Review Article

Clinical Characteristics of ASIA Syndrome in Patients with Silicone Breast Implants: A Scoping Review

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ABSTRACT

Background: Adjuvant-induced autoimmune syndrome (ASIA), described in 2011, includes autoimmune reactions triggered by environmental adjuvants, such as silicone breast implants (SBI). Symptoms include fatigue, sleep disturbances, appetite changes, muscle pain, fever, among others, with pathophysiology involving a combination of genetic predisposition and adjuvant exposure, leading to abnormal immune responses. We aimed to define clinical profiles and outcomes of patients with SBI, clarify ASIA's clinical implications, and guide future research.

Methods: Using the PRISMA-ScR framework, a scoping review was conducted to identify clinical profiles, preexisting conditions, prosthetic anomalies, and outcomes of patients with ASIA syndrome associated with SBI. Searches were performed in Medline, Scopus, Lilacs, and Google Scholar to locate relevant studies.

Results: Of 35 selected studies, 21 were case reports, 6 case series, and 8 cohort studies, identifying 848 patients, predominantly from the Netherlands (n=513), with an average age of 45-47 yr. Common medical histories included autoimmune diseases and breast cancer, while frequent implant-related anomalies were capsular contracture and rupture. Musculoskeletal symptoms and fatigue were the most prevalent, and implant explantation was the primary treatment, resulting in symptom improvement for most patients.

Conclusion: This review highlights the clinical features of ASIA syndrome in patients with SBI, particularly musculoskeletal symptoms, fatigue, and the presence of positive antinuclear antibody as a potential marker. However, the relationship between SBI and ASIA remains controversial. Despite limitations in current evidence, ongoing clinical monitoring and further research are crucial to better understanding and managing ASIA syndrome in patients with SBI.

KEYWORDS
Adjuvant-induced autoimmune syndrome (ASIA); ASIA syndrome; Breast implants; Plastic surgery; Scoping review

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INTRODUCTION

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), first described in 2011, includes a range of autoimmune reactions triggered by environmental adjuvants, such as silicone, used in breast implants (SBI). ASIA is characterized by symptoms like fatigue, memory disturbances, muscle and joint pain, fever, lymphadenopathy, and the presence of antibodies. It encompasses various diagnoses, including siliconosis and Gulf War syndrome [1].

ASIA syndrome is a complex disorder resulting from a combination of genetic predisposition and environmental factors, particularly exposure to adjuvants, which are substances that enhance the immune response [2]. Theories suggest that immune overstimulation and activation of transcription factors by adjuvants lead to cytokine and chemokine production, driving immune response expansion [3]. There is growing concern about the association between silicone breast implants (SBI) and ASIA syndrome, given the increasing use of SBI in cosmetic and reconstructive surgeries.

Initially thought to be biologically inert when introduced in 1960 [4], silicone has had various immunological effects [5], raising concerns about long-term safety and autoimmune risks. Millions of procedures have been performed, yet many women have reported complications and systemic symptoms aligning with ASIA syndrome [6], prompting requests for implant removal.

The diagnosis of ASIA syndrome is challenging due to its heterogeneous presentation and overlap with other autoimmune disorders, alongside a variable latency period between implant placement and symptom onset.

We aimed to characterize the clinical profiles, medical records, prosthetic abnormalities, clinical manifestations, laboratory abnormalities, and outcomes of patients diagnosed with ASIA syndrome related to SBI. By synthesizing available data, the review seeks to improve understanding of ASIA syndrome's clinical implications and inform future research directions.

METHODS

We chose a scoping review methodology in line with the Arksey and O'Malley framework [7] and reported according to the PRISMA-ScR guidelines [8]. The aim was to explore the characteristics of research on ASIA syndrome in patients with SBI and their clinical features.

A systematic search was conducted in the databases Medline (PubMed), Scopus, Lilacs, Google Scholar using Medical Subject Headings (MeSH), Health Sciences Descriptors (DeCS), and free terms in both Spanish and English (Supplementary 1). Two independent reviewers (JEOG and MGLA) conducted the searches, and discrepancies were resolved by consensus with a third researcher (CCR). Articles discussing ASIA syndrome and SBI, published up to the search date (2011- 01/19/2024) were included. Exclusions were based on secondary source studies, animal studies, conferences, books, book chapters, conference reviews, notes, errata, editorials, letters to the editor, and other non-scientific documents. Subsequently, all full-text documents were reviewed by the researchers, and those not addressing our research question were excluded.

An electronic matrix was designed for data extraction using Google Sheets. The following variables were extracted: patient characteristics, clinical manifestations, diagnoses, laboratory abnormalities, treatments, and outcomes. Articles were categorized into case reports/series or cohorts/other studies for better data presentation. Based on the extracted data, an inductive content analysis of the information was conducted. The synthesis of results was presented in the form of tables, according to the objective and research question.

RESULTS

Selection of articles

Figure 1 presents the PRISMA diagram for article selection in this review. Initially, 193 articles were identified from databases, and 82 duplicates were removed using the Rayyan QCRI platform [9]. Subsequently, titles and abstracts were screened, excluding 69 articles that did not meet the inclusion criteria (not addressing ASIA syndrome, SBI, reviews, or not available). Forty-two articles were selected for full-text review, and seven were excluded for not meeting criteria.

General characteristics of the articles

Of the 35 selected articles, most were case reports

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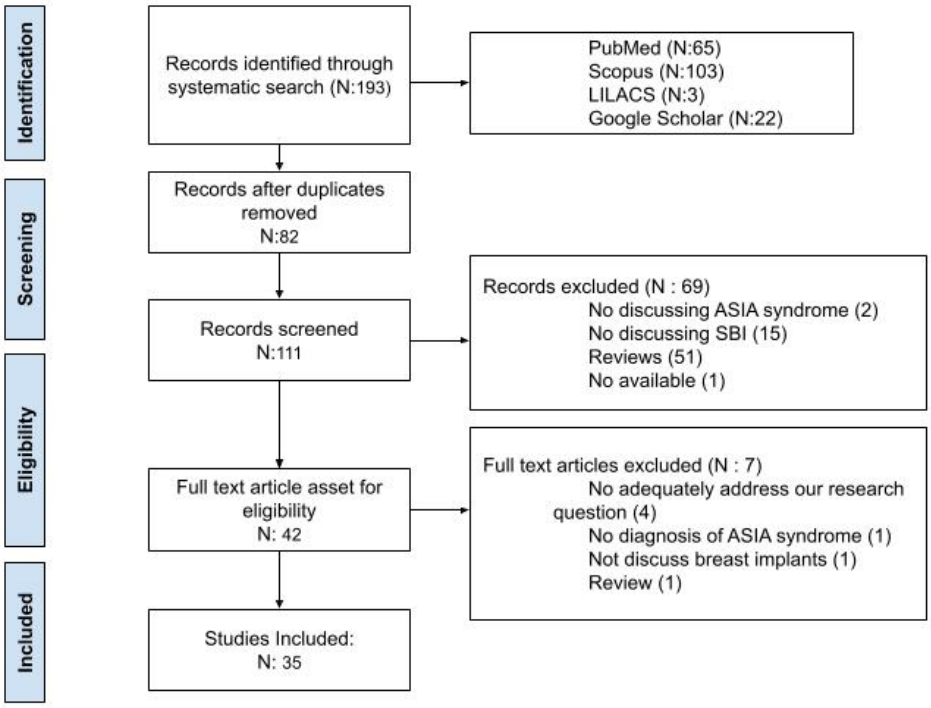

Figure 1: PRISMA flowchart illustrating the study selection process. The diagram outlines the number of studies identified, screened, assessed for eligibility, and included in the review, along with the reasons for exclusion at each stage

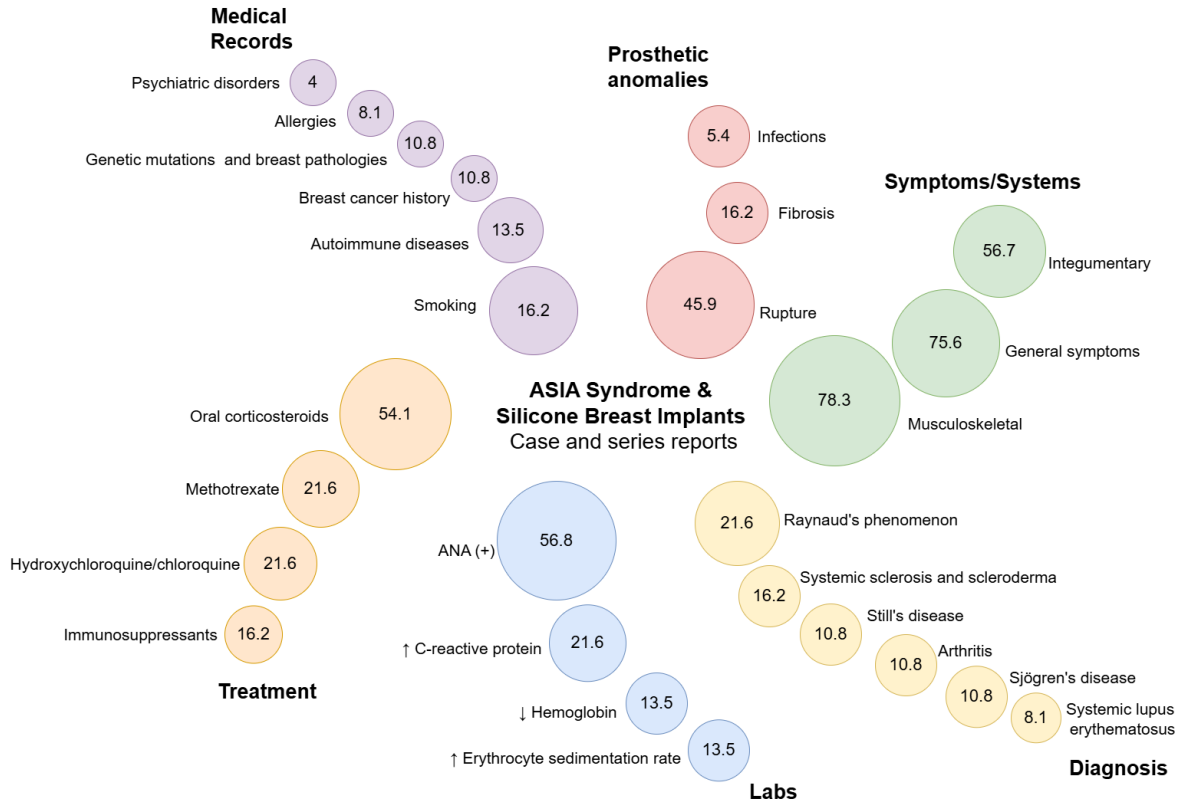

Figure 2: Summary of the findings from the case reports and case series. The circles represent the main categories. Each color represents a category, and the size of each circle is proportional to the percentage described inside it

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(21) [10–30] and case series (6) [31–36], followed by cohorts and other studies (8) [37–44]. A summary of the findings from the case reports and case series is presented in Figure 2. Only one field study and one cross-sectional study were found. Detailed characteristics of each study are presented in Supplementary material (Supplementary 2).

Patient demographics

The study included 848 patients, with 37 from case reports and series, and 811 from cohorts and other studies. The Netherlands had the highest number of patients (513), followed by Israel (168), the United States (100), Brazil (31), and Argentina (14). The mean age in case reports and series was 45.1 yr (23-64 yr), while the age range in cohorts and other studies was 17-83 yr, with a range between 17-83 yr old.

Medical records

In case reports, the most common medical history was smoking (16.2%), followed by autoimmune diseases such as Sjögren's syndrome and lupus (13.5%), and breast cancer history (10.8%). Preventive mastectomies due to genetic mutations or breast pathologies were reported in another 10.8% of patients. Allergies (8.1%), psychiatric disorders (4%), and other conditions were also noted. Some patients (14) had no history or it was unreported.
In the cohort data, allergies were the most prevalent medical history, affecting 60% of cases in one cohort [42], 40.7% in another [37], and were also reported in a third cohort [43]. Thyroid diseases were found in two cohorts [37,42], with a prevalence of 30% and 7.9%. Autoimmune diseases were common, affecting 30% and 7.9% of patients in different cohorts [37,42]. Malignant tumors were reported in 9% of one cohort [40], while benign tumors were noted in 15.5% of cases. Other histories included chronic diseases, psychiatric disorders, cardiovascular diseases, and chronic fatigue. Three cohorts did not mention any personal histories.

Prosthetic anomalies

Prosthetic abnormalities were reported in 27 of the 37 (72%) patients from case reports and series. Among these, 17 patients had SBI rupture, six had fibrosis and two had infections. Less frequent abnormalities included prosthetic displacement, capsulitis, with only one case each.
In cohort studies, capsular contracture was the most frequent complication, reported across three cohorts [37,40,43]. The Colaris cohort [40] documented 29 cases of capsular contracture, while Bird [37] reported a 25.7% prevalence. Implant rupture was also significant, with Colaris noting 25 cases, and Bird reporting a 14.2% rupture rate. Silicone leakage was seen in 13 cases in the Colaris cohort. Additional complications in the Bird cohort included implant discoloration (12.9%), excess fluid around the implant (4.3%), and implant malposition or rotation (1.4%). Less common issues were excess scar tissue or calcification (2.8%), intraoperative rupture (2.1%), siliconoma (1.4%), and a volume decrease greater than 50 cc (1.4%). Four cohorts did not report any prosthetic anomalies.

Time to symptom onset

The average time from implantation to symptom onset in case reports and series was 5.58 yr, ranging from 6 wk to 20 yr. In the included cohorts, the time to symptom onset ranged from 5 d to 40 yr.

Symptoms

The main symptoms observed across case reports, series, and cohort studies were musculoskeletal symptoms such as polyarthralgia, myalgia, arthritis, and pain. These were present in 78.37% of cases (29 cases) and in all eight cohorts. Fatigue, fever, malaise, and weight loss were also common, appearing in 75.67% of case reports (28 cases) and all cohorts.
Integumentary symptoms, including erythema, rosacea, cyanosis, telangiectasia, and rashes, were noted in 56.75% of case reports (21 cases), but only in three of the eight cohorts [38,40,42] and other studies. Neurological symptoms, such as memory loss and cognitive issues, ranked third in the cohorts, and were present in 10 case reports. Ophthalmological manifestations were reported in five cohorts. Less frequently affected systems included the auditory system [41], and the gynecological [25,32,36] and urinary system [13,19,22,40].

Diagnoses

In the review of case reports and series, the most frequent diagnosis was Raynaud's phenomenon,

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present in eight cases (21.6%), followed by systemic sclerosis and scleroderma in six cases (16.2%). Other notable diagnoses included Still's disease, arthritis, and Sjögren's syndrome (10.8% each), and systemic lupus erythematosus (8.1%). Less common diagnoses, each with a single report (2.7%), included Takayasu's arteritis, sarcoidosis, and myofibrillar myopathy, among others.

In cohort studies, Raynaud's phenomenon was also the most common diagnosis, appearing in three cohorts [38,40,44]. Connective tissue diseases were reported in 18% of patients [40], while systemic autoimmune diseases were present in 53.1% of patients [39]. Sjögren's syndrome and limited systemic scleroderma were documented too [38], along with vasculitis (5%) and granulomatous disease (3%) [40].

Labs

In the case reports, the most frequent laboratory finding was the presence of antinuclear antibodies (ANA), including variants such as anticentromere, anti-Ro, anti-RP155, and anti-CenpB, observed in 21 out of 37 cases (56.8%). Elevated C-reactive protein (CRP) was noted in eight cases (21.6%), while low hemoglobin and increased erythrocyte sedimentation rate (ESR) were each identified in five cases (13.5%). Elevated lactate dehydrogenase (LDH) was found in four cases (10.8%), and antineutrophil cytoplasmic antibodies (ANCA) were positive in five cases (13.5%). Other abnormalities, such as increased eosinophils and creatine kinase were reported, among others.

In the cohorts, ANA positivity was also the most common finding, present in 60% of patients [38] and 19.38% [40]. Acute phase reactants were elevated in 40% of cases in Cavallasca's cohort. The Colaris cohort reported increased immunoglobulins in 15.5% of patients and decreased levels in 21.2%. The Cohen cohort found decreased immunoglobulins in 46.8% of cases. Rheumatoid factor was positive in 7.7% of Colaris cohort cases. Five cohorts did not report any lab results.

Treatment

In the review of case reports and series, oral corticosteroids, particularly prednisone and prednisolone, were the most frequently used treatments, prescribed in 54.1% of cases (20 out of 37). These were often combined with methotrexate or hydroxychloroquine/chloroquine, each used in 21.6% of cases (8 cases). Immunosuppressants like azathioprine and cyclophosphamide were administered in 16.2% of cases (4 cases each). Additional therapies included NSAIDs, opioids, vitamin D3 supplements, and cytotoxic agents like rituximab. Combined therapies included ACE inhibitors, aspirin, and vitamins C and E. Explantation of breast implants was a key treatment in 56.7% of cases (21 reports), leading to symptom improvement in most patients.

In cohort studies, explantation was the primary treatment in 6 cohorts [37,40–44]. In De Miranda et al.'s cohort, all patients showed symptom improvement after explantation, whereas in Colaris et al.'s cohort, only 50% of patients improved. Other treatments were limited, except in Cavallasca's cohort, where prednisone, hydroxychloroquine, and calcium channel blockers were used, leading to symptom improvement. Cohen et al.'s cohort did not clearly document treatment outcomes. Most cohorts focused on explantation as the main therapeutic approach.

DISCUSSION

Relationship between ASIA syndrome and SBI

SBIs, first developed in 1963, consist of silicone gel within a silicone shell [4]. In 1982, safety concerns emerged due to complications like gel leakage, capsular contracture, and autoimmune diseases (e.g., lupus, rheumatoid arthritis) following implantation [4]. However, expert evaluations in 2000 by the European Parliament [45] and U.S. courts [46] found no scientific evidence linking SBIs to cancer or autoimmune diseases, though they acknowledged common local complications such as implant rupture.

Shoenfeld and Agmon-Levin introduced the concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA), proposing that silicone in implants could trigger inflammatory and autoimmune diseases [47]. ASIA diagnostic criteria were established, but their validity remains controversial due to the nonspecific nature of symptoms, leading to concerns about overdiagnosis. Social media has exacerbated patient fears, with misinformation contributing to symptom misinterpretation as autoimmune disease.

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To address this, healthcare professionals must provide accurate, evidence-based information to mitigate the effects of misinformation and prevent unnecessary diagnoses based on nonspecific symptoms.

Age and medical record

Age is a crucial factor in ASIA syndrome development related to SBI, influencing susceptibility and symptom progression. Studies show it mainly affects middle-aged individuals; for example, Watad et al.'s international registry reported an average onset age of 37.6 yr (range: 4-82) [48]. In our review, most patients were aged 18-83, with an average onset of 46.89 yr. This suggests a link between surgical age and ASIA onset, as Becherer et al.'s registry showed augmentation procedures between ages 31-36 and reconstruction between 41-49 [49], aligning with our findings.

Medical records highlight genetic predisposition as a key factor. Watad et al. found immune susceptibility in 20.3% of cases, supporting genetics' role in ASIA onset. Our review also noted a high prevalence of autoimmune diseases (13.5%) like Sjögren's syndrome and lupus, and allergies (8.1%). Kappel et al.'s case series described three sisters with BRCA1 mutations developing ASIA post-breast reconstruction [34], emphasizing genetic predisposition's impact on ASIA risk.

Most common prosthetic abnormalities associated with ASIA Syndrome

This review found a high prevalence of prosthetic abnormalities in patients with SBI, especially in case studies and series, emphasizing the need for close monitoring. Silicone leakage can trigger immune responses, fibrosis, and granuloma formation [35,50]. The body forms a fibrous capsule around the implant, and ruptures can be intracapsular (contained) or extracapsular (leaking outside) [51]. Although rupture types were often unspecified, extracapsular ruptures are hypothesized to be more strongly linked to ASIA syndrome.

Onset time of symptoms

The onset of ASIA syndrome symptoms varies widely. Puerta et al reported an average onset of seven years for ASIA caused by biopolymers and silicone implants [52]. In contrast, symptoms appeared three weeks after COVID-19 infection in a patient with biopolymer injection [53], and two weeks after receiving the AstraZeneca vaccine in a case of subacute thyroiditis [54]. Factors such as adjuvant type, exposure route, and immune response likely influence this variability in symptom onset.

Associated symptoms

Significant similarities were observed in symptoms between ASIA cases related to vaccines and SBI, despite different adjuvants. Musculoskeletal symptoms, such as polyarthralgia and myalgia, were prevalent in both groups; in our study, these symptoms were present in 78.37% of cases, while in the vaccine-induced ASIA study, myalgia and arthralgia were reported in 50.8% and 73.8% of patients, respectively. Fatigue was also prevalent, affecting 75.67% of implant patients and 65.6% of vaccinated individuals. Neurological symptoms, including memory and concentration issues, were present in both, with a 35% prevalence in vaccinated patients. Raynaud's phenomenon was the most common diagnosis, suggesting a shared immunological mechanism, despite variations in adjuvants. These findings underscore the notion that ASIA symptoms are nonspecific and challenging to quantify, contributing to ongoing controversy surrounding its diagnosis and management. This highlights the urgent need for further studies to explore this association in greater depth [55].

Associated diagnoses

Comparing ASIA syndrome diagnoses from SBI to those induced by cosmetic injections [56], Raynaud's phenomenon (21.6%) was the most frequent in our study, followed by systemic sclerosis (16.2%) and Sjögren's syndrome (10.8%). These findings align with similar autoimmune diagnoses in ASIA cases related to injectable materials. Despite differing adjuvants (silicone vs. mineral oil), both studies suggest that immune activation by external adjuvants triggers autoimmune responses. This highlights the nonspecificity of ASIA symptoms and diagnoses, reinforcing the idea that different adjuvants can lead to similar autoimmune mechanisms and conditions.

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Paraclinical tests

Laboratory results in ASIA syndrome highlight its autoimmune and autoinflammatory nature. ANAs are the most frequently altered biomarker, found in 51.7% of patients from the international ASIA registry [46], consistent with our findings. While ANAs detect autoantibodies across many autoimmune diseases, their low specificity means they can also appear in healthy individuals [57], indicating a potential predisposition in susceptible patients.
Additionally, elevations in acute phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were observed in 21.6% and 13.5% of cases, respectively, suggesting a systemic inflammatory pattern in ASIA [58]. However, biomarkers such as ANCA and elevated muscle enzymes (CK and LDH) were less common. These variations indicate heterogeneity in the serological profiles of ASIA syndrome, reflecting differences in disease severity or individual immune responses to adjuvants. Overall, while common inflammatory markers are consistent, variability in less frequent biomarkers underscores the complexity of ASIA syndrome.

Effects of explantation on ASIA Syndrome symptoms

Analysis of ASIA syndrome criteria reveals that symptom improvement following the removal of adjuvants, specifically SBI, is a key indicator of recovery. In 21 case reports, most patients experienced symptom relief after explantation. Spit et al [59] have compared symptom improvement in patients who underwent explantation to those who did not. They found that 30% of women explanted experienced significant improvement, particularly those who had their implants for over 10 years. Conversely, patients who did not undergo explantation demonstrated only a 12% improvement (OR = 2.86; CI 1.31-6.24, with a statistically significant *P*-value).
Although ASIA syndrome's exact pathophysiology is unclear, removing silicone breast implants leads to significant clinical improvement. This occurs by reducing chronic immune activation, halting molecular mimicry that produces autoantibodies, and eliminating silicone particles that increase antigenic load. These mechanisms restore immune balance, decrease inflammation, and alleviate symptoms. Explantation effectively addresses these triggers, leading to symptom improvement [3].

Study limitations

This review has limitations, including reliance on case reports and case series, which may introduce publication bias. The variability in patients' clinical presentations complicates generalization of findings, and the lack of detailed treatment data limits the ability to establish specific therapeutic recommendations.

Future directions

Future studies should involve larger, well-defined cohorts to validate findings and improve understanding of ASIA syndrome in breast implant patients. Research on treatment effectiveness and the link between prosthetic characteristics and symptom onset is also crucial for clinical management.

CONCLUSION

This scoping review provides a comprehensive overview of the clinical characteristics of patients with ASIA syndrome and SBI. Musculoskeletal symptoms and fatigue are prevalent, and the presence of positive ANAs can be an important marker of the disease. The link between SBI and ASIA syndrome remains unclear, and the syndrome itself is controversial, with limited robust evidence from primary studies. Nevertheless, these findings underscore the necessity for ongoing clinical surveillance and additional research to enhance patient management and outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AVAILABILITY OF SUPPLEMENTARY DATA

All supplementary data are accessible via sending email to the corresponding author based on reasonable application.

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