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Systematic Review

Autoimmune hepatic involvement in systemic sclerosis—systematic review and meta-analysis

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Abstract

Systemic sclerosis (SSc) is a heterogeneous, multisystem autoimmune disease characterized by fibrosis in genetically predisposed individuals. It can involve multiple organ systems, but hepatic involvement is rare.

In this study, we aim to find the correlation of liver disease, especially primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), in the population with SSc. Further, the correlation of anti-mitochondrial antibody (AMA) and other autoantibodies were done.

Databases were searched for liver disease in SSc, and studies were selected for analysis. Cochrane risk of bias tools and meta-analysis online were used. Controls were taken from the prevalence in the respective countries around the same time.

There was a significant association between PBC and AIH, AMA positivity, and SSc. There was no association with liver fibrosis.

Keywords: Primary biliary cholangitis, Autoimmune hepatitis, Systemic sclerosis, Anti-mitochondrial antibody

Background

Systemic sclerosis (SSc) is a heterogeneous, multisystem autoimmune disease characterized by fibrosis in genetically predisposed individuals. It has unclear pathogenesis but a strong predisposition in first-degree family members. It has a varying extent and often differs in clinical manifestations, skin involvement, complications, and mortality. It is more prevalent in middle-aged women, with incidence more common in North American countries. Poor prognostic factors include male gender and African American race [1].

In SSc, endothelial dysfunction and resultant microvascular damage promote tissue hypoxia and hence inflammation, including overproduction of transforming growth factor-β (TGF-β), resulting in fibrosis, which can affect the gastrointestinal tract from mouth to anus, with smooth muscle atrophy and fibrosis on biopsy. Liver involvement with this pathway is rare and seldom documented. Liver biopsy is similar to PBC, ranging from intrahepatic bile duct damage to portal inflammation, necrosis, and lymphocyte invasion [2,3].

Autoimmunity, such as through anti-mitochondrial antibodies (AMA) is a common driver of cholangiocyte activation and dysfunction as seen in primary biliary cholangitis (PBC) [2,4].

Primary biliary cholangitis, autoimmune hepatitis, and overlap syndrome are common hepatic associations with SSc [5]. A review of 35 patients with AIH identified only 2 patients with SSc. Patients with SSc have increased rates of PBC compared with the general population (2% versus 0.04%) [6,7].

In this systematic review and meta-analysis, we aim to look at studies that examine the incidence of liver disease in patients with SSc. Some of the studies also focus on the extent of liver injury, including steatosis, fibrosis, and cirrhosis.

Methods

The study aimed to observe the incidence of liver disease, associated antibodies, and degree of fibrosis in people diagnosed with scleroderma. PRISMA guidelines were followed (**Figure 1**).

Inclusion criteria for studies included:

1. Patients aged more than 18 years
2. Patients with a confirmed diagnosis of scleroderma
3. Patients with pre-existing scleroderma with elevated transaminases
4. Observational cohort studies, systematic reviews or meta-analyses

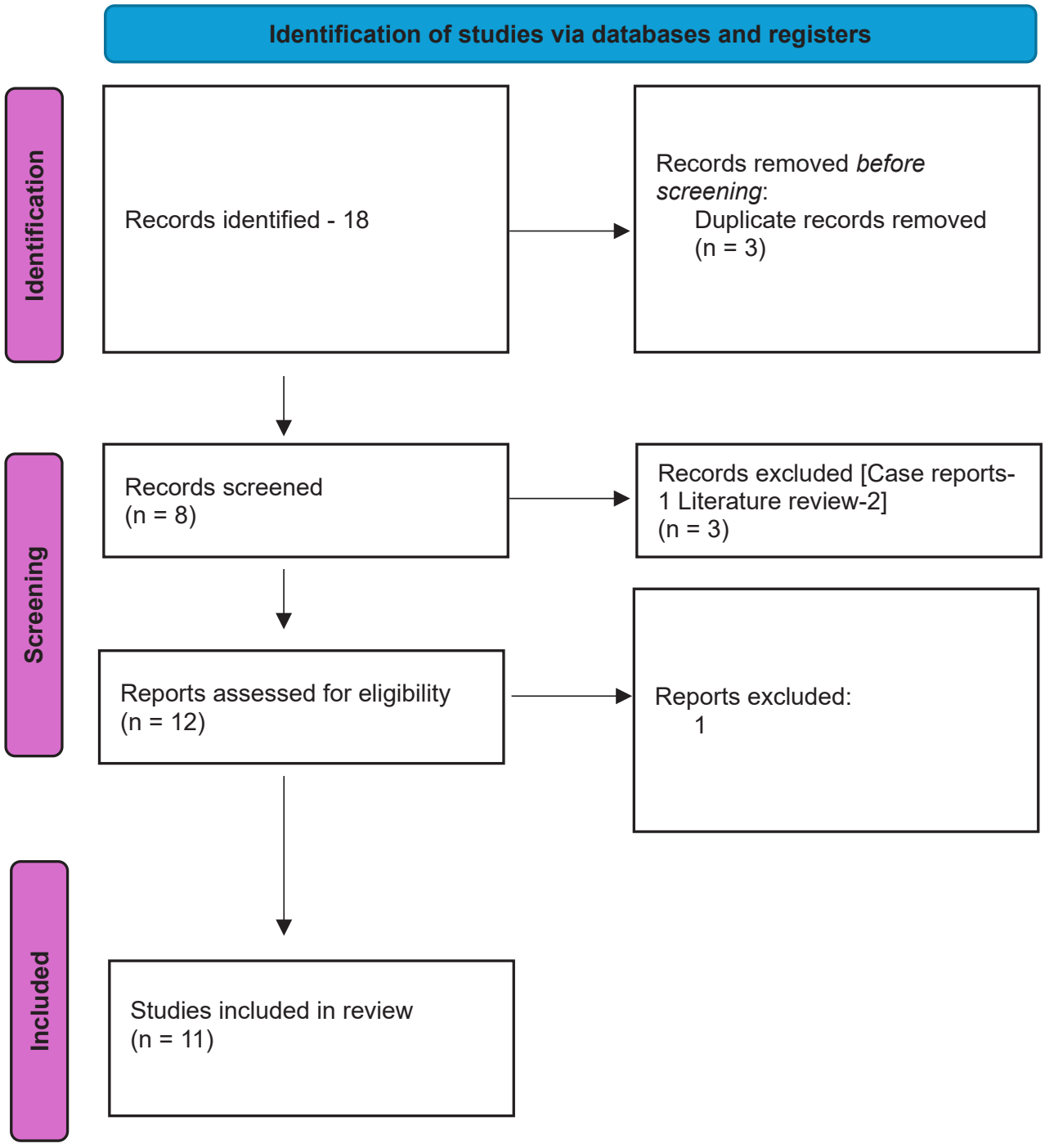


Figure 1. PRISMA flowchart.

Exclusion criteria for the studies:

1. Patients less than 18 years

2. Studies focusing on multi-organ involvement

3. Case reports, case series, or literature reviews were excluded

Databases explored included PubMed, PubMed Central, Scopus, Google Scholar, and Cochrane Library. MeSH terms included ("Scleroderma, Systemic"[MeSH] OR scleroderma) AND ("Liver Diseases"[MeSH] OR liver disease).

The literature search yielded 11 articles; 3 articles were duplicates and were excluded. Amongst 8 leftover articles, there were 2 literature reviews and one case report. These were excluded as well. Five articles, all observational cohort studies, were included in the study, as shown in **Figure 1**. The Cochrane risk of bias 2.0 tool was used, and the risk of bias calculated is shown in **Figure 2**.

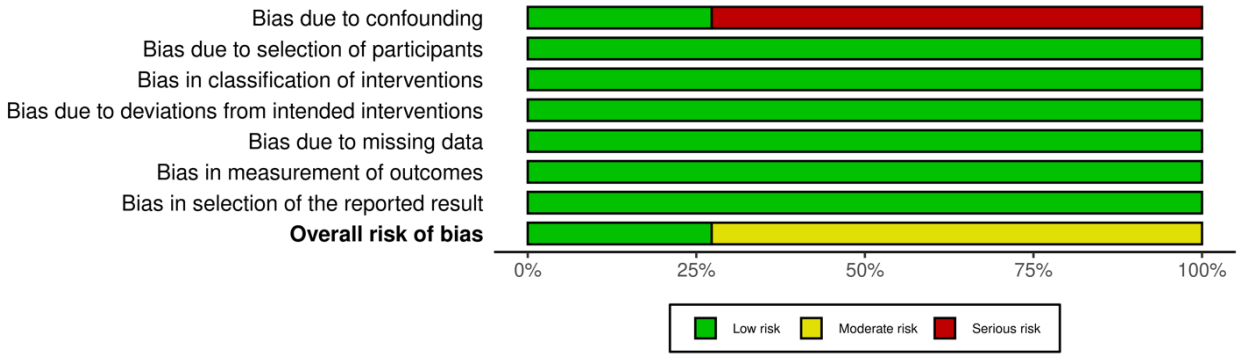


Figure 2. ROBVIS RoB

Three analyses were done. The incidence of patterns of liver injury, especially PBC, was examined. Secondly, the prevalence of different antibodies was determined. Lastly degree of fibrosis as a result of liver injury was checked. Meta-analysis online software was used to derive forest plots.

Results

Table 1 shows the name of the study, type, number of participants, year of study, and country.

Table 2 shows patients who were diagnosed with liver disease. In 2 of the studies, a clear-cut diagnosis of PBC was not made, but transaminase elevation showed a cholestatic disease pattern in 37 and 14 patients, respectively. However, given the lack of formal diagnosis, it shall not be used in the calculation of prevalence in this study. Two thousand seven hundred ninety-seven patients with SSc were investigated, and 190 of them were diagnosed with liver disease. It, however, included 33 patients with alcoholic, metabolic, and viral liver disease, and the last 3 studies only studied PBC. Exclusively,

Table 1. Studies included in the review.

Study	Author	Type	Number	Year	Place
Clinical relevance of liver involvement in the clinical course of systemic sclerosis	Lorena *et al.* [8]	Retrospective observational cohort	97	2018–2020	Italy
Hepatobiliary involvement in systemic sclerosis and the cutaneous subsets characteristics and survival of patients from the spanish registry	Alfonso *et al.* [9]	Retrospective observational cohort	1572	2015	Spain
Liver involvement in patients with systemic sclerosis: role of transient elastography in the assessment of hepatic fibrosis and steatosis	Cuomo *et al.* [10]	Cross sectional	59	2013	Italy
Incidence and predictors of an abnormal liver function test among 674 systemic sclerosis patients: a cohort study	Sawadpanich *et al.* [11]	Retrospective observational cohort	674	2012–2019	Thailand

Study	Author	Type	Number	Year	Place
Evaluation of liver function tests in scleroderma patients	Salem *et al*. [12]	Retrospective observational cohort	40	2012	Saudi arabia
Presence of organ specific antibodies in patients with systemic sclerosis	Wielosz *et al*. [13]	Retrospective observational cohort	86	2006	Poland
Primary biliary cirrhosis (pbc), pbc autoantibodies, and hepatic parameter abnormalities in a large population of systemic sclerosis patients	Assassi *et al*. [5]	Retrospective observational cohort	817	2009	Usa
High prevalence of primary biliary cirrhosis and disease-associated autoantibodies in japanese patients with systemic sclerosis	Imura-kumada *et al*. [14]	Retrospective observational cohort	225	2012	Japan
Primary biliary cirrhosis-related autoantibodies in a large cohort of italian patients with systemic sclerosis	Cavazzana et al. [15]	Retrospective observational cohort	201	2011	Italy
Is prevalence of pbc underestimated in patients with systemic sclerosis?	Norman *et al*. [16]	Retrospective observational cohort	52	2009	Poland
Liver autoantibodies in patients with scleroderma	Skare *et al*. [17]	Retrospective observational cohort	63	2011	Brazil

Table 2. Prevalence of PBC, AIH, and other autoimmune liver diseases in SSc.

AUTHOR	Number of patients with SSc	Liver disease	PBC	AIH	Others
Lorena *et al.* [8]	97	11	7	1	1 PSC 1 NRH 3 Viral Hepatitis 3 Alcoholic Hepatitis
Alfonso *et al.* [9]	1,572	118	67 AMA positive 6 AMA negative	19	26 Secondary liver diseases (n = 11), SSc-related HBI (n = 7), nodular regenerative hyperplasia (n = 3), liver cirrhosis (n = 3), and HBI of unknown origin (n = 2, 0.1%)
Sawadpanich *et al.* [11]	674	430	Possibly 37	NA	NA
Salem *et al.* [12]	40	14	Possibly 12	NA	2
Wielosz *et al.* [13]	86	10	10	NA	NA
Assassi *et al.* [5]	817	16	16	NA	NA
Imura-Kumada *et al.* [14]	225	35	35	NA	NA

157 people had autoimmune-associated liver diseases, accounting for a 6.7% prevalence in SSc patients. PBC accounted for 5%, AIH for 1.20% (not studied in the last 3 studies, so calculated amongst studies 1 and 2). PSC was only seen in 1 patient across the studies. **Figures 3** and **4** show forest plots for the prevalence of PBC and AIH, respectively in patients with SSc and general populations from the respective countries around the same time frame [18–20].

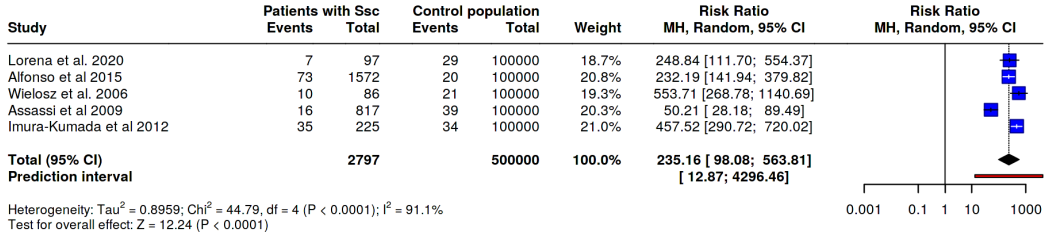
The incidence of AMA positivity was 172 in 1581 patients, accounting for 10.87%, as shown in **Table 3**. The second most common antibody is Anti-sp100 with 3.1% positivity.

Eighteen out of 156 patients had significant fibrosis, accounting for 12.5%. However, the distribution amongst the 2 studies was different as in **Table 4**. In study 1, the prevalence was 16.5%, and most associations were with autoimmune disease. On the other hand, Cuomo *et al.* had a low prevalence of 3.4%. A commonly associated risk factor was triglyceride levels. **Figure 5** shows the forest plot indicating an insignificant relationship with the SSc despite it being a primarily fibrosing condition.

Discussion

Systemic sclerosis (SSc) is a clinically and serologically heterogeneous disease rather than a single entity. The classic division is into limited cutaneous SSc (lcSSc) and Diffuse cutaneous SSc (dcSSc) based on the extent of skin fibrosis. Pulmonary fibrosis, renal crisis are more frequent in dcSSc. Pulmonary arterial hypertension and overlap autoimmunity are more common in lcSSc. Primary biliary cholangitis (PBC) is most strongly associated with the limited cutaneous subtype of systemic sclerosis (lcSSc). However, it has not been explored in this study. Patients with internal organ disease and SSc-specific autoantibodies but minimal/absent skin thickening are called Sine scleroderma (ssSSc) [21].

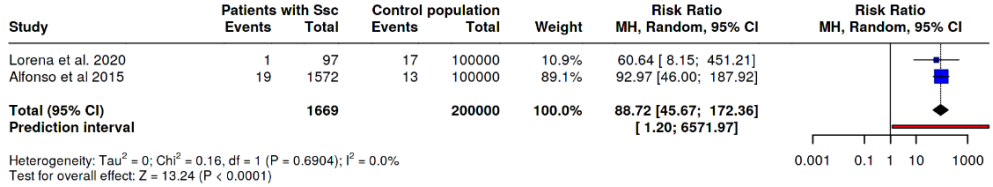
Recent cross-phenotype and genetic-correlation studies show a nontrivial shared genetic background between SSc and PBC. Shared loci include immune-regulatory and HLA-region signals. This genetic overlap plausibly explains why PBC is the most reported autoimmune liver disease co-occurring with SSc. AIH appears in some series as part of overlap syndromes (AIH–PBC overlap rather than isolated AIH). Overlapping features such as shared regulatory T cell abnormalities and common genetic variants (e.g., STAT4, IRF5, NF-κB, IRF8) justify a potential pathogenetic link. The prevalence of disease-specific autoantibodies is considerably higher, indicating a broader subclinical spectrum of hepatic involvement [21]. Hence investigation into associated autoimmune liver disease and antibody profile was also carried out.



Conclusion:

- All together 5 studies were analyzed with a total of 2797 subjects in the Patients with Ssc cohort and 5e+05 subjects in the Control population cohort.
- Based on the analysis performed using random effects model with Mantel-Haenszel method to compare the risk ratio, there is a statistical difference between the two cohorts, the overall risk ratio is 235.16 with a 95% confidence interval of 98.08 - 563.81.
- The test for overall effect shows a significance at p<0.05.
- A significant heterogeneity was detected (p<0.01), suggesting inconsistent effects in magnitude and/or direction. The I2 value indicates that 91% of the variability among studies arises from heterogeneity rather than random chance.

Figure 3. Prevalence of PBC in SSc compared to the general population.



Conclusion:

- All together 2 studies were analyzed with a total of 1669 subjects in the Patients with Ssc cohort and 2e+05 subjects in the Control population cohort.
- Based on the analysis performed using random effects model with Mantel-Haenszel method to compare the risk ratio, there is a statistical difference between the two cohorts, the overall risk ratio is 88.72 with a 95% confidence interval of 45.67 - 172.36.
- The test for overall effect shows a significance at p<0.05.
- We did not observe significant heterogeneity, signaling that the effect sizes across cohorts were consistent in both magnitude and direction.

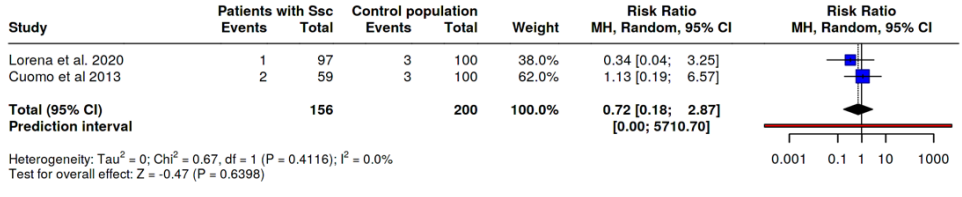
Figure 4. Prevalence of AIH in SSc compared to the general population.

Table 3. Incidence of AMA positivity.

AUTHOR	Number of patients with SSc	AMA	Others
Lorena *et al.* [8]	97	18	Anti SP-100- 4 Anti gp120- 1
Alfonso *et al.* [9]	1572	NA	NA
Cuomo *et al.* [10]	59	NA	NA
Sawadpanich *et al.* [11]	674	NA	NA
Salem *et al.* [12]	40	1	NA
Wielosz *et al.* [13]	817	56	sp100 -26 gp210 -3
Assassi *et al.* [5]	225	37	sp100 -13 gp210 -3
Imura-Kumada *et al.* [14]	86	11	
Cavazzana *et al.* [15]	201	36	sp100 -5 gp210 -1
Norman *et al.* [16]	52	7	sp100-1
Skare *et al.* [17]	63	6	

Table 4. Studies showing differential distribution of Fibrosis.

AUTHOR	Number of patients with SSc	Fibrosis	Comments
Lorena *et al.* [8]	97	16 patients	AMA positivity and ALP were independently associated with liver fibrosis
Cuomo *et al.* [10]	59	2	TAG levels were associated



Conclusion:

- All together 2 studies were analyzed with a total of 156 subjects in the Patients with Ssc cohort and 200 subjects in the Control population cohort.
- Based on the analysis performed using random effects model with Mantel-Haenszel method to compare the risk ratio, there is no statistical difference between the two cohorts, the overall risk ratio is 0.72 with a 95% confidence interval of 0.18 - 2.87.
- The test for overall effect does not show a significant effect.
- We did not find notable variability, implying that the effect sizes across studies were uniform in both size and direction.

Figure 5. Forest plot indicating the relationship of liver fibrosis with the SSc in 2 Italian studies.

This review of 11 retrospective observational studies highlights liver involvement in patients with systemic sclerosis (SSc), a primarily fibrosing autoimmune disease. Out of 2,797 patients with SSc across these studies, 190 were found to have liver disease, with 157 cases attributed to autoimmune etiologies, establishing a 6.7% prevalence of autoimmune liver diseases in this population.

Primary biliary cholangitis (PBC) emerged as the most common autoimmune liver disease associated with SSc, with a prevalence of approximately 5%. This is markedly higher than the general population prevalence of PBC, which ranges from 0.02% to 0.04% depending on the geographic region, underscoring a significant association between PBC and SSc. The association is further strengthened by the notable presence of antimitochondrial antibodies (AMA), detected in 10.87% of patients, which is considerably higher than in the general population and indicates subclinical or evolving PBC in many SSc patients.

Autoimmune hepatitis (AIH) was identified in 1.2% of SSc patients, a figure derived from studies 1 and 2 where a definitive diagnosis was made. This prevalence also exceeds general population estimates for AIH (approximately 0.02%-0.05%), further indicating that SSc patients may be predisposed to broader autoimmune liver involvement.

Serological profiles from studies focusing on PBC revealed the presence of disease-specific autoantibodies in a substantial proportion of SSc patients. Apart from AMA, anti-sp100 and anti-gp210 antibodies were frequently observed. Anti-sp100, found in 3.1%, and anti-gp210, although less frequent, serve as useful markers for PBC diagnosis and prognosis.

Two studies specifically addressed liver fibrosis using elastography. Notably, 16.5% of patients in the first study exhibited liver fibrosis, which was independently associated with AMA positivity and elevated alkaline phosphatase (ALP). In contrast, the rest of the studies found fibrosis in only 3.4%, with elevated triglyceride levels being a more prominent association than autoimmunity. The different incidence of actual fibrosis, possibly confounded by metabolic factors including triglyceride levels, needs further matching. Cholestatic fibrogenesis follows different cell-cell signaling and may be slower in many patients, especially if recognized and treated. SSc is primarily a vasculopathic disease. There's no clear reason why SSc would accelerate hepatocellular fibrogenesis.

Although SSc is recognized as a fibrosing condition, the data do not strongly support a consistent or predominant hepatic fibrosing phenotype across all cohorts. **Figure 5** underscores this variability, showing no significant pooled association between SSc and liver fibrosis, despite localized trends in select populations such as Italy.

Geographic variability was notable, with a higher prevalence of autoimmune liver diseases observed in Italian and Japanese cohorts. This could reflect regional differences in diagnostic practices, genetic predisposition, or environmental triggers.

Conclusion

Hepatic involvement in SSc is under-investigated. Autoimmune conditions, including PBC and AIH, had a significant association as mentioned in the literature. The statistically significant elevation of anti-mitochondrial antibodies also consolidates it. As per fibrosis, despite the fibrosing nature of the disease, a significant association was not seen, and it was mostly associated with pre-existing conditions.

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