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IGOR MESQUITA LAMEIRA

Síndrome de Sjögren em Homens: Revisão Sistemática da Literatura Sobre os Aspectos Clínicos, Complicações e Abordagens Terapêuticas

Sjögren's Syndrome in Male patients: A Systematic Review of Literature on the Clinical Aspects, Complications and Approach Therapy

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestre em Estomatopatologia, na Área de Estomatologia.

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Orientador: Prof. Dr. Helder Antonio Rebêlo Pontes

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RESUMO

Objetivos: O objetivo desta revisão sistemática foi avaliar casos de Síndrome de Sjögren (SS) em pacientes do sexo masculino para determinar as principais características clínicas, complicações e conduta terapêutica.

Métodos: Cinco bases de dados foram avaliadas de acordo com as diretrizes PRISMA. Os casos de SS na América/Europa que atenderam aos critérios ACR/EULAR 2016 e para pacientes diagnosticados na Ásia pelos critérios japoneses (1999).

Resultados: Dos 3.809 artigos identificados, foram selecionados 63 relatos de 15 países, abrangendo 68 pacientes. A SS mais comum foi a primária (58 casos; 85,29%). A idade média dos homens foi de 56.6 anos. Na SS secundária, a Artrite Reumatoide (AR) esteve presente em sete deles, sendo que nesses casos a média de idade foi de 60,25 anos. Os sinais e sintomas mais frequentes foram complicações oculares (72,05%), seguidas de boca seca (61,5%) e características inespecíficas (fadiga, tosse, febre e dispneia) (60,2%). Envolvimento musculoesquelético, como artralgia, miopatia e mialgia, foi observado em 32,3% dos pacientes, e complicações do sistema nervoso foram relatadas em 38,2% dos casos. O desenvolvimento de linfoma ocorreu em cinco casos, sendo quatro deles linfoma MALT (5,8%) e um caso como linfoma de células T. Os medicamentos imunomoduladores/imunossupressores foram a abordagem terapêutica mais comum (34 casos).

Conclusões: Nos homens existem alguns aspectos clínicos peculiares. Pacientes idosos apresentam mais sintomas glandulares e menos envolvimento extraglandular do que adultos jovens. Em geral, os homens apresentaram menor envolvimento linfonodal, metade da incidência de aumento de parótida, menos síndrome seca e mais complicações neurológicas quando comparados às mulheres.

Palavras-chave: Síndrome de Sjögren; Síndrome Sicca; Pacientes do sexo masculino; Complicação, Revisão Sistemática

ABSTRACT

Objectives: The objective of this systematic review was to evaluate cases of Sjögren Syndrome (SS) in male patients to determine the principal clinical features, complications, and the therapeutic approach.

Methods: Five databases were evaluated in accordance with the PRISMA guidelines. The SS cases in America/Europe that met the ACR/EULAR 2016 criteria and for patients diagnosed in Asia by Japanese criteria (1999).

Results: Of the 3,809 articles identified, 63 reports from 15 countries were selected, comprising 68 patients. The most common SS was primary (58 cases; 85.29%). The mean age for men was 56.6 years. In secondary SS, Rheumatoid Arthritis (RA) was presented in seven of them, and for those cases, the mean age was 60.25 years. The most frequent signs and symptoms were ocular complications (72.05%), followed by dry mouth (61.5%), and non-specific features (fatigue, cough, fever, and dyspnea) (60.2%). Musculoskeletal involvement, such as arthralgia, myopathy, and myalgia, were observed in 32.3% of patients, and nervous system complications were reported in 38.2% of cases. Lymphoma development occurred in five cases, with four of them being MALT (5.8%) lymphoma and one case as T-cell Lymphoma. Immunomodulatory/immunosuppressive drugs were the most common therapeutic approach (34 cases).

Conclusions: In men, there are some peculiar clinical aspects. Elderly patients show more glandular symptoms and less extra-glandular involvement than young adults. In general, men showed minor lymph node involvement, half of the parotid enlargement incidence, less sicca syndrome, and more neurological complications when compared to women.

Keywords: Sjögren's Syndrome, Sicca Syndrome, Male Patients, Complication, Systematic Review

SUMÁRIO

1 INTRODUÇÃO

A Síndrome de Sjögren (SS) deve seu nome ao oftalmologista sueco Henrik Samuel Conrad Sjögren que foi o primeiro a correlaciona em um ensaio clínico a ceratoconjuntivite seca, xerostomia e poliartrite em 1933 (SJOGREN et al., 1933). A SS é uma doença autoimune crônica sistêmica de etiologia desconhecida caracterizada pelo dano imuno mediado causado as glândulas salivares e lacrimais, resultando em boca seca (xerostomia) e olhos secos (xeroftalmia). O ressecamento pode afetar outras superfícies de mucosas como vias aéreas, trato digestivo e vagina resultando no aspecto clínico da "síndrome sicca" (BRITO-ZERON et al., 2016). A SS apresenta uma ampla gama de manifestações clínicas sistêmicas, podendo afetar essencialmente grande parte dos órgãos (pulmões, pele, olhos, marcha, músculos). O envolvimento do sistema nervoso (central e periférico) e o desenvolvimento de linfoma não-Hodgkin são as principais complicações observadas.

A SS pode ser categorizada em SS Primária (pSS), quando se apresenta isoladamente, e SS Secundária (SSs), ocorrendo quando o distúrbio está associado a uma doença autoimune estabelecida, sendo a artrite reumatoide a associação mais comum, mas lúpus eritematoso sistêmico e doença do IgG4 também podem estar relacionadas (ALANI et al., 2018). A SS é a segunda doença autoimune mais comum no mundo, tendo incidência aproximada em metade da artrite reumatoide (AR) ou afetando 0,5% a 1% da população (SHIBOSKI et al., 2016).

Esta condição afeta predominantemente mulheres entre 45 e 55 anos, poucos casos foram relatados na literatura afetando homens. (BRANT et al., 2015). Em mulheres a SS atua de forma diversificada, afetando principalmente as glândulas exócrinas, causando xerostomia e xeroftalmia, na maioria dos casos. Os efeitos extra glandulares afetam a maioria dos pacientes, causando efeitos não específicos como fatiga, ansiedade

e depressão, mas podendo afetar orgãos levando a complicações severas (BRITO-ZERON et al., 2016). Demograficamente, a proporção entre homens e mulheres tendem a alterar, podendo variar entre 9-20:1. As populações que mais apresentam discrepâncias são relacionadas ao território asiático (RAMIREZ et al., 2017).

A SS é a segunda doença autoimune mais comum, tendo incidência de aproximadamente metade da artrite reumatoide (AR) ou afetando 0,5% a 1% da população (SHINBOSKI et al., 2017) . Os principais critérios diagnósticos foram criados em 2016 pelo American College of Rheumatology/European League Against Rheumatism. A doença pode ser categorizada em SS Primária, quando a síndrome aparece isoladamente, e SS Secundária (SSS), que ocorre quando o distúrbio está associado a uma doença autoimune estabelecida, sendo a artrite reumatoide a associação mais comum, mas lúpus eritematoso sistêmico e IgG4 doenças também são relatadas (QIN BI et al., 2014).

A principal característica histológica é representado por uma infiltração linfocítica ao redor das glândulas salivares, levando à destruição dos acinos. Em lesões avançadas pode-se observar um padrão conhecido como lesão linfoepitelial benigna (sialoadenite mioepitelial). Na biópsia de glândula salivar menor pode-se observar a presença de agregados inflamatórios crônicos focais com 50 ou mais linfócitos (DANIELS et al., 2011).

As células mononucleares infiltrantes, fatores humorais como anticorpos e citocinas, ou ambos, supostamente causam disfunção das glândulas exócrinas, principalmente glândulas lacrimais e glândulas salivares. (GOULES et al., 2017). Nos últimos anos, a confirmação de que o fator-chave na patogénese da SS é de fato a ativação persistente do sistema interferon tipo I (IFN) juntamente com células B e T autorreativas

e auto-anticorpos associados à doença, oferecendo um alvo interessante para uma abordagem terapêutica individualizada. em SS. (BOHBARDIERI et al. 2020).

Ao todo, no mundo, existem 11 critérios para classificação da Síndrome de Sjögren, mas os principais critérios utilizados atualmente são o American College of Rheumatology/European League Against Rheumatism 2016 (ACR/EULAR) e o critério Japonês (1999), pois ambos atingiram os maiores percentuais de eficácia no diagnóstico (referenciar). Os critérios de diagnóstico da SS foram alterados em 2016 pela ACR/EULAR. Os critérios ACR/EULAR incluem a presença de soro positivo anti-SSA/Ro (três pontos), biópsia de glândula salivar labial exibindo agregados inflamatórios crônicos focais com pontuação de foco > 1 foco/4mm² (três pontos), pontuação de coloração ocular > 5 (um ponto), teste de Schirmer < 5mm (um ponto) e fluxo salivar total não estimulada < 0,1 ml (um ponto), necessitando atingir a pontuação de $\leq$ 4 como condição para o diagnóstico (VIRDE et al., 2017). O critério japonês (1999) possui condições semelhantes a ACR/EULAR 2016, mas inclui a aceitação do soro positivo anti-SSB/La, a biópsia de glândulas lacrimais e o fluxo de saliva não estimulado observado em cintilografia. O Diagnóstico é alcançado quando dois desses critérios são observados no paciente (RAMIREZ et al., 2017).

Os pacientes diagnósticados com SS apresentam um risco maior de desenvolvimento de linfomas, principalmente linfoma de Non-Hodking (referenciar). Estudos anteriores relatam o maior acometimento desses pacientes, levando a criação de fatores de risco que podem prever o desenvolvimento de linfomas, classificando os pacientes em baixo, médio e alto risco (NOCTURNE et al.,2014)

O objetivo deste estudo é realizar uma revisão sistemática da literatura sobre os aspectos clínicos, complicações e terapia responsiva em pacientes do sexo masculino com síndrome de Sjögren descritos na literatura.

2 ARTIGO: Artigo: Sjögren's Syndrome in Male patients: A Systematic Review of Literature on the Clinical Aspects, Complications and Therapeutic Approach

Artigo submetido para publicação no Annals of Rheumatic Diseases (Anexo2)

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ABSTRACT

Objectives: The objective of this systematic review was to evaluate cases of Sjögren Syndrome (SS) in male patients to determine the principal clinical features, complications, and the therapeutic approach.

Methods: Five databases were evaluated in accordance with the PRISMA guidelines. The SS cases in America/Europe that met the ACR/EULAR 2016 criteria and for patients diagnosed in Asia by Japanese criteria (1999).

Results: Of the 3,809 articles identified, 63 reports from 15 countries were selected, comprising 68 patients. The most common SS was primary (58 cases; 85.29%). The mean age for men was 57.4 years. In secondary SS, Rheumatoid Arthritis (RA) was presented in seven of them, and for those cases, the mean age was 60.25 years. The most frequent signs and symptoms were ocular complications (75%), followed by dry mouth (61.7%), and non-specific features (fatigue, cough, fever, and dyspnea) (60.2%). Musculoskeletal involvement, such as arthralgia, myopathy, and myalgia, were observed in 32.3% of patients, and nervous system complications were reported in 38.2% of cases. Lymphoma development occurred in five cases, with four of them being MALT (5.8%) lymphoma and one case as T-cell Lymphoma. Immunomodulatory/immunosuppressive drugs were the most common therapeutic approach (34 cases).

Conclusions: In men, there are some peculiar clinical aspects. Elderly patients show more glandular symptoms and less extra-glandular involvement than young adults. In general, men showed minor lymph node involvement, half of the parotid enlargement incidence, less sicca syndrome, and more neurological complications when compared to women.

Keywords: Sjögren's Syndrome, Sicca Syndrome, Male Patients, Complication, Systematic Review

INTRODUCTION

Sjögren Syndrome (SS) is named after the Swedish ophthalmologist Henrik Samuel Conrad Sjögren, who first correlated the triad of keratoconjunctivitis sicca, xerostomia, and polyarthritis in 1933.[1] SS is a systemic chronic autoimmune disorder of unknown etiology characterized by immune-mediated damage to the salivary and lacrimal glands, resulting in dryness of the mouth (xerostomia) and eyes (xerophthalmia). This dryness can affect other mucosal surfaces such as the airways, digestive tract, and vagina, resulting in the clinical aspect of "sicca syndrome".[2] The systemic disease SS manifests a wide range of manifestations, affecting the lungs, skin, eyes, spleen, muscles, and other sites. The involvement of the nervous system, both central and peripheral, and the development of non-Hodgkin lymphoma are also important complications.

Sjögren Syndrome (SS) is the second most common autoimmune disease, with an incidence of approximately one-half that of rheumatoid arthritis (RA), affecting 0.5% to 1% of the population.[3] The principal diagnostic criteria were established in 2016 by the American College of Rheumatology/European League Against Rheumatism.[4] The disease can be categorized as Primary SS and Secondary SS (sSS), the latter occurring when the disorder is associated with an established autoimmune disease, particularly rheumatoid arthritis, and less frequently systemic lupus erythematosus, and IgG4 disease.[5]

The disease predominantly affects women between the ages of 45 and 55 years, with few cases reported in the literature involving men.[6] The ratio of women to men can be as high as 20:1 in the Asian population, but this proportion may vary in other regions.[7-9]

The objective of this study was to conduct a systematic literature review of the clinical aspects, complications, and therapeutic approaches in male SS patients as described in the English-language literature.

METHODS

Protocol and Registration

The report of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] A protocol was developed and registered in the International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42023414369).

Eligibility criteria

This systematic review included publications reporting cases of SS in male patients written in English. For inclusion, the studies needed to provide sufficient information to support the diagnosis. The diagnosis confirmation of SS was based on the American College of Rheumatology/European League Against Rheumatism classification criteria of primary SS of 2016.[4] The Asian cases described in the literature had their diagnoses confirmed according to the Japanese criteria of 1999.[11]

Information source and search strategies

An electronic search without time restrictions was conducted up to December 2023 in the following databases: PubMed, ScienceDirect, Web of Science, Embase, and Scopus. The search terms used were "(Sjögren's syndrome OR Sjögren Syndrome OR Sicca Syndrome) AND (male OR man) AND (Complications OR associated disease OR Coexistent Disease OR Associated conditions OR Concomitant disease)." Additionally, the reference lists of the selected studies and relevant reviews were scanned for possible additional studies. Grey literature searches were also conducted using Google Scholar, with the search limited to the first 100 hits.

Selection process

The titles and abstracts of all articles identified through the electronic searches were independently reviewed by two authors (IML and CAP). Articles meeting the inclusion criteria—official publications with robust clinical records providing sufficient information for accurate diagnosis according to the ACR/EULAR (2016)[4] and Japanese criteria (1999),[11] written in English, and comprising case reports or case series—were obtained as full paper copies. Cases that raised doubts were discussed by the authors. All papers excluded after full evaluation were documented, along with the reasons for exclusion. The clinical aspects, complications, and therapeutic approaches reported were assessed by two authors (FSCP and HARP), who are experts in oral medicine and oral pathology.

Quality assessment

The risk of bias assessment was conducted using the Joanna Briggs Institute Critical Appraisal Checklist for case reports and case series in Figure 3 and Figure 4.[12] This checklist evaluates various aspects including the study population, demographics, clinicopathological information, diagnosis, and follow-up. Studies were categorized based on responses such as "yes," "no," "unclear," and "not available." Following classification, studies were rated as having a "high," "moderate," or "low" risk of bias. Assessment was carried out by two authors (IML and CAP), with any disagreements resolved through consultation with a third author, HARP.

Data extraction

The necessary information from the eligible papers was gathered and documented by two reviewers (IML and CAP) using a specially designed data extraction form in Microsoft Excel® software. A standard form was utilized for collecting the following data, when available: author/year of publication, country, number of patients, sex (male/female),

type, age (years), diagnosis time and method, clinical and histological aspects, complications, lymphocyte foci, biopsy results of minor glands (when available), treatment, follow-up time, and prognosis.

Synthesis Methods and Analysis

Qualitative and quantitative data were descriptively analyzed using Microsoft Excel® software. Additionally, a narrative synthesis of the findings from the included publications was conducted.

RESULTS

PRISMA flowchart

The study selection process is summarized in Figure 1. The search strategy identified 2,809 papers through the databases and registries, and 1,000 papers via grey literature. Among these, 91 were cited in more than one database (duplicates). The authors screened the titles and abstracts for articles related to the study question. Of all papers identified through databases and registries, 2,383 were excluded for not being related to the topic, and 31 were excluded due to unavailability for access, resulting in 304 reports. Out of the 1,000 reports via grey literature, 100 were selected, but only 93 papers were available for access. The full text reports of the 397 articles were evaluated, leading to the exclusion of 334 papers for reasons including wrong study design (58), publication type (49), foreign language (27), wrong population (178), and lack of information (24). This resulted in 63 reports, comprising 44 reports from databases and registries, and 19 from grey literature.

Description of the studies

Demographics/epidemiological

The demographic distribution of Sjögren's syndrome (SS) cases is shown in Figure 2. The research revealed that Japan (25 publications) and the United States of America (11 publications) were the most frequent countries, followed by China (8 publications) and France (5 publications). The research identified a total of 68 cases of SS. In men, the prevalence of Primary SS was evident in 58 (85.29%) patients, with Secondary SS comprising 10 cases (14.7%). Among these ten reports of Secondary SS, seven (70%) were associated with rheumatoid arthritis (RA), two with systemic lupus erythematosus, and one with IgG4-related disease. The mean age was 56.6 years (ranging from 26 to 87), with a mean age of diagnosis of 55.3 years (ranging from 26 to 87) (Table 1).

Complications and follow-up

The mean follow-up duration was 18.7 months (ranging from 1 to 120 months) in 37 cases. Among these, only four patients (5.8%) were discharged from treatment, while 33 patients (48.5%) were still undergoing therapy. Six cases (8.8%) resulted in death due to various complications (pulmonary transplantation surgery, bacteremic pneumococcal pneumonia, myocardial infarction, and cerebral hemorrhage). The follow-up status of patients was not reported in 23 reports (33.8%).

Clinical Features

The data regarding clinical features is presented in Table 2.

Glandular Features

The complications of SS showed a variable panorama. The most common complication was ophthalmic involvement (51 cases, 75%), followed by dry eyes (52.9%; 36 cases) and low lacrimal flux (44.1%; 30 cases). Oral symptoms (49 cases; 72.05%) were the

second most frequent alteration observed, with dry mouth affecting 61.7% (42 cases) of cases, followed by Sicca syndrome (dry eyes/dry mouth) with 26 cases (38.2%). Swelling of the parotid glands was observed in 11 cases (16.1%), with 8 cases showing unilateral enlargement (11.7%), two cases with bilateral enlargement (2.9%), and one case with recurrence of unilateral enlargement of the parotid gland (1.4%).

Extra glandular Features

Other relevant complications included involvement of the articular and muscular systems (22 cases; 32.3%), cutaneous manifestations (21 cases; 30.8%), pulmonary disease (20 cases; 29.4%), peripheral nervous system involvement (17 cases; 25%), nephron-urological involvement (14 cases; 20.5%), central nervous system manifestations (13 cases; 19.1%), cardiovascular involvement (12 cases; 17.6%), gastrointestinal complications (nine cases; 13.2%), and lymph node involvement (six cases; 8.8%). Only five cases (7.3%) progressed to lymphomas (four MALT lymphomas and one T-cell cutaneous lymphoma).

Nonspecific features such as fever, fatigue, dyspnea, cough, and weight loss were present in 60.2% (41 cases) of patients. Cutaneous manifestations (30.8%; 21 cases) were diverse, including xerosis cutis, purpura, annular erythema, and generalized anhidrosis as the principal manifestations. Among musculoskeletal manifestations (32.3%; 22 cases), arthralgia/joint pain, myopathy, and myalgia were the most common findings. Pulmonary manifestations (29.4%; 20 cases) were recurrent features leading to interstitial lung disease, bilateral pleural effusion, and two cases of MALT lymphoma as principal complications.

Nervous system (NS) complications were significant factors in male patients with SS. Peripheral nervous system complications (PNS) were present in 17 cases (25%) affecting

mostly sensory neuropathies (painful sensory neuropathy and 'mixed' dorsal root ganglionitis) and cranial neuropathies (diplopia, Bell's palsy, and neural deafness). Central nervous system complications (CNS) were present in 13 cases (19.1%) and included diseases resembling multiple sclerosis, encephalopathies, and ataxia. Simultaneous PNS and CNS complications were described in five cases (7.3%).

The risk of lymphoid malignancy was assessed following the study by Fragkioudaki et al. (2016),[13] with 24 patients (35.29%) classified as low risk, seven patients (10.2%) as moderate risk, and 37 patients (54.4%) showing no degree of lymphoma risk (Table 4).

Laboratorial Features

In terms of laboratory results, when men were affected by SS, most of them showed a positive Anti-RO/SSA test (44 cases; 64.7%), 13 tested negative (19.1%), and 11 patients (16.1%) did not report their test results.

Regarding histological findings, the results of minor salivary gland biopsies in men showed that out of 68 cases, 37 were positive (54.4%), six were negative (8.8%), three patients did not undergo the biopsy as they already had the diagnosis (4.4%), nine patients (13.2%) underwent biopsies of other organs (lungs, kidneys, heart, and skin), one patient refused the biopsy, and information on nine patients (13.2%) was not reported. Only 12 reports included information on the foci score, with a mean score of 3.5.

Responsive Therapy

In this survey, it was demonstrated that the most common treatment was immunomodulatory/immunosuppressive drugs such as oral prednisolone and methylprednisolone (34 cases; 50%), followed by biological agents such as intravenous immunoglobulin G or methotrexate (14 cases; 20.5%). The combination of treatments

used was quite diverse, with immunosuppressives being used orally in 22 cases (32.3%) or in conjunction with intravenous application followed by oral dosage in 11 cases (16.1%). Additionally, the association with biological agents was observed in nine cases (13.2%), such as rituximab, cyclosporine, and cyclophosphamide in combination with prednisolone or methylprednisolone (Table III).

Eye drops alone were used in only one case (1.4%) for ocular dryness. Other types of treatment were utilized in only three cases (4.4%), such as intravenous vitamin B12, intravenous potassium, and cefmetazole, and treatment was not reported in five cases (7.3%).

Quality assessment (Risk of bias)

According to the Joanna Briggs Institute risk of bias classification, case reports were categorized as overall low risk (39 studies), moderate overall risk (15 studies), and high overall risk of bias (five studies). Case series were categorized as overall low risk (two studies) and moderate overall risk of bias (two studies).

DISCUSSION

SS is a chronic, systemic autoimmune connective tissue disorder mediated by B and T cells that principally affects the salivary and lacrimal glands. The typical symptoms of SS include sicca syndrome, dry mouth, and dry eyes.[2] SS is more prevalent in women, with a female-to-male ratio of 12:1 in several studies.[7,11] Due to its rarity in men and the signs and symptoms being easily confused with those of other autoimmune diseases, diagnosis is often delayed in most cases. This fact was confirmed in this review, where there was an average delay of one year in the diagnosis of the described cases.

This survey utilized the two main criteria with the best performance in the diagnosis of SS, EULAR/ACR 2016,[4] and The Japanese criteria (1999).[11] The principal differences are the inclusion of SSB/La positivity and lacrimal gland biopsy by the Japanese criteria as diagnostic factors. In contrast, the EULAR/ACR 2016 criteria do not consider these options as inclusive factors; rather, positive anti-Ro/SSA or minor salivary gland biopsy (score >1) are necessary for diagnosis according to the EULAR/ACR 2016 criteria.[4]

To date, at least 68 cases of SS in men have been published in the English-language literature. The mean age of patients observed in this review was 56.6 (26-87) years, with half the cases being diagnosed in elderly patients. Confirming previous articles, young adult patients (26-59 years) showed major extra-glandular involvement, while older patients were more affected by glandular symptoms.[14,15] In adult men (up to 59 years), the principal extra-glandular alterations were lymphadenopathy, cutaneous manifestations, muscular complications (arthralgias and myalgia), nephron-urological manifestations, systemic peripheral nervous system involvement, and parotid enlargement. Elderly men (above 60 years) showed higher glandular complications and more involvement of pulmonary complications than young adults. They also exhibited fewer extra-glandular features compared to younger men.

Men showed a decrease in glandular manifestations such as dry eyes or dry mouth in 72%-75% of cases and sicca syndrome in only 38% of cases, while studies with 95% female patients showed an incidence of dry eyes or dry mouth in 72%-98% of cases and sicca syndrome in 86%.[16,17,18]. The enlargement of the parotid gland is present in one-third of the female population with SS,[19] but men showed a prevalence of 16.1% in the current study, with the most common form being bilateral enlargement (11.7%).

According to Ramos-Casal et al. fatigue is the most prevalent manifestation affecting women (70%-80%).[19] In our research, men were affected by fatigue in only 16% of the cases. In addition, dyspnea, fever, and cough were also reported affecting this population.

Musculoskeletal manifestations are common in female SS patients, such as myalgia, arthralgia, and morning stiffness, affecting 90% of patients.[20] Other studies have shown a prevalence of muscular involvement up to 75%, with arthralgia being the most common aspect, even in secondary SS patients.[18] In this survey, men showed an involvement of 32.3% in musculoskeletal manifestations, with arthralgia also being the most relevant aspect.

In women, there is a high prevalence of cutaneous manifestations, with xerosis cutis (dry skin) and annular erythema being the most common features.[2,16] Our research showed cutaneous manifestations in 30% of male patients, with xerosis cutis (7.3%) also being the most common manifestation, followed by annular erythema and cutaneous vasculitis (1%-4.4%).

Regarding pulmonary manifestations in men, the results were similar to the female population, with a prevalence of 29.4%, while studies with female predominance showed development rates of 5%-24%.[21] The most common pulmonary manifestation in both women and men was interstitial lung disease (ILD), affecting 28% and 10.2%, respectively.[22]

Previous studies have shown a low frequency of cardiac complications in female patients.[23] The cardiac manifestations include Raynaud's phenomenon, pericarditis, and vasculitis as the most common presentations.[2] This survey yielded similar results, with only 17.6% of cases affected by cardiac diseases such as hypertension, orthostatic hypotension, pericarditis, and Raynaud's phenomenon.

According to Evans et al.,[23] renal involvement is generally considered low in women, with studies reporting rates of involvement reaching 5%. In middle-aged women with renal complications, tubulointerstitial nephritis is the principal manifestation, affecting 71% of cases.[23] In men, the proportion of patients affected reaches 20.5%, with proteinuria and hypokalemic paralysis being the most frequent aspects.

Gastrointestinal symptoms can affect up to 23% of female SS patients, typically presenting as central upper abdominal pain, nausea, vomiting, and early satiety.[24] They may include chronic pancreatitis in 5% of cases, liver manifestations such as primary biliary cirrhosis, and acceleration of hepatitis C.[25] Gastrointestinal complications in the analyzed survey were observed in 13.2% of male patients, represented by constipation, bleeding, chronic atrophic gastritis, and ulcerative colitis. Pancreatic manifestations affect 5.8% of men, with no complication being more predominant.

As described in the studies by Tobon et al.,[26] and Ramos-Casals et al.,[27] the prevalence of NS involvement in female SS patients is small, with PNS involvement being more common than CNS involvement. Painful sensory neuropathy and sensorimotor neuropathies are the most prevalent diseases affecting the PNS, while in the CNS, the manifestations are heterogeneous, presenting with focal or diffuse involvement such as ataxia, encephalitis, dizziness, memory loss, and visual disturbance.[28] In NS involvement in men, we observed a slight increase in frequency, reaching 38.2%. We found that the most common involvement in the PNS was painful sensory neuropathy (11.7%) and cranial neuropathy such as Bell's palsy, diplopia, and neural deafness (10.2%). In CNS involvement, ataxia (7.3%) was the most prevalent manifestation among dizziness, memory loss, encephalopathy, and multiple sclerosis-like disease.

Female SS patients have a high risk of developing lymphoma, as many studies have shown that this risk can be higher than in SLE and RA.[16,18] In the latest systematic

review on the risk of lymphoma development in women with SS, it was estimated to be 13.7%, indicating an increased risk of lymphomas.[29] The most common type associated with SS is low-grade B-cell non-Hodgkin lymphomas, with MALT being the most prevalent.[30] In this survey, men presented with 24 patients (47.69%) showing low risk, seven patients (10.2%) presenting middle risk. Lymphoma development was observed in five cases (7.3%), with four of them being MALT lymphoma.

Antinuclear antibodies (ANA), rheumatoid factor (RF), and Ro/SSA and La/SSB autoantibodies are important laboratory findings for SS cases. ANA can be present in up to 85% of SS patients, and RF positivity is usually common in the female population.[31] In the ACR/EULAR 2016 criteria, ANA, RF, and Anti/SSB were excluded as diagnostic criteria. In this study, we observed that the male population showed positivity for Anti-Ro/SSA in 64.7%, Anti-LA/SSB in 44%, ANA in 45.5%, and RF in 22% of cases. Most of the laboratory results showed similarity with the female population, regardless of RF.

Regarding treatment and management, SS remains one of the most complicated among autoimmune rheumatic disorders. Treatment decisions in SS are based on the initial evaluation of symptoms and extra-glandular manifestations.[32] For non-life-threatening signs such as fatigue, arthralgia, arthritis, and cutaneous signs, immunosuppressant drugs such as hydroxychloroquine, oral prednisolone, and methylprednisolone are the first choice. In life-threatening situations, the recognized therapy must include intravenous methylprednisolone followed by other medications as alternatives.[33] In this survey, oral therapy with prednisolone or methylprednisolone was reported in 50% of cases, followed by a tapered dose until reaching stabilization of symptoms with a small dose (41.1%) or withdrawal of the medicine (8.8%). Biological agents have been an alternative line of treatment, with studies showing efficacy in primary results.[34] This review also showed that rituximab had a positive result in improving sicca syndrome, fatigue, and extra-

glandular manifestations, being included as an effective and safe strategy for SS patients. In this study, the use of biological agents was observed in only 14 cases (20.5%), including methotrexate, rituximab, cyclophosphamide, and intravenous immunoglobulin G, with nine of them in combination with immunomodulatory therapy such as prednisolone and methylprednisolone.

CONCLUSION

According to the results, SS in male patients is a rare autoimmune disease with a heterogeneous presentation, typically occurring in the mid-50s. Elderly patients show more glandular symptoms and less extra-glandular involvement than young adults. Compared to women, men show a lower prevalence of sicca syndrome and minor enlargement of the parotid gland. Neurological complications were more frequent in men, with painful sensory neuropathy affecting the peripheral nervous system and ataxia affecting the central nervous system.

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CONTRIBUTORS

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Not applicable

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ETHICS APPROVAL

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No

DATA AVAILABILITY STATEMENT

Not applicable

SUPPLEMENTAL MATERIAL

Articles information (supplement table 1)

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KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC:

Sjogren's Syndrome (SS) is the second most common autoimmune disease worldwide. The pathogenesis of the disease involves the infiltration of target tissues by lymphocytes, leading to dysfunction.

WHAT THIS STUDY ADDS:

To the best of our understanding, there are no systematic reviews addressing the disease exclusively in men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY:

Greater knowledge of the main clinical aspects of SS in men will serve as a diagnostic tool. Additionally, detailed information on the main complications will aid in the development of protocols for the disease.

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FIGURE LEGENDS

FIGURE 1. Study screening process

FIGURE 2. Graphic showing countries with cases of Sjögren Syndrome described in the literature associated with the number of cases in each country.

FIGURE 3. Risk of bias analysis chart for each article, according to the Joanna Briggs Institute Critical Appraisal Checklist.

FIGURE 4. Chart of the summarized risk of bias analysis, according to the Joanna Briggs Institute Critical Appraisal Checklist.

FIGURE 5. Lip biopsy showing a minor salivary gland lymphocytic infiltrate around a ductulus. Epithelial hyperplasia is visible around the ductulus. Hematoxylin & Eosin original magnification 10× (A), 20× (B) and 40× (C).

Table I. Demographic and Laboratory Features of Sjögren's Syndrome Cases Described in the Literature.

Variables	**N = 68**	**(%)**
Type		
Primary SS	58	85.2
Secondary SS	10	14.7
Rheumatoid Arthritis	7	10.2
Systemic Lupus Erythematosus	2	2.9
IgG4 Related Disease	1	1.4
Gender		
Male	68	100.0
Age, (mean age: 56.6 years)		
≤ 56.6	68	100.0
Diagnosis Age (mean age, 55.3 years)		
≤ 55.3	68	100.0
Follow-up time (mean time: 18.7 months)		
≤ 18.7	45	66.17
NR	23	33.82
Laboratory		
Anti-Ro/SSA		
Positive	44	64.7
Negative	13	19.1
NR	11	16.1
Minor Salivary Gland Biopsy		
Positive	37	54.4
Negative	6	8.8
Not Performed	13	19.1
Diagnosed	3	4.4
Mean Foci Score	12	3.5 (foci score)
NR	9	13.2

Abbreviations: N, total number; NR, Not Report.

Table II. Clinical features organ by organ systemic manifestation of Sjögren's Syndrome described in the literature.

Variables	**N = 68**	**(%)**
Oral Symptoms	**49**	**72.05**
Xerostomia/Dry Mouth	42	61.7
Oral ulcers	2	2.9
Uveitis	1	1.4
Swelling of salivary glands	2	2.9
Multiple Caries	1	1.4
Hyposalivation/low salivary flux	2	2.9
Taste disorder	2	2.9
Furrowed Tongue	1	1.4
Nodular Scleritis	1	1.4
Oral ulcers	2	2.9
Uveitis	1	1.4
Ocular symptoms	**51**	**75**
Xerophthalmia/Dry eyes	36	52.9
Swelling of lacrimal glands	1	1.4
Low lacrimal flux	30	44.1
Conjunctival inflammation	2	2.9
Corneal Melt	1	1.4
Ocular Ischemic Syndrome	1	1.4
Orbital Myositis	1	1.4
Conjunctival Hyperemia	1	1.4
Burning Eyes	1	1.4
Cornea Edema	2	2.9
Cornea Melt	3	4.4
Sicca Syndrome (Xeroftalmia/Xerostomia)	**26**	**38.2**
General Symptoms	**41**	**60.2**
Fever	15	22
Fatigue	11	16.1
Dyspnea	10	14.7
Cough	9	13.2
Weight loss/Appetite Loss	8	11.7
Headaches	4	5.8
Chest Pain	4	5.8
Nausea	2	2.9
Dizziness	1	1.4

Lymph and node complications	**6**	**8.8**
Reactive Multiple Lymphadenopathy (Swelling of the lymph nodes)	3	4.4
Generalized Swelling of Lymph Nodes	3	4.4
Cutaneous Manifestation		
Xerosis Cutis (Dry skin)	**21**	**30.8**
Purpura	5	7.3
Annular Erythema	3	4.4
Generalized Anhidrosis/Hypohidrosis	3	4.4
Gyrate Erythema	2	2.9
Skin Eruptions	1	1.4
Cutaneous Vasculitis	1	1.4
Ulcerative Wounds (hands)	1	1.4
Pyomyositis Diffuse	1	1.4
Generalized Edema	1	1.4
Ecchymoses	1	1.4
Vascular Purpura Legs	1	1.4
Pretibial Edema	1	1.4
Articular and Muscular Complications	**22**	**32.3**
Arthralgia/Joint Pain	8	11.7
Muscular weakness/Myopathy	4	5.8
Myalgia	4	5.8
Areflexia	3	4.4
Paralysis	2	2.9
Synovitis	2	2.9
Symmetric Flaccid Paralysis	2	2.9
Peripheral Arthritis	2	2.9
Rhabdomyolysis	1	1.4
Muscular Dystrophy	1	1.4
Muscular Atrophies (lower limbs)	1	1.4
Pulmonary Complications	**20**	**29.4**
Interstitial Lung Disease	5	7.3
Bilateral Pleural Effusion	4	5.8
MALT Lymphoma	2	2.9
Pleural Effusion	2	2.9
Bronchiectasis	1	1.4
Pleuritis	1	1.4
Chronic Eosinophilic Pneumonia	1	1.4
Acute Respiratory Failure	1	1.4
Interstitial Pulmonary Fibrosis	1	1.4
Sarcoidosis	1	1.4
Bronchiolitis	1	1.4

Lymphocytic Interstitial Pneumonitis	1	1.4
Cardiovascular Complications	12	**17.6**
Hypertension	5	7.3
Orthostatic Hypotension	3	4.4
Angiitis	1	1.4
Vasculitis	1	1.4
Raynaud's Phenomenon	1	1.4
Inflammatory Aortic Aneurysm	1	1.4
Constrictive Pericarditis	1	1.4
Pancreatic Complication	4	**5.8**
Autoimmune Pancreatitis	1	1.4
Distal Renal Tubular Acidoses	1	1.4
Obstructive Icteric	1	1.4
Sclerosing Cholangitis	1	1.4
Enlargement of Liver and Spleen	1	1.4
Cancer of the Head of Pancreas	1	1.4
Swelling of Pancreas	1	1.4
Nephro-Urological Complications	14	**20.5**
Proteinuria	4	5.8
Hypokalemic Paralysis	2	2.9
Splenomegaly/Enlargement kidney	2	2.9
Nephrocalcinosis	2	2.9
Primary Biliary Cirrhosis	1	1.4
Interstitial Cystitis	1	1.4
Mild Proteinuria	1	1.4
Dysuria;	1	1.4
Nocturia;	1	1.4
Pauci-immune Glomerulonephritis	1	1.4
Renal Parenchymal Disease	1	1.4
Hypokalemic Myopathy	1	1.4
Kidney Failure	1	1.4
Distal Renal Tubular Acidosis	1	1.4
Kidney transplant	1	1.4
Hematuria	1	1.4
Interstitial Nephritis	1	1.4
Hepatomegaly	1	1.4
Gastro-intestinal Complications	**9**	**13.2**
Constipation	2	2.9
Irritable Bowel Syndrome	1	1.4
Gastrointestinal Dysmotility	1	1.4
Bleeding	1	1.4
Ulcerative Colitis	1	1.4
Chronic Atrophic Gastritis	1	1.4

Protein Losing Gastroenteropathy	1	1.4
Nervous System Complication	**26**	**38.2**
Peripheral Nervous System Complications		
Sensory Neuropathy	8	11.7
Cranial Neuropathy	7	10.2
Sensorimotor Neuropathy	4	5.8
Central Nervous System Manifestation		
Ataxic	5	**7.3**
Acute Neurological Abnormalities	2	2.9
Encephalitis	2	2.9
Memory Loss	1	1.4
Multiple Sclerosis	1	1.4
Ear, Nose and Throat Complications	**11**	**16.1**
Swelling/Enlargement of the Parotid Gland	8	11.7
Bilateral Enlargement of the Parotid	2	2.9
Recurrent enlargement of the Parotid	1	1.4

Abbreviations: N, total number; NR, Not Reported.

Table III. Treatment of Sjögren's Syndrome.

Treatment	**N = 68**	**(%)**
Immunomodulatory/Immunosuppressive	**34**	**50**
Only oral Prednisolone/Methylprednisolone	22	32.3
Oral Prednisolone + IV therapy	11	16.1
Hydroxychloroquine	1	1.4
Biologic Agents	**14**	**20.5**
Methotrexate	6	8.8
Intravenous Immunoglobulin G (IVIG)	5	7.3
Cyclophosphamide	2	2.9
Rituximab	1	1.4
Immunomodulatory + Biologic Agents	**9**	**13.2**
Prednisolone + Cyclosporine	3	4.4
Methylprednisolone + Methotrexate	2	2.9
Prednisolone + Rituximab	1	1.4
Immunoglobulin G IV + Prednisolone	1	1.4
Prednisolone + Cyclophosphamide	1	1.4
Not specific	1	1.4
Eyes Drops	**1**	1.4
Immunomodulatory + Eye Drops	**1**	1.4
Methylprednisolone + Artificial Tears	1	1.4
Immunomodulatory + Eye Drops + Biologic Agents	**1**	1.4
Methylprednisolone + Methotrexate + Artificial Tears	1	1.4
Other treatment	**3**	4.4
NR	**5**	7.3

Abbreviations: N, total number; NR, Not Reported.

Table 4: Independent risk factors for Non-Hodgkin lymphoma development.

Article	SALIVARY GLAND ENLARGEMENT	LYMPHADENOPATHY	RAYNAUD'S PHENOMENON	ANTI-Ro/SSA or ANTI-La/SSB POSITIVITY	RHEUMATOID FACTOR POSITIVITY	MONOCLONAL GAMMOPATHY	C4 HYPOCOMPLEMENTEMIA	SCORE ≥3	RISC LEVEL	LYMPHOMA RISC
Koite et al., 2008	-	-	-	-	-	-	-	-	0	-
JAMES et al., 2006	-	+	-	-	-	-	-	+	02 FACTOR	LOW RISK
H, Yasui, 2015	-	+	-	-	-	-	-	-	01 FACTOR	-
M, yoshikawa, 2020	-	-	-	+	-	-	-	-	01 FACTOR	-
Y, Peng et al., 2021	-	+	-	+	-	-	-	-	02 FACTOR	LOW RISK
C, Lv et al 2022	-	-	-	+	-	-	-	-	01 FACTOR	-
S, Yasuda et al., 2004	+	-	-	-	-	-	-	-	01 FACTOR	-
Y, Lu et al., 2022	+	-	-	+	+	-	-	-	03 FACTOR	MIDDLE RISK
A, Awad et al., 2010	-	-	-	+	-	-	-	-	01 FACTOR	-
DB, Dublin et al., 1998	+	+	-	-	-	-	-	-	02 FACTOR	LOW RISK
Y, Yamamoto., 2021	-	-	-	+	+	-	-	-	02 FACTOR	LOW RISK
T, Watanabe et al., 1996	+	-	-	+	+	-	-	-	03 FACTOR	MIDDLE RISK

WJ, Wang et al. 2011	-	-	-	+	-	-	-	-	01 FACTOR	-
N, Pasçalau et al., 2016	+	-	-	+	-	-	-	-	02 FACTOR	LOW RISK
L, Michel et al., 2011	-	-	-	-	-	-	-	+	01 FACTOR	-
Y, Takahashi et al., 2003	-	-	-	+	+	-	-	-	02 FACTOR	LOW RISK
K, Migita et al., 1999	-	-	-	+	-	-	-	-	01 FACTOR	-
K, Waseda et al., 2015	-	-	-	+	+	-	-	-	02 FACTOR	LOW RISK
FB, Vivino et al., 2001	-	-	-	+	-	-	-	+	02 FACTOR	LOW RISK
Y, Cao et al., 2020	-	-	-	+	-	-	-	-	01 FACTOR	-
JS, Van Den Berg et al., 1999	-	-	-	-	-	-	-	-	0	-
T, Matsumura et al., 1995	-	-	-	+	-	-	-	-	01 FACTOR	-
CC, Huang et al., 2010	-	-	-	+	-	-	-	-	01 FACTOR	-
BP, Goodman et al., 2017	-	-	-	+	-	-	-	-	01 FACTOR	-
K, Sughimoto et al., 2006	-	-	-	+	+	-	-	-	02 FACTOR	LOW RISK
S, Yamada et al., 2005	-	-	-	+	-	-	-	-	01 FACTOR	-

S, Morozumi et al., 2009 (2)	-	-	-	+	-	-	-	+	02 FACTOR	LOW RISK
R, Verma et al., 2020	-	-	-	+	-	-	-	-	01 FACTOR	-
PG, Ferreira et al., 2014	-	-	+	+	-	-	-	-	02 FACTOR	LOW RISK
N, Sutcliffe et al., 2000 (2)	+	+	-	-	-	-	-	-	02 FACTOR	LOW RISK
NA, Polanco et al., 2013	-	-	-	+	-	-	-	-	01 FACTOR	-
CD, Johnson et al., 1989	-	-	-	-	-	-	-	-	0	-
M, Euch El et al., 2020	-	-	-	-	-	-	+	+	02 FACTOR	LOW RISK
FX, Danlos et al., 2015	-	+	-	+	+	-	-	-	03 FACTOR	MIDDLE RISK
A, Ghinoi et al., 2007	-	-	-	+	-	-	-	+	02 FACTOR	LOW RISK
Mafla et al., 2018	-	-	-	-	-	-	+	-	01 FACTOR	-
L, Medina-Paz et al ., 2016	-	-	-	+	-	-	-	+	02 FACTOR	LOW RISK
K, Teshigawara et al., 2008	-	-	-	+	-	-	-	-	01 FACTOR	-
R, Sharma et al., 2014	-	-	-	+	-	-	-	-	01 FACTOR	-

JE, Ferreiro et al., 1987	+	-	-	-	-	-	-	-	01 FACTOR	-
I, Quiquandon et al., 1997	-	-	-	-	-	-	-	+	01 FACTOR	-
J, Pedro-Botet et al., 1993	-	-	-	-	-	-	-	+	01 FACTOR	-
Y, Hayashi et al, 2008	-	-	-	-	-	-	-	-	0	-
T, Nagashima et al., 2009	-	-	-	+	-	-	-	-	01 FACTOR	-
H, Yu et al., 2009	-	-	-	-	-	-	-	-	0	-
A.J.O., Davis et al., 2021	-	+	-	+	-	-	-	-	02 FACTOR	LOW RISK
AN, Baer et al., 2012	+	-	-	-	-	-	-	-	01 FACTOR	-
V, Ooms et al., 2005	-	+	-	-	-	-	-	-	01 FACTOR	-
M, Matsuda et al., 2007(2)	-	-	-	+	-	-	-	-	01 FACTOR	-
IO, Kara et al., 2004	+	+	-	+	-	-	-	-	03 FACTOR	MIDDLE RISK
T, Ogihara et al., 1995	-	-	-	+	+	-	-	-	02 FACTOR	LOW RISK
K, Matsuo et al., 2013	-	-	-	+	-	-	-	-	01 FACTOR	-
T, Seeliger et al., 2020	-	-	-	+	-	-	-	-	01 FACTOR	-

X, Xu et al., 2018	-	-	-	+	-	-	+	-	02 FACTOR	LOW RISK
EP, Flanagan et al., 2013	-	-	-	+	--	-	-	-	01 FACTOR	-
P, Cacoub et al., 1996	+	+	-	-	-	-	+	-	03 FACTOR	MIDDLE RISK
T, Isono et al., 2021	-	-	-	+	-	-	-		01 FACTOR	-
SJC, Shan et al., 2009 (2)	-	-	-	-	-	-	-		0	-
Y, Horita et al., 2000	-	-	-	+	-	-	-	+	02 FACTOR	LOW RISK
CJ, Cheng et al., 2005 (2)	-	-	-	+	+		+		03 FACTOR	MIDDLE RISK

FIGURE 1. Study screening process

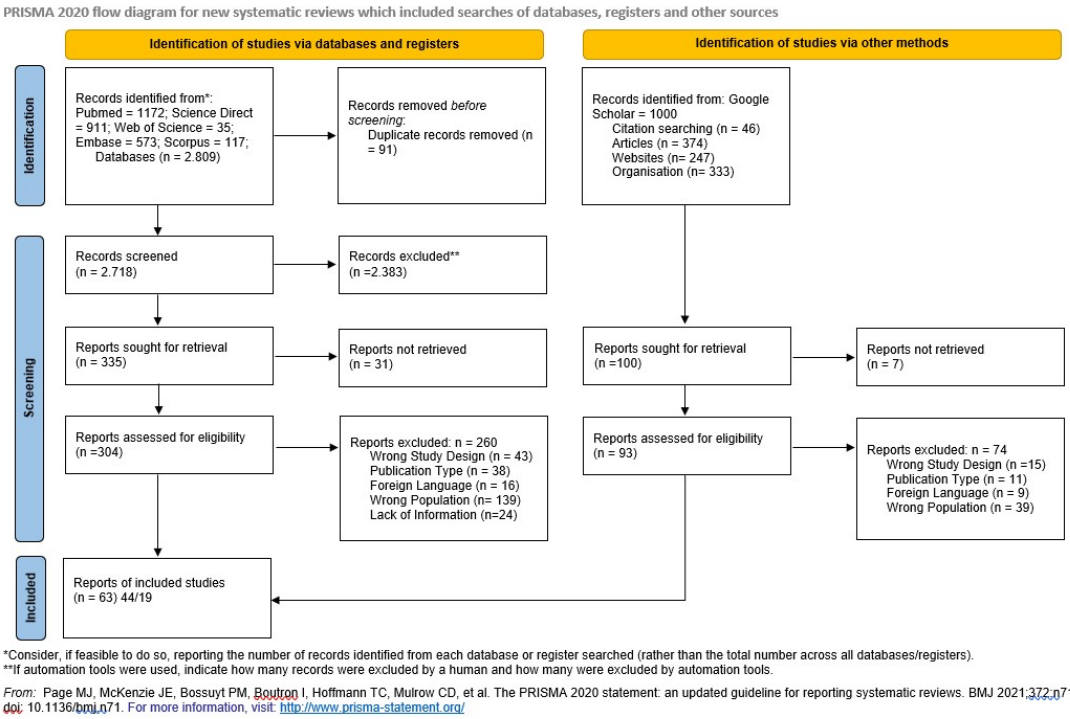


FIGURE 2. Graphic showing countries with cases of Sjögren Syndrome described in the literature associated with the number of cases in each country.

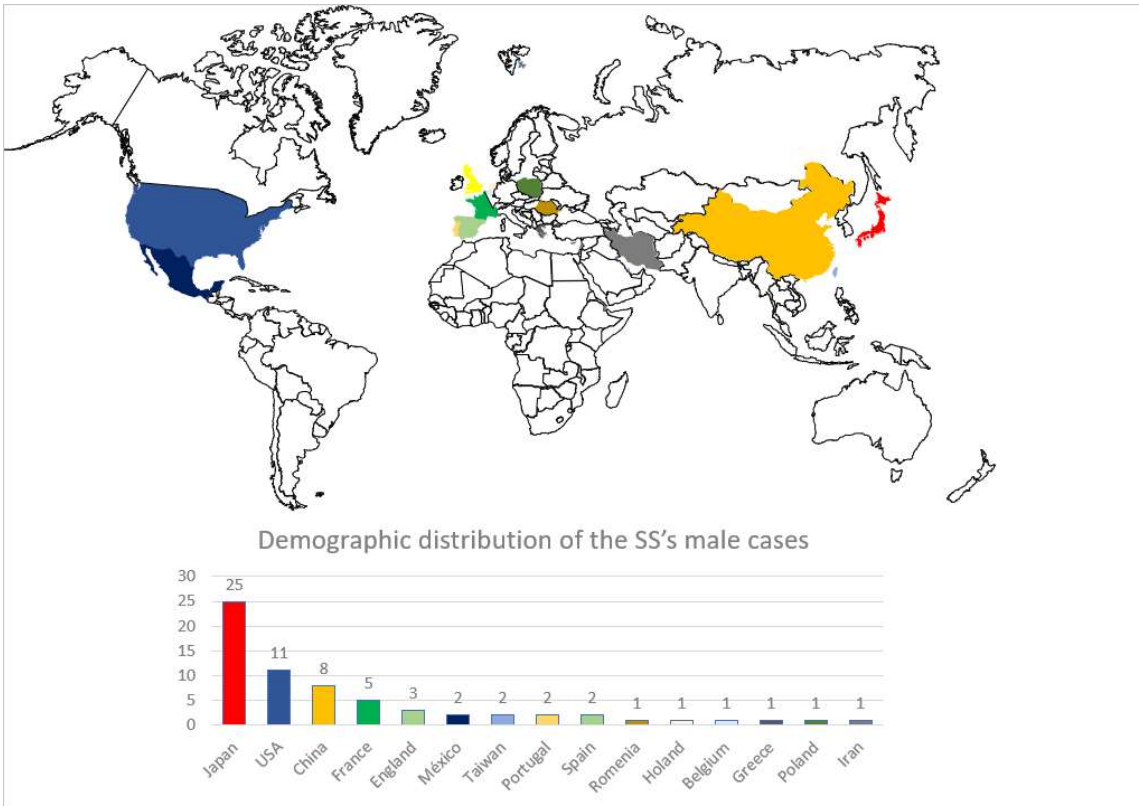


FIGURE 3. Risk of bias analysis chart for each article, according to the Joanna Briggs Institute Critical Appraisal Checklist.

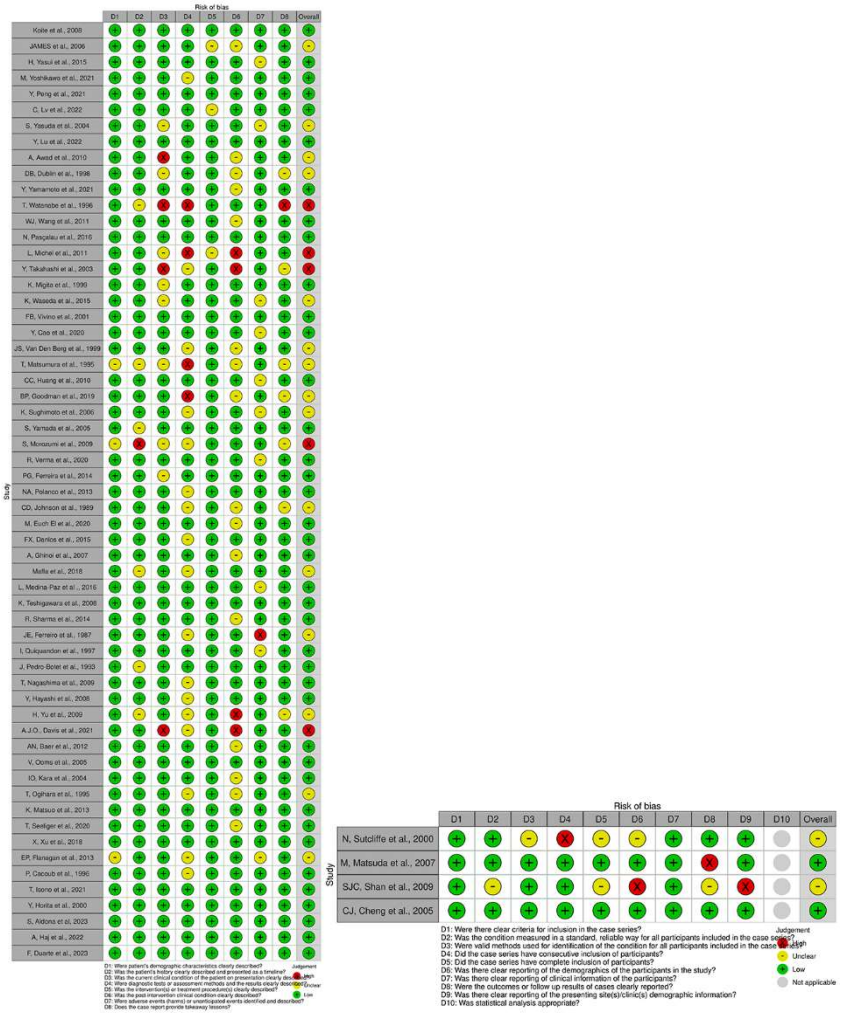


FIGURE 4. Chart of the summarized risk of bias analysis, according to the Joanna Briggs Institute Critical Appraisal Checklist.

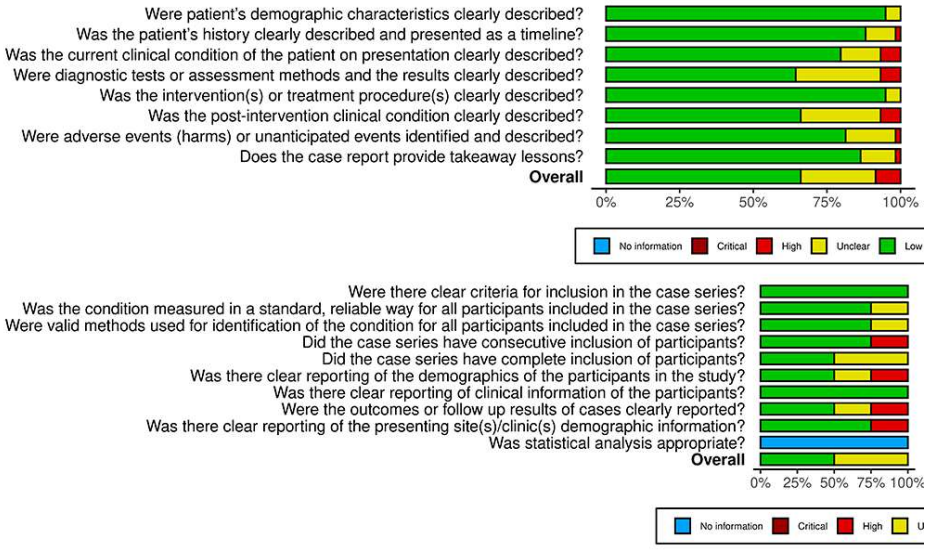
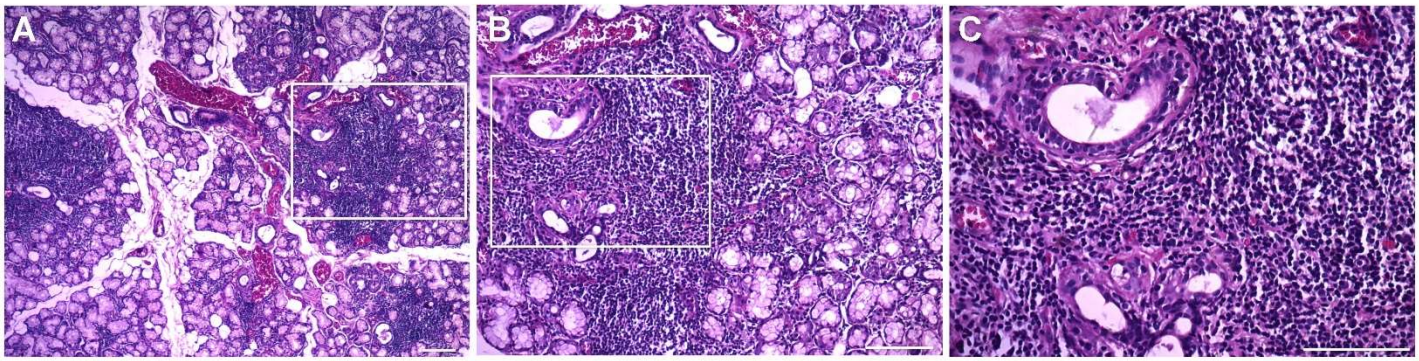


FIGURE 5. Lip biopsy showing a minor salivary gland lymphocytic infiltrate around a ductulus. Epithelial hyperplasia is visible around the ductulus. Hematoxylin & Eosin original magnification 10× (A), 20× (B) and 40× (C).



3 CONCLUSÃO

Com base nas informações obtidas através do estudo apresentado nesta dissertação podemos concluir que:

- Os resultados dessa pesquisa oferecem uma compreensão mais profunda sobre os aspectos clínicos que mais afetam os homens com síndrome de Sjögren
- Esses resultados mostram como pacientes idosos estão mais propícios a desenvolver aspectos glandulares do que adultos jovens
- Os adultos jovens apresentam maior envolvimento extra glandular quando comparado com pacientes idosos, mas apresentam menor predominância de síndrome sicca
- Os homens tendem a desenvolver maior acometimento do sistema nervoso, com predominância de neuropatias sensoriais e craniais envolvendo o sistema nervoso periférico e ataxia envolvendo o sistema nervoso central.

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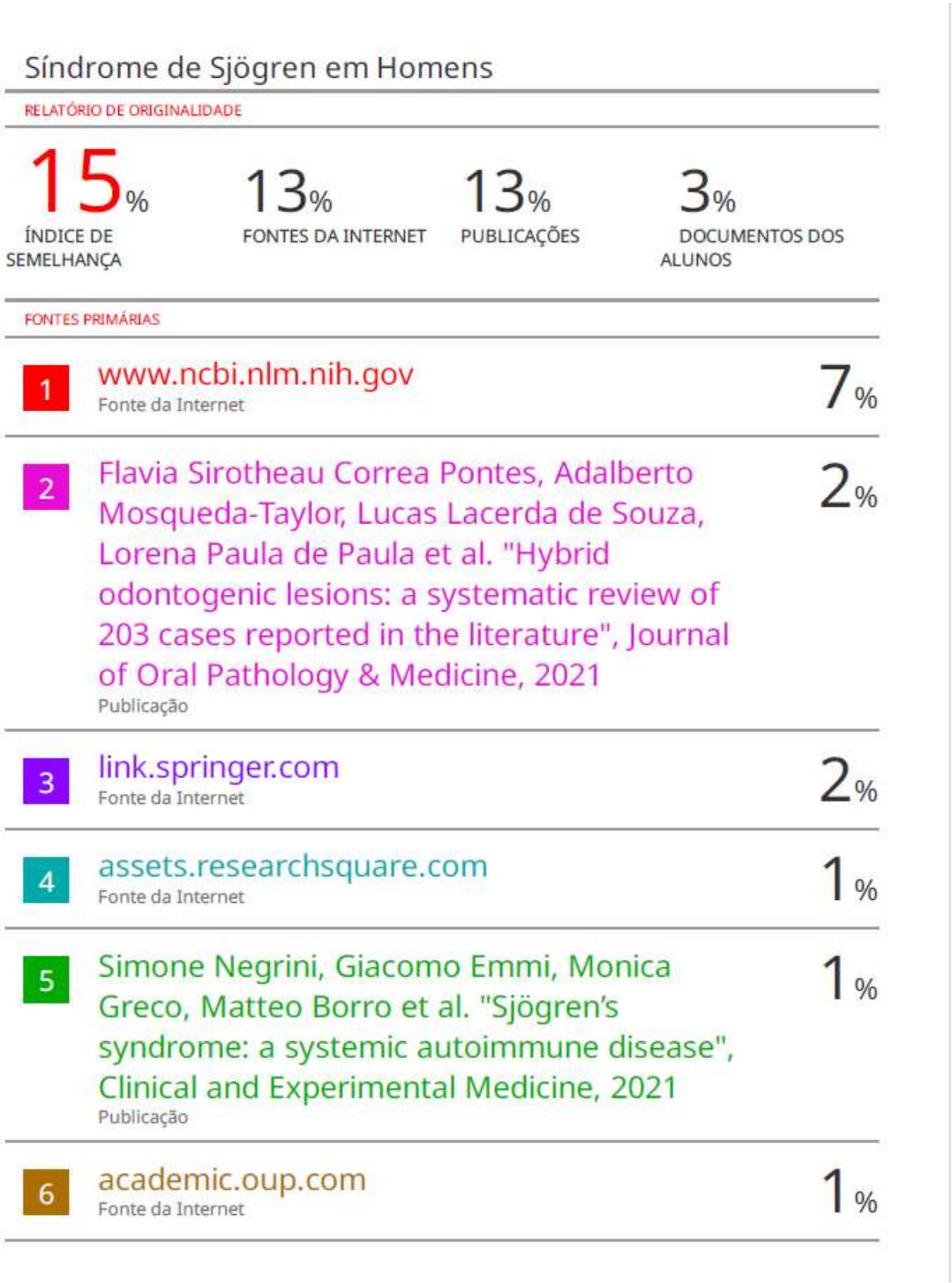
ANEXOS

ANEXO 1 – Verificação de originalidade e prevenção de plágio



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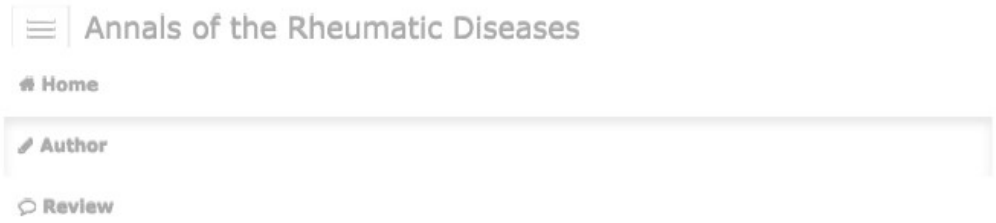

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Title
Sjögren's Syndrome in Male patients: A Systematic Review of Literature on the Clinical Aspects, Complications and Therapeutic Approach

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