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Recommendations for evaluation and diagnosis of extra-glandular manifestations of primary Sjögren syndrome: results of an epidemiologic systematic review/meta-analysis and a consensus guideline from the Brazilian society of rheumatology (hepatic, gastrointestinal and pancreatic)

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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, some systemic manifestations, mainly liver, gastrointestinal, and pancreatic are not routinely evaluated. To address these manifestations, the *Sjögren's Syndrome Committee of the Brazilian Society of Rheumatology* conducted a broad systematic review of the literature on studies investigating prevalence and diagnosis of these symptoms in Sjogren´s patients and made recommendations based on the findings. Agreement between the experts was achieved using the Delphi method. This is the second part of this guideline, providing 6 recommendations for liver, gastrointestinal, and pancreatic care of SS patients.

Keywords: Sjögren's syndrome, Gastrointestinal diseases, Clinical guidelines

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Background

Sjogren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and other organs [1]. The disease may occur in isolation,

when it is called primary Sjogren's Syndrome, or in conjunction with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or other rheumatic diseases, when it is called secondary Sjogren's Syndrome [2]. Primary Sjogren's Syndrome (pSS) is a common disease that affects 0.04% to 0.08% of people worldwide and has a female to male ratio of 9–14 to 1 [3]. As the process leads to progressively reduced or absent glandular secretion, along with mucosal dryness, Sjogren's Syndrome (SS) is characterized by symptoms ranging from xerophthalmia, xerostomia, fatigue, myalgias, and arthralgia to severe systemic symptoms with cutaneous, vascular, renal, pulmonary, or neurological involvement [2, 4].

Besides these well-known symptoms, several gastrointestinal manifestations have been reported in Sjogren's syndrome, with varying degrees of gastrointestinal, liver, or pancreatic involvement.

To address these manifestations, the *Sjögren's Syndrome Committee of the Brazilian Society of Rheumatology* conducted a broad systematic review of the literature on studies investigating those symptoms in Sjogren´s patients. The Committe then gathered the experts in the field and developed recommendations for the screening and management of SS patients with these manifestations. Therefore, the current paper represents an effort by the Brazilian Society of Rheumatology, with the objective of retrieving the best available evidence and providing guidance for the identification of symptoms, diagnosis, monitoring, prognosis, and treatment of gastrointestinal manifestations of Sjogren's Syndrome.

Methods

A literature and systematic review was conducted of papers about the prevalence and the diagnosis of liver, gastrointestinal and pancreatic manifestations of Sjogren's Syndrome. This is the second part of a guideline proposed by the Brazilian Society of Rheumatology about recommendations for evaluation and diagnosis of extra-glandular manifestations of Primary Sjögren Syndrome that was published in 2022. The methodology used was similar. 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. For evaluating the diagnosis of systemic manifestations, diagnostic accuracy studies were preferably considered. 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.

To the meta-analyses, 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). Forest plots for the prevalence of extra-glandular manifestations in patients with Sjogren's Syndrome are presented in Appendix 1 (Figs. 1, 2, 3, 4). A flowchart was created with the studies identified through databases searching, including studies screened and used for qualitative analyses. (Appendix 1—Fig. 5).

After the analysis, the study group wrote the paper and proposed the initial recommendations on each organ. Final recommendations were provided during the meeting which gathered the whole Sjogren's Syndrome Committee of the Brazilian Society of Rheumatology, after full consensus on the writing. Agreement between these recommendations was achieved with the Delphi Method.

Results

Liver involvement

Recommendation

1. Liver involvement in pSS is frequently subclinical. We recommend performing liver biochemical tests (alkaline phostatase, gamma-glutamyltransferase, and transaminases) every six months in asymptomatic patients, and immediately in patients with symptoms such as pruritus and fatigue. If canalicular enzyme abnormalities are observed, it is recommended that investigations be carried out for Primary Biliary Cholangitis and other causes of hepatic cholestasis. If a disproportionate increase in transaminases is observed, we recommend continuation of the investigation for autoimmune liver disease with the analysis of antibodies.

Sjögren's syndrome (SS) is associated with liver abnormalities, including (usually mild) abnormal biochemical tests and histological patterns of Primary Biliary Cholangitis (formerly called Primary Biliary Cirrhosis) or Autoimmune Hepatitis. Alterations in liver function tests can be hepatocellular or present a predominantly cholestatic pattern and are persistent in 5 to 26% of patients [5, 6]. Other causes of liver dysfunction in SS include Hepatitis C, nonalcoholic steatohepatitis, and drug toxicity [7].

Patients with Primary Biliary Cholangitis (PBC) have a prevalence of pSS of around 38% [8]. However, clinical evidence of PBC is found in less than 2% of patients with SS in large cohorts [9–11]. Likewise, Autoimmune Hepatitis (AIH) is present in less than 2% of patients with pSS [7, 9]. In large cohorts, anti-mitochondrial (AMA) and anti-smooth muscle antibodies are present, respectively, in 8 and 62% of patients, raising the possibility that subclinical liver disease is more common in SS [10].

The prevalence of silent but significant hepatic fibrosis in patients with pSS assessed by hepatic elastography was 11.9% and its clinical predictors were leukopenia ≤ 4000, serum albumin ≤ 3.8 mg/dL, and aspartate aminotransferase ≥ 27 [11, 12].

Pseudolymphoma, a process usually found in salivary and lacrimal glands, has been described in the liver of patients with SS. Reactive hyperplasia of the liver, clinically known as pseudolymphoma in the liver, has a pathology similar to malignant lymphoma, with a completely benign clinical course, and is rare in the literature [13, 14].

Primary biliary cholangitis

Primary Biliary Cholangitis (PBC) is characterized by T lymphocyte-mediated attack of the small intralobular bile ducts. The continuous aggression to the epithelial cells of the bile ducts leads to their gradual destruction and eventual disappearance. Loss of intralobular bile ducts (ductopenia) causes signs and symptoms of cholestasis and can eventually result in cirrhosis and liver failure [15, 16]. With the advent of ursodeoxycholic acid treatment, the majority of patients currently have a normal life expectancy and only a minority of patients develop cirrhosis [17, 18].

Approximately 50 to 60% of patients with PBC are asymptomatic at the time of diagnosis and are diagnosed with abnormalities through liver biochemical tests performed for other reasons [19]. In patients with symptoms, fatigue and pruritus are the most common and 17% may report discomfort in the upper quadrant of the abdomen [17, 20]. In the advanced stage they may develop malabsorption and steatorrhea, with findings of fat-soluble vitamin deficiency and signs and symptoms of complications from PBC such as cirrhosis [20].

Findings from physical examination in patients with PBC vary widely and depend on the stage of the disease. Physical examination is often normal in asymptomatic patients. Common cutaneous findings, present in 40% of patients, are hyperpigmentation, excoriations, jaundice, xanthomas, xanthelasmas, xerosis, and dermographism. Jaundice is a more advanced sign of illness. Hepatomegaly can be detected in asymptomatic patients, but is more common with disease progression. Splenomegaly is more common with the advance of the disease and is usually a sign of portal hypertension [20, 21].

Common laboratory abnormalities in patients with PBC include increased cholestatic patterned liver enzymes, antimitochondrial antibodies (AMA), positive antinuclear factor (ANA), and hyperlipidemia [20, 21].

Alkaline phosphatase is almost always very high, with values tending to plateau early in the course of the disease and then commonly fluctuating by 20% of this value. Serum levels of gamma-glutamyl-transpeptidase parallel those of alkaline phosphatase. Serum aminotransferases may be normal or slightly elevated. Serum bilirubin concentration is usually normal early in the disease but becomes elevated in many patients as the disease progresses, both the direct and indirect fractions rise and elevated bilirubin is a sign of poor prognosis [21].

Antimitochondrial antibodies (AMA) are the serological marker of PBC, present in 95% of patients. ANA is present in 70% of patients with PBC. Two immunofluorescence patterns are considered "PBC-specific": the multiple nuclear dots pattern and the rim-like/membranous pattern. In some patients, anti nuclear antibodies, particularly anti glicoprotein 210 (anti-gp210) and /or anti-sp100, are present and may correlate with prognosis. Other antibodies such as anticentromere, anti-SSA /Ro, and anti-dsDNA can also be found in PBC [22–26].

Hyperlipidemia can be very marked, with serum cholesterol exceeding 1000 mg/dL in patients with xanthomas. Other abnormalities in PBC include elevated serum immunoglobulin M (IgM), ceruloplasmin, and bile acids. Antithyroid antibodies are often seen in patients with PBC and are not always associated with clinically evident thyroid disease [27].

Noninvasive imaging evaluation of the liver and biliary tree is mandatory in all patients with biochemical evidence of cholestasis. Ultrasound is usually the first imaging exam to be performed to exclude extrahepatic biliary obstruction [14].

In patients with chronic intrahepatic cholestasis, investigation of AMA (antimitochondrial antibodies), highly specific to PBC, is useful for diagnostic confirmation. In individuals with negative AMA, it is recommended that ANA be investigated, which can be performed by indirect immunofluorescence or by Elisa, gp210 and sp100, found in up to 30–50% of patients with PBC [14].

The diagnosis of PBC is established if there is no extrahepatic biliary obstruction, no comorbidities affecting the liver, and at least two of the following items are present [18]:

- Elevated alkaline phosphatase at least 1.5 times the upper limit of normality;

- Presence of antimitochondrial antibodies (AMA) in titer of 1:40 or higher or other PBC-specific autoantibodies, including sp100 and gp210, if AMA is negative;
- Histological evidence of PBC (non-suppurative destructive cholangitis and destruction of the interlobular bile ducts).

Liver biopsy is not often required for diagnosis, however it provides useful information for assessing disease stage and prognosis. Serologically, the diagnostic marker of PBC is the presence of significant AMA titers. Early diagnosis of PBC can be made by determining serum antimitochondrial antibodies (AMA) by indirect immunofluorescence (IFI), with titers $\geq$ 1: 40 considered as the serological marker of PBC. Many AMA research tests are 95% sensitive and 98% specific for PBC [28, 29].

Several studies have analyzed the prevalence of AMA in patients with pSS. Studies that used IFI found a prevalence of 1.6 to 13%, while studies using ELISA/ Western blot found a higher prevalence (22 to 27%) [4, 7, 13]. The discrepancy in prevalence can be explained by the low sensitivity of the IFI. Therefore, in patients who are strongly suspected of having PBC, but with negative AMA by IFI, more sensitive techniques are recommended. When AMA is negative by all the methods described, despite clinical and biochemical findings suggesting PBC, the diagnosis must be confirmed by liver biopsy [30].

Antimitochondrial antibodies are found in 2 to 8% of patients with pSS. Antimitochondrial antibody is the most sensitive indicator of liver pathology in Sjögren's Syndrome. When a patient with SS has high alkaline phosphatase, it is necessary to search for antimitochondrial antibodies (AMA) and perform a liver biopsy. PBC associated with pSS tends to be asymptomatic, or subclinical with histological findings predominantly of Primary Biliary Cirrhosis stage I [5, 10, 30].

In a Spanish cohort of 335 patients with pSS, *Nardi* et al. detected AMA in 28 patients (8%), although only 14 had clinical and laboratory evidence of liver involvement [10]. Hatzis, in an evaluation of 410 patients with pSS, found biochemical alterations with a cholestatic pattern in 8.8%, of which 5.1% were AMA positive. The prevalence of PBC was 6.6%, stage I, mild form, with slow progression [27].

Ramos-Casals et al., in 475 patients with SS, showed that liver involvement was significant, detected in 27%, and many cases had chronic hepatitis C (13%). Autoimmune hepatic involvement was detected in 24 patients (5%), with PBC in 16 patients (4%) and type-1 autoimmune hepatitis in 8 patients (2%). Patients with autoimmune liver disease had higher ESR and gamma globulin values and a higher prevalence of ANA, and antimitochondrial, anti-smooth muscle, and anti-Ro and anti-La antibodies, while patients with chronic viral liver disease had a higher frequency of cryoglobulinemia and hypocomplementemia [7].

The literature shows that PBC and SS share several clinical, serological, and histological findings. A large number of patients with PBC have "sicca syndrome", among them, patients who have classic Sjögren's syndrome. Characteristics such as dry mouth and dry eyes are commonly found in 47–73% of PBC. Objective findings of dry eyes and dry mouth (abnormal Schirmer test and decreased salivary flow) were found in 30 to 50% of patients with PBC [6, 8, 29, 31].

Regarding the immunological profile, ANA is frequently observed in both conditions, with a higher prevalence in pSS compared to PBC. Patients with pSS also demonstrate a significantly higher frequency of anti-Ro and anti-La, while patients with PBC have a higher frequency of AMA. AMA is an early immunological marker of PBC, suggesting the existence of incipient or incomplete PBC in some patients with pSS [7].

Patients with PBC frequently (26–93%) manifest histological abnormalities in salivary gland biopsies compatible with SS, especially in the early stages of PBC when CD4 + lymphocyte infiltration predominates [8, 31].

Both PBC and pSS diseases share etiopathogenic mechanisms. In both, "environmental triggers" (infectious agents) can cause apoptosis of biliary and salivary epithelial cells. Both are characterized by inflammation of "target" epithelial elements. In both, autoimmunity appears to be directed towards epithelial ductal cells. PBC can be considered Sjögren's Syndrome in the liver while Sjögren's Syndrome can also be considered PBC of the salivary glands, both epithelial disorders [31].

Few studies have evaluated the progression of PBC in patients with pSS. Hatzis and colleagues studied 410 patients with pSS, analyzing clinical, biochemical, and histological data during a follow-up of 66 months after the diagnosis of PBC, and concluded that PBC in patients with pSS appears to progress slowly [27].

After eliminating viral hepatitis, PBC should be considered the leading cause of liver disease in patients with pSS [7]. The inclusion of AMA research in the immunological follow-up of patients with pSS is recommended, regardless of whether the serum liver profile is altered or not, because there is a strong association between the presence of AMA and the development of PBC in patients with pSS and because these patients may have underlying asymptomatic PBC.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a chronic necroinflammatory disease of the liver characterized by circulating autoantibodies and high levels of serum globulins. AIH predominantly occurs in women and can present at any age. The disease has a variety of clinical phenotypes and can manifest as an acute or a chronic illness with a fluctuating condition. It is included in the differential diagnosis for patients with abnormal liver biochemical tests, acute hepatitis, cirrhosis, or liver failure [32, 33]. AIH is heterogeneous and fluctuating in nature, which leads to very varied clinical manifestations. The spectrum of the disease ranges from asymptomatic patients to patients who present with nonspecific symptoms such as fatigue, pruritus, anorexia, nausea, abdominal pain, and even acute liver failure [33].

AIH is characterized by an increase in aminotransferases, with levels reaching values above 50 times the upper limit of normality. In cases of more advanced liver disease or with less necroinflammatory activity on biopsy, elevation of aminotransferases less than or equal to five times the normal can be found. Alkaline phosphatase values, on the other hand, are normal or slightly elevated. Varying degrees of liver dysfunction can be noted, characterized by hyperbilirubinemia, extended prothrombin time, and hypoalbuminemia. A characteristic finding of AIH is polyclonal hypergammaglobulinemia, with increased levels of immunoglobulin G. IgA and IgM levels are typically normal. Hypergammaglobulinaemia is usually associated with circulating autoantibodies [33, 34].

The autoantibody positivity profile allows the classification of AIH into two types: type-1 AIH and type-2 AIH. The main autoantibodies that may be present are as follows [33–37]:

- Antinuclear antibodies (ANA) are the most common in type-1 disease and may be the only autoantibody present, titers of ≥ 1:80 are considered positive in adults. ANA is the most nonspecific antibody of AIH and the most commonly found immunofluorescence patterns are homogeneous and dotted.
- Anti-smooth muscle antibodies (ASMA) are more specific than ANA, especially if present at titers ≥ 1:80 in adults, but less prevalent. Anti-smooth muscle antibody is the main marker of AIH, present in 70% of patients in association with ANA or alone (30%).
- Anti-actin antibodies (AAA) are more specific than ANA for type-1 autoimmune hepatitis. ASMA titers ≥ 1:320 usually reflect the presence of AAA and may serve as a marker for these antibodies.
- -Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP) have been found in approximately 10 to 30% of adult patients with type-1 AIH.
- Anticytoplasm antibodies of atypical neutrophils. Atypical p-ANCA has been identified in patients with type-1 AIH, and arealso found in Inflammatory Bowel Disease and Primary Sclerosing Cholangitis.
- Antimitochondrial antibodies (AMA) may occur in type-1 AIH, with a frequency < 5%. It is the classic, most specific marker for Primary Biliary Cholangitis.
- Anti-single stranded DNA (ssDNA) and double stranded (dsDNA) antibodies can be found in patients with autoimmune hepatitis types 1 and 2.
- Antibodies to liver and kidney microsome type-1 (ALKM-1), this is the most important marker for type-2 AIH, present in 90% of cases.
- Antibodies to liver and kidney microsome type-3 (ALKM-3), rarely found in patients with type-2 disease.
- Anti-hepatic cytosol-1 antibodies is the second marker of type-2 AIH.

Autoantibody titers do not reflect the extent of immune response and disease severity and may be absent in 10% of cases and negative with treatment. Regarding liver histological findings, although they are not pathognomonic, some aspects are characteristic of AIH, including interface hepatitis, with the presence of lymphoplasmocytic infiltrate, plasma cell predominance, which attacks the limiting plate and invades the liver parenchyma, and hepatocytic rosettes. More severe cases, with liver failure, present a greater degree of interface hepatitis, lobular disarrangement, hepatocyte necrosis, submassive necrosis, and less fibrosis than cases of gradual evolution. The finding of fibrosis is almost universal [37].

AIH does not have pathognomonic characteristics and does not have markers with sufficient sensitivity and specificity to define its diagnosis in isolation. Although the positivity of autoantibodies is important for the diagnosis and classification of the disease, it may be present in other liver, rheumatologic, and infectious diseases, and be absent in up to 10% of cases. A definitive diagnosis is made by combining clinical, laboratory, and histological findings, with the exclusion of other causes of liver disease [37].

The use of the 2008 simplified criteria is recommended for the diagnosis of AIH (Table 1) [30].

The disease is considered probable if the patient reaches 6 points, and definitive if the patient reaches 7 or more points

Type-1 AIH is the second most frequent autoimmune liver disease associated with pSS [34]. All cases of AIH reported in patients with pSS are type-1. Two-thirds

Table 1 Simplified criteria for AIH diagnosis—2008 [30]

Parameter	Cut-off point	Score
Positive ANA or positive smooth muscle	≥ 1:40	+1
Positive ANA or positive smooth muscle	≥ 1:80	+2
or anti-LKM positive	≥ 1:40	+2
or anti-SLA/LP positive	Any value	+2
IgG or gamma-globulin	Above the normal limit	+1
	> 1.1 instead of the upper limit	+2
Liver biopsy (evidence of hepatitis is indispensable)	Compatible	+1
	Typical	+2
	Atypical	0
Viral hepatitis	Yes	0
	No	+2

Table 2 Prevalence of PBC and AIH in patients with pSS

References	Country	pSS (n)	PBC n (%)	AIH n (%)
Lindgren et al. [44]	Sweden	45	4 (9%)	2 (4%)
Ramos-Casals et al. [7]	Spain	475	16 (4%)	8 (2%)
Montaño-Loza et al. [11]	Mexico	95	5 (5%)	2 (2%)
Hatzis et al. [26]	Greece	410	27 (6.6%)	–
Karp et al. [39]	USA	58	–	1 (1.7%)

Table 3 Prevalence of pSS in patients with PBC

References	Country	PBC n	pSS n (%)
Marasini et al. [22]	Italy	170	6 (3.5%)
Valera et al. [46]	Chile	115	38%
Wang et al. [32]	China	322	121 (36.2%)

(2/3) of the cases of type-1 AIH associated with pSS were reported in Asian countries. There are no cases of type-2 AIH in patients with pSS, a disease in which anti-LKM was not detected. AIH is found in 1 to 4% of patients with pSS [6, 17, 27, 38–40]. Table 2 summarizes the studies on the prevalence of PBC and AIH in patients with pSS and Table 3 presents the research on the prevalence of pSS in patients with PBC. The pooled proportion of AHI and PBC was 2% (95% CI 1% to 3%) and 5% (95% CI 4% to 5%), respectively (see Appendix 1, Figs. 1 and 2).

Review of the literature

Tsianos et al., in Greece, evaluated 38 patients with PBC. Symptoms of Sjögren's Syndrome were present in 18 (47.4%) patients. Nineteen patients were evaluated using the Schirmer-I test, salivary flow, serum autoantibodies, lip biopsy, and HLA typing. Salivary biopsy was positive in 5 (26.3%) patients. Serologic tests and HLA were not similar to those described in the pSS, but similar to those described in patients with RA and SS. The findings indicated that Sjögren's Syndrome associated with Primary Biliary Cirrhosis is a secondary form of SS, resembling that associated with Rheumatoid Arthritis [4].

Skopouli et al., in Greece, published a cross-sectional study, investigating hepatic impairment in 300 patients with pSS. Seven percent of patients presented evidence of liver disease (subclinical in 2%, asymptomatic in 5%, with increased liver enzymes). In 6.6% of the patients, anti-mitochondrial antibodies (AMA) were detected by immunofluorescence, of which 92% showed liver biopsy compatible with stage I PBC. The authors concluded that liver involvement in pSS is rare and subclinical, with histologic biopsy aspects mainly in PBC stage 1. AMA was the most sensitive indicator for liver disease in patients with pSS [1].

Csepregi et al. published a cohort study that aimed to assess the clinical value of AMA and ASMA antibodies as serological markers in predicting the development of autoimmune liver disease in patients with pSS. Both antibodies were investigated in one hundred and eighty patients with no history of liver involvement, and the patients were followed for five years. Nine patients (5%) had autoimmune liver disease (five PBC, two type 1 autoimmune hepatitis, one autoimmune hepatitis and hepatitis C overlap, and one diagnosed with autoimmune cholangiopathy). Three patients were positive for AMA at the baseline, two of them developed symptomatic PBC, while the other, who did not undergo the biopsy remained asymptomatic during the 5 years of follow-up. Twenty seven patients (39%) had positive ASMA, most with titers of 1:80, and only three, who were those who developed autoimmune hepatitis, presented titers ≥ 1:160 [30].

High titers of ASMA and AMA are the most specific indicators for AIH and PBC. It is suggested that patients with high titers of ASMA and AMA, even in the absence of any biochemical and clinical evidence of chronic liver disease, should have regular liver biochemical tests and follow-up with a hepatologist [26].

Kaplan et al. in a retrospective study of 73 cases of pSS, found that 49.1% of patients had abnormal liver function tests, including 20.3% with clinically evident liver disease. Hepatic involvement was significantly more common in patients with pSS who also had evidence of pulmonary, renal, and hematological involvement. Patients with abnormal liver function tests had more elevated ESR and positive ANA during the course of the disease. The authors concluded that hepatic involvement is a common

complication in pSS. Its presence correlates with systemic disease and this complication should be considered in patients with pSS, especially those with positive ANA and evidence of systemic inflammatio [2].

Nardi et al. analyzed the prevalence and clinical significance of autoantibodies in a cohort of 335 patients with pSS in Spain. The authors detected positive ANA in 83%, anti-Ro in 33%, anti-La in 23%, anti-RNP in 2%, anti-Sm in 1%, anti-smooth muscle antibody in 62%, and anti-parietal cell in 27%. AMA was detected in 28 patients (8%), although only 14 had evidence of liver involvement. The presence of anti-smooth muscle antibody, despite the high prevalence (62%), did not present clinical significance in pSS. AMA and anti parietal cell positivity suggest an association with some organ-specific autoimmune diseases (thyroiditis, Primary Biliary Cirrhosis) [6].

Ramos-Casals et al., in Barcelona, investigated 475 patients with SS. Liver involvement was detected in 129 (27%) patients. The main etiologies were chronic viral liver disease in 64 (13%) (chronic hepatitis C in 63 and HBV infection in 1), and autoimmune disease in 24 (5%) of the cases (PBC in 16 patients and autoimmune hepatitis type-1 in 8 patients). Chronic viral disease, mainly because of HCV, was the main cause of liver involvement in SS, with a prevalence of 13%, nearly 3 times higher than autoimmune liver involvement (5%). Patients with autoimmune liver disease had higher ESR and gamma globulin values and a higher prevalence of ANA, antimitochondrial, anti-smooth muscle, anti-Ro, and anti-La antibodies, while patients with chronic viral liver disease had a higher frequency of cryoglobulinemia and hypocomplementemia [3].

Hatzis et al. published a cross-sectional study that aimed to assess the prevalence of PBC and its progression in patients with pSS. The authors evaluated 410 patients with pSS, without a previous history of liver disease, and found biochemical alterations with a cholestatic pattern in 36 patients (8.8%), of which 21 patients (5.1%) had positive antimitochondrial antibodies (AMA). The prevalence of PBC was 6.6% (27 cases), with stage 1 PBC lesions found in most cases. Five patients underwent a second liver biopsy and there was no significant histological worsening after a mean interval of 46 months. The authors concluded that PBC is uncommon in patients with pSS. The disease appears to be pathologically mild, with slow progression in clinical, biochemical, and histological evaluations [23].

Malladi et al. assessed the prevalence of specific extra-glandular manifestations in the SICCA Registry among 1.927 participants enrolled at 9 SICCA sites in 7 countries. The authors found that the prevalence of specific organ manifestations in pSS is relatively low. Among 886 participants who met the 2002 American-European Consensus Group (AECG) criteria for pSS, PBC was found in 17 patients (1.9%) and AIH in 9 patients (1%) [9].

Zhu et al., in China, evaluated 76 AIH cases, 40 AIH cases with SS and 36 AIH cases without SS. Comparing the two groups, the proportion of women was 97.5% in the first and 77.8% in the second, age at diagnosis < 60 years in 70% and 47.2%, mean course of the disease of 30 months and 9 months, all statistically significant differences. The main complaints in both groups were cutaneous (52.5% vs 38.9%), abnormal transaminases (17.5% vs 44.4%), and dry mouth and eyes (15.0% vs 2.8%), all with significant differences. The average levels of total bilirubin, direct bilirubin, and IgM in the AIH + SS group were higher than in the AIH group. The mean albumin and C3 level in the AIH + SS group was lower than in the AIH group. The positivity rate for AMA, anti-Ro, and anti-La in the AIH + SS group was higher. There was no significant difference in histological changes in hepatocytes and bile duct injury. In young or middle-aged women with AIH, it is necessary to be vigilant with SS if the patient presents cutaneous manifestations and high titers of autoantibodies [39].

Yan SM and colleagues in China retrospectively analyzed 60 patients with pSS with antibody anticentromere (ACA) compared to patients with pSS without ACA. The mean age of patients at onset of pSS with ACA was higher than those without ACA. Patients with ACA had a higher prevalence of liver involvement and a lower prevalence of renal involvement, neuropathy, and hypergammaglobulinemia. Although both groups had the same ANA prevalence, the immunofluorescence patterns of ANA were different, a slight speckled pattern was more frequent in patients with ACA and occurred in 61.7%. Patients with ACA had a lower prevalence of anti-SSA, anti-SSB, Rheumatoid Factor, and anti-U1RNP and a higher prevalence of antimitochondrial antibodies. The authors concluded that patients with ACA-positive pSS are at high risk of liver involvement and may be a special subtype of SS [40].

Montaño-Loza et al., in Mexico, analyzed 95 patients with pSS, of which 42 patients (44%) had abnormal liver biochemical tests, and of these 19 patients (20%) had clinical liver disease. Patients with abnormal liver biochemistry had a higher frequency of autoimmune hypothyroidism, arthritis, vasculitis, and Raynaud's phenomenon, higher ESR, and a higher frequency of AMA than patients with normal liver biochemical tests. Patients with clinical liver disease had a higher frequency of arthritis, vasculitis, and AMA than patients without clinical liver disease. Twenty-one patients were diagnosed with specific liver disease such as hepatitis C (n = 11), autoimmune hepatitis (n = 2), primary biliary

cirrhosis (n = 5), nonalcoholic steatohepatitis (n = 2), and virus B infection (n = 1). The authors concluded that hepatic involvement is frequent in patients with pSS and its presence is associated with clinical manifestations of systemic diseases and markers of autoimmunity and inflammation [7].

Machida et al., in Japan, reported a case of Reactive Lymphoid Hyperplasia of the liver, clinically known as pseudolymphoma, in a 53-year-old woman with a liver tumor and suspected hepatocellular carcinoma. Surgical resection of three small lesions was performed. Histopathological examination with immunohistochemistry diagnosed reactive lymphoid hyperplasia, a rare condition, with only 12 cases reported in the English literature. Most reported cases are in middle-aged women that have an immune disease, such as autoimmune thyroiditis, Sjögren's Syndrome, Primary Biliary Cirrhosis, Primary Immunodeficiency. Although the pathology is similar to malignant lymphoma, the clinical course is completely benign. Differential diagnosis of liver Reactive Lymphoid Hyperplasia with hepatocellular carcinoma is necessary [10].

Valera et al., in Chile, in a retrospective review of 13 years, analyzing the medical records of 115 patients with PBC (110 women, aged between 30 and 76 years), found that 78% were symptomatic on presentation (itching, fatigue) and 56% of cases were AMA positive. Sjögren was present in 38%, hypothyroidism in 13%, scleroderma in 7%, and RA in 5% [41].

Zhang et al., in China, reviewed the clinical manifestations and laboratory findings in 40 patients with PBC (37 women with a mean age at diagnosis of 50.5 ± 7.8 years). The most frequent symptoms were fatigue (67.5%), jaundice (60%), and pruritus (32.5%). Eight patients (20%) had an associated autoimmune disease (Sjögren and/or RA). Very high levels of alkaline phosphatase and GGT were found in all cases (100%), with slightly elevated transaminases. Thirty-five patients (87.5%) had elevated serum IgM and 97.5% (39/40) were AMA/AMA2 positive. Therefore, the finding of elevated alkaline phosphatase and GGT together with positive AMA/AMA2 could help in the diagnosis of PBC. Liver biopsy is useful to confirm the diagnosis and to differentiate the histopathological stages [42].

A significant number of patients with PBC have "sicca syndrome", among them patients who have classic Sjögren's syndrome. Both PBC and SS are characterized by inflammation of the "target" epithelial elements. Both diseases can be considered on the basis of a number of other related clinical aspects, including unique apoptotic findings of target tissue, the role of secretory IgA, and the frequency with which both diseases overlap [27].

Lee and colleagues in South Korea investigated the prevalence and predictors of silent, but substantial liver fibrosis in 101 patients with pSS with normal liver function and no significant liver disease or other conditions affecting the liver. Hepatic stiffness was analyzed by elastography. Twelve patients (11.9%) had significant liver fibrosis and their predictors were leukopenia ≤ 4000/mm [3], serum albumin ≤ 3.8 mg/dL, and aspartate aminotransferase ≥ 27 [8].

There are few cases of pSS in childhood with gastrointestinal and liver lesions reported in the literature. Kashiwagi and collaborators, in 2017, reported five cases in Japan, four cases with atrophic gastric antrum or chronic gastritis. Liver biopsies in two cases revealed non-alcoholic steatohepatitis [43].

Lindgren and colleagues, in Sweden, investigated autoimmune liver disease in 45 patients with pSS. Liver function tests were abnormal in 12 patients (27%), in 8 cases with cholestatic pattern. Elevated IgM levels (> 2 g/l) were observed in 9 patients, AMA positive in 6 patients, and anti-smooth muscle antibody positive in 3 patients, with a percutaneous liver biopsy diagnosis of PBC in 4 patients and chronic active AIH in 2 patients. The study showed that abnormal liver function tests in patients with pSS are frequent and may indicate autoimmune-associated liver disease [44, 45].

Wang and colleagues in China evaluated 322 patients with PBC and investigated the presence of connective tissue disease (CTD) and systemic involvement. One hundred and fifty patients (46.6%) had one or more CTDs, with pSS being the most frequent (121 cases, 36.2%). Compared with patients with only PBC, patients with PBC + pSS had more frequent fever, higher ESR, higher serum IgG levels, a higher frequency of Rheumatoid Factor, and a higher incidence of Interstitial Pulmonary Disease [46].

Karp et al. retrospectively in 2010, based on the AECG criteria, established the diagnosis of pSS and secondary Sjögren's Syndrome in 202 patients referred to the Sjögren Syndrome Clinic, 58 patients met the criteria for pSS and 8 for secondary Sjögren's Syndrome. Among the 58 patients with pSS, there was 1 case of AIH (1.7%). One symptomatic patient who did not meet the pSS criteria had AIH. No patients with secondary Sjögren's Syndrome had AIH. Of the 194 patients with pSS or clinical symptoms, 2 patients (1%) had Primary Biliary Cirrhosis [47].

The prevalence of PBC in patients with pSS ranges from 4 to 9%, with two studies including more than 400 patients with pSS [3, 7, 23, 35, 45]. In some studies that analyzed the prevalence of autoimmune diseases in patients with PBC, pSS was the most prevalent. Wang et al. found that 36.2% of 322 patients with PBC had pSS,

and Valera et al. found 38% pSS in 115 patients with PBC. Marasini reported lower prevalences of pSS in patients with PBC (3.5% of 170 patients) [18, 41, 46, 47].

Esophagus involvement

Recommendation

2. Subjective swallowing difficulties, heartburn, and symptoms associated with LPR (Laryngopharyngealreflux) are more prevalent in pSS patients than in controls. All symptomatic patients should be investigated in accordance with specific clinical guidelines and we recommend that treatment should be established, even in the absence of objective abnormalities.

Dysphagia is a relatively common gastrointestinal complaint in pSS and has been reported in 33% to 92% of patients [37, 48–54]. This wide range in prevalence may be explained by two factors: the small series of patients studied and the different criteria used for SS diagnosis.

Theoretically, saliva has an essential role in food processing inside the oral cavity and in transferring the bolus through the pharynx and esophagus. The lack of saliva, esophageal dysmotility, or even esophageal webs are hypothesized to be the major reasons for dysphagia [48]. However, the majority of studies failed to show any correlation between salivary flow or esophageal webs and the dysphagia [52, 54]. The pooled proportion of dysphagia was 70% (95% CI 58% to 79%) (see Appendix 1, Fig. 3).

In Mandl T et al., pSS patients experienced significantly more dysphagia compared with controls (65% vs. 3%; $p<0.001$). In addition, pharyngeal (45% vs. 7%; $p<0.01$), esophageal (80% vs. 7%; $p<0.001$), and gastro-esophageal reflux symptoms (60% vs. 23%; $p<0.01$) were also more prevalent in pSS patients. In spite of this, pharyngeal (15% vs. 17%; $p=$NS) and esophageal dysmotility (40% vs. 30%; $p=$NS) were not different between the groups [49]. Likewise, as summarized in Table 4, the majority of studies which evaluated dysphagia and GI motility disorders showed that these are not consistently associated [48–52, 55].

With regard to the heartburn symptom, it has been reported in 24% to 62% of SS patients. Although it might be correlated with abnormal 24-h pH recordings and the presence of tertiary waves [50, 51], some studies found it to be rare or absent [48, 49, 54]. One study from the National Health Insurance Database in Taiwan, evaluated 4650 patients with SS and found that the risk of gastroesophageal reflux disease was 2.41-fold greater than that for the comparison cohort after adjusting for age, sex, and comorbidities. In addition, in age stratified analyses, the youngest Sjögren's syndrome cohort (age: 20–44 years old) had the highest risk (HR 3.02; 95% CI 2.48–3.69) [56].

Laryngopharyngealreflux (LPR) has been associated with dysphonia, chronic cough, reactive airway disease, middle ar effusion, throat pain, excessive throat mucus, post nasal drip, dental caries, and laryngeal cancer. Interestingly, these symptoms frequently occur in the absence of heartburn and esophagitis, and, thus, a high index of suspicion for LPR must be maintained [56].

In summary, subjective swallowing difficulties, heartburn, and symptoms associated with LPR are more common in pSS patients than in controls and diagnosis must rely on clinical settings since they are, in general, poorly correlated with endoscopy images or other objective signs of dysmotility.

Gastric involvement

Recommendation

3. Epigastric pain, dyspepsia, and nausea are all more prevalent in pSS patients than in controls, in spite of being poorly correlated with objective signs of dyspepsia. All symptomatic patients should be investigated in accordance with specific clinical guidelines and we recommend that treatment should be established, even in the absence of objective abnormalities.

Epigastric pain, dyspepsia, and nausea are common clinical symptoms in pSS. In general, symptoms tend not to correlate with endoscopic or histologic findings [57, 58]. However, if so, there might be an association with an unspecific chronic gastropathy [59]. In studies in which pSS patients underwent endoscopy and histological examination, chronic atrophic gastritis was reported to have an increased prevalence (25% to 85%) in comparison to the general population [57, 58, 60,

Table 4 Dysphagia and GI motility disorders in Sjogren syndrome

References	Study type	n	Dysphagia (%)	GI motility disorder
Kjellen et al. [48]	Case–control	22	73	No
Grande et al. [52]	Cross-sectional	20	75	No
Palma et al. [51]	Case–control	21	70.6	No
Anselmino et al. [54]	Cross-sectional	27	74	Yes
Rosztoczy et al. [55]	Case–control	25	92	Yes
Volter et al. [50]	Case–control	21	33	No
Turk et al. [53]	Case–control	40	65	Yes
Mandl et al. [49]	Case–control	22	65	No

61]. In addition, high prevalences of hypopepsinogenemia and hypergastrinemia have been reported in the same patients. In addition, the lowest pepsinogen levels were associated with high levels of SS-B antibody, raising the point of a possible role of serologic parameters in the severity of the gastritis. Taken together, these data could reinforce the hypothesis for a physiopathological connection between pSS and chronic atrophic gastritis. However, published studies showed that gastric parietal cell antibodies were found in only 13% of patients with chronic atrophic gastritis and pSS or in 10 to 27% of patients with isolated pSS [58, 62]. Furthermore, low vitamin B12 levels or pernicious anemia have rarely been described, even considering the group of patients that are positive for the antibody [61, 63]. Therefore, although dyspepsia is relatively common in pSS, the exact physiopathology associated with this finding is not well understood. The prevalence of chronic atrophic gastritis is increased in this population, but there is no straight forward correlation between the histopathological findings and the presence of the specific antibodies or nutritional deficiencies.

With regard to *H. pylori* infection, some reports have been published suggesting a possible pathophysiologic link with Sjögren's syndrome. Although *H. pylori* infection is usually asymptomatic, it has been identified as an antigenic stimulus in the gastric mucosa for accumulation of lymphoid tissue, including the subsequent development of gastric lymphoma. Miedany et al. found that patients with SS were more prone to have *H. pylori* infection, in comparison to other connective tissue diseases or normal controls. The authors also described that the serum antibody titer to *H. pylori* correlated with an index for clinical disease manifestations, age, disease duration, and CRP [64]. Aragona et al. corroborated these results with similar findings [65]. In spite of this, others obtained opposite results, demonstrating a similar prevalence of *H. pylori* infection between patients and controls [66, 67]. In a recent meta-analysis, which included nine studies with 1958 participants, the total infection rate of *H. pylori* was 53.83% (1054/1958). Patients with SS had a significantly higher *H. Pylori* infection rate than control groups (OR 1.19, 95% CI 1.01–1.41, $p = 0.033$) [68]. These controversial data probably occur because of the small number of published studies, associated with the variability in the use of the diagnostic criteria of SS and heterogeneity in the control groups used. Consequently, we do not have a definitive understanding on this matter and more data are necessary to come to an exact conclusion.

Bowel involvement

Recommendation

4. Considering the increased prevalence of celiac disease (CD) in Sjogren's syndrome, patients with GI symptoms should undergo laboratory screening (mainly antibodies) and proceed with a small bowel biopsy if they test positive.

Abdominal discomfort occurs in up to 37% of patients with SS, constipation in up to 23%, diarrhea in up to 9%, and iron deficiency anemia due to malabsorption in up to 5% [38]. However, documented intestinal involvement, such as inflammatory bowel disease, vasculitis, neoplasia or pseudo-obstructions are rarely described.

Celiac disease (CD) is a chronic autoimmune disorder primarily affecting the small bowel and induced by an abnormal immune response directed against gluten ingestion in genetically susceptible individuals. The relationship between CD and autoimmune diseases has been investigated in various studies. It is hypothesized that both conditions might have common genotypes, or systemic immune reactions triggered by food antigens, or even that the intestinal villus damage could lead to a "leaky gut". Several studies that show an increased prevalence of CD or its immunolaboratory features in patients suffering from SS. *Luft* et al. demonstrated that anti-tissue transglutaminase antibody (a highly sensitive and specific test in CD) was present in 12% of SS patients compared to 4% of normal controls. Additionally, 5/6 of the patients with the antibody presented symptoms, signs or a small bowel biopsy compatible with CD [69]. In *Itanen* et al., 34 patients with pSS and 28 controls underwent a small bowel biopsy. Five (14.7%) SS patients presented alterations compatible with CD. None of them had diarrhea, but three complained of abdominal discomfort which was alleviated by a gluten free diet [70]. *Szodoray* et al., evaluated 111 SS patients for clinical or immunolaboratory signs of CD. Six patients had positive serology for CD and underwent jejunoscopy and a small bowel biopsy to confirm the diagnosis. In five patients, the diagnosis was established histologically, demonstrating that the prevalence of CD in SS is higher than expected in the general population (4.5 in 100×4.5–5.5 in 1000) [71]. In contrast, the findings of a higher prevalence of SS or its associated antibodies have been controversial in CD [72–76]. In addition, a gluten free diet ameliorates symptoms associated with CD, but does not ameliorate sicca symptoms [77]. On the basis of these data, we recommend active clinical and laboratory screening of CD in SS, proceeding with a small bowel biopsy on those patients who

test positive. Furthermore, in a high suspicion clinical scenario, as 2 to 3% of patients have a negative transglutaminase antibody, a biopsy should also be performed.

Pancreas involvement

Recommendation

5. Patients with pSS are at a low risk of developing symptomatic acute or chronic pancreatitis. Subclinical involvement is more frequent and 25% of patients present abnormal amylase rates. It is recommended that amylase and lipase dosages be requested in symptomatic patients with pSS, especially in the presence of other risk factors for pancreatitis (alcoholism, cholelithiasis, diabetes, and use of prednisone > 5 mg/day).
6. We recommend screening for exocrine pancreatic insufficiency and imaging tests such as USG, CT, MRI, or ERCP in symptomatic patients, according to clinical guidelines. Differential diagnosis with Igg4 disease and other causes of pancreatic diseases should be addressed.

The pancreas exerts both exocrine and endocrine functions and pancreatitis may be fatal or lead to severe complications [78]. As an exocrine gland, the pancreas is functionally and histologically comparable to the salivary glands, so its dysfunction in SS has long been postulated [79]. However, despite the similarities of both tissues, symptomatic involvement of the pancreas as acute or chronic pancreatitis is, fortunately, a rare event in pSS patients [80–83]. Pancreatic symptoms in Sjogren´s syndrome patients are usually mild and subclinical and might not be correlated with morphological or imaging findings.

Acute pancreatitis prevalence in Sjögren´s syndrome ranges from 0.5% [79, 84] to 3% [85]. In Taiwan, 44 cases of acute pancreatitis (Table 5) were found among 9468 pSS patients, an incidence significantly higher than in the control group (0.46% versus 0.28%, respectively) [86]. An attending study on autoimmune pancreatitis (AIP) in Japan pointed to the diagnosis of SS in 25% of 54 AIP patients [87]. Patients with pSS exhibit a 2.9-fold risk for acute pancreatitis and patients with secondary SS (sSS) exhibit a 4.1-fold risk compared to non-SS controls (3.85, 4.3, and 2.8, respectively), for systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis sSS [88]. The use of cyclophosphamide seems to be associated with an increased risk of acute pancreatitis, possibly due to direct toxicity or, perhaps, because it is a marker of more severe systemic disease. Hydroxychloroquine use reduces the risk [86]. In addition to the typical exposures such as alcoholism, gallstone, and metabolic factors, autoimmune diseases also increase the chance for pancreatitis [78, 85–88] and primary SS is an independent risk factor for its occurrence. The pooled proportion of acute pancreatitis was 0% (95% CI 0% to 1%) (see Appendix 1, Fig. 4).

The concept of pancreatitis associated or caused by autoimmune mechanisms has been occasionally described since the reports of Sarles et al. [89]. The main features established for the AIP diagnosis are: increased serum gamma-globulin or IgG levels; presence of autoantibodies; diffuse enlargement of the pancreas; narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (ERP); lymphocytic infiltration and fibrosis of the pancreas; only mild symptoms or asymptomatic courses; constriction of the common bile duct in the pancreas with dilatation of the bile duct upstream; cholestatic liver dysfunction and hyperbilirubinemia; no pancreatic calcification; no pancreatic cysts; occasional association with other autoimmune diseases; and effectiveness of steroid therapy [90, 91].

The international consensus diagnostic criteria for autoimmune pancreatitis [91] classified AIP into type 1 and type 2. In type 1 AIP, the pancreas is affected as part of a systemic IgG-4–positive disease, also known as lymphoplasmacytic sclerosing pancreatitis, with high IgG4 levels and a recurrent course. Type 2 AIP is rarer, restricted to the pancreas, and characterized by histological duct centric pancreatitis, often with granulocytic epithelial lesions withoutIgG-4 [91–94]. There is a strong association between AIP and other immune-mediated disorders, including IgG-4–associated cholangitis, mediastinal fibrosis, retroperitoneal fibrosis, and tubule interstitial disease (type 1 AIP) [93], or inflammatory bowel disease (type 2 AIP) [94].

The most frequent laboratorial reports are increased pancreatic enzymes and exocrine dysfunction. Serum amylase, pancreatic isoamylase, lipase, and trypsin are often normal or slightly increased in symptomatic or asymptomatic subjects, indicating a mild subclinical inflammatory process in 25% to 33% of SS patients [95, 96]. Even though trypsin was found to be the most commonly increased enzyme (35.3% of pSS patients), it does

Table 5 Acute pancreatitis prevalence in Sjögren syndrome (pSS)

References	Country	Study type	pSS, n	Acute pancreatitis (%)
Ramos Casals et al. [7]	Spain	Retrospective Cohort	1010	5 (0.5%)
Chang et al. [86]	Taiwan	Retrospective Cohort	9468	44 (0.46%)

not seem to be related to clinical or radiological findings [95]. Hypergammaglobulinemia and IgG serum level increases have been reported in percentages ranging from 37 to 76% in AIP [91]. A high serum IgG-4 concentration in IgG4-related disease is striking, but a minor IgG-4 elevation can be seen, rarely, in pancreatic cancer, chronic pancreatitis, and Sjogren´s syndrome [97]. Non-specific autoantibodies, such as antinuclear antibodies, anti-mitochondrial antibodies, and rheumatoid factor have low sensitivity in autoimmune pancreatitis. Currently, there is no definitive serological marker for AIP, although some studies searched for antibodies to salivary and pancreatic duct epithelial cells [98]. Serum antibodies were detected against carbonic anhydrase II in patients with idiopathic chronic pancreatitis and pSS patients [99–101] (30–59%), and lactoferrin antibodies were also detected in 50–76%, however, these antibodies do not present reasonable sensitivity and specificity to separate out patients with AIP from patients with pancreatic malignancy and have not been widely assessed [96, 99].

Evaluation of the alleles of major histocompatibility complex genes mentioned that DRB1*0405 and DQB1*0401 are significantly recurrent in patients with autoimmune pancreatitis when compared to chronic calcifying pancreatitis [102]. Further studies are required to evaluate the meaning of each laboratory indicator and to identify the most reliable.

The exocrine dysfunction in AIP is due to the loss of acinar cells caused by inflammatory infiltration [38, 99], and is reported in 18%-37.5% of patients with pSS. The secretin stimulation test is the optimal trial for detecting exocrine pancreatic insufficiency. However, it is an invasive and technically difficult procedure [38, 86]. Alternative methods such as fecal elastase, lipase, or chymotrypsin measurement are useful only in cases of advanced pancreatic dysfunction. Fecal fat excretion in 24 h, after receiving a diet of 100 g of fat for 3 days, is considered abnormal when fat loss is greater than 7 g/day [103]. Table 6 (Additional file 1) shows studies on pancreatic exocrine dysfunctions in pSS. The endocrine dysfunction could be triggered by blood flow disturbance in pancreatic islets due to parenchyma fibrosis, and may be monitored with glycated hemoglobin [86, 99, 103, 104].

Imaging evaluation is indispensable for the diagnosis of autoimmune pancreatitis [105]. Ultrasound is often the first imaging technique used in patients with obstructive jaundice or upper abdominal pain [105]. A focal, multifocal, or diffuse swelling of the pancreatic gland and involvement of the main pancreatic duct and biliary duct are well-described in USG, computed tomography (CT), and magnetic resonance imaging (MRI) [105, 106]. Pancreatic calcifications, invasion of vessels, vascular encasement, mass effect, and fluid collections are rarely seen in AIP and SS patients [105, 106]. There are no differences insensitivity and specificity between the methods so the evaluation routine depends on the feasibility and experience of the health services. Endoscopic retrograde cholangiopancreatographic (ERCP) may be requested in select cases. There is no characteristic in ECRP related to salivary gland involvement. The benchmarks for autoimmune pancreatitis diagnosis include diffuse irregular narrowing of the main pancreatic duct and wide improvement after steroid therapy [84, 86, 104]. The correlation between the structural (by imaging) and functional pancreatic alterations is fragile in patients with pancreatic insufficiency of different etiologies. A patient presenting with conspicuous exocrine insufficiency may have a structurally normal pancreas. These discrepancies range from 12 to 29% [86].

With regards to histology, the loss of pancreatic parenchyma, its replacement by fibrosis, and mononuclear cell infiltrate are the main features of AIP [87, 106]. In type 1 AIP, extrapancreatic organs have marked lymphoplasmacytic without granulocytic infiltration, storiform fibrosis, obliterative phlebitis, and abundant IgG-4–positive cells. In this case, the pancreas is affected as part of a systemic IgG-4–related disease [91–93]. Autopsies of asymptomatic patients with SS show variable degrees of chronic pancreatitis. Histopathological findings include acinar atrophy, lymphocytic and plasma cell infiltration, typically around interlobular ducts, as well as interstitial fibrosis [86, 106]. It is recommended that a differential diagnosis be made with pancreatic cancer, using the duodenal papilla core biopsy, in atypical cases such as a mass in the pancreas head, obstructive jaundice, and ductal dilation [84].

Referring to treatment, corticosteroids are the most widely used treatment for AIP. The recommendation is an initial dose of 30-40 mg/day for 1–2 months with a decrease of 5 mg every 2–4 weeks and a following maintenance dose of 5–10 mg/day. An adequate response to corticosteroid therapy can be seen in 2–4 weeks by imaging and laboratorial exams and a complete response rate reaches 97–98% of cases [107]. Long-term maintenance doses are recommended to prevent recurrence. Relapsing disease is common and retreatment is often sufficient to re induce remission. When there is a lack of response, reconsideration of diagnosis and exclusion of malignancy is essential [84]. Although steroids remain the mainstay of treatment for patients diagnosed with AIP, immunemodulating agents in conjunction with rituximab have been shown to induce remission in those intolerant to steroid maintenance or weaning [10]. The use of analgesics, enzyme replacement, and other therapeutic options in the management of symptomatic patients, the

interventional management of both uncomplicated and complicated cases, and the role of endoscopic and surgical modalities are well defined in the context of the best available evidence, combined with the experience of the group. It is recommended that AIP should be managed in a multidisciplinary team. All patients with AIP should be advised to stop smoking and to abstain from alcohol consumption [107]. We summarize the recommendations in Additional file 1: Table 7 and included in Additional file 1: Appendix 2—Tables 8, 9 and 10 with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for the different involvements.

Conclusion

The systemic manifestations of SS are not adequately incorporated in clinical practice. This is the second part of a guideline proposed by the Brazilian Society of Rheumatology to cover this gap and we provide 6 recommendations based on evidence and with a high level of agreement between experts for liver, gastrointestinal, and pancreatic care of patients with SS.

Appendix 1

Meta-analyses of Extra-Glandular Manifestations of Primary Sjogren Syndrome (Figs. 1, 2, 3, 4 and 5).

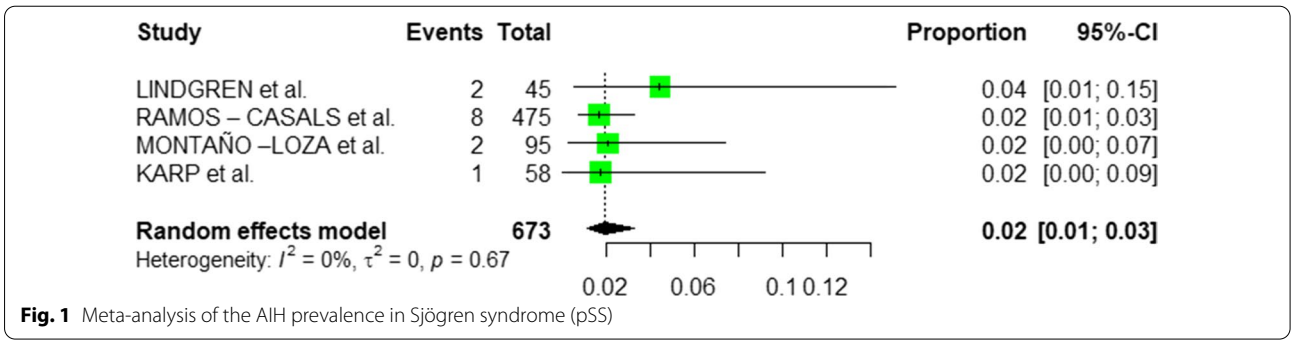

Fig. 1 Meta-analysis of the AIH prevalence in Sjögren syndrome (pSS)

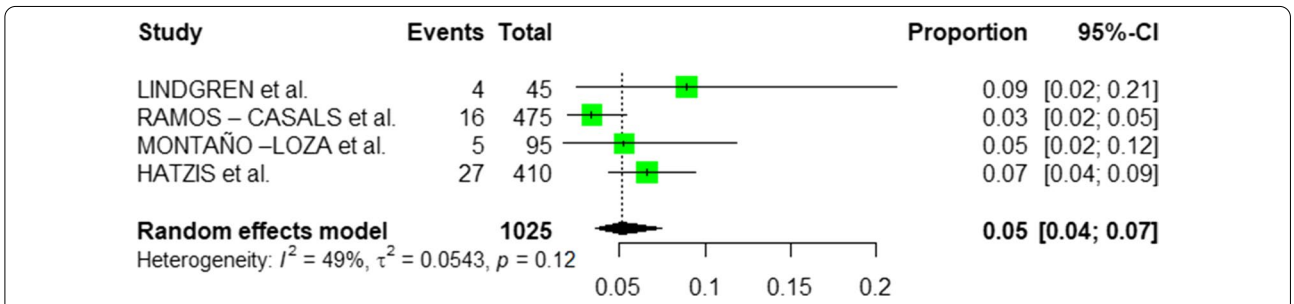

Fig. 2 Meta-analysis of the PBC prevalence in Sjögren syndrome (pSS)

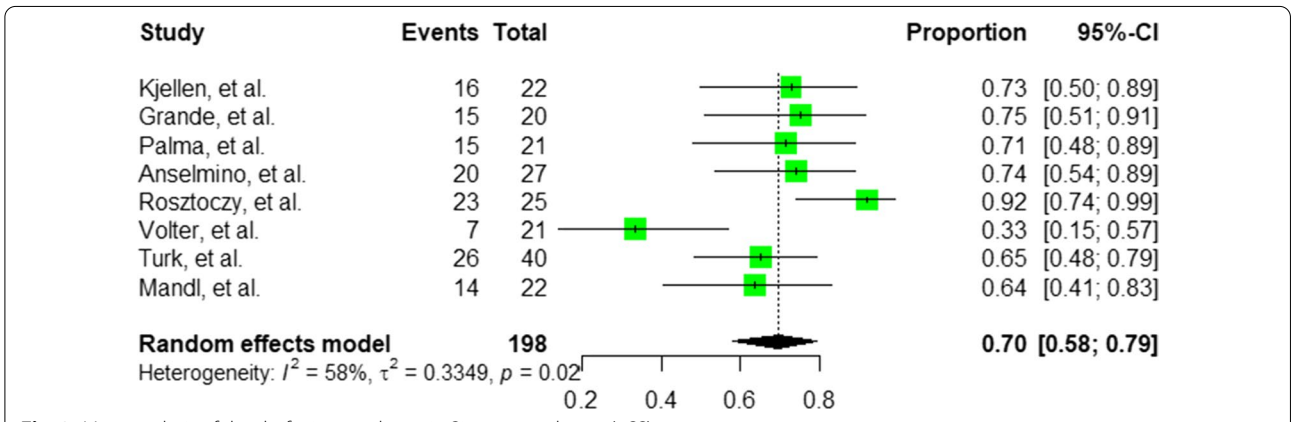

Fig. 3 Meta-analysis of the dysfagia prevalence in Sjögren syndrome (pSS)

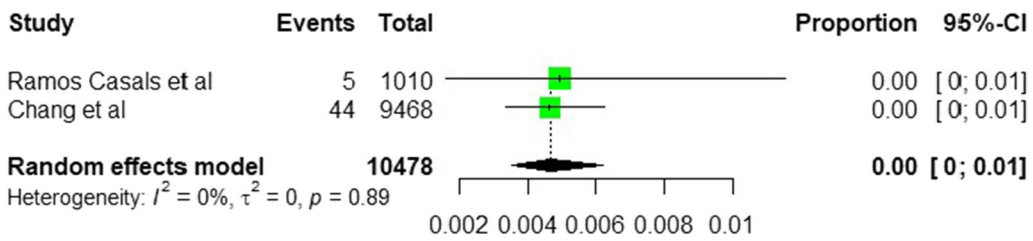

Fig. 4 Meta-analysis of the Acute pancreatitis prevalence in Sjögren syndrome (pSS)

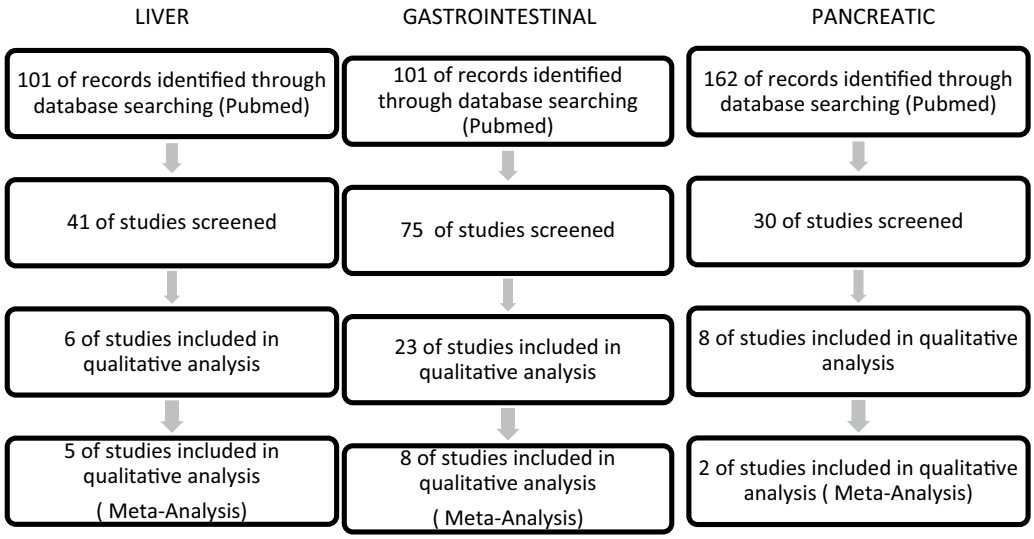

Fig. 5 Study flow diagram

Supplementary Information

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Additional file 1: Search strategy/ Summary of recommendations and Joanna Briggs Institute (JBI) Critical Appraisal Checklist.

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Author contributions
All authors made contributions to the acquisition of data, have been involved in drafting the manuscript or revising it critically for important intellectual content, participated in the voting rounds, gave final approval of the version to be published and have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors read and approved the final manuscript.

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Competing interests
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