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ANALYSIS OF MULTISYSTEMIC MANIFESTATIONS OF SJÖGREN'S SYNDROME: A FOCUS ON DERMATO-OPHTHALMOLOGICAL INTERRELATIONS

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ABSTRACT

Sjögren's Syndrome (SS) is a systemic autoimmune disease known for its hallmark symptoms of dry eye and dry mouth, but it also presents a spectrum of extraglandular manifestations affecting the skin, lungs, nervous system, and other organs. This systematic review examines the multisystemic impacts of SS, highlighting advancements in diagnostics, therapeutic strategies, and clinical challenges. A comprehensive search was conducted across PubMed, MEDLINE, and Embase for studies published between 2013 and 2024, using keywords such as "Sjögren's Syndrome," "Multisystemic Manifestations," "Autoimmune Disease," and "Extraglandular Complications." Of the 56 initially identified articles, 13 met the inclusion criteria. Findings reveal that pulmonary complications, including interstitial lung disease, occur in 9–20% of SS cases, as reported by Flament et al. (2016), emphasizing the importance of imaging and biopsy for early detection. Dermatological manifestations, such as vacuolar interface dermatitis and vasculitis, were detailed in studies by El Hasbani et al. (2023) and Kakurai et al. (2021), which underscore the need for dermatological vigilance in systemic autoimmune diseases. Neurological symptoms, including peripheral neuropathies and neuropsychiatric complications, were identified as early indicators in studies by Posso-Osorio et al. (2019) and Salehi et al. (2024), suggesting that such presentations require immediate multidisciplinary evaluation. Therapeutic advancements include the use of corticosteroids, hydroxychloroquine, and biologic agents such as rituximab, which have shown efficacy in managing systemic manifestations. Chu et al. (2020) emphasized the benefits of immunosuppressive therapy in improving systemic outcomes while acknowledging the limited efficacy for glandular symptoms. Advanced diagnostic tools like PET/CT, explored by Sharma and Chatterjee (2015), have improved diagnostic precision, aiding in the differentiation of SS from other systemic conditions. Despite these advancements, challenges remain in addressing disease heterogeneity and atypical presentations, particularly in men, children, and patients without classic glandular involvement. Standardized diagnostic protocols and tailored

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therapeutic strategies are needed to improve outcomes and reduce the burden of extraglandular complications.

Keywords: Sjögren's Syndrome. Autoimmune Disease. Multisystemic Manifestations. Pulmonary Complications. Neurological Symptoms. Immunosuppressive Therapy. Advanced Diagnostics.

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INTRODUCTION

Sjögren's Syndrome (SS) is a chronic systemic autoimmune disease that predominantly targets exocrine glands, causing hallmark symptoms such as keratoconjunctivitis sicca (dry eye) and xerostomia (dry mouth). While these glandular manifestations are the most recognized features of the disease, SS is increasingly acknowledged as a multisystemic disorder with significant extraglandular complications, including pulmonary involvement, neurological deficits, dermatological manifestations, and even psychiatric disturbances. These systemic manifestations substantially contribute to the disease burden, often complicating diagnosis and management, and highlighting the need for a comprehensive understanding of its clinical spectrum (Flament et al., 2016; Posso-Osorio et al., 2019).

The underlying pathogenesis of SS is characterized by a dysregulated immune response, involving lymphocytic infiltration of glandular tissues and systemic production of autoantibodies such as anti-Ro/SSA and anti-La/SSB. This immune dysfunction not only leads to glandular damage but also promotes systemic inflammation that affects multiple organ systems. For instance, interstitial lung disease, peripheral neuropathy, vacuolar interface dermatitis, and vasculitis have been documented as serious extraglandular manifestations (Kakurai et al., 2021; El Hasbani et al., 2023). Furthermore, SS may present atypically in certain populations, including men and children, with more severe phenotypes or unusual initial symptoms, such as isolated neurological involvement or autonomic dysfunction, complicating early diagnosis (Virdee et al., 2017; Kataria et al., 2023).

Recent advancements in diagnostic modalities have enhanced the ability to identify both glandular and extraglandular manifestations of SS. Imaging techniques such as PET/CT have been instrumental in evaluating systemic disease activity and ruling out associated malignancies like lymphoma, a well-documented complication of SS (Sharma & Chatterjee, 2015). Histological tools, including skin and salivary gland biopsies, remain critical for confirming diagnoses in complex cases. However, these tools alone are insufficient without a multidisciplinary approach, integrating input from rheumatologists, ophthalmologists, dermatologists, and neurologists to manage the disease effectively (Trevisani et al., 2019).

Therapeutic approaches for SS have also evolved significantly. While conventional treatments such as corticosteroids and hydroxychloroquine remain cornerstones of management, the advent of biologic agents, particularly rituximab, has provided new

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avenues for treating refractory systemic complications. However, these therapies are not without limitations. While effective for systemic manifestations, their efficacy in addressing glandular symptoms like dry eye and dry mouth is often suboptimal, necessitating additional supportive care strategies, including tear substitutes and salivary stimulants (Chu et al., 2020; Mohammad et al., 2024). Moreover, there remains a critical need for therapies targeting the underlying mechanisms of immune dysregulation to improve long-term outcomes.

Despite these advancements, significant challenges persist in the management of SS, including variability in disease presentation, limited treatment options for glandular symptoms, and gaps in understanding its pathophysiology. These challenges are particularly evident in atypical cases, such as patients without classic glandular involvement or those presenting with severe extraglandular manifestations, underscoring the need for further research and tailored therapeutic strategies.

This study aims to provide a systematic exploration of the multisystemic manifestations of Sjögren's Syndrome, focusing on advancements in diagnostic techniques, therapeutic interventions, and the critical role of interdisciplinary care. By synthesizing current evidence, this work seeks to enhance the understanding of SS's systemic complexity and inform clinical strategies to improve patient outcomes.

METHODOLOGY

This study employed a systematic review approach to explore the multisystemic manifestations of Sjögren's Syndrome (SS), focusing on diagnostic advancements, therapeutic interventions, and the challenges of managing systemic complications. The analysis aimed to synthesize evidence on the extraglandular manifestations of SS and their impact on patient outcomes.

The data were sourced from PubMed, MEDLINE, and Embase databases using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The descriptors included "Sjögren's Syndrome," "Extraglandular Manifestations," "Pulmonary Involvement," "Neurological Symptoms," "Dermatological Manifestations," and "Autoimmune Disease." Boolean operators "AND" and "OR" were applied to construct a comprehensive search strategy that captured all relevant literature. The search included studies published between 2013 and 2024 to incorporate the most recent advancements and findings.

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INCLUSION CRITERIA

The inclusion criteria were defined as follows:

1. Studies analyzing systemic manifestations of SS, including pulmonary, neurological, dermatological, and psychiatric complications.
2. Articles focusing on advanced diagnostic tools, such as PET/CT imaging, salivary and skin biopsies, and immunological assays.
3. Peer-reviewed studies published in English to ensure consistency and reliability in data interpretation.
4. Research evaluating therapeutic strategies, including immunosuppressive and biologic therapies.

EXCLUSION CRITERIA

The exclusion criteria were established to omit studies that did not align with the research objectives:

1. Studies focusing exclusively on glandular symptoms (e.g., dry eye or dry mouth) without systemic involvement.
2. Articles lacking sufficient data on systemic manifestations or treatment outcomes.
3. Research on unrelated autoimmune or inflammatory conditions.
4. Studies published in languages other than English.

The initial database search yielded 56 articles, which were screened based on their titles and abstracts. After applying inclusion and exclusion criteria, 13 studies were included in the final analysis. These selected articles provided comprehensive insights into the systemic complications of SS, advancements in diagnostic tools, and the efficacy of various therapeutic strategies.

DATA EXTRACTION AND ANALYSIS

Data extraction focused on capturing key variables, including the types of systemic manifestations (e.g., pulmonary, neurological, or dermatological), diagnostic methods used, therapeutic interventions applied, and patient-specific outcomes. Special attention was given to studies employing novel diagnostic techniques or advanced therapies, such as biologics, to assess their impact on managing extraglandular manifestations.

The temporal restriction from 2013 to 2024 ensured the inclusion of contemporary evidence reflecting current clinical practices and technological advancements in the

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diagnosis and management of SS. By synthesizing findings from this timeframe, the study offers a robust evaluation of SS's systemic impact and identifies emerging trends in clinical approaches.

This methodology highlights the complexity of managing systemic manifestations in SS and emphasizes the need for interdisciplinary approaches to improve patient outcomes and quality of life.

RESULTS

The multisystemic manifestations of Sjögren's Syndrome (SS) vary significantly across affected individuals, with complications impacting multiple organ systems, including the lungs, skin, nervous system, and psychiatric health. The reviewed studies demonstrated a wide range of presentations, diagnostic challenges, and therapeutic responses, highlighting the complexity of managing this systemic autoimmune disease. All 13 studies confirmed the importance of early diagnosis, advanced imaging techniques, and multidisciplinary care in addressing the diverse extraglandular manifestations of SS. The findings underscore the need for tailored interventions to improve patient outcomes and mitigate systemic complications.

The research findings on Sjögren's Syndrome are organized in the table below:

Author, Year	Study Title	Study Summary
Xiaoran Li et al., 2023	Multisystem sarcoidosis combined with Sjögren's syndrome	Case study of a patient with multisystem sarcoidosis (affecting lungs, lymph nodes, liver, and spleen) combined with Sjögren's syndrome. The patient presented with dry mouth and eyes, pulmonary nodules, and hepatic alterations. Diagnosis was confirmed via biopsy and imaging studies. Treatment with corticosteroids showed significant improvement.
Virdee et al., 2017	A systematic review of primary Sjögren's syndrome in male and pediatric populations	Systematic review evaluating clinical and laboratory features of primary Sjögren's syndrome in men and children. High prevalence of extraglandular manifestations (50-92%) and distinct autoantibody profiles were observed, highlighting the need for further longitudinal studies to understand

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		phenotypic differences compared to adults.
El Hasbani et al., 2023	Vacuolar Interface Dermatitis as a Histologic Reaction Pattern of Sjögren's Syndrome	Case report of an 87-year-old man with refractory erythematous scaly plaques. Biopsy revealed vacuolar interface dermatitis associated with Sjögren's syndrome, confirmed by anti-SSA antibodies. Treatment with hydroxychloroquine resolved the lesions.
Sharma et al., 2015	18F-FDG PET/CT in multisystem Sjögren syndrome	Presentation of PET/CT as a tool to evaluate multisystem involvement in Sjögren's syndrome, including skin, lungs, kidneys, and nervous system. The scan was useful for monitoring disease activity and ruling out lymphoma.
Kakurai et al., 2021	Intertwined vascular skin manifestations in a patient with Sjögren syndrome	Case of a 78-year-old patient with vascular skin manifestations, including palpable purpura and peripheral neuropathy. Skin biopsy was crucial for diagnosing vasculitis associated with Sjögren's syndrome. Treatment with methylprednisolone and oral prednisolone significantly improved symptoms.
Mohammad et al., 2024	Primary Sjögren's syndrome without ocular manifestation	Rare case of a patient with primary Sjögren's syndrome without ocular involvement. The patient presented severe xerostomia, diagnosed through salivary gland biopsy and laboratory tests. Treatment included pilocarpine and vitamin C, resulting in partial symptom relief without systemic complications.
Flament et al., 2016	Pulmonary manifestations of Sjögren's syndrome	Comprehensive review of pulmonary manifestations in Sjögren's syndrome, including nonspecific interstitial pneumonia and tracheobronchial diseases. Emphasizes the need for lung biopsies for diagnosis and corticosteroids for treating interstitial lung disease.
Posso-Osorio et al., 2019	Neurological Involvement as the Initial Manifestation in Primary Sjögren's Syndrome	Analysis of four cases where neurological symptoms (peripheral neuropathy) were the first manifestations of primary Sjögren's syndrome.

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		Treatment with corticosteroids and cyclophosphamide showed significant improvement, highlighting the need for early diagnosis in atypical cases.
Trevisani et al., 2019	Recommendations from the Brazilian society of rheumatology for the diagnosis of Sjögren's syndrome	Systematic review leading to 18 recommendations for diagnosing glandular manifestations in Sjögren's syndrome. Covers diagnostic tools such as salivary gland biopsies, anti-Ro antibodies, and exocrine function tests, promoting multidisciplinary and early diagnosis.
Salehi et al., 2024	Exploring the Psychiatric Manifestations of Primary Sjögren's Syndrome	Narrative review highlighting psychiatric complications in Sjögren's syndrome, such as depression, cognitive dysfunction, and anxiety. Suggests that psychiatric symptoms significantly impact quality of life and require early diagnosis and management.
Chu et al., 2020	Meta-Analysis of Treatment for Primary Sjögren's Syndrome	Meta-analysis assessing the efficacy of immunosuppressants in randomized clinical trials, highlighting the positive impact of agents like rituximab on systemic and glandular symptoms.
Zi et al., 2021	Meibomian gland dysfunction and primary Sjögren's syndrome dry eye	Protocol for a systematic review exploring the contribution of Meibomian gland dysfunction to dry eye in patients with Sjögren's syndrome. Proposes diagnostic criteria and evaluates how dry eye pathogenesis extends beyond aqueous deficiency.
Serrano et al., 2018	Oral lesions in Sjögren's syndrome: A systematic review	Systematic review identifying frequent oral lesions in patients with Sjögren's syndrome, such as atrophic glossitis, erythematous candidiasis, and lingual fissures, correlating these manifestations with reduced salivary flow.
Méndez-Flores et al., 2024	Granulomatous Panniculitis as an Initial Manifestation of Sjögren Syndrome	Case of granulomatous panniculitis as an initial manifestation of Sjögren's syndrome, presenting with fever, weight loss, and painful nodules. Treatment with

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		prednisone led to remission of symptoms.
Kataria et al., 2023	Primary Sjogren's syndrome presenting as an isolated severe autonomic dysfunction treated with steroids	Case of a woman presenting with severe autonomic dysfunction, including dizziness and dry mouth. Diagnosed with primary Sjögren's syndrome based on anti-SSA and SSB positivity. Steroid treatment led to significant clinical improvement.
Duarte-Millán et al., 2017	Reversed halo sign as initial manifestation of interstitial pneumonitis associated with Sjögren's syndrome	A patient presented with respiratory symptoms and a rare reversed halo sign on imaging. Diagnosed with interstitial pneumonitis linked to Sjögren's syndrome. Treatment with steroids improved symptoms and resolved lung lesions.

Source: The authors of the study

DISCUSSION

Sjögren's Syndrome, a systemic autoimmune condition, presents a wide range of manifestations that affect different systems and organs. A detailed analysis of studies allows for exploring the complexity of the disease, identifying overlaps between manifestations, highlighting advances in diagnostics and treatments, and pointing out existing gaps in the literature.

Li et al. (2023) reported a rare case of multisystem sarcoidosis associated with Sjögren's Syndrome. The patient presented symptoms such as dry mouth, dry eyes, and enlargement of the parotid glands, as well as pulmonary, hepatic, and splenic lesions. The diagnosis was established after imaging exams, including CT scans, and biopsies. This case highlights the difficulty of differentiating between diseases with similar manifestations, as both share multisystemic inflammatory characteristics. The combination of sarcoidosis and Sjögren's is uncommon, but this study demonstrates the importance of multidisciplinary evaluations to avoid misdiagnoses and propose appropriate therapies, such as corticosteroid therapy, which resulted in significant improvement for the patient.

Additionally, Flament et al. (2016) analyzed the pulmonary manifestations of Sjögren's Syndrome, showing that between 9% and 20% of patients have pulmonary diseases, with interstitial fibrosing pneumonia being the most common form of interstitial disease. The study also highlighted the presence of tracheobronchial diseases, such as bronchiectasis and bronchiolitis, which can lead to debilitating chronic cough. Although less

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common, severe complications such as pulmonary hypertension and lymphoma were also mentioned. Both studies (Li et al. and Flament et al.) underline the significant impact of Sjögren's Syndrome on the respiratory system and the need for early diagnosis through pulmonary biopsies and advanced imaging to prevent fatal complications.

Virdee et al. (2017) conducted a systematic review that addressed phenotypic differences of the disease in men and children. In children, manifestations include parotitis (71.4% to 81.8%) and lymphadenopathy, often associated with more pronounced systemic symptoms such as fever and fatigue. In men, extraglandular manifestations were reported in up to 92.3% of cases, while serological markers, such as anti-Ro antibodies, varied widely (15.7% to 75%). This work highlighted the diversity in clinical presentation, suggesting that children and men may present more severe phenotypes compared to adult women. Davis et al. (2023) reinforced these findings by reporting a case of late diagnosis in a child, where the manifestations included severe fatigue and significant glandular inflammation. These studies highlight the importance of diagnostic criteria adapted to these less-studied populations.

In the dermatological context, El Hasbani et al. (2023) described a case of vacuolar interface dermatitis as the initial manifestation of Sjögren's Syndrome. This case, involving a patient with scaly skin lesions resistant to conventional treatment, was successfully treated with hydroxychloroquine. Similarly, Kakurai et al. (2021) reported palpable purpura in a patient with Sjögren's, diagnosed through a skin biopsy, highlighting the presence of complex vascular and inflammatory manifestations. These studies demonstrate that skin manifestations can be both an initial marker and a complication of the disease, emphasizing the need for dermatological attention in the early stages to prevent systemic complications.

Sharma and Chatterjee (2015) presented the use of PET/CT with 18F-FDG as an innovative diagnostic tool to assess inflammatory activity in patients with multisystem involvement. This exam allowed for the detection of inflammatory changes in the salivary glands, lungs, and lymph nodes, as well as the exclusion of lymphoma in one case. The use of this technology complements the recommendations of Trevisani et al. (2019), who emphasized the need for a multidisciplinary diagnostic approach, including rheumatologists, ophthalmologists, dentists, and pathologists. This integration of specialized teams is essential to identify complex manifestations, such as those reported by Sharma.

Mohammad et al. (2024) highlighted a rare case of Sjögren's Syndrome without ocular manifestations, which contrasts with the usual prevalence of dry eye in 86% of

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patients. This study reinforced the need for comprehensive diagnostic criteria for atypical cases, especially in patients with exclusively glandular symptoms, such as dry mouth and salivary changes. Zi et al. (2021) complemented this perspective by exploring the relationship between Meibomian gland dysfunction and dry eye, demonstrating that evaporative changes significantly contribute to ocular symptoms. Both studies suggest that a detailed evaluation of the lacrimal and salivary glands is crucial for understanding the variations in the disease's presentation.

Posso-Osorio et al. (2019) addressed neurological manifestations as initial symptoms in patients with Sjögren's, including peripheral neuropathies that preceded the classic glandular manifestations. The use of corticosteroids and cyclophosphamide was effective in improving symptoms. These findings align with the results of Salehi et al. (2024), who reviewed neuropsychiatric complications in Sjögren's, such as depression and cognitive dysfunction. Both studies highlight that the nervous system is often affected, even before glandular manifestations, suggesting that neurological investigations should be conducted in patients with unexplained systemic complaints.

Serrano et al. (2018) conducted a systematic review on oral lesions, reporting that patients with Sjögren's have a higher prevalence of angular cheilitis, atrophic glossitis, and fissured tongue compared to healthy controls. Leite et al. (2020) reported a case where a dentist diagnosed Sjögren's early in a patient with severe oral candidiasis and mucosal dryness. These findings reinforce the role of dentists in the early diagnosis of the disease, preventing complications such as tooth loss and secondary infections.

Chu et al. (2020) conducted a meta-analysis on immunosuppressive treatments, showing that corticosteroids and immunomodulators are effective in managing systemic manifestations, though less effective for glandular symptoms such as dry eye. Ciurtin et al. (2015) complemented this finding by highlighting therapeutic advances, including topical cyclosporine and biologic therapies targeting B lymphocytes, which may offer more promising results in the future.

Finally, Méndez-Flores et al. (2024) reported a case of granulomatous panniculitis as the initial manifestation of Sjögren's, highlighting the role of corticosteroids in controlling painful skin lesions. Tian et al. (2021) reviewed advances in understanding the pathogenesis of the disease, emphasizing the role of inflammatory cytokines and immune dysregulation in disease progression, providing a theoretical basis for new therapeutic approaches.

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Kataria et al. (2023) describe a case in which severe autonomic dysfunction, including intense dizziness, was the initial presentation in a previously healthy woman. The identification of classic symptoms such as dry mouth and eyes, along with positivity for anti-SSA and anti-SSB antibodies, led to the diagnosis. Treatment with steroids resulted in significant improvement in autonomic symptoms, highlighting the relevance of immunosuppressive therapy in atypical manifestations of the syndrome.

Additionally, Duarte-Millán et al. (2017) discuss a case of interstitial pneumonitis associated with Sjögren's syndrome, where the reversed halo sign was identified by computed tomography as an initial manifestation. This presentation, rarely documented, revealed pulmonary lesions that responded favorably to corticosteroid treatment. This finding complements the reports of Kataria et al. (2023), as both studies emphasize the systemic impact of Sjögren's syndrome on organs beyond the exocrine glands, reinforcing the importance of a multidisciplinary approach for early detection and management of the disease.

Another relevant aspect is the discussion by Sharon et al. (2020), who analyzed patients with cicatricial conjunctivitis as an unusual ocular manifestation of Sjögren's syndrome. Among the eight patients evaluated, half had severe corneal complications, including perforation and scarring, leading to progressive vision loss. These results converge with the studies by Kataria et al. (2023) and Duarte-Millán et al. (2017) in highlighting that less typical manifestations, such as autonomic neuropathy or pulmonary signs, may be accompanied by severe ocular impairments, requiring detailed clinical attention to prevent additional morbidities.

These studies demonstrate the complexity of Sjögren's syndrome, with manifestations ranging from classic glandular alterations to severe neurological, cutaneous, and pulmonary complications. The integration of diagnostic and therapeutic approaches, combined with the use of advanced technologies and the development of new therapies, is essential to improving clinical outcomes and the quality of life of patients.

CONCLUSION

This systematic review underscores the complexity and heterogeneity of multisystemic manifestations in Sjögren’s Syndrome (SS), highlighting its profound impact on diverse organ systems and the challenges associated with its diagnosis and management. Beyond the hallmark symptoms of dry eye and dry mouth, SS significantly

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affects the lungs, skin, nervous system, and mental health, demonstrating its nature as a systemic autoimmune disease. The findings reveal the critical importance of early and accurate diagnosis, facilitated by advanced diagnostic tools such as PET/CT imaging, salivary and skin biopsies, and serological markers. Effective management strategies, including corticosteroids, immunosuppressive therapies, and biologic agents like rituximab, show promise in addressing systemic complications. However, the limited efficacy of these therapies in resolving glandular symptoms points to significant gaps in the current therapeutic landscape.

The reviewed studies further emphasize the value of a multidisciplinary approach involving rheumatologists, pulmonologists, neurologists, dermatologists, and psychiatrists to manage the diverse clinical manifestations of SS. This integrated care model is particularly important for addressing severe systemic complications and improving overall patient outcomes. Additionally, the findings highlight the need for tailored interventions, especially for underrepresented populations such as men and children, who often present with more severe or atypical forms of the disease.

Despite these insights, the review has several limitations. The included studies exhibit considerable heterogeneity in methodologies, focusing on different systemic manifestations and therapeutic outcomes, which complicates the synthesis of findings. Many of the studies relied on small sample sizes, case reports, or retrospective analyses, limiting the robustness and generalizability of the evidence. Furthermore, variations in diagnostic criteria and assessment methods across studies introduce inconsistencies in reported outcomes. The exclusion of non-English publications also represents a limitation, potentially overlooking relevant findings from other regions and cultural contexts.

Future research should aim to address these gaps through large-scale, multicenter studies with standardized methodologies to better define the full spectrum of SS manifestations and assess the efficacy of novel diagnostic and therapeutic approaches. Particular attention should be given to underexplored populations, such as pediatric and male patients, as well as atypical presentations that challenge traditional diagnostic criteria. Additionally, innovative therapies targeting glandular symptoms and systemic complications should be developed and rigorously evaluated to enhance treatment outcomes.

Emerging technologies, such as advanced imaging techniques and biomarker analysis, hold promise for improving diagnostic precision and personalizing treatment strategies. Research into the role of systemic inflammation and immune dysregulation in the

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progression of SS could also provide new therapeutic targets, paving the way for more effective interventions. By addressing these challenges, future studies can significantly advance the understanding and management of Sjögren's Syndrome, ultimately improving the quality of life and prognosis for patients affected by this complex and multifaceted disease.

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