ефективного лікування. Всебічний огляд літератури розкриває тонкий зв'язок між спондилоартропатіями та легеневою гіпертензією (ЛГ), розширюючи наше розуміння цих станів, що ведуть за межі суглобової патології. Аналіз результатів різних досліджень дає цінне уявлення про складну взаємодію факторів, що спричинюють розвиток ЛГ в осіб із SpA.

Отримані наукові результати послідовно вказують на збільшену поширеність підвищеного артеріального тиску в легеневій артерії серед пацієнтів з анкілозивним спондилоартритом та псоріатичним артритом. Однак обмеженість досліджень реактивного артриту та інших підтипу потребує подальшого вивчення з метою визначення розповсюдженості та особливостей перебігу ЛГ в усьому спектрі SpA.

Виявлені прогалини підкреслюють важливість майбутніх досліджень, які охоплюють весь профіль спондилоартропатій, щоб забезпечити більш повне розуміння зв'язку з ЛГ. Вкрай важливо розглянути всі патогенетичні механізми, включаючи вплив хронічного персистуючого запалення, ендотеліальної дисфункції та інших релевантних факторів. Визнання важливості цих механізмів є суттєво важливим для всебічного розуміння складної взаємодії між обома патологіями, спрямування розробки цілеспрямованих заходів та вдосконалення стратегій догляду за пацієнтами. Дискусія слугує основою для майбутніх напрямків досліджень та клінічних міркувань у мінливому ландшафті спондилоартропатій. Огляд літератури створює основу для глибшого вивчення складних аспектів SpA, включаючи його системні наслідки та нові терапевтичні стратегії.

Ключові слова: спондилоартрит, псоріатичний артрит, анкілозивний спондилоартрит, реактивний артрит, спондилоартропатії, легенева гіпертензія.

Spondyloarthritis (SpA) represents a group of chronic inflammatory rheumatic diseases characterized by axial involvement of the spine, peripheral arthritis, enthesitis, and a strong association with the human leukocyte antigen B27 (HLA-B27). This cluster of disorders includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), and other related conditions (such as undifferentiated

spondyloarthritis (UnSpA), juvenile spondyloarthritis (JuSpA) (fig. 1) [1–3].

As a collective term, SpA encompasses a spectrum of clinical manifestations that extend beyond mere joint inflammation, involving various organ systems and presenting unique challenges for both diagnosis and management. These conditions are known to have a genetic basis, and, as



Fig. 1. Classification of disease overlap in spondyloarthropathies

of now, there is no scientific evidence supporting the possibility of preventing the onset of the diseases [4].

According to research findings, the prevalence of SpA significantly varies across different regions of the world, ranging from 0.20% in Southeast Asian populations to 1.61% in northern arctic communities, specially 2,5% in Alaska's region. The geographical clustering of SpA is likely associated with the genetic characteristics of the population, particularly the presence of HLA-B27 [5].

Researchers have also attempted to ascertain specific prevalence figures for each subgroup of SpA, but meta-analyses could only be conducted for AS and PsA. The prevalence of AS ranged from a minimum of 0.02% in Sub-Saharan Africa to 0.35% in the North Arctic. PsA prevalence varied from 0.01% in the Middle East to 0.19% in Europe (southern regions). Japan reported the world's lowest PsA prevalence at 0.001%, with China showing a prevalence range of 0.01% to 0.10% [5–7].

The data on ReA are notably limited and understated, primarily due to the perception of its relative safety and the insufficient awareness among healthcare professionals regarding potential complications. In Europe, the prevalence ranged from 0.04% in Greece to 0.10% in Serbia and Germany. Lebanon reported the highest global prevalence of ReA at 3.4% [5].

Unfortunately, obtaining a global estimate of SpA prevalence is currently unfeasible as many parts of the world lack comprehensive and reliable prevalence data. In fact, it was only in 2012 that the Centers for Disease Control and Prevention provided national estimates for the prevalence of axial SpA, revealing its potential impact on approximately 1% of adults in the United States, or roughly 2.7 million individuals [5].

The hallmark feature of SpA is its predilection for axial involvement, resulting in inflammatory back pain and stiffness. AS, a prototypical form of SpA, predominantly affects the axial skeleton, leading to progressive fusion of the sacroiliac joints and the spine. However, the clinical spectrum of SpA extends to peripheral joints, enthesal sites (insertion points of tendons and ligaments into bone), skin, eyes, and other organs [3, 4].

The pathogenesis of SpA is multifactorial, involving a complex interplay of genetic predisposition, environmental triggers, and dysregulated immune responses. The strong association with HLA-B27 highlights the genetic component, yet environmental factors, such as microbial infections, are believed to contribute to disease initiation and perpetuation. Dysregulation of immune pathways, particularly involving tumor necrosis factor-alpha (TNF- α), plays a pivotal role in the chronic inflammatory process characteristic of SpA [3, 8].

The heterogeneity within the SpA spectrum necessitates a thorough understanding of its diverse clinical presentations. PsA, for instance, is characterized by the coexistence of inflammatory arthritis and psoriasis, while ReA often follows gastrointestinal or genitourinary infections. This diversity challenges clinicians to adopt a holistic approach, considering not only joint symptoms but also the potential involvement of extra-articular manifestations [1, 9, 10].

SpA encompasses a group of disorders affecting the joints and adjacent tissues, manifesting a wide spectrum of clinical presentations. Beyond the evident joint symptoms, these conditions can also manifest in unexpected locations. One such manifestation is pulmonary hypertension (PH), which arises in patients with spondyloarthropathies [11]. It manifests as a condition characterized by elevated arterial pressure within the pulmonary circulation. This pathological process contributes to an increased vascular resistance, subsequently leading to excessive strain on the right ventricle of the heart and potentially giving rise to severe complications [12].

PH, stemming from vascular disturbances in the lungs, poses a significant challenge for individuals with SpA. Despite the predominant focus on joint involvement in spondyloarthropathies, it is crucial to explore the broader systemic consequences of these disorders.

In this literature review, we delve into the current state of research and knowledge regarding the connection between SpA and the development of PH, expanding our comprehension of these diseases beyond the realm of joints.

Our literature review involved the PubMed, MEDLINE (Ovid), Cochrane Central Register of Controlled Trials (Wiley), Scholar (Google), Scopus and Embase (Elsevier) databases, limited to full-text publications in the English language for the period from December 1970 to December 2023. The keywords used in the search were «pulmonary hypertension, and one of the following: «spondyloarthropathy», «spondyloarthritis», «ankylosing spondylitis», «psoriatic arthritis», and «reactive arthritis».

As shown in fig. 2, our initial searches yielded a total of 77 (100%) studies, and after eliminating duplicates, 31 studies (40.3%) underwent a comprehensive full-text review. Among these, 19 studies (61.3%) did not meet the pre-defined criteria: were published outside our search range, or were not available in English or presented as conference abstracts, which may not provide comprehensive scientific details. Consequently, our scoping review incorporated 12 studies (38.7%) that successfully met the established criteria, contributing valuable insights to our analysis.

The development of PH in patients with SpA is influenced by a complex interplay of various factors and mechanisms. Inflammatory processes inherent in spondyloarthropathies can trigger a systemic response, involving immune system reactions that lead to the deposition

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

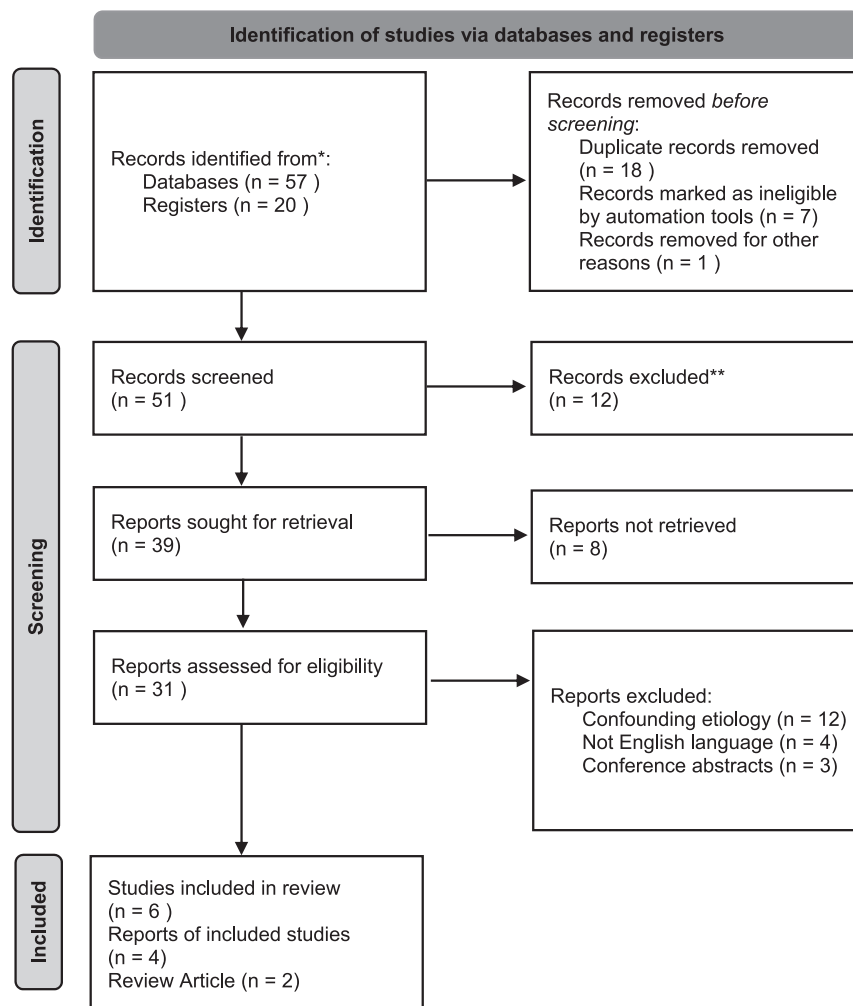


Fig. 2. PRISMA 2020 study selection flow diagram

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

of immune complexes and activation of inflammation in the pulmonary vessels [11–13]. Additionally, these conditions may cause anatomical changes in joints and adjacent tissues, including the formation of calcific deposits affecting blood vessels and disruptions in vascular structure, potentially leading to increased resistance and elevated pressure in the pulmonary circulation. A specific yet significant risk factor for PH development in this context is pulmonary hypoventilation associated with restricted chest excursion.

The substantial limitation of spinal mobility, ankylosis of thoracolumbar and costovertebral joints in patients with SpA, significantly reduces overall chest mobility. While diaphragmatic excursion compensates partially, this mechanism is often insufficient, resulting in decreased respiratory volumes, the onset of pulmonary hypoventilation, and hypoxemia. These respiratory challenges unfavorably impact endothelial function [13, 14].

In addition to alveolar hypoventilation and hypoxemia, which undeniably influence endothelial function, patients

with SpA face another persistent factor contributing to endothelial dysfunction (ED) – systemic inflammation. The systemic inflammatory response, characteristic of AS, becomes an additional element in the development of ED, emphasizing the multifactorial nature of pulmonary hypertension in spondyloarthropathies. Prolonged inflammatory reactions and imbalances between pro-capillary and anti-inflammatory mechanisms can result in an inadequate vasoconstriction/vasodilatation process and pathological elevation of pressure in the pulmonary artery [15, 16].

Moreover, prolonged stress on the cardiovascular (CV) system due to chronic inflammation and arthritic involvement may lead to structural and functional modifications in the heart and vessels, contributing to the onset of PH. These factors intricately interact and collaborate, determining individual risks and peculiarities in the development of PH within the context of SpA [13]. The primary pathogenetic mechanisms leading to elevated pressure in the pulmonary artery among patients with spondyloarthropathies are illustrated in fig. 3.

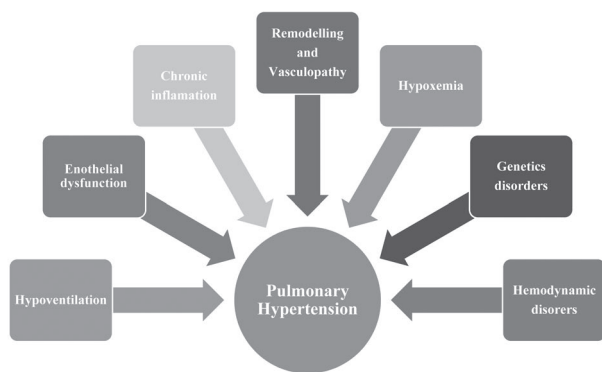


Fig. 3. The main pathogenetic mechanisms underlying pulmonary hypertension development in spondyloarthritis

In the context of recent decades, and especially in light of recent events related to the discovery of advanced and effective immunobiological drugs, interest in autoimmune diseases of joints and spine has surged multiple times [17, 18]. There is a growing emphasis on comorbid conditions associated with these diseases [19, 20]. Additionally, in recent times, scientists have been intrigued by the impact on the CV system, particularly emphasizing attention on arterial hypertension, often overlooking the significant influence of pulmonary hypertension and underestimating the existing pathophysiological mechanisms that may contribute to its occurrence [24]. However, there is relatively limited research in this area, and most studies are centered on individuals with Rheumatoid arthritis (RA) and systemic scleroderma (SSD) [22, 23].

Concerning SpA, there is very limited research on the association with PH. Most existing studies revolve around diseases that constitute a group of seronegative spondyloarthropathies, namely AS and PsA (table). For instance, the first case was described in 1971 at Nottingham General Hospital by Talbot S, focusing on the development of Cor pulmonale in ankylosing spondylitis in a patient [24].

The most extensive research in terms of volume was conducted in South Korea in 2021 under the leadership of Ji Hyoun Kim [25]. Sixteen studies were analyzed, encompassing a review of approximately 100,000 individuals with SpA. These studies were sourced from scientific databases covering the years 2017–2019. With the exception of one study (Hung YM et al, 2016), no elevated prevalence of pulmonary diseases was identified compared to the general population. However, reports indicated that this cohort of individuals exhibited significantly increased mortality due to CV complications, including incidents such as heart attacks and strokes.

Similar findings were also reported by Paolo Spagnolo and colleagues. Despite the substantial prevalence of comorbid pathology, they did not provide information on the presence of pulmonary complications and specially PH [26].

However, studies focusing on individual nosologies, particularly AS and PsA, indicate different disease trajectories but consistently point towards an increased frequency of pulmonary hypertension in these patients. Notably, some of these studies specifically exclude patients with ReA of various etiologies. These excluded individu-

als often exhibit a milder course and less disease activity, suggesting a less pronounced impact of the inflammatory process on the endothelium [27, 28].

For instance, one of the most recent investigations conducted by Morvai-Illes et al. (2022) revealed a significant difference in pulmonary artery pressure between individuals with AS and PsA compared to the control group (control: 12.6 ± 6.4 mmHg; AS: 22.8 ± 7.6 mmHg; $p < 0.001$; PsA: 21.4 ± 7.0 mmHg; $p < 0.001$). The researchers concluded that there are subclinical cardiopulmonary changes among AS and PsA patients [29].

In another study involving the examination of 1776 patients with SpA, more precise data indicated a prevalence of PH in 1.2% against the backdrop of 23.4% chronic lung diseases [30]. This suggests that elevated arterial pressure in the pulmonary artery was detected in about 1 out of 100 patients and in 1 out of 20 patients with underlying lung pathology.

Regarding the analysis of pulmonary manifestations, including elevated arterial pressure in pulmonary artery, in patients with AS, there is extensive data from a large-scale study involving the examination of 2080 patients. These investigations revealed a clear correlation between comorbid lung pathologies and the activity and duration of the underlying disease. In addition to typical pulmonary conditions for these patients (such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), observations included apical nodularity, pleural thickening, enlargement of the lung hila, and the development of multiple thin-walled or thick-walled cysts or cavities, along with pleural calcification [31].

Simultaneously, there exists a substantial body of scientific literature analyzing cardiopulmonary pathology in patients with psoriasis (PS) and PsA. Notably, many studies distinguish themselves through their extensive participant numbers [32, 33]. In summary, this information reveals that the pooled odds ratio (OR) for COPD in individuals with PsA, compared to controls, is 1.90 (95% CI 1.36–2.65). This association is notably more pronounced among patients with severe PS, revealing an odds ratio of 2.15 (95% confidence interval, 1.26–3.67). The examined cohort demonstrates an elevated risk of developing PH, and a clear correlation has been identified between the tendency for joint involvement and the development of pulmonary hypertension. Furthermore, a correlation has been observed between disease activity and the occurrence of elevated arterial pressure in a pulmonalis.

Regarding the analysis of individual cases (case reports), there is sufficient data on the prevalence of PH in individuals with PsA, AS, and ReA [34–36]. However, further research, incorporating larger cohorts and multicenter studies, is warranted to determine whether these occurrences are isolated cases.

In recent decades, there has been a heightened focus on individuals with a rheumatological profile, spurred by the emergence of advanced diagnostic methods and the availability of diverse and efficacious yet notably expensive pharmaceuticals [37, 38]. This shift not only improves the quality of medical care but also places significant responsibility on the scientific community, necessitating a deeper understanding of the impact of modern technologies and therapeutic approaches on patients with rheumatological conditions.

Summary of selected articles included in literature review

References	Type of study and aim	Study population	Key findings
Shahane A, 2013 (21)	Review (a comprehensive search for relevant studies by querying four database MEDLINE published between 1970 and 2012)	14 studies with 11,387 patients with SpA	Pulmonary arterial hypertension associated with rheumatic diseases carries a particularly grim prognosis with faster progression of disease and poor response to therapy. Though largely associated with systemic sclerosis, it is being increasingly recognized in other rheumatic diseases. Several pathophysiologic processes have been identified including an obliterative vasculopathy, veno-occlusive disease, formation of microthrombi and pulmonary fibrosis.
S Talbot, 1971 (24)	A single-centre case report	1 patient	Presented case history of cor pulmonale and PH in patient with AS. This case highlights the intricate connection between AS and cardiovascular complications, underscoring the importance of early recognition and targeted intervention in managing these complex comorbidities.
Kim JH et al, 2021 (25)	meta-analysis of population-based studies published between January 1997 and September 2019	16 articles (18 cases). Aprox. 100, 000 patients	Confirmed the increased risks of MI and stroke in patients with SpA. The overall CV risk and all-cause mortality remains higher in patients with SpA than in the general population. But there is no significant data about prevalence of PH in patients with spondyloarthropathies compare to general population.
Spagnolo P et al 2016, (26)	Review Article	-	Pulmonary complications encompass chest wall restriction, pleuroparenchymal abnormalities, and common yet clinically significant upper lobe fibrobullous disease, affecting less than 2% of patients, with additional manifestations including apical fibrosis, interstitial lung disease, pleural thickening and effusion, and spontaneous pneumothorax, but no PH.
Morvai-Illes B et al, 2022 (29)	A single-centre case-control study	71 AS and PsA patients	Investigation revealed a significant difference in pulmonary artery pressure between individuals with AS and PsA compared to the control group .
Redeker I et al, 2020 (30)	A nationwide population-based study from 2014 to 2015 (Germany)	1776 patients with SpA	Comorbidities are common in SpA patients and are associated with higher disease activity and higher levels of functional impairment. Pulmonary involvements in 23,4 % while PH in 1,2 %
Lynch et al 2009 (31)	Observational cohort study	2080 patients with AS	Pleuropulmonary involvement is a rare complication of ankylosing spondylitis, found in 1.3% of 2080 patients. It almost always involves males, with long duration of disease.
Li X et al, 2015 (32)	A single-centre case-control study	A retrospective meta-analysis of 2 cohort and 2 case-controlled studies; 42,150 patient with PsA and PS	The pooled OR for COPD was 1.90 (95% CI 1.36-2.65) for PsA versus controls. the association between of psoriasis and with chronic obstructive pulmonary disease was stronger among patients with severe psoriasis (odds ratio, 2.15; 95% confidence interval, 1.26–3.67). The examined cohort had an increased risk of developing pulmonary hypertension, and a clear correlation was observed between the tendency for joint involvement and the development of pulmonary hypertension, as well as between disease activity and its occurrence.
Choi YM et al, 2017 (33)	A retrospective cohort study	13936 patients with PsA and PS	The systemic inflammatory process underlying psoriasis may be a cause for an increased risk of PH, but there are numerous secondary causes of PH, some of which were not accounted for in our study. Further prospective, randomized controlled trials are necessary to establish psoriasis as a risk factor for PH
Hung YM, 2015 (34)	A single-centre case report	1 patient	Present patient was confirmed to have both AS and PAH. Further large-scale epidemiologic studies regarding the incidence of PH among patients with AS are needed to elucidate the actual relationship between these two conditions.
Yang TY et al, 2022 (35)	A single-centre case report	1 patient	Early echocardiographic screening is necessary for symptomatic patients. Further epidemiologic studies are needed to disclose the association between AS and PH.
Collini V . et al 2022 (36)	A single-centre case report	1 patient	This case provides additional evidence supporting the rare but increasingly recognized association of leflunomide in patients with PsA and PH

PH - Pulmonary Hypertension; AS - Ankylosing Spondylitis; MI - Myocardial Infarction; CV - Cardiovascular; PSA - Psoriatic Arthritis; PS - Psoriasis; LEF - Leflunomide; COPD - Chronic Obstructive Pulmonary Disease; SpA – spondyloarthritis.

The findings of this literature review shed light on the intricate relationship between SpA and the development of PH. The collective evidence underscores the need to broaden our understanding of SpA, recognizing its impact beyond joint inflammation and encompassing systemic manifestations.

The literature review has identified gaps in knowledge, emphasizing the necessity for further research to explore the intricate relationship between SpA and pulmonary hypertension comprehensively. If the pathophysiological mechanism of pulmonary hypertension is well-known [39], its development in inflammatory diseases, especially of autoimmune nature, is the subject of many scientific discussions [12, 40]. Addressing these gaps will enhance our ability to diagnose, manage, and potentially prevent the development of pulmonary hypertension in individuals with spondyloarthritis.

The heterogeneity within the SpA spectrum, characterized by diseases like AS, PsA, and ReA, necessitates a tailored approach to research and clinical management. While there is extensive research on the association of PH with AS and PsA, the specific connection with ReA and other subtypes remains understudied. Existing literature has predominantly focused on elucidating the relationship between PH and AS or PsA, leaving a notable gap in our understanding of how ReA contributes to or differs in its association with pulmonary hypertension. This underscores the need for targeted investigations to fill this knowledge void and provide a comprehensive understanding of the diverse SpA spectrum.

The pathogenesis of SpA, influenced by genetic predisposition, environmental triggers, and dysregulated immune responses, contributes to the multifaceted clinical presentations. The identified risk factors for PH in SpA, including inflammatory processes, immune reactions, anatomical changes in joints, and pulmonary hypoventilation, underscore the need for a holistic assessment in clinical practice.

Despite the meticulous attention given to this patient cohort, often prioritizing arterial hypertension, due consideration to pulmonary hypertension is lacking. This oversight underscores the importance of conducting echocardiography with pulmonary artery pressure measurement in patients with a rheumatological profile, as recommended by Al-Mohaissen MA et al. (2016) and Sade LE et al. (2019) [41, 42]. This diagnostic step is crucial in capturing the potential development of pulmonary hypertension, a facet often underestimated in the existing literature. Consequently, in many studies evaluating the CV system in patients with SpA using echocardiography, pulmonary artery pressure was not assessed.

The consistent findings of increased pulmonary hypertension frequency in studies focusing on AS and PsA suggest a potential shared mechanism within these specific nosologies. However, the exclusion of patients with ReA in some studies raises questions about the impact of disease activity on the development of PH and emphasizes the importance of recognizing the variability within the SpA spectrum, which may lead to an underestimation of the prevalence.

The studies by Morvai-Illes et al. (2022) and Redeker et al. (2020) provide specific insights into the differences in pulmonary artery pressure among individuals with AS and PsA compared to the control group. These findings contribute to our understanding of subclinical cardiopulmonary changes and the prevalence of PH in SpA populations.

In addition to the identified research gaps, further investigation is needed to explore the impact of medications on the development of PH in patients with inflammatory arthropathies. Recent reports have highlighted concerns regarding the potential negative influence of leflunomide on the occurrence of PH [36, 43]. As medication choices play a crucial role in the management of spondyloarthritis, understanding their specific effects on cardiovascular manifestation, particularly PH, is imperative. Therefore, future research endeavors should not only focus on the broader epidemiological aspects but also delve into the nuanced relationship between specific medications, including leflunomide, and the risk of pulmonary hypertension in individuals with inflammatory arthropathies.

CONCLUSION

In conclusion, this literature review highlights the complex interplay between spondyloarthropathies and the development of PH; contributes to the growing body of knowledge on the association between SpA and PH, providing a foundation for future research directions and clinical considerations in the management of these complex rheumatic conditions. Beyond joint inflammation, SpA exhibits systemic manifestations that impact the CV system, leading to structural and functional modifications. PH emerges as a significant consequence, influenced by inflammatory processes, immune reactions, and joint-related anatomical changes.

The literature underscores the need for a comprehensive approach to spondyloarthropathies management, considering both joint symptoms and CV implications. Recognizing the diversity within the spectrum of this condition is crucial for customizing research and clinical strategies. Future investigations should focus on larger cohorts, multicenter studies, and a holistic understanding of the CV impact to fill existing knowledge gaps and enhance the care of individuals with SpA and PH.

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