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Recommendations for evaluation and diagnosis of extra-glandular manifestations of primary sjogren syndrome: results of an epidemiologic systematic review/meta-analysis and a consensus guideline from the Brazilian Society of Rheumatology (articular, pulmonary and renal)

Virginia Fernandes Moça Trevisani[1,2], Alisson Pugliesi[3*], Sandra Gofinet Pasoto[4], Maria Lucia Lemos Lopes[5], Lissiane Karine Noronha Guedes[4], Samira Tatiyama Miyamoto[6], Marilena Leal Mesquita Silvestre Fernandes[7], Sonia Cristina de Magalhães Souza Fialho[8], Aysa César Pinheiro[9], Laura Caldas dos Santos[10], Simone Appenzeller[3], Tania Fidelix[10], Sandra Lúcia Euzébio Ribeiro[11], Danielle Christinne Soares Egypto de Brito[12], Tatiana Nayara Libório-Kimura[11], Maria Carmen Lopes Ferreira Silva Santos[13], Diego Ustárroz Cantali[14], Juliana D'Agostino Gennari[15], Vinicius Tassoni Civile[1], Ana Carolina Pereira Nunes Pinto[1], César Ramos Rocha-Filho[1], Fabiola Reis Oliveira[16], Aline Pereira da Rocha[1] and Valeria Valim[17]

Abstract

Sjogren's Syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and other organs, associated with sicca syndrome but also with systemic involvement with varying degrees of severity. Despite their importance, these systemic manifestations are not routinely evaluated and there is no homogenous approach to their diagnosis or evaluation. To close this gap, a panel of experts from the Brazilian Society of Rheumatology conducted a systematic review and meta-analysis on the identification of epidemiologic and clinical features of these manifestations and made recommendations based on the findings. Agreement between the experts was achieved using the Delphi method. The first part of this guideline summarizes the most important topics, and 11 recommendations are provided for the articular, pulmonary, and renal care of SS patients.

*Correspondence: alissonvigano@gmail.com

[3] Departamento de Ortopedia, Reumatologia e Traumatologia, Universidade Estadual de Campinas, R. Tessália Vieira de Camargo, 126 - Cidade Universitária, Campinas, SP CEP: 13083-887, Brazil
Full list of author information is available at the end of the article

Background

Primary Sjögren's syndrome (pSS) is a systemic, chronic, immune-mediated inflammatory disease, characterized by the presence of lymphocytic infiltrate in the salivary and lacrimal glands, autoantibodies, and glandular disorders clinically expressed by xerostomia and

xerophthalmia [1]. Systemic manifestations occur in around 40–50% of patients and can be severe, showing an association with the prognosis and development of lymphoma [2]. The assessment of disease activity is performed using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), which evaluates the systemic involvement of pSS [3]. Despite its importance, these manifestations are not routinely evaluated and there is no homogenous approach to the diagnosis or evaluation.

Methods

We conducted a systematic review of the diagnosis and prevalence of systemic manifestations in patients diagnosed with pSS according to the 2002, 2012, and 2016 classification criteria [4–6], following the recommendations proposed by the Cochrane Collaboration Handbook [7]. Questions were asked about the diagnosis and prevalence of different systemic manifestations in pSS. An individualized search strategy on the different systemic manifestations was performed (Additional file 1) for the Cochrane Central, MEDLINE, Embase, and LILACS databases. The strategy was conducted with no restriction of language or publication date. Observational studies in which the primary research question concerned the diagnosis and prevalence of individualized systemic manifestations were included. Duplicate articles found in different databases were excluded, as were those not focused on diagnosis and prevalence. For evaluating the diagnosis of systemic manifestations, diagnostic accuracy studies were preferably considered. In the absence of this type of studies, we considered for inclusion any observational study reporting the use of diagnostic tests for detecting systemic manifestations in pSS. For estimating the prevalence of systemic manifestations, studies specifying the number of patients affected by the systemic manifestation and the total number of pSS patients included in the studies were considered. The statistical heterogeneity detected in these metaanalyses was already expected by our review group, as it is commonly found in prevalence meta-analyses, and since these recommendations were planned to address a large number of patients characteristics and all the available classification criteria (2002, 2012, and 2016), and methods to evaluate the systemic manifestations. Risk of bias was assessed (Additional file 2) using the Joanna Briggs Institute Prevalence Critical Appraisal Tool [8]. To the Meta-Analysis, we pooled clinical data by extracting the number of events and total patients to perform proportion meta-analysis. To estimate an overall proportion and present pooled results with their respective 95% confidence intervals (CI), we used a generalized linear mixed model (GLMM) method with a random-effects model for pooling the results. Results were calculated using logit transformation in the "meta" and "metafor" packages from R software (version 3.6.1). Based on data from systematic review and Meta-Analysis, recommendations were done by Rheumatologists from Sjogren Syndrome Committee of Brazilian Society of Rheumatologist. Agreement between these recommendations was achieved in online and presential meetings and the Delphi Method was used.

Results

Figure 1 summarizes the steps of the systematic review. Important topics were described in sections reserved to each extra glandular manifestation. Based on it and in agreement between the panel of specialists, 11 recommendations were made (Table 1). And the Forest Plots of prevalence Meta-Analysis were showed at the end of each manifestation topic. In Additional file 1, we summarize: description of all the studies of prevalence; the terms used strategies used to the systematic review; tables and charts to evaluation of the renal manifestations; evaluation of biases of the studies that were selected.

Evaluation of systemic manifestations

Recommendation

(1) The ESSDAI should be used as a measurement tool for diagnosing and evaluating the activity of systemic manifestations.

Level of Agreement: 88%, Strength of Recommendation: conditional recommendation for using in the ESSDAI manifestations

The ESSDAI is an activity assessment tool for pSS, created in 2009 by a group of European and North American specialists. It consists of 12 domains and includes systemic involvement in pSS (articular, cutaneous, muscular, ganglionic, pulmonary, renal, central and peripheral nervous systems, hematological and biological manifestations, in addition to assessing constitutional and glandular symptoms). Each domain is classified into between 3 and 4 levels, according to the activity observed at the time of the assessment. The ESSDAI has a score ranging from 0 to 123, with low activity < 5; moderate activity between 5 and 13; and high activity ≥ 14. The ESSDAI is used mainly in the evaluation of clinical trial participants, but there is a worldwide effort to apply the instrument in clinical practice [3]. Despite of that, twelve percent of our panelists didn't agree with these first recommendations. Possible reasons for this disagreement are the requirement of complex exams (as chest images or electroneuromyography) and the lack of evaluation of some systemic manifestations commonly presented in pSS (such as cardiovascular disease and Raynaud´s phenomenon).

Articular manifestations

Recommendation

(2) Inflammatory arthralgia and/or non-erosive arthritis are frequent manifestations in pSS that should be classified according to the number and location of joints involved. Cases of suspected arthritis should be confirmed by physical examination and, if necessary, imaging tests.

Level of Agreement: 100%, Strength of Recommendation: Strong

Arthralgia is a symptom characterized by joint pain without inflammatory signs. In the ESSDAI, the presence of arthralgia in the hands, wrists, ankles, and feet, accompanied by morning stiffness (> 30 min.), is classified as low activity. Arthritis is the inflammation of one or more joints, characterized by arthralgia, heat, erythema, and edema on physical examination. The classification of arthritis activity in the ESSDAI is performed according to the number of joints involved (moderate: 1 to 5 joints; high: 6 or more joints) [9, 10]. According to the international multicenter registry Big Data Sjögren Consortium, the ESSDAI domain with the highest frequency of active patients at diagnosis is the biological domain (51.0%), followed by the articular domain (37.7%)—the same pattern is observed in different ethnicities and continents. In this study, 3,541 (37.9%) women and 231 (35.3%) men, from a total of 10,007 patients, presented joint impairment at diagnosis according to the ESSDAI [11].

The prevalence of joint impairment, including both arthralgia and arthritis, ranges from 13% [12] to 98% [13], while the prevalence of arthritis alone ranges from 0 [14] to 48% [15] (Additional file 1: Table A). The results of our meta-analysis have showed a prevalence of joint impairment of 59% (95% CI 48–69%), with Arthritis affecting 19% (95%CI 15–23%) of patients with pSS (Figs. 2, 3).

The joints most affected by arthritis are the proximal interphalangeal (PIP) (22% [16] to 91% [17]), metacarpophalangeal (MCP) (22% [18] to 59% [17]), and wrist (28% [16] to 45% [17]) (Additional file 1: Table A). Anti-CCP was evaluated in 28 studies, with positivity ranging from 0 [19] to 33% [20]. Bone erosions were observed by high resolution ultrasound (US) of hands and wrists in approximately 27% of pSS patients compared with 7% of healthy controls with comparable sex,

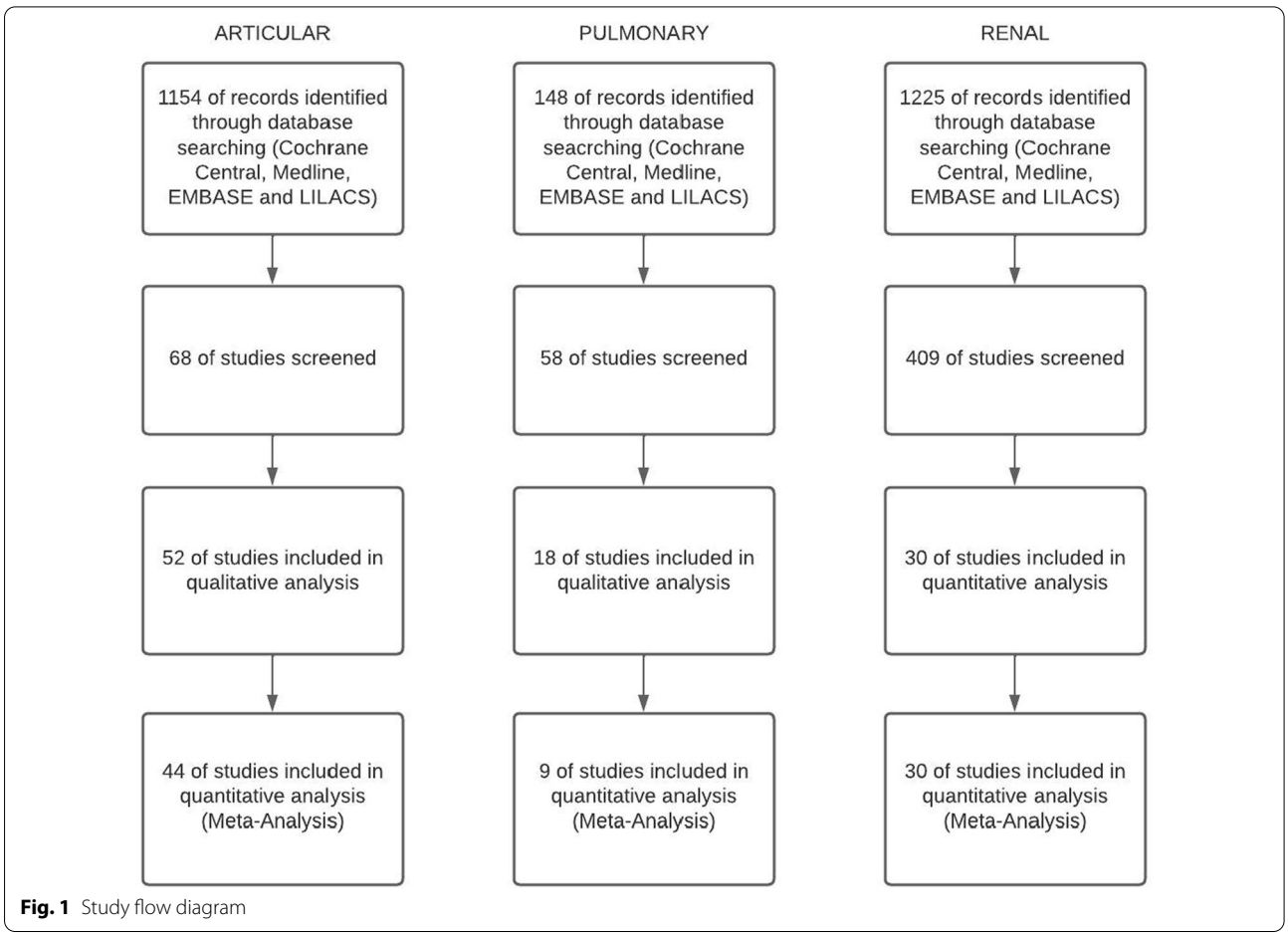

Fig. 1 Study flow diagram

Table 1 Summary of recommendations

(1) The ESSDAI should be used as a measurement tool for diagnosing and evaluating the activity of systemic manifestations. (Level of Agreement: 88%, Strength of Recommendation: conditional recommendation)
(2) Inflammatory arthralgia and/or non-erosive arthritis are frequent manifestations in pSS that should be classified according to the number and location of joints involved. Cases of suspected arthritis should be confirmed by physical examination and, if necessary, imaging tests. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(3) Respiratory impairment in pSS is frequent, polymorphic, and may be associated with decreased quality of life, development of lymphoma, and worse prognosis. Thus, we recommend that every patient should be accurately assessed for the presence of respiratory signs and symptoms at diagnosis and follow-up visits. For the confirmation of pulmonary involvement, the most frequently used tests are high-resolution chest tomography and the complete pulmonary function test. Level of Agreement: 100%, Strength of Recommendation: Strong
(4) Considering that pulmonary involvement can be asymptomatic, we recommend that all patients be evaluated by these tests at least once during their evolution, especially those with risk factors for lung function impairment, such as the male sex, presence of rheumatoid factor, antinuclear antibodies (ANA), anti-Ro/SSA and anti-La/SSB, hypergammaglobulinemia, lymphopenia, Raynaud's phenomenon, peripheral arthritis, changes in the pulmonary function test (decreased FVC and FEV1), smoking history, advanced age, gastrointestinal involvement, and focal score ≥ 4 on the labial salivary gland biopsy. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(5) For patients with pulmonary involvement, monitoring with high-resolution chest tomography and the complete pulmonary function test is recommended at least every two years (as proposed in ESSDAI) or earlier, if necessary, according to the clinical judgment. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(6) Renal manifestations are underdiagnosed, as they do not often present evident symptoms; thus, an adequate and systematic assessment of renal function is required. When investigating, we must consider the two types of renal impairment: distal tubulointerstitial nephritis (Type I) and proximal tubulointerstitial nephritis (Type II), with or without renal tubular acidosis (RTA); and glomerulonephritis (GN).; (Level of Agreement: 100%, Strength of Recommendation: Strong)
(7) Initial and follow-up evaluations are recommended even in asymptomatic patients, with the measurement of serum creatinine, glomerular filtration rate (GFR), type I urine (pH and density always assessed in fresh morning urine), serum electrolytes (Na, K, Cl), venous blood gases (HCO3, blood pH), and plain abdominal radiography or renal bladder ultrasound. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(8) The diagnosis of tubulointerstitial involvement requires an active search for RTA signs and symptoms: cramps, muscle weakness, hypokalemic periodic paralysis, renal lithiasis, nephrocalcinosis, polyuria, polydipsia, nocturia, nephrogenic diabetes insipidus, bone pain, and pathological fractures secondary to osteomalacia. (Additional file 1: Chart S2) In these cases, in addition to the initial laboratory evaluation, serum calcium and phosphorus, 24-h proteinuria, or the protein creatinine index (PCI) should be assessed. Hypocitraturia is a frequent and early finding in distal tubular dysfunction, being a risk factor for urolithiasis and nephrocalcinosis (Level of Agreement: 100%, Strength of Recommendation: Strong)
(9) Distal renal tubular acidosis (dRTA) is secondary to tubulointerstitial nephritis (TIN) when urinary pH > 5.5 in the presence of metabolic acidosis, with normal blood anion gap and positive urinary anion gap. If urinary pH > 5.5 in the absence of metabolic acidosis, incomplete distal renal tubular acidosis (idRTA) should be considered. Urinary acidification tests with ammonium chloride or furosemide and hydrocortisone confirm the diagnosis if urinary pH remains > 5.5. If these tests are not available, the patient should be monitored more frequently. In cases of urinary pH > 7.5, proximal renal tubular acidosis (pRTA) should be suspected, which may course with normal glycosuria and glycemia, hyperphosphaturia, hyperuricosuria, aminoaciduria, hypophosphatemia, and hypouricemia. Assessment of these tests should be required. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(10) Glomerular involvement is much less frequent, but presents evident symptoms in most cases and may be associated with cryoglobulinemia. (Additional file 1: Chart S2) Laboratory findings are suggestive of impaired kidney function, proteinuria, hematuria, leukocyturia, cylindruria, and hypocomplementemia. Assessment of this test should be required. (Level of Agreement: 100%, Strength of Recommendation: Strong)
(11) Renal biopsy is indicated for suspected glomerulopathies, cases of tubulointerstitial nephritis with kidney failure or severe electrolyte imbalance, and differential diagnosis. (Level of Agreement: 100%, Strength of Recommendation: Strong)

age, and ethnicity [21]. Anti-CCP values three times higher than the upper reference limit were associated with the presence of bone erosions [21]. The characteristics of erosions and the presence of the Power Doppler signal on US of hands and wrists can help in the differential diagnosis between pSSp and RA [21]. In pSS, erosions were mostly of small size, contrasting with moderate/large size in RA, and positive Power Doppler synovitis predominated in RA [21]. The finding of bone erosion in the second MCP joint on US showed sensitivity of 28.8% and specificity of 100% to distinguish patients with Sjögren's syndrome secondary to rheumatoid arthritis from patients with pSS. As for the presence of erosion in at least one of the joints, the sensitivity and specificity were 83.3% and 82.3%, respectively [22]. Studies evaluating articular symptoms with US in pSS patients showed a predominance of synovitis in the knees (76%) [22], wrists (37% [23] to 76% [22]), and hand joints (25%) [23]. Nineteen percent of patients had synovial hypertrophy (MCP or PIP) [13]; 42% had joint effusion (MCP or PIP) [13]; and 13% [13] to 28% [21] had bone erosions (wrist, MCP, and/or PIP). Considering the number of joints evaluated, synovial hypertrophy was present in 48% of the knees [24], 30% of the wrists [23], and 3% [23] to 16% [25] of the hand joints. Joint effusion was evident in 44% of the wrists [23] and 6% of the knees [24]. Magnetic resonance imaging (MRI) of hands and wrists in

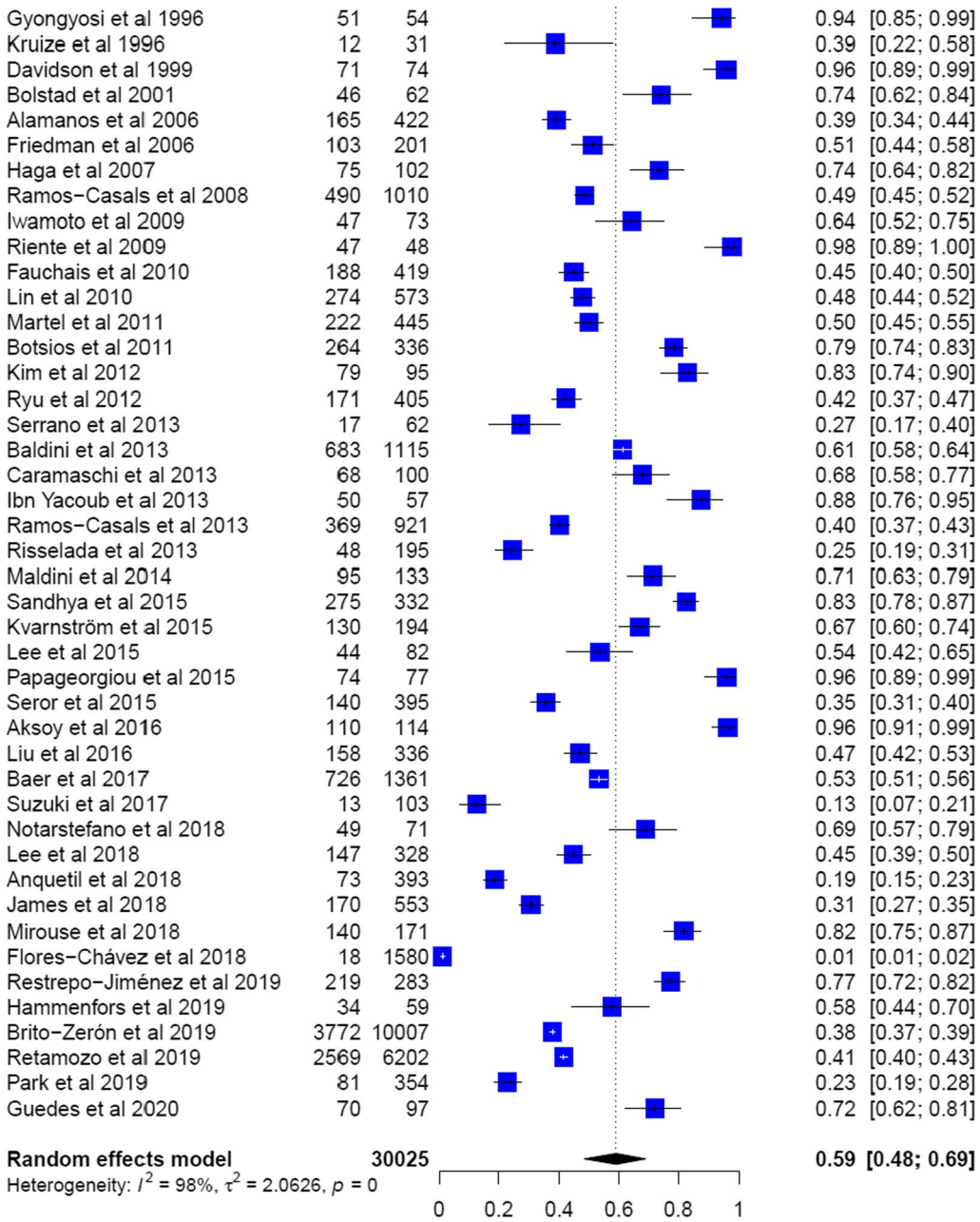

Fig. 2 Meta-analysis of prevalence of articular manifestations in patients with pSS

five patients with severe polyarthritis demonstrated moderate erosive lesions in only two individuals, with progression to rheumatoid arthritis occurring in one of them [26]. In another study with 20 patients, only 1 (5%) had bone erosion [27]. Studies that evaluate the psychometric properties of joint assessment methods or compare them in pSS are scarce.

Pulmonary manifestations

Recommendations

(3) Respiratory impairment in pSS is frequent, polymorphic, and may be associated with decreased quality of life, development of lymphoma, and worse prognosis. Thus, we recommend that every patient should be accurately

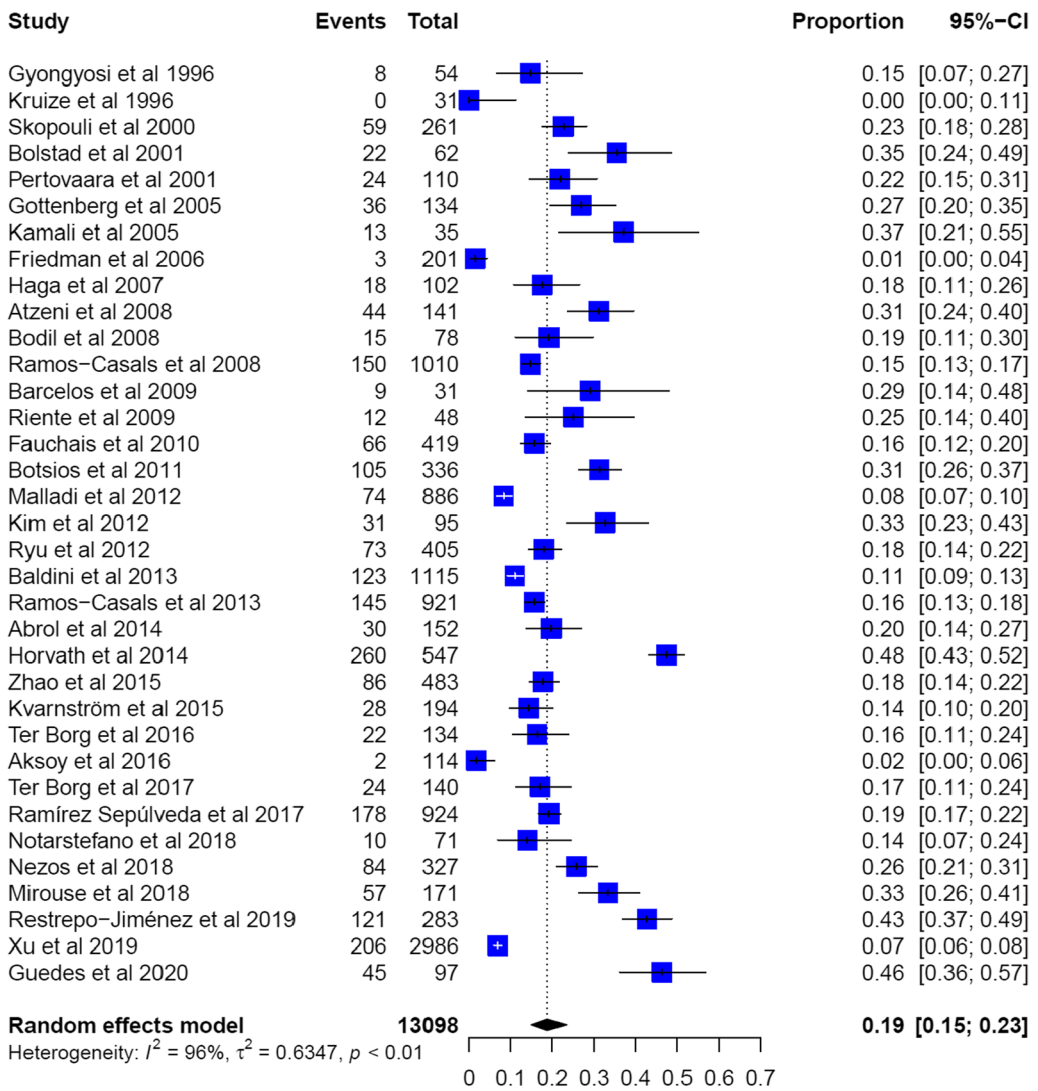

Fig. 3 Meta-analysis of the Arthritis in patients with Sjogren's syndrome

assessed for the presence of respiratory signs and symptoms at diagnosis and follow-up visits. For the confirmation of pulmonary involvement, the most frequently used tests are high-resolution chest tomography and the complete pulmonary function test.

Level of Agreement: 100%, Strength of Recommendation: Strong

(4) Considering that pulmonary involvement can be asymptomatic, we recommend that all patients be evaluated by these tests at least once during their evolution, especially those with risk factors for lung function impairment, such as the male sex, presence of rheumatoid factor, antinuclear antibodies (ANA), anti-Ro/SSA and anti-La/SSB, hypergammaglobulinemia, lymphopenia, Raynaud's phenomenon, peripheral arthritis, changes in the pulmonary function test (decreased FVC and FEV1), smoking history, advanced age, gastrointestinal involvement, and focal score ≥ 4 on the labial salivary gland biopsy.

Level of Agreement: 100%, Strength of Recommendation: Strong

(5) For patients with pulmonary involvement, monitoring with high-resolution chest tomography and the complete pulmonary function test is recommended at least every two years (as proposed in ESSDAI) or earlier, if necessary, according to the clinical judgment.

Level of Agreement: 100%, Strength of Recommendation: Strong

Pulmonary manifestations of pSS are common, polymorphic, and present a wide spectrum of severity and a significant impact on patient morbidity and mortality [28–30]. Pulmonary involvement of pSS is symptomatic in approximately 6–27.3% of patients, typically with exertional dyspnea and dry cough and a predominance in females [30–35]. The prevalence of pulmonary manifestations, however, may vary widely 0–65%, as they are influenced by the selection of patients, pSS classification criteria, presence or absence of respiratory symptoms, and different methods of assessing pulmonary involvement (Additional file 1: Table B) [30, 33, 36–40].

Studies with high-resolution computed tomography (HRCT) performed systematically in pSS (even when asymptomatic) have shown pulmonary involvement in 42–65% of patients. The association with the pulmonary function test and/or bronchoalveolar lavage (BAL) increases pulmonary alterations in pSS to 75% [38–41].

Pulmonary manifestations of pSS include airway diseases, interstitial lung disease (ILD), pulmonary lymphoma, pulmonary embolism, pulmonary hypertension, and more rare disorders. We emphasize that airway diseases and ILD are the most common manifestations and can occur in association. We also point out that infections or drug-induced pneumonia should always be considered in the differential diagnosis of pulmonary conditions [42].

We identified a prevalence of 21% (95% CI 12% to 34%) of ILD in pSS (Fig. 4). Several histopathological patterns of ILD have been described in pSS: non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) (which leads to a worse prognosis), organizing pneumonia, and lymphocytic interstitial pneumonia (LIP) [33, 42, 43]. The results of our meta-analysis of prevalence of the different types of ILD in are: non-specific interstitial pneumonia (NSIP) affects 36% (95% CI 30–43%) (Fig. 5), usual interstitial pneumonia (UIP) affects 14% (95% CI 7–26%) (Fig. 6), lymphocytic interstitial pneumonia (LIP) 6% (95% CI 3–10%) (Fig. 7), organizing pneumonia 6% (95% CI 3–12%) of patients (Fig. 8) and Indeterminate pattern in 14% (95% CI 8–24%) (Fig. 9).

NSIP is the most commonly observed ILD pattern, presenting a characteristic tomographic aspect and a good histopathological correlation; therefore, a routine lung biopsy is not recommended. However, radiographic findings suggestive of lymphomas, such as consolidation, large nodules, and pleural effusion, require invasive investigation [36, 44].

In a study of 85 patients with pSS, followed from 1976 to 2005, the annual incidence of ILD (diagnosed through clinical data, a pulmonary function test, X-ray, high-resolution chest CT, and thoracoscopic or open lung biopsy) was 10% (±3%) 1 year after the diagnosis of pSS and 20% (±4%) 5 years after [45].

Some reports suggest that pulmonary involvement in pSS is mild and stable [46], while others describe a disease with significant mortality: risk of death of 16% in 5 years [47, 48] and 4 times greater in 10 years [33, 37]. In addition, the presence of lymphocytic alveolitis detected by BAL was associated with a higher occurrence of death in pSS [49].

Lung involvement may precede the diagnosis or dry symptoms of pSS in up to 10% of patients [50–52] and pulmonary adenocarcinoma (90%) has an increased incidence in pSS compared to the normal population [53].

Thus, in patients with pSS, pulmonary involvement should be investigated and monitored regularly, according to the severity of the clinical framework. The use of screening in asymptomatic patients is still under question, but we know that HRCT offers high sensitivity and specificity for the diagnosis and that a complete pulmonary function test detects extra cases (15%) [33].

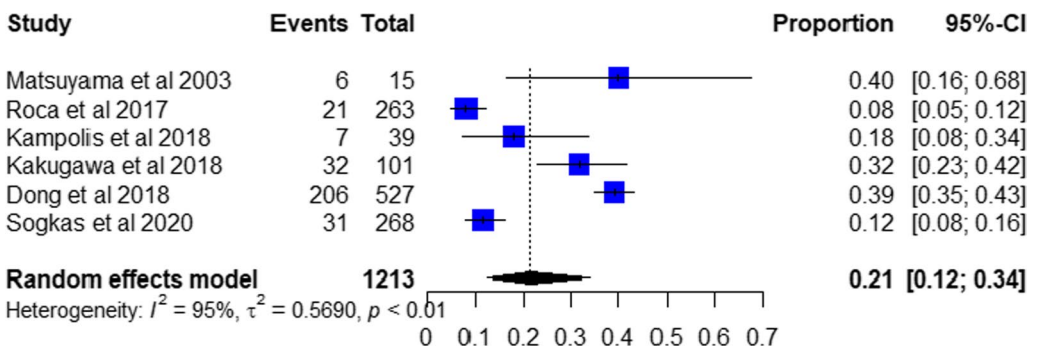

Fig. 4 Meta-analysis of the General Interstitial Lung Disease in patients with Sjogren's syndrome

Forms of pulmonary involvement and clinical manifestations in pSS

Airway disease is considered the most frequent form of pulmonary involvement in pSS [32], with impairment of upper and lower airways by lymphocytic infiltration, with a predominance of CD4+T lymphocytes and the destruction of the exocrine glands of the airways. Its main symptom is a nonproductive cough, which can result from xerotrachea and xerobronchitis and impact patients' quality of life [30]. When it reaches the lower

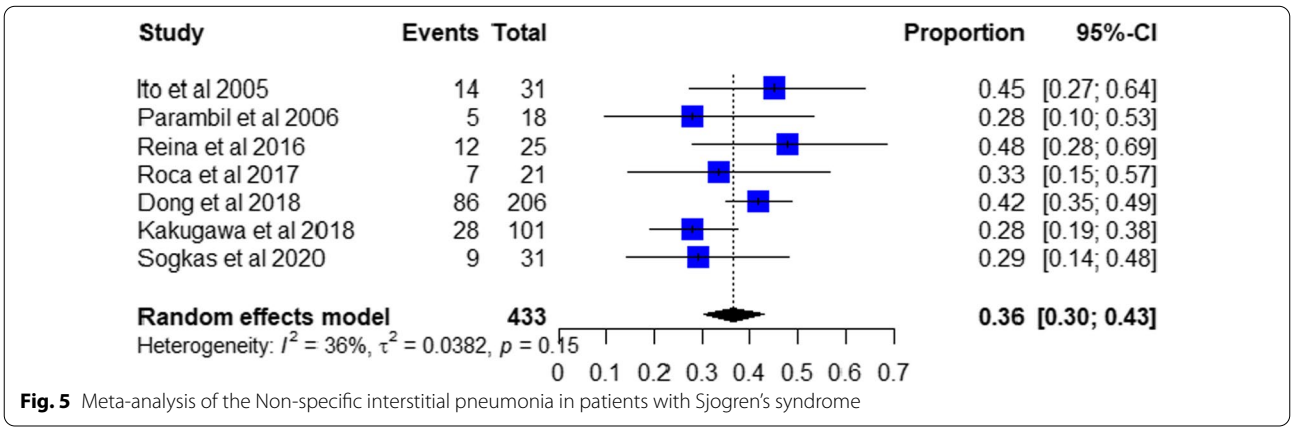

Fig. 5 Meta-analysis of the Non-specific interstitial pneumonia in patients with Sjogren's syndrome

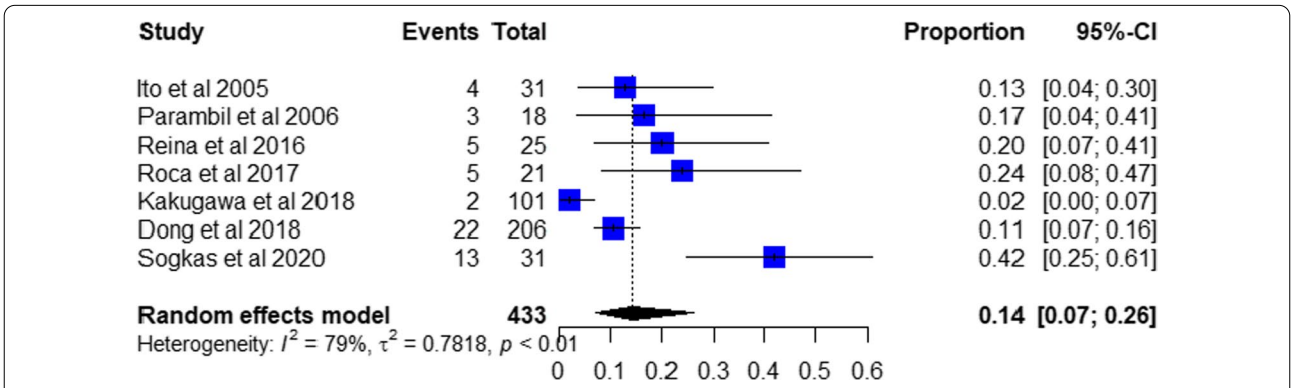

Fig. 6 Meta-analysis of the usual interstitial pneumonia in patients with Sjogren's syndrome

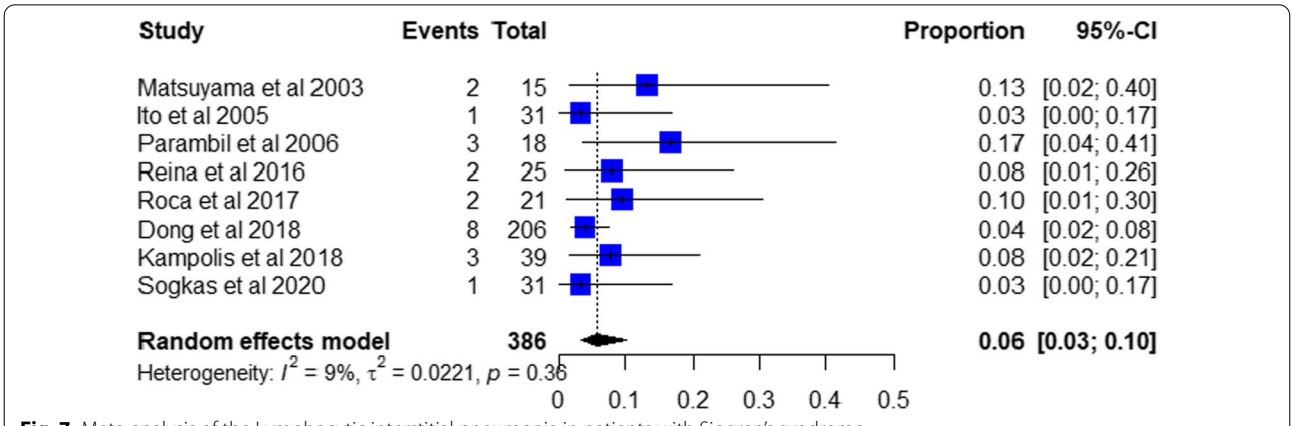

Fig. 7 Meta-analysis of the Lymphocytic interstitial pneumonia in patients with Sjogren's syndrome

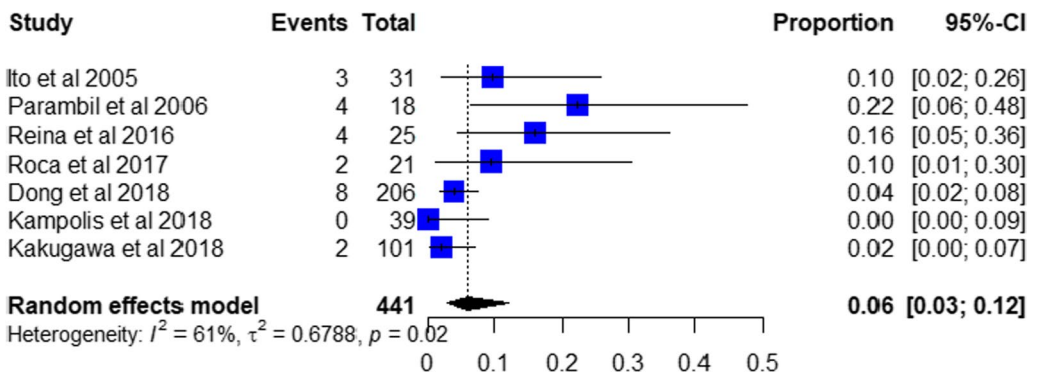

Fig. 8 Meta-analysis of the Organizing pneumonia in patients with Sjogren's syndrome

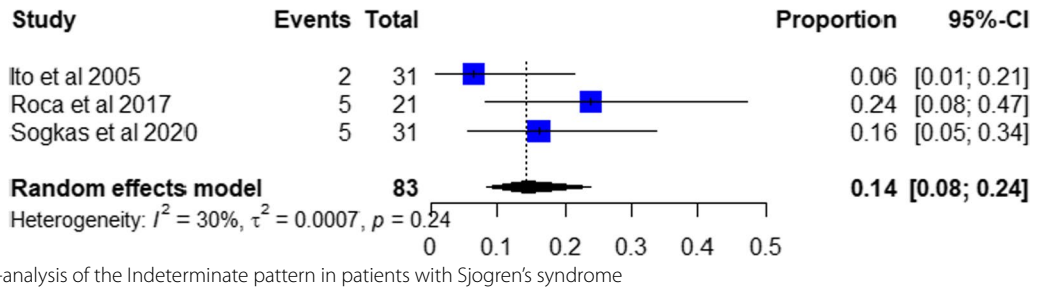

Fig. 9 Meta-analysis of the Indeterminate pattern in patients with Sjogren's syndrome

airways, it can also cause dyspnea and wheezing [29, 30, 42].

Inflammation of the bronchioles (bronchiolitis) is the most frequent lower airway involvement in pSS [30, 47] and may present alone or in combination with ILD. Biopsy studies show a 12% prevalence of bronchiolitis in pSS [47]; however, this rate can vary widely from 9.7 to 58.4% with the use of HRCT and PFT (Additional file 1: Table B). The most common histological pattern is follicular bronchiolitis, which is characterized by the presence of hyperplastic lymphoid follicles with germinal centers [48, 54, 55]. Permanent airway enlargement (bronchiectasis) is also found in 0–43.6% of patients with pSS. Its clinical manifestations include a productive cough, wheezing, dyspnea, and even hemoptysis [30]. Our meta-analysis identified bronchiolitis in 35% of patients (95% CI 20–54%) (Fig. 10) and bronchiectasis in 6% (95% CI 0–52%) (Fig. 11).

Interstitial pulmonary involvement can present with dyspnea (94% of cases), cough (67%), chest pain (22%), crackles (67%), and wheezing (17%) [32].

B-cell non-Hodgkin's lymphoma is a major concern in pSS and may comprise primary lung MALT (mucosa-associated lymphoid tissue) lymphoma [30, 56], which has a prevalence of 1–20% in patients with pSS [28, 32, 47, 57]. Symptoms can be nonspecific, such as cough and dyspnea [30, 42]. The main risk factors for the development of lymphoma in pSS are parotid gland enlargement, vasculitic purpura, cryoglobulinemia, hypocomplementemia, and lymphopenia, particularly with a reduction in the CD4+/CD8+ ratio [56, 58].

Pulmonary amyloidosis is a rare complication of pSS that mainly affects women and can cause cough, dyspnea, hemoptysis, and pleuritic chest pain, with a prevalence of 5.5–6.5%in patients with pSS [30, 32, 47, 59, 60].

It should also be noted that sarcoidosis is a differential diagnosis of pSS. However, these diseases can overlap [61], with the frequency of sarcoidosis in pSS being 1–2% [62].

Pulmonary vascular involvement is less frequent but can also be found in patients with pSS, mainly comprising pulmonary hypertension and pulmonary embolism. Pulmonary hypertension in pSS can be caused by pulmonary arterial hypertension, pulmonary veno-occlusive disease, heart valve disease, or ILD [28, 30]. The exact frequency of pulmonary hypertension in pSS is not known. When using echocardiography, signs of pulmonary hypertension can be observed in 12.5–23.4% of patients [63–65].

A higher risk of developing venous thromboembolism was observed in pSS patients compared to the general population [66, 67]. The mechanisms that could explain this high prevalence are still poorly understood, but it is

interesting to note that antiphospholipid antibodies can be detected in patients with pSS [68].

Although less frequent, pleural thickening and pleural effusion are observed in patients with pSS [37, 38, 69]. Finally, rare cases of shrinking lung syndrome without parenchymal changes on the chest CT have been described in pSS [70, 71].

Diagnostic methods of pulmonary involvement in pSS

Subclinical involvement is the most frequent manifestation in pSS. When investigated systematically, that is, in symptomatic and non-symptomatic patients, the prevalence of changes in the pulmonary function test is 43%, including a reduction in forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DLCO) [72, 73]. These changes suggest an inflammatory process in the small airways [74].

Changes on the chest X-ray occur in about 20% of cases of pSS [75]. X-ray findings include bilateral interstitial infiltrate (linear and reticular opacities) in 56–83% of cases [32, 75], bilateral interstitial and alveolar infiltrate (ground-glass opacities) in 22–25% [32, 75], bilateral nodular infiltrate in 11% [32], bilateral consolidative infiltrate in 11–25% [32, 75], honeycombing in 8% [75], and pulmonary cysts in 8% [75].

Comparatively, HRCT changes occur in approximately 50% of patients, most of whom are asymptomatic [75]. This is the most sensitive method for detecting ILD [30] and commonly reveals linear parenchymal opacities and bronchiolar abnormalities [76] in the form of peribronchovascular interstitial thickening (27%), interlobular septal thickening (6–60%), intralobular interstitial thickening (60%), centrilobular abnormalities (67%), reticular opacities (56%), ground-glass opacities (80–89%), lung consolidation (7–56%), honeycombing (17–20%), pulmonary cysts (17–27%), traction bronchiectasis (22–53%), mosaic attenuation (33%), small nodules (30–44%), and large nodules and mass (11–13%) [32, 75].

Recently, a statement [77] on pulmonary manifestations of pSS recommended chest x-ray and PFT as screening tests for pulmonary involvement. Due to the low accuracy of chest radiography to detect ILD and the superiority of CT to this purpose [78, 79], this guideline recommends HRCT as the image preference to detect asymptomatic lung involvement in addition to PFT.

According to tomographic changes, pulmonary involvement can present characteristic patterns of interstitial pneumonia (40% NSIP, UIP, and LIP), bronchiolitis (33% with organizing pneumonia), or LPD (13% lymphoma or LIP) [42, 43, 75].

NSIP appears on a high-resolution chest CT, mainly as linear and ground-glass opacities, sparing the subpleural region and spreading mainly in the lower lobes [80]. UIP

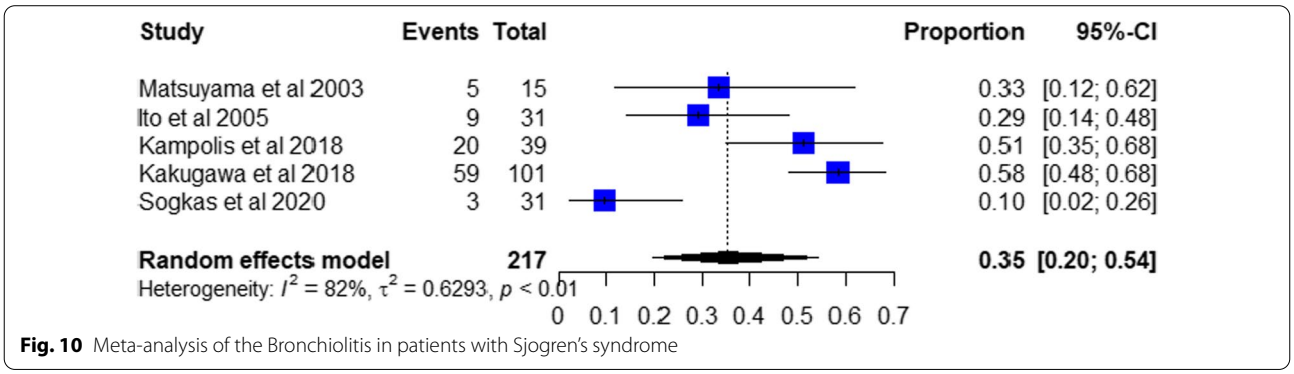

Fig. 10 Meta-analysis of the Bronchiolitis in patients with Sjogren's syndrome

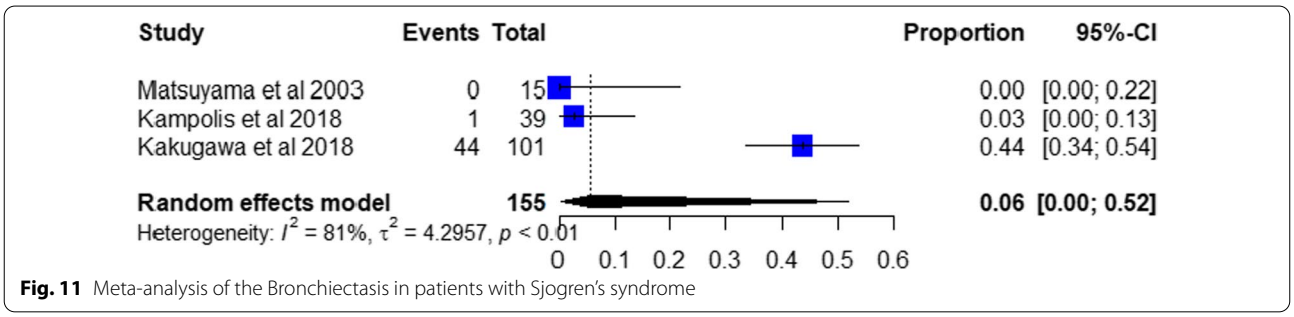

Fig. 11 Meta-analysis of the Bronchiectasis in patients with Sjogren's syndrome

is characterized by interlobular septal thickening, honeycomb, and traction bronchiectasis, spreading mainly in the lower lobes and in the lung periphery [80]. Organized pneumonia is characterized by areas of heterogeneous consolidation, ground-glass opacities, and centrilobular changes [28, 29]. Mixed HRCT patterns can be observed: NSIP with OP (43.9%), NSIP mixed with UIP (35.4%), and NSIP mixed with LIP (19.5%) were the most frequent [81].

LIP is considered the most classic form of ILD in pSS, but NSIP is reported as the most frequent histological subtype [32, 35, 47, 82–84] The histological finding of LIP includes peribronchiolar lymphocytic infiltration leading to interlobular septal thickening, bronchovascular bundles, centrilobular changes, subpleural nodules, ground-glass opacities, and stenotic bronchioles that result in the formation of thin-walled pulmonary cysts and bronchiectasis [42, 85–87]. Parenchymal cysts may also occur in lymphoma and pulmonary amyloidosis [48]. In these cases, they are commonly associated with solitary or multiple nodules [28, 42]. In lymphoma, masses with areas of consolidation, ground-glass opacities, pleural effusions, and lymphadenomegaly are described [30, 42]. For differential diagnosis, a lung biopsy is usually required [30].

It is worth mentioning that there was good agreement between the histological pattern and HRCT findings [72]. However, tomographic abnormalities often do not correlate with respiratory symptoms or changes detected in the pulmonary function test [48].

Bronchoalveolar lavage can be used for the diagnosis of pulmonary involvement in pSS and for the differential diagnosis of concomitant infectious processes [88].

Risk factors associated with pulmonary involvement in pSS

Some risk factors have been described in symptomatic pulmonary involvement of pSS, such as the male sex, presence of rheumatoid factor, antinuclear antibodies (ANA), anti-Ro/SSA and anti-La/SSB, hypergammaglobulinemia, lymphopenia, Raynaud's phenomenon, peripheral arthritis, changes in the pulmonary function test (decreased FVC and FEV1), smoking history, advanced age, and gastrointestinal involvement [35, 36, 42, 89]. The last two were associated with ILD deterioration [90].

Considering pulmonary involvement on the chest CT (with or without symptoms), dry mouth and focal score ≥ 4 on the labial salivary gland biopsy were risk factors for airway disease. Advanced age, male sex, and focal score ≥ 4 on the labial salivary gland biopsy were risk factors for ILD [91].

Renal manifestations

Recommendations

(6) Renal manifestations are underdiagnosed, as they do not often present evident symptoms; thus, an adequate and systematic assessment of renal function is required. When investigating, we must consider the two types of renal impairment: distal tubulointerstitial nephritis (Type I) and proximal tubulointerstitial nephritis (Type II), with or without renal tubular acidosis (RTA); and glomerulonephritis (GN). **Level of Agreement: 100%, Strength of Recommendation: Strong.**

(7) Initial and follow-up evaluations are recommended even in asymptomatic patients, with the measurement of serum creatinine, glomerular filtration rate (GFR), type I urine (pH and density always assessed in fresh morning urine), serum electrolytes (Na, K, Cl), venous blood gases (HCO3, blood pH), and plain abdominal radiography or renal bladder ultrasound. **Level of Agreement: 100%, Strength of Recommendation: Strong** (Additional file 1: Chart S1).

(8) The diagnosis of tubulointerstitial involvement requires an active search for RTA signs and symptoms: cramps, muscle weakness, hypokalemic periodic paralysis, renal lithiasis, nephrocalcinosis, polyuria, polydipsia, nocturia, nephrogenic diabetes insipidus, bone pain, and pathological fractures secondary to osteomalacia (Additional file 1: Chart S2). In these cases, in addition to the initial laboratory evaluation, serum calcium and phosphorus, 24-h proteinuria, or the protein creatinine index (PCI) should be assessed. Hypocitraturia is a frequent and early finding in distal tubular dysfunction, being a risk factor for urolithiasis and nephrocalcinosis. **Level of Agreement: 100%, Strength of Recommendation: Strong.**

Distal renal tubular acidosis (dRTA) is secondary to tubulointerstitial nephritis (TIN) when urinary pH > 5.5 in the presence of metabolic acidosis, with normal blood anion gap and positive urinary anion gap. If urinary pH > 5.5 in the absence of metabolic acidosis, incomplete distal renal tubular acidosis (idRTA) should be considered. Urinary acidification tests with ammonium chloride or furosemide and hydrocortisone confirm the diagnosis if urinary pH remains > 5.5. If these tests are not available, the patient should be monitored more frequently. In cases of urinary pH > 7.5, proximal renal tubular acidosis (pRTA) should be suspected, which may course with normal glycosuria and glycemia, hyperphosphaturia, hyperuricosuria, aminoaciduria, hypophosphatemia, and hypouricemia. Assessment of these tests should be required. **Level of Agreement: 100%, Strength of Recommendation: Strong.**

Glomerular involvement is much less frequent, but presents evident symptoms in most cases and may be associated with cryoglobulinemia. (Additional file 1: Chart S2) Laboratory findings are suggestive of impaired kidney function, proteinuria, hematuria, leukocyturia, cylindruria, and hypocomplementemia. Assessment of this test should be required. **Level of Agreement: 100%, Strength of Recommendation: Strong.**

Renal biopsy is indicated for suspected glomerulopathies, cases of tubulointerstitial nephritis with kidney failure or severe electrolyte imbalance, and differential diagnosis. **Level of Agreement: 100%, Strength of Recommendation: Strong.**

Clinically relevant renal involvement in pSS occurs in about 5–10% of patients, and, although its evolution is often benign and slow, it can lead to chronic kidney disease and impact long-term prognosis [35, 80, 92–97]. The prevalence of kidney disease varies widely in the literature (1–52%), not only because studies in the last 20 years have adopted different diagnostic criteria, but also due to different definitions of kidney failure and different methods of diagnostic evaluation (clinical, biochemical, and anatomopathological findings) [39, 42, 52, 53, 98–105], in addition to geographic and ethnic influences [106–110] (Additional file 1: Table C). Our meta-analysis have found a prevalence of 9% (95% CI 6% to 13%) of Renal Manifestations in pSS (Fig. 12).

A recent international, multicenter epidemiological study of systemic impairment in pSS (Big Data Sjögren Consortium) highlights the difference between ethnic groups and the greater frequency of renal involvement in Asian patients [11]. In addition, renal involvement is underestimated, as it frequently presents few or no symptoms. Its diagnosis, therefore, requires an adequate and systematic assessment of renal function [35, 80, 111, 112]. Renal involvement rate in retrospective studies is generally lower than in prospective studies, being much higher (6–52%) in studies that carried out an active search for the identification of kidney impairment [97, 107, 111] Although using different methodologies, all the prevalence studies reviewed were performed with pSS patients who met the 2002 [4], 2012 [5], or 2016 [6] classification criteria for pSS, even if previously diagnosed. (Additional file 1: Table C).

The kidney may undergo two distinct immunological processes in pSS: periepithelial lymphocytic infiltration and immune complex deposition by B cell hyperactivation [80, 94, 113]. TIN, in its chronic form, is the most common kidney disease in pSS, but can also occur in the acute form [93, 111, 112, 114]. TIN is present in more than 75% of nearly all studies [2, 29, 42, 54, 60, 98–101, 103, 105, 115–122], and, similarly to what is observed in the exocrine glands, it is caused by lymphoplasmacytic infiltration in the interstitium and around the renal tubules (periepithelial involvement) [35, 80, 94, 113, 123].

Glomerular involvement secondary to immune complex deposition and autoantibody production is much less frequent, and membranoproliferative glomerulonephritis (MPGN) is the most common finding in the majority of studies, frequently in association with cryoglobulinemia [2, 35, 92, 93, 95, 124, 125]. Other forms of glomerulonephritis (GN) were described, with varying prevalence according to the study: mesangioproliferative glomerulonephritis (MesP) [41, 94, 95, 124, 126] membranous glomerulonephritis (MGN) [73, 124, 127], focal segmental glomerulosclerosis (FSGS) [92, 123, 128], IgA nephropathy (IgAN) [73, 107, 127], and antineutrophil cytoplasmic antibody (ANCA)-associated rapidly progressive glomerulonephritis (RPGN) [35, 93, 123, 124, 128, 129], in addition to rare cases of podocytopathy [80, 128, 130–132] and two cases of fibrillary glomerulonephritis (FGN) [125, 133].

Among the 30 studies on the prevalence of renal involvement in pSS, the histopathological type—interstitial or glomerular—was specified in 16. The prevalences of isolated TIN, isolated GN, and TIN associated with GN in these 16 studies were 37.1% [95] to 100% [134–137]; 0% [107, 134–137] to 48.6% [95]; and 0% [2, 108, 126, 129, 134–141] to 20.1% [107], respectively (Additional file 1: Table D). Our meta-analysis have found TIN in 83% (95% CI 69–91%) (Fig. 13) and GN in 12% (95% CI 5–26%) (Fig. 14).

Among the renal manifestations, tubulointerstitial nephritis is the most common (83%) 95% CI (69–91%) (Fig. 12). Glomerulonephritis affects 12% of patients 95% CI (5–26%) (Fig. 13). Tubulointerstitial nephritis plus glomerulonephritis is a rare manifestation, affecting 1% of patients (95% CI 0–9%) (Fig. 14).

Kidney disease in pSS generally occurs in patients older than 50 years of age and 2–7 years after the diagnosis of pSS [35, 80, 92–95]. Renal involvement in pSS is heterogeneous, ranging from a simple electrolyte imbalance to quite evident changes in renal function [35, 80].

Immunological markers have been associated with the risk of renal involvement [142, 143]. Patients with hypergammaglobulinemia [73, 96, 124, 141], hypocomplementemia, anti-Ro/SSA antibodies, anti-La/SSB antibodies, and cryoglobulinemia are at an increased risk for renal impairment [35, 50, 96, 138, 141, 142]. Some studies, however, did not reproduce the association between Anti-Ro/SSA and renal disease in pSS [73, 124, 134, 138, 144]. Due to the important relationship between hypergammaglobulinemia and kidney disease, Ren et al., investigating TIN, suggested assessing and monitoring renal

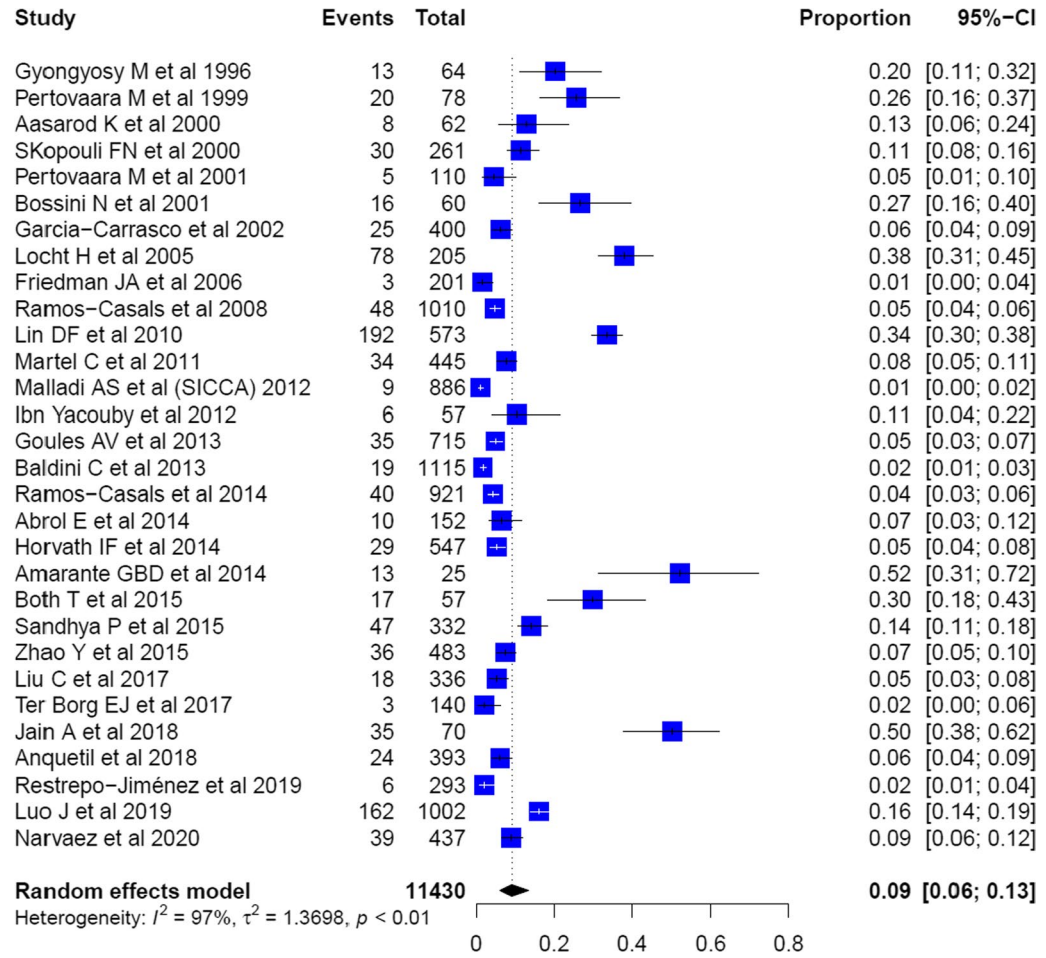

Fig. 12 Meta-analysis of the Renal Manifestations in pSS in patients with Sjogren's syndrome

acidification ability in all pSS patients with high levels of gamma globulins [124].

Cryoglobulinemia, which is one of the major complications of systemic involvement in pSS [35, 50, 95, 145, 146], is strongly associated with GN (50–80% of cases) [35, 50, 142, 145, 146]. pSS is the disease most frequently associated with cryoglobulinemia unrelated to the hepatitis C virus [115, 147]. The increase in serum $ß_2$-microglobulin, described as a biomarker of B cell activation and systemic inflammatory activity of pSS [106, 116, 117, 148], has also been linked to the risk and activity of renal disease [100, 118, 149], while the increase in urinary $ß_2$-microglobulin may be indicative of tubular injury [134]. The international, multicenter pSS registry (Big Data Sjögren Consortium), which includes 22 countries and 10,500 patients, found a strong association between renal involvement and the presence of anti-Ro/SSA, anti-La/SSB, cryoglobulinemia, and low C3 and C4 levels ($p < 0.001$) [142].

Renal impairment plays a significant role in the ESSDAI [3]. The ESSDAI includes patients with no disease activity (normal urinary sediment, proteinuria < 500 mg/24 h, absence of acidosis, and stable renal function) and with disease activity (mild, moderate, or high), according to changes in renal function or urinalysis, suggesting RTA or GN and TIN or GN confirmed by biopsy.

The patient with RTA is classified as having TIN, and the disease staging varies according to the GFR or the histopathological findings. Patients with GFR < 60 mL/min or lymphocytic infiltrate at biopsy, for example, are considered to have moderate activity [3, 9, 10, 101]. The ESSDAI, however, does not include TIN in its subclinical form (when there are only changes in urinary concentration or isolated electrolyte abnormalities). Although less severe, these findings also indicate an active disease with evolutionary potential [35, 80, 141].

For patients with GN, the staging varies according to the GFR, the presence of proteinuria, or the histopathological findings. For example, patients with proteinuria > 1.5 g/day, GFR < 60 mL/min, or proliferative disease at biopsy are considered to have high activity.

Recently, data from 437 patients from the Registry of Adult pSS patients of the Spanish Society of Rheumatology showed that patients with renal disease have higher ESSDAI scores when compared to patients without this manifestation (9 ± 9 vs. 4 ± 5, $p < 0.01$) [96].

Tubulointerstitial involvement

RTA is the main clinical presentation of TIN [102, 103, 111]. This disorder is a result of tubular dysfunction, leading to acid retention (distal tubules) or loss of bicarbonate (proximal tubules). Type I (distal) RTA (95% of cases) and type II (proximal) RTA (Fanconi syndrome) are the most frequently described forms of RTA in pSS [35, 124, 134]. Complete Fanconi syndrome is rare (3% of TINs in pSS), but isolated findings of proximal tubular cell dysfunction, such as mild, low molecular weight proteinuria, are not uncommon [106, 134, 141]. Type IV (distal) RTA (Gitelman syndrome) may also occur [80, 98, 99, 104, 105].

Clinical findings of RTA are greatly varied and generally secondary to electrolyte imbalance and metabolic acidosis, which is typically hypokalemic and hyperchloremic. The findings may include cramps, muscle weakness, flaccid paralysis, or hypokalemic quadriparesis, sometimes described as recurrent attacks [150], renal colic, polyuria, polydipsia, nocturia and nephrogenic diabetes insipidus (in dRTA), bone pain, and pathological fractures, sometimes bilateral and multiple [151]. Known as pseudofractures, or looser zones, these pathological fractures are described as broad, transverse lines, generally at a right angle to the involved cortex, secondary to osteomalacia (in pRTA and dRTA).

Osteomalacia caused by TIN is probably secondary to the combination of acidosis and hypophosphatemia, both resulting from a resorption defect. The associated vitamin D deficit can be an aggravating factor [119, 152]. Hypokalemic periodic paralysis may progress to respiratory failure and even cardiac arrest [120, 134, 153–156]. Severe potassium deficiency can cause ischemia followed by muscle necrosis and even rhabdomyolysis [157]. All these clinical findings were described prior to or at the diagnosis of pSS [80, 95, 158]. In the Ramos-Casals et al. systematic review, clinical presentations of RTA were responsible for the diagnosis of TIN in pSS in two-thirds of cases, with hypokalemic weakness being the most frequent finding [35].

Distal RTA is considered secondary to TIN when urine pH > 5.5 and there is metabolic acidosis with normal blood anion gap [$Na - (Cl + HCO_3)$] and positive urinary anion gap [(Na U + K U) − Cl U]. If urinary pH is always > 5.5 and there is no evident metabolic acidosis, incomplete distal RTA should be considered [103, 124, 134]. In this case, a urinary acidification test with ammonium chloride [121] or furosemide and hydrocortisone should be performed [122]. If urinary pH after the test ≤ 5.5, there is no RTA; if urinary pH > 5.5, incomplete distal RTA is confirmed, acknowledging the kidney's inability to acidify urine (these tests are difficult to perform and not used in daily clinical practice).

Incomplete distal RTA due to the absence of acidemia may justify the oligosymptomatic—and sometimes

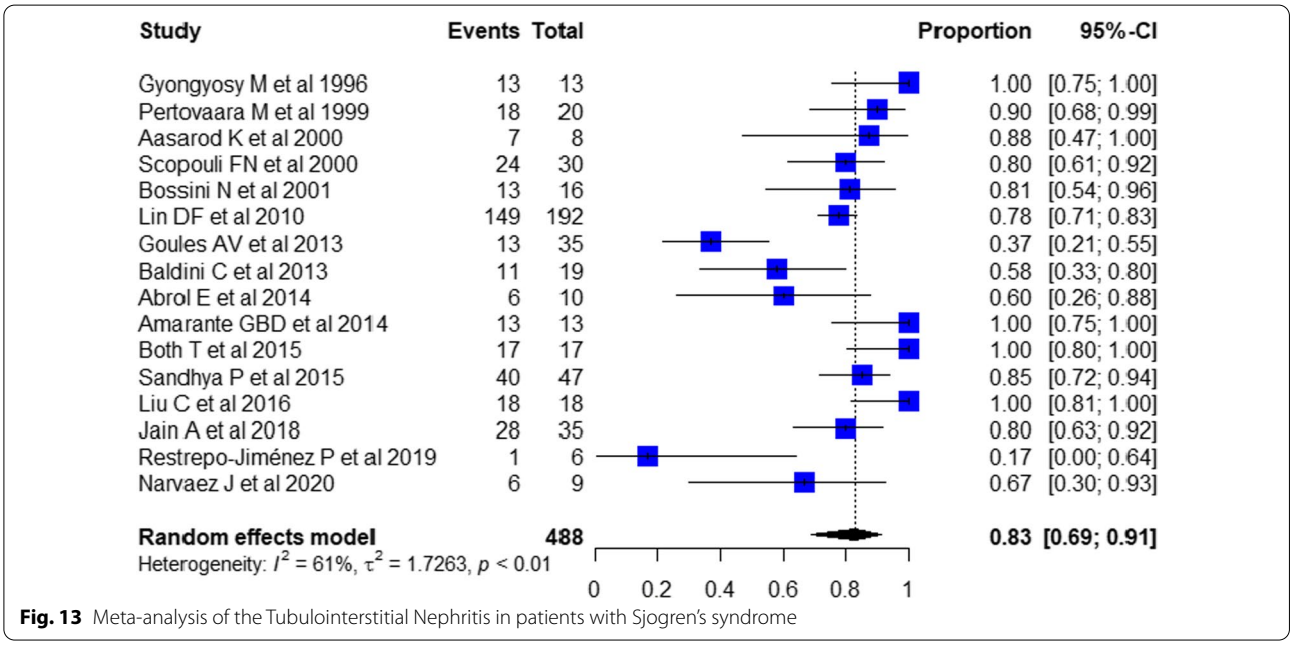

Fig. 13 Meta-analysis of the Tubulointerstitial Nephritis in patients with Sjogren's syndrome

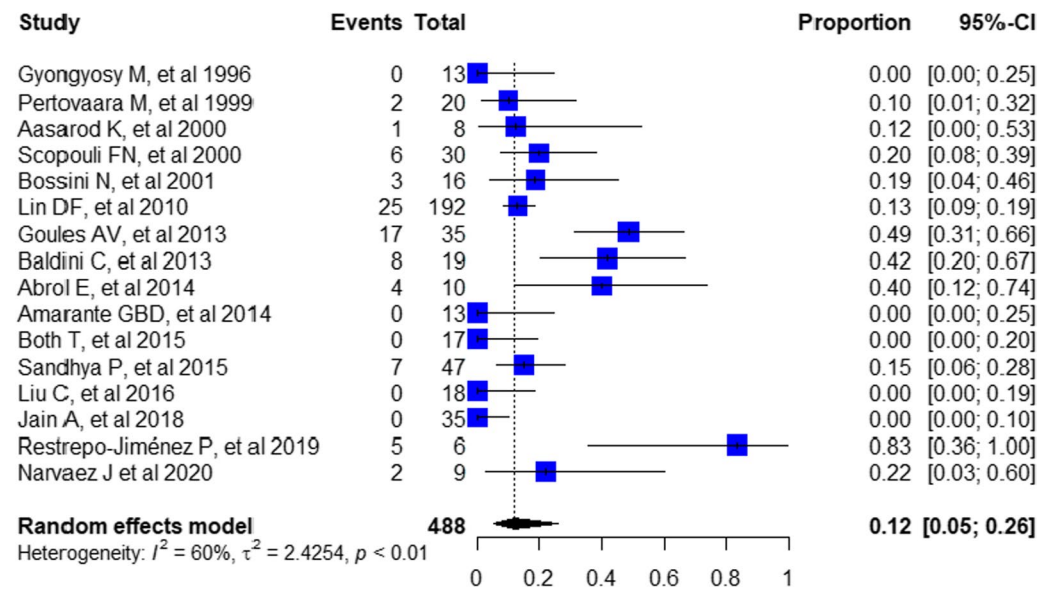

Fig. 14 Meta-analysis of the Glomerulonephritis in patients with Sjogren's syndrome

asymptomatic—presentation of TIN [124, 134]. In pRTA, where urinary bicarbonate excretion is increased, urinary pH is persistently > 7.5 and urinary anion gap is negative (unlike dRTA, where it is positive), with increased chlorine loss in the urine and no increase in serum chlorine. Glycosuria with normal glycemia (identified in type I urine test), hyperphosphaturia, hyperuricosuria, aminoaciduria, hypophosphatemia, and hypouricemia can also occur in proximal tubule involvement [103, 159]. dRTA and pRTA may occur simultaneously [160, 161].

Urolithiasis and nephrocalcinosis are frequent findings in dRTA and pRTA due to hypercalciuria and acidosis [162–164]. Renal biopsy puncture (RPB) is not required for confirming TIN, except in cases of significant renal function impairment, severe electrolyte imbalance, or differential diagnosis (sarcoidosis, IgG4-related disease) [97, 100, 165, 166].

This review identified studies that followed three main groups of patients with renal involvement in pSS: unselected patients; patients with suspected renal impairment; and patients with renal impairment confirmed by clinical and/or laboratory assessment, or biopsy. The present study includes information from registry-based studies, case series, and case reports of interstitial or glomerular involvement (Additional file 1: References). All patients met the 2002, 2012, or 2016 classification criteria for pSS, even if previously diagnosed [41, 167, 168].

Considering TIN patients from prevalence studies, renal biopsy studies, and case reports, we found a male-to-female ratio of 13.6:1 in 307 patients and a median age of 41 years (13–84) at diagnosis of nephritis in 184 patients. In 695 TIN cases, RTA was diagnosed as complete in 621 (89.4%) and incomplete in 74 patients (10.6%). Its types were specified in 557 cases: 487 (87.4%) were type I (distal) RTA; 66 (11.9%) type II (proximal) RTA (Fanconi syndrome); and 4 (0.7%) type IV (distal) RTA (Gitelman syndrome). In 19 of the patients (3.4%), type I (distal) RTA and type II (proximal) RTA were observed.

Clinical findings were described in 762 individuals. Of the symptomatic patients, 185 (24.3%) had muscle weakness and/or hypokalemic periodic paralysis, 121 (15.9%) renal lithiasis/renal colic, 54 (7.1%) radiological nephrocalcinosis, 56 (7.3%) osteomalacia/pathological fractures, 39 (5.1%) polyuria/polydipsia, and 17 (2.2%) nephrogenic diabetes insipidus. Changes in renal function (Cr > 1.2 mg/dL and/or GFR < 60 mL/min) were identified in 176 (24.2%) of 727 patients with TIN. Electrolyte dosages were reported in 616 cases, and hypokalemia ($K^+ < 3.4$ mEq/L) was the most frequent electrolyte imbalance, present in 383 (62.2%) patients, followed by low serum bicarbonate ($HCO_3^- < 22$ mEq/L), in 163 (26.5%) patients, and hyperchloremia ($Cl^- > 107$ mEq/L), in 153 (24.8%) patients. In the 4 reports of type IV RTA [60, 76, 169, 170], serum bicarbonate and blood pH were high (metabolic alkalosis). Immunological markers showed the presence of anti-Ro/SSA in 403 (76.0%) of 531, anti-La/SSB in 257 (55.9%) of 460, antinuclear antibodies (ANA) in 281 (77.6%) of 362, and rheumatoid factor in 215 (67.0%) of 321 patients. Complement C_3 and C_4 levels were low in 79 (28.6%) of 276 and 68 (24.6%) of 276 patients, respectively, and hypergammaglobulinemia

(> 1.6 g/L) occurred in 238 (71.7%) of 332 individuals (Additional file 1: Table E).

Renal biopsy was performed in 572 patients with pSS and renal involvement, and TIN was found in isolation in 298 (52.1%) and associated with GN in 69 (12.1%) of cases. Renal injury correlated to other causes was identified in 14 (2.4%) of the biopsies. Not all patients with biopsy-diagnosed TIN had RTA.

Glomerular involvement

According to the new classification, pSS-associated GN belongs to the immune-complex glomerulonephritis group, which includes autoimmune diseases, infections, IgAN, and FGN. It is characterized by the deposition of immunoglobulins and complement fractions, detected by immunofluorescence or immunohistochemistry staining, with deposits varying in type and location [169–171]. In pSS, these glomerular immune deposits are secondary to the continuous stimulation of B cell activation and the production of autoantibodies [80, 94].

Glomerular disease is much less frequent than TIN in pSS but easily detected in routine laboratory testing, as it usually associates with kidney failure (altered Cr and GFR), altered urinalysis (glomerular proteinuria, hematuria, leukocyturia, and cylindruria), and, in most cases, evident symptomatology (systemic arterial hypertension—SAH, lower limb and periorbital edema, nephrotic syndrome, and nephritic syndrome); however, asymptomatic proteinuria may also occur [80, 93, 129, 169, 172] (Additional file 1: Chart S1). The presence or history of purpura (mainly palpable) may suggest glomerular renal involvement due to the association with cryoglobulinemia and GN [2].

RPB is mandatory for the diagnostic confirmation of glomerulopathy, the identification of GN type, and differential diagnosis. Another important histopathological finding of GN that frequently occurs in pSS is the concomitant tubulointerstitial involvement, with characteristic lymphoplasmacytic infiltration [80, 114, 173].

In this systematic review, we have found 143 patients with glomerular involvement. A 14.1:1 rate between female and male participants and a 53-year-old median age at diagnosis of GN (25–86 years of age) were found as epidemiological characteristics in 85 patients. Considering the clinical findings, edema and nephrotic syndrome were reported in 82 (66.1%) of 124 patients, SAH in 23 (36.5%) of 63 patients, and purpura in 19 (57.6%) of 33 patients with cryoglobulinemia and GN. Kidney failure (Cr > 1.2 and/or GFR < 60 mL/min) was identified in 59 (63.4%) of the 93 renal function cases, and 24-h proteinuria or PCI were described in 100 (89.3%) of 112 patients. Of these 100 patients, 5 (5.0%) had levels below 500 mg/24 h; 6 (6.0%) between 500 mg and 1 g; 13 (13.0%) between 1 and 1.5 g; and 58 (58.0%) above 1.5 g. In 18 (18.0%) cases, proteinuria was not quantified. As for the immunological profile, anti-Ro/SSA was found in 69 (69.7%) of 99 patients, anti-La/SSB in 43 (51.2%) of 84, antinuclear antibodies, in 68 (88.3%) of 77, rheumatoid factor in 62 (67.4%) of 92, decreased C_3 in 29 (33.4%) of 87, decreased C_4 in 37 (41.1%) of 90, and hypergammaglobulinemia in 33 (63.5%) of 52. Ninety-six patients were tested for cryoglobulinemia, which was positive in 33 (34.4%). ANCA was positive in 10 (66.7%) of 15 cases (9 p-ANCA with anti-myeloperoxidase positive and 1 cytoplasmic c-ANCA with antiproteinase-3 positive). (Additional file 1: Table F) Eight of 10 ANCA-positive patients had RPGN, 1 had FSGS, and 1 had IgAN.

Of the 572 patients with pSS and renal impairment who underwent renal biopsy that we have analyzed in this review, isolated GN was found in 191 (33.4%) and GN associated with TIN in 69 (12.1%), totaling 260 cases of GN (Additional file 1: Table F). The biopsy revealed different pathological findings, including 81 (31.1%) cases of MGN, 52(20%)) of MesP, 50(19.2%) of MPGN, 20 (7.7%) of FSGS, 15 (5.8%) of IgAN, 11 (4.2%) of MCD, 11 (4.2%) of RPGN, 8 (3.0%) of DPGN, 5 (1.9%) of FPG, 4 (1.5%) of podocytopathy (podocytic infolding glomerulopathy), 2 (0.8%) of FGN, 1 (0.4%) of TBMD, and 3 (1.1%) of unspecified GN. (Additional file 1: Table F). Of the 50 cases of MPGN detected by biopsy, cryoglobulin dosages were described in 29 cases, 22 (75.9%) of which were positive. Eight of the 11 patients with RPGN underwent ANCA testing, all of whom presented p-ANCA pattern and anti-MPO antibodies. Amicrobial pustulosis was reported in two patients with pSS and IgAN [174, 175]. In three biopsies, more than one type of histological alteration was described [131, 133, 176].

Podocytopathy and FGN are electron microscopy findings and may present different patterns under optical microscopy. In a study prior to the publication of the two cases of pSS-associated FGN included in this review [125, 133], Nasr et al. described 66 cases of FGN associated with different systemic diseases, including one patient with pSS [177]. In the described cases of podocytopathy, podocytic infolding causes irregularities and thickening of the basement membrane that resemble MPGN under optical microscopy. In addition, there is an involvement that can extend up to the epithelial wall of the vessel (where the podocytes are), with immune complex deposition that is generally not very expressive. Electron microscopy identifies microspheres, microtubules, and podocytic folding, causing irregular thickening of the basement membrane [130–132].

The most frequent histological type of GN found in this review was MGN, unlike most studies, which reported

MPGN associated with cryoglobulinemia as the main finding [92, 93, 95, 123, 125, 178]. The recent systematic review by Ramos-Casals et al. also describes MPGN as the most frequent glomerulopathy [35]. The findings of the current review of 260 cases of GN documented by biopsy may be different because we included 2 recent Chinese studies with a significant number of biopsies, in which the most frequent histological type was MGN, with no cases of MPGN [73, 127].

In a study with 103 renal biopsies, Yang et al. found 50 cases of GN, 37 of which were MGN [73]. Luo et al., in a study with 30 biopsies [127], described 15 MGN among 25 cases of GN. In another Chinese study, Lin et al. did not find MPGN in any of the 42 cases of GN documented by renal biopsy, with mesangial proliferative glomerulonephritis (MesPGN) being the most frequent histological type (50% of biopsies) [41]. Ethnic and geographical factors are a possible explanation for these Chinese findings, considering the remarkably low prevalence of MPGN (0.6–1.5%) in primary glomerular disease documented in China [179].

Conclusion

The evaluation of the systemic manifestations of SS are not properly incorporated in clinical practice. In this first part of a guideline being produced by the Brazilian Society of Rheumatology to cover this gap, we provide 11 recommendations, based on evidence and with a high level of agreement between experts, for the articular, pulmonary, and renal care of patients with SS. Due to the low and heterogeneous level of scientific evidence available, we suggest caution and individualization of the application of recommendations in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42358-022-00248-1.

Additional file 1. Prevalence of articular, pulmonary, and renal manifestations: Descriptive summary of the studies.

Additional file 2. Joanna Briggs Institute (JBI) Critical Appraisal Checklist.

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Declarations

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Not applicable.

Consent for publication
Not applicable.

Competing interests
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Author details
[1]Disciplina de Medicina de Urgência e Medicina Baseada em Evidências, Escola Paulista de Medicina – Universidade Federal de São Paulo (EPM-UNIFESP), Rua Botucatu, 740, Vila Clementino, São Paulo, SP CEP: 04023-062, Brazil. [2]Disciplina de Reumatologia, Universidade de Santo Amaro (UNISA), Rua Enéas Siqueira Neto, Jardim das Imbuias, São Paulo, SP CEP: 04829-300, Brazil. [3]Departamento de Ortopedia, Reumatologia e Traumatologia, Universidade Estadual de Campinas, R. Tessália Vieira de Camargo, 126 - Cidade Universitária, Campinas, SP CEP: 13083-887, Brazil. [4]Disciplina de Reumatologia, Laboratório de Autoimunidade (DLC + LIM17), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, R. Dr. Ovídio Pires de Campos, 225 – Cerqueira César, São Paulo, SP CEP: 05403-010, Brazil. [5]Disciplina de Especialidades Clínicas, Departamento de Clínica Médica, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), R. Sarmento Leite, 245 - Centro Histórico de Porto Alegre, Porto Alegre, RS CEP: 90050-170, Brazil. [6]Departamento de Educação Integrada em Saúde, Universidade Federal do Espírito Santo (UFES), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29040-090, Brazil. [7]Serviço de Reumatologia, Hospital Federal dos Servidores do Estado do Rio de Janeiro, R. Sacadura Cabral, 178, Saúde, Rio de Janeiro, RJ CEP: 20221-903, Brazil. [8]Centro Catarinense de Imunoterapia, R. Santos Dumont, 182 – Centro, Florianópolis, SC CEP: 88015-020, Brazil. [9]Serviço de Reumatologia, Universidade Federal de Pernambuco (UFPE), Av. Prof. Moraes Rego, 1235, Cidade Universitária, Recife, PE CEP: 50670-901, Brazil. [10]Departamento de Oftalmologia, Escola Paulista de Medicina – Universidade Federal de São Paulo (EPM-UNIFESP), Rua Botucatu, 820, Vila Clementino, São Paulo, SP CEP: 04023-062, Brazil. [11]Departamento de Patologia e Medicina Legal, Universidade Federal do Amazonas, Rua Afonso Pena, 1053, Manaus, AM CEP: 69020-160, Brazil. [12]Disciplina de Reumatologia, Departamento de Medicina Interna, Centro de Ciências Médicas, Universidade Federal da Paraíba (UFPB), Campus I - Lot. Cidade Universitária, Paraíba, PB CEP: 58051-900, Brazil. [13]Departamento de Patologia, Hospital Universitário Cassiano Antônio de Moraes, Universidade Federal do Espírito Santo (UFES), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil. [14]Serviço de Reumatologia, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande de Sul (PUCRS), Av. Ipiranga, 6690 - Jardim Botânico, Porto Alegre, RS CEP: 90610-000, Brazil. [15]Serviço de Reumatologia da Santa Casa de São Paulo, R. Dr. Cesário Mota Júnior, 112, Vila Buarque, São Paulo, SP CEP: 01221-020, Brazil. [16]Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (HCFMRP-USP), Av. Bandeirantes, 3900, Vila Monte Alegre, Ribeirão Preto, SP CEP: 14049-900, Brazil. [17]Serviço de Reumatologia, Hospital Universitário Cassiano Antônio de Moraes, Universidade Federal Do Espírito Santo (UFES), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil.

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