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Pathogenesis, Non-Invasive Assessments and Treatment of Hepatic Fibrosis in Autoimmune Liver Diseases

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ABSTRACT

Background and Aims: Autoimmune liver diseases (AILD), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), can lead to progressive liver fibrosis, development of cirrhosis, decompensation, hepatocellular carcinoma (HCC), and need for liver transplantation (LT).

Methods: This review aims to provide a comprehensive overview of the mechanisms of liver fibrogenesis, non-invasive methods to assess hepatic fibrosis and potential anti-fibrotic interventions in AILD.

Results and Conclusions: Current management for AILD should incorporate non-invasive methods to evaluate changes in hepatic fibrosis and consider potential interventions aiming at controlling the progression of the disease, interruption and, potentially, reversal of liver fibrosis. Several laboratory tests can help distinguish patients with advanced fibrosis or cirrhosis but their utility in discriminating earlier histological stages of fibrosis is unclear. A current shift toward non-invasive radiological methods, such as vibration-controlled transient elastography, shear wave elastography, acoustic radiation force impulse imaging and magnetic resonance elastography, opens promising avenues for their wide application; however, their performances may be compromised by hepatic inflammation, ascites, biliary obstruction, or concomitant obesity and metabolic dysfunction-associated steatotic liver disease. Corticosteroids and immunomodulators have been shown to regress fibrosis in AIH patients. In PBC, treatment with either synthetic bile acids, farnesoid X receptor agonists or peroxisome proliferator-activated receptor agonist leads to the improvement or stabilization in the fibrosis stage. There is an urgent need for effective medical treatment in PSC, and available evidence of antifibrotic treatment is particularly limited. Promising anti-fibrotic interventions in AILD encompass conventional pharmacological agents as well as potential new treatments, such as fibrates, monoclonal antibodies, and site- and organelle-specific agents.

Summary

- The progression of hepatic fibrosis in autoimmune liver diseases (AILD) involves key pathophysiological mechanisms, such as cytokines- and chemokines-mediated inflammatory activity, oxidative and nitrosative stress, and apoptosis.
- Blood-based biomarkers and scores along with radiological tools including vibration-controlled transient elastography, shear wave elastography, acoustic radiation force impulse imaging and magnetic resonance elastography provide a non-invasive assessment of liver fibrosis in AILD.
- Liver fibrosis can improve with corticosteroids and immunomodulators in autoimmune hepatitis, synthetic bile acids, farnesoid X receptor agonists and peroxisome proliferator-activated receptor agonist in primary biliary cholangitis; however, there is an urgent need for anti-fibrotic treatment in primary sclerosing cholangitis

1 | Introduction

Autoimmune liver diseases (AILD) are immune-mediated conditions that can present as acute or chronic hepatocellular inflammation and parenchymal damage in the case of autoimmune hepatitis (AIH), and chronic inflammatory destruction and stricturing of bile ducts with cholestasis in the case of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [1–3].

The natural history of AILD is characterised by progressive hepatic fibrosis and, in some cases, cirrhosis development, which is secondary to the severity and duration of inflammatory activity and cholestatic damage [4]. In AIH, progression to cirrhosis is largely influenced by the success of the immunosuppressive treatment and the achievement of complete treatment response [5]. Cirrhosis can develop in as many as 40% of treated AIH patients, and the incidence of histologically proven cirrhosis is approximately 3% per year. Cirrhosis development in AIH increases the risk of liver-related death and the need for LT by over three-fold [6, 7].

PBC is usually a slowly progressive disease and cirrhosis can develop decades after the onset of the disease, although rates vary across studies with some reporting the 5- and 10-year event-free survival rates being 90% and 79%, respectively [8]. In the absence of treatment, the median time to develop extensive liver fibrosis can be as short as 2 years and approximately 50% of people with PBC will progress to histologically proven cirrhosis in 4–6 years from the time of diagnosis [9, 10]. In PSC, over 90% of patients develop fibrosis over 5 years of observation, and the median survival to either LT or liver-related death ranges from 9.6 to 21.0 years [11].

The main factors associated with liver fibrosis include inflammatory activity, pro-inflammatory cytokines, pro-fibrotic chemokines, hepatic cell apoptosis, oxidative and nitrosative stress, gut microbiome composition and diversity, in a complex interplay with environmental aspects [12]. These factors have the potential to maintain and expand liver injury and eventually culminate in an imbalance between accumulation and degradation of extracellular matrix (ECM) leading to fibrosis progression. These pathways constitute key targets for anti-fibrotic intervention.

Non-invasive assessment of hepatic fibrosis has been an active area of research because of the limitations of liver biopsy due to its invasiveness, sampling error, potential complications, and inter-observer variation. Non-invasive assessment tools for hepatic fibrosis include blood-based biomarkers and aggregate biomarker scores, vibration-controlled transient elastography (VCTE), shear wave elastography (SWE), acoustic radiation force impulse (ARFI) imaging, and magnetic resonance imaging elastography (MRE).

The overarching goal of AILD treatment is to suppress inflammatory and cholestatic damage to prevent the progression of fibrosis and the development of cirrhosis and its complications. Liver fibrosis can improve on treatment with corticosteroids and immunomodulators in AIH, and ursodeoxycholic acid (UDCA), obeticholic acid (OCA) and fibrates in PBC, while available evidence for anti-fibrotic treatment in PSC is scarce. Novel anti-fibrotic agents to prevent and reverse liver fibrosis are now emerging with a promise to block established pathophysiological pathways and expand treatment options for AILD.

In this review, we present the pathways of fibrosis in AILD, non-invasive laboratory and radiological assessments of hepatic fibrosis along with their clinical challenges, and potential anti-fibrotic interventions that could be used in AILD.

2 | Pathogenesis of Liver Fibrosis in AILD

2.1 | Inflammatory Activity

Inflammatory activity has a main role in triggering and promoting hepatic fibrosis. $CD4^+$ helper T-lymphocytes become sensitised to self-antigens and separate according to the cytokine paths into intrahepatic $CD8^+$ cytotoxic T- and B-lymphocytes which subsequently evolve into antibody-producing plasma cells [13]. The immune response can trigger cell apoptosis involving the intrinsic or mitochondrial-mediated or the extrinsic or receptor-mediated routes (Figure 1) [14].

The inflammatory state is regulated through the activation of toll-like receptors (TLRs) [12, 15]. Hepatic stellate cells (HSCs), the primary effectors for liver fibrosis, express TLR4, and its activation promotes adhesion molecules and pro-inflammatory chemokines in the damaged tissue [16]. In addition, TLR4 signalling stimulates the action of transforming growth factor-beta (TGF-β), which promotes fibrosis activity on HSCs and myofibroblasts [12]. A circle of inflammatory response and imbalance between pro- and anti-inflammatory responses magnifies damage to the liver cells leading to the production of apoptotic bodies [17].

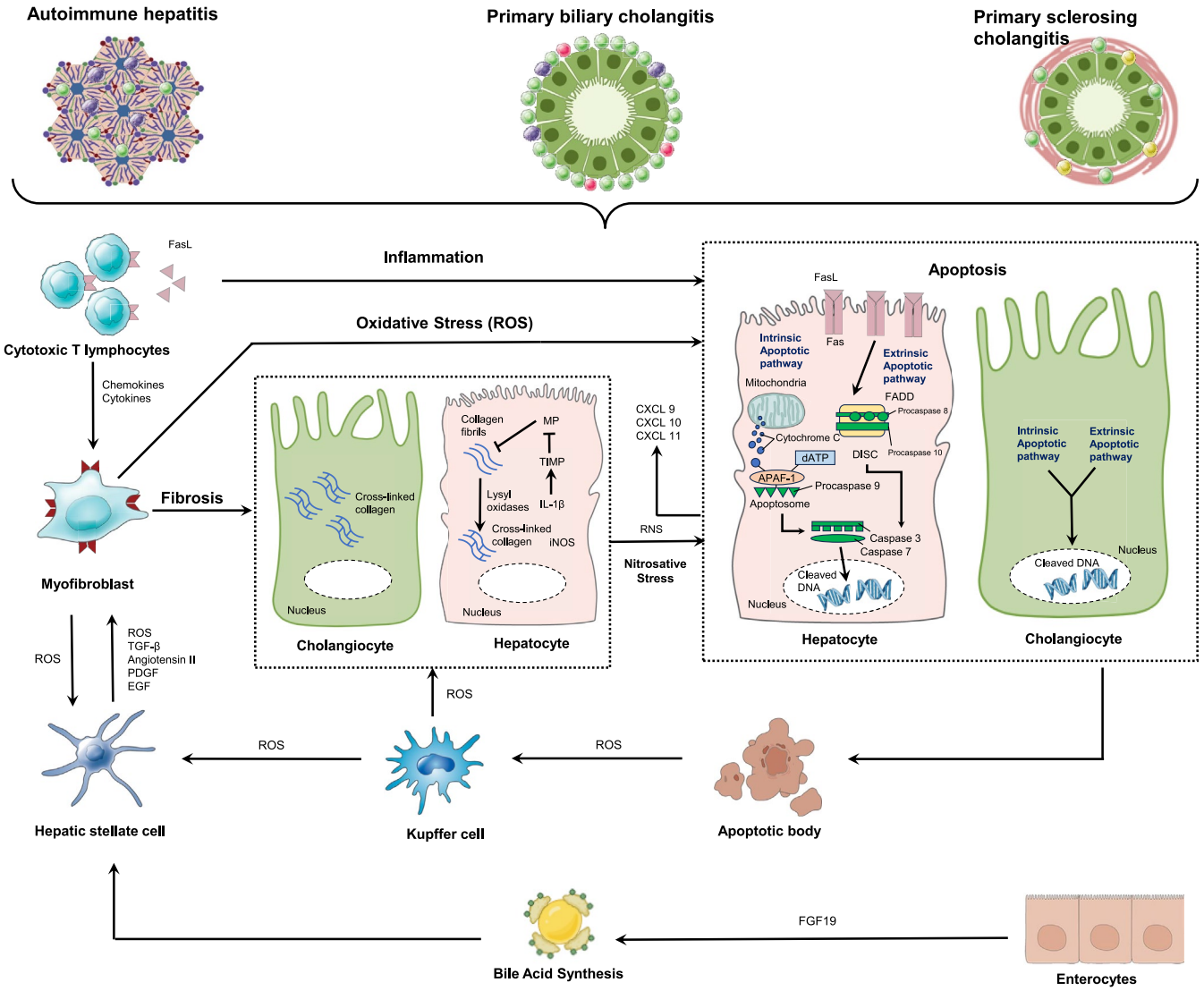

FIGURE 1 | Mechanisms of hepatic fibrosis associated with liver inflammation, oxidative stress, nitrosative stress and apoptosis in AILD.

2.2 | Cytokines and Chemokines

Cytokines are mainly secreted by immune cells and can modulate inflammatory and immune reactions. In AILD, cytokines that promote inflammation and seem to have a major role are tumour necrosis factor (TNF)-α, interferon-gamma (IFN-γ), and interleukins (IL)-1, IL-6, IL-8, and IL-12 [18]. TGF-β, IL-6, and IL-23 activate T helper (Th0) cells to Th17 cells, and Th17 lymphocytes produce TNF-α, IL-1, IL-17A, and IL-17F which also promote an inflammatory state [13]. TGF-β is a major profibrotic cytokine which activates myofibroblast subtypes Smad1 to Smad8 through carboxy-terminal phosphorylation promoting liver fibrosis [19, 20].

Damaged liver cells can release IFN-γ induced chemokines. Chemokines involved in fibrogenesis are the CC chemokine receptors type two (CCR2), type five (CCR5), and C-X-C chemokine ligands (CXCL9, CXCL10 and CXCL11) [17, 21]. These chemokines have the potential to attract immune and inflammatory cells to the areas of liver tissue damage, which promotes apoptosis and fibrosis. In AIH, these chemokines are increased and correlate with the severity and progression of fibrosis [13]. CXCL9 and CXCL10 are also increased in PBC, suggesting an important role in attracting Th1 cells that contribute to liver injury [22]. More recently, the clinical significance of other chemokines, such as CCL4, CXCL12 and CXCL16, and their role in fibrogenesis and resolution of fibrosis, is being explored [23].

2.3 | Apoptosis

Apoptosis constitutes the main pathway of cell death in AILD [14, 24]. The apoptotic bodies promote the generation of reactive oxygen species (ROS), and function as self-antigens which maintain the adaptive immune system stimulation and boost fibrogenesis [24]. In AILD, $CD8^+$ cytotoxic T-lymphocytes can stimulate Fas receptors and caspases 8 and 10, which activate caspases 3 and 7, which can slice chromosomal DNA and lead to cellular death. Inactivated HSCs become active by swallowing up the apoptotic bodies of dying liver cells, and they transition to myofibroblasts through angiotensin II, platelet-derived growth factor (PDGF), TGF-β1, and endothelial growth factor (EGF) [14, 25]. These myofibroblasts produce collagen fibrils that are

cross-linked by lysyl oxidase like-2 (LOXL2) enzymes, which play important roles in ECM by oxidative deamination of the ε-amino groups of lysine and hydroxylysine residues on substrate proteins, such as collagen and elastin.

2.4 | Oxidative and Nitrosative Stress

Oxidative stress is defined as a disruption of the oxidant/antioxidant balance in favour of the former that can lead to tissue damage, thus promoting fibrogenesis in AILD [26, 27]. When HSCs and Kupffer cells become activated, they can produce ROS that cause damage to lipids, proteins and DNA. In addition, nicotinamide adenine dinucleotide phosphate oxidases (NOXs) are a major source of ROS and are linked to oxidative damage, HSC stimulation and liver fibrosis [28].

2.5 | Gut Microbiota

Gut microbiota and its biodiversity seem to play an essential role in AILD fibrogenesis [29, 30]. Bacteria that translocate from the intestine could stimulate TLR4, a key activator of the innate immune response, and gut microbiota could contribute to sustaining tissue inflammation and ECM extension; although some commensal bacteria may even limit liver inflammation [31]. The relationship between the liver and the gut is often bidirectional, and as liver disease progresses, dysbiosis can occur and persist, in turn impairing the intestinal barrier and increasing permeability with the augmented translocation of bacteria and their endotoxins to the liver, fostering inflammation and fibrosis [32].

In AIH, compared to healthy controls, studies showed a reduction in the biodiversity of the intestinal microbiome along with the transformation of microbiota from anaerobic to aerobic [32, 33]. Those alterations of luminal contents, both compositionally and functionally, lead to the imbalance of regulatory T-cells, the activation of natural killer T (NKT) cells, the decrease of short-chain fatty acids (SCFAs) and secondary bile acids, subsequently resulting in the increased permeability of the intestinal barrier, breakdown of luminal immune homeostasis, augmentation of inflammatory injury and progression of fibrosis [34]. In PBC, increased relative abundance of the genus *Weissella* was observed in advanced fibrosis ($F \geq 3$) and associated with decreased overall microbial richness and elevated faecal acetate and SCFAs [35]. While no intestinal microbiota genera were found to be associated with fibrosis in PSC, some studies demonstrated decreased microbiota richness and overrepresentation of *Enterococcus*, *Lactobacillus, Fusobacterium* and *Veillonella* genera [36, 37].

2.6 | Accumulation and Degradation of ECM

Liver fibrosis per se is the process of excessive and progressive accumulation of ECM proteins, including collagen I, III and IV, fibronectin, undulin, elastin, laminin, hyaluronic acid (HA), proteoglycans, tissue inhibitor of metalloproteinase type 1 (TIMP-1), matrix metalloproteinase (MMP), type III and V pro-collagen (PRO-C3, PRO-C5), biglycan (BGM), citrullinated vimentin (VICM) and YKL (chitinase-3-like)-40 accompanied by a reduced enzymatic degradation of the hepatic ECM [38]. Protein accumulation is a restorative reaction to reiterated tissue damage, and, overall, liver fibrosis in AILD represents a quintessence of liver injury with a reflection of the severity and duration of necro-inflammatory and cholestatic damage of hepatocytes and bile ducts [4]. ECM can be remodelled followed by restoration of liver structure and function or degrade further eventually leading to cirrhosis with the formation of regenerative nodules later encapsulated into fibrotic septae accompanied by major angio-architectural changes of the liver maintained by parenchymal and non-parenchymal cells such as macrophages and endothelial cells [39]. In response to liver injury, hepatic progenitor cells (HPC) have the ability to differentiate into hepatocytes and bile duct epithelia; however, HPC activation via ductular reaction has been associated with fibrosis [40–43].

2.7 | Concurrent Intra- and Extrahepatic Disorders and Their Potential Impact on Liver Fibrogenesis

In a large multi-centric international cohort of over 600 AIH patients, fibrosis progression and development of cirrhosis did not differ between patients with and without hepatic steatosis [44]. In the same cohort, AIH patients developed cirrhosis twice as frequently during follow-up if they had type 2 diabetes and almost 2.5 times more frequently if they had dyslipidemia [44].

In parallel with these findings, metabolic-associated steatotic liver disease (MASLD) and inflammatory bowel disease were not found to be predictors of the development of cirrhosis in a large Western Canadian AIH cohort [45–47]. Similar results were obtained upon studying the impact of MASLD in a large Western Canadian cohort of PBC patients, demonstrating no association between MASLD and the development of cirrhosis [48].

2.8 | Lifestyle, Dietary and Environmental Factors Contributing to Liver Fibrogenesis

Several features and factors along with vitamin and micronutrient deficiencies have a role in hepatic fibrogenesis. A history of smoking ≥ 10 pack-years was shown to be a significant predictor of advanced fibrosis in PBC, even when age, sex and history of significant alcohol use were all considered as cofounders [49]. In a French cohort of PBC patients, each smoking pack-year was associated with a 5.0% increase in the likelihood of advanced fibrosis [50]. Several mechanisms might be involved, such as high levels of pro-inflammatory cytokines IL-6, IL-8, IL-10 and IL-13, hypoxia, insulin resistance, exertion of the anti-estrogenic effects, and imbalance of the Th-1/Th-2 response [51].

Several studies demonstrated that coffee consumption above two cups per day has an anti-fibrotic effect in AILD [52]. The benefits are thought to relate to detoxification, inhibition of expression of connective tissue growth factor (CTGF), up-regulation of peroxisome proliferator-activated receptor gamma (PPARγ), and inhibition of the TGFβ pathway [52].

Zinc has important antioxidant, anti-inflammatory and anti-apoptotic effects, playing a critical role in a broad spectrum of biological processes [53]. Zinc deficiency leads to dysregulation of apoptosis via regulation of different caspases, an increase in ROS stimulating oxidative stress, and aggravating inflammation [54–56]. The relationship between zinc and chronic liver disorders is often bidirectional, as the liver is responsible for zinc metabolism, which is negatively impacted in chronic liver conditions; at the same time, zinc deficiency exacerbates pathophysiological processes in hepatocytes and ECM [53]. Serum zinc concentration was shown to decrease gradually with the progression of liver fibrosis; however, this relationship was not specifically elucidated in AILD yet [57]. In AIH patients, serum zinc levels inversely correlate with liver fibrotic biomarkers, such as serum procollagen type III, collagen type IV and HA [58].

Vitamin D has an anti-fibrotic effect exhibited through attenuation of TGF-β-induced fibrosis, suppressing collagen production in stromal HSCs, and expression of collagen I and III, and MMP-8, which is a protease enzyme directly regulating ECM degradation [59, 60]. Moreover, vitamin D plays an immunomodulatory role and prevents inflammatory processes by suppressing T- and B-cell auto-aggression, thus indirectly decreasing the risk of fibrosis progression. In AIH, serum vitamin D levels were shown to be significantly lower compared to the general population, and severe vitamin D deficiency was associated with inflammatory activity and advanced fibrosis [61]. Moreover, vitamin D deficiency was independently associated with advanced fibrosis and progression to cirrhosis in AIH, PBC and PSC [62–64]. Several studies also revealed an association between other liposoluble vitamins (A and E) deficiencies and fibrosis progression in AILD [65].

2.9 | Clinical Risk Factors for the Development of Advanced Liver Fibrosis

Risk factors for advanced fibrosis in AIH include male sex, ethnicity (African American, Hispanic and Indigenous), younger or older age at onset, insufficient treatment response and the development of cirrhosis, all of which present an increased risk of progressive disease [66]. Lack of normalisation of ALT at 6 months and age at diagnosis younger than 20 or older than 60 years were significant independent predictors of liver-related mortality or need for liver transplant. Ethnicity has also been implicated as a risk factor for the progression of AIH, with studies showing worse outcomes and more advanced disease at diagnosis in Hispanic and African American populations compared to Caucasians [67, 68]. In large retro- and prospective cohort studies with over 1100 AIH and 1500 PBC patients, Indigenous Canadians had worse clinical outcomes compared to other ethnicities, but the impact of ethnic background on the progression of fibrosis is yet to be explored [69, 70].

Similarly, risk factors for advanced fibrosis in PBC have been identified as younger age at onset, male sex, and results from selected biochemical/serological indices (bilirubin, albumin) pre- and post-therapy with UDCA [71]. Younger age at onset is associated with poorer treatment response to UDCA and higher rates of liver-related mortality [72, 73]. Serum baseline bilirubin and albumin can be used to stratify UDCA-treated patients into low, medium and high-risk groups; however, these tests are not recommended for patients in the early stage [74].

Finally, risk factors for advanced fibrosis in PSC are described as symptoms such as jaundice, persistent alkaline phosphatase (ALP) >1.5 ULN, abnormal bilirubin, albumin, platelets or international normalised ratio (INR), and extensive biliary changes (especially intra-hepatic biliary dilatation) on magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) [75].

While many of the above-mentioned clinical risk factors are non-modifiable, achieving biochemical response through personalised treatment, proper monitoring and consideration of second-line treatments if needed are fundamental to prevent the development of advanced fibrosis in patients with AIH and PBC; unfortunately, there is no effective treatment to prevent fibrosis progression in PSC [7, 76].

3 | Non-Invasive Assessment of Liver Fibrosis in AILD

3.1 | Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI)

Overall, APRI has good performance characteristics with an area under the receiver operating characteristic curve (AUROC) exceeding 0.80 to detect advanced fibrosis [77]. Unfortunately, APRI revealed a relatively suboptimal performance in identifying significant fibrosis ($F \geq 2$), advanced fibrosis, and cirrhosis in AIH with AUROC of 0.66, 0.71 and 0.75, respectively (Tables 1 and 2) [78]. It is important to note that the summary sensitivity of APRI for the diagnosis of significant fibrosis in AIH was 0.90 (which might support its utility as a screening test); however, it was coupled with a relatively low specificity of 36% [78]. Summary sensitivity and specificity for the diagnosis of advanced fibrosis and cirrhosis were 0.78 and 0.55, and 0.77 and 0.61, respectively [78]. In PBC, APRI showed a good correlation with the histopathological stage with a cut-point of 0.54 allowing identification of individuals with advanced fibrosis [88, 89]. A cut-off of 0.75 displayed good accuracy (AUROC 0.71, sensitivity of 0.33 and specificity of 0.96) [79]. In PSC, increased APRI was shown to have an association with the risk of progression to cirrhosis at 2 years [90].

3.2 | Fibrosis 4 (FIB-4) Score

The FIB-4 score is a simple measure based on demographic and laboratory parameters and, overall, has good performance characteristics for estimating hepatic fibrosis, although, the accuracy of FIB-4 for fibrosis assessment in AILD remains less robust. In AIH, a meta-analysis of 14 studies including over a thousand patients revealed the summary AUROC values of 0.75, 0.73 and 0.79 for the prediction of significant fibrosis, advanced fibrosis, and cirrhosis, with the summary sensitivity and specificity being 0.70 and 0.70, 0.65 and 0.70, and 0.78 and 0.65, respectively [78]. Among PBC patients, FIB-4 demonstrated good performance for diagnosis of advanced fibrosis and cirrhosis with AUROC of 0.82 and 0.89, respectively [79, 91]. In PSC, the FIB-4 score at baseline and weeks 12, 24 and 48, was associated with

TABLE 1 | Non-invasive biomarker-based scores for liver fibrosis and parameters required for their calculation.

Score	Age	Sex	ALT	AST	GGT	Platelet count	RDW	INR	PT	Albumin	Total bilirubin	Urea	HA	Hyaluronate	PIIINP	TIMP-1	α-2-macroglobulin
APRI				X		X											
FIB-4 score	X		X	X		X											
AAR			X	X													
GPR					X	X											
ELF score													X		X		
ALBI grade										X	X						
FibroQ	X		X	X		X		X									
Fibrometer	X			X		X			X			X		X			X
Hepascore	X	X			X						X		X				X
RPR						X	X										

Abbreviations: AAR, AST/ALT ratio; ALBI grade, Albumin-Bilirubin grade; ALT, alanine transaminase; APRI, AST/platelet ratio index; AST, aspartate transaminase; ELF score, Enhanced Liver Fibrosis score; FIB-4 score, Fibrosis-4; GGT, gamma-glutamyl transferase; GPR, GGT to platelet ratio; HA, hyaluronic acid; INR, international normalised ratio; PIIINP, propeptide of type III procollagen; PT, prothrombin time; RDW, red cell distribution width; RPR, RDW to platelet count ratio; TIMP-1, tissue inhibitor of metalloproteinase type 1; α-2-macroglobulin, alpha-2-macroglobulin.

the development of cirrhosis at 2 years, and FIB-4 measured at 48 weeks was associated with a 66% increased risk of a 2-point increase in fibrosis stage at 2 years [90].

3.3 | AST to Alanine Aminotransferase (ALT) Ratio (AAR)

In a meta-analysis with over 1500 AIH patients, the performance of AAR in detecting advanced fibrosis was suboptimal with a summary AUROC of 0.73 [77]. In the meta-analysis with over 3000 PBC patients, AAR performed better in diagnosing cirrhosis with summary AUROC of 0.88, sensitivity of 0.81 and specificity of 0.77 for cut-off 1.00–1.10 [77].

3.4 | Gamma-Glutamyl Transpeptidase (GGT) to Platelet Ratio (GPR)

In PBC, GPR showed satisfactory performance in distinguishing between early and advanced fibrosis with an AUROC of 0.84, a sensitivity of 0.41 and a specificity of 0.96 [79].

3.5 | Enhanced Liver Fibrosis (ELF) Score

The ELF score is a validated measure of liver fibrosis based on circulating biomarkers of ECM metabolism that are expressed during the early stages of hepatic collagen deposition. In AIH, ELF scores were found to be higher in patients with significant fibrosis than those with mild fibrosis (10.60 vs. 8.62, $p < 0.001$). In the ROC analysis, a cut-off point of 8.84 had 0.92 sensitivity and 0.78 specificity for significant fibrosis with a good AUROC of 0.88 [80]. ELF is also a sensitive fibrosis marker with good accuracy in identifying PBC patients with advanced fibrosis (AUROC 0.81) [81]. In PSC, patients with elevated ELF scores at baseline and weeks 12, 24 and 48 were three times more likely to develop cirrhosis at 2 years. Moreover, those elevated ELF scores were associated with a 2-point increase in fibrosis stage at 2 years, thus doubling the risk [90].

3.6 | Emerging Blood-Based Fibrosis Markers

Emerging blood-based fibrosis biomarkers and scores used to evaluate fibrosis along with their performance in AILD are summarised in Tables 1 and 2. TGF-β1 serum levels have a good correlation with the Ishak fibrosis score and might serve as a tool to monitor decreasing or progression of fibrosis [92]. TGF-β1 high-producer genotype (25GG) is linked with worse clinical outcomes in paediatric AIH patients [19, 93].

Levels of LOXL2 in serum adequately detect cirrhosis (AUROC 0.78) in patients with PSC [86]. Among newly discovered serological biomarkers of ECM turnover, PRO-C3 performed best, showing excellent (AUROC > 0.80 in PSC and PBC) or good (AUROC 0.77 in AIH) ability to discriminate advanced fibrosis from non-advanced fibrosis and tight (in PSC and PBC) or moderate (in AIH) correlation with liver stiffness measurement (LSM) and the ELF and APRI scores [87]. In PBC and AIH, PRO-C5, C3M and C4M (both aetiologies) and VICM and BGM (in PBC) discriminated between advanced and non-advanced disease [87].

TABLE 2 | Selected non-invasive biomarkers and scores for Liver Fibrosis and their Performance in AILD.

Liver fibrosis biomarkers and scores	Calculation or description	Performance in AILD
APRI	$\text{APRI} = \left(\frac{\text{AST}}{\text{AST}_{\text{ULN}}}\right) \times \frac{100}{\text{PLT}}$ • AST (U/L) • PLT (10^9/L)	• **AIH:** ◦ Chen et al. 2023 [77]: – Significant fibrosis: summary AUROC 0.67 (95% CI 0.63–0.71) – Advanced fibrosis: summary AUROC 0.71 (95% CI 0.67–0.75) – Cirrhosis: summary AUROC 0.71 (95% CI 0.67–0.75) ◦ Dong et al. 2022 [78]: – Significant fibrosis: AUROC 0.66 (95% CI 0.61–0.70); Sn 0.90; Sp 0.55 – Advanced fibrosis: AUROC 0.71 (95% CI 0.67–0.75); Sn 0.36; Sp 0.77 – Cirrhosis: AUROC 0.75 (95% CI 0.71–0.79); Sn 0.78; Sp 0.61 • **PBC:** ◦ Chen et al. 2023 [77]: – Significant fibrosis: summary AUROC 0.77 (95% CI 0.73–0.80); Sn 0.84; Sp 0.63; PLR 1.98; NLR 0.34 (cut-off: 0.26–1.20) – Advanced fibrosis: summary AUROC 0.70 (95% CI 0.66–0.74) – Cirrhosis: summary AUROC 0.83 (95% CI 0.79–0.86); Sn 0.75; Sp 0.51; PLR 2.19; NLR 0.31 (cut-off: 0.65–1.39) ◦ Avcioğlu et al. 2022 [79]: – Advanced fibrosis: AUROC 0.71 (95% CI 0.54–0.89); Sn 0.33; Sp 0.96 (cut-off: 0.75)
FIB-4 score	$\text{FIB}-4 = \frac{\text{Age} \times \text{AST}}{\text{PLT} \times \sqrt{\text{ALT}}}$ • Age (years) • AST (U/L) • PLT (10^9/L) • ALT (U/L)	• **AIH:** ◦ Chen et al. 2023 [77]: – Significant fibrosis: summary AUROC 0.74 (95% CI 0.70–0.78) – Advanced fibrosis: summary AUROC 0.73 (95% CI 0.69–0.76) – Cirrhosis: summary AUROC 0.72 (95% CI 0.68–0.76); Sn 0.87; Sp 0.61; PLR 2.79; NLR 0.16 (cut-off: 2.05–4.60) ◦ Dong et al. 2022 [78]: – Significant fibrosis: AUROC 0.75 (95% CI 0.71–0.79); Sn 0.70; Sp 0.70 – Advanced fibrosis: AUROC 0.73 (95% CI 0.69–0.77); Sn 0.65; Sp 0.70 – Cirrhosis: AUROC 0.79 (95% CI 0.75–0.82); Sn 0.78; Sp 0.65 • **PBC:** ◦ Chen et al. 2023 [77]: – Advanced fibrosis: summary AUROC 0.79 (95% CI 0.75–0.82) – Cirrhosis: summary AUROC 0.88 (95% CI 0.85–0.91) ◦ Avcioğlu et al. 2022 [79]: – Advanced fibrosis: AUROC 0.82 (95% CI 0.68–0.96); Sn 0.33; Sp 0.96 (cut-off: 2.96)
AAR	$\text{AAR} = \frac{\text{AST}}{\text{ALT}}$ • AST (U/L) • ALT (U/L)	• **AIH:** ◦ Chen et al. 2023 [77]: – Advanced fibrosis: summary AUROC 0.73 (95% CI 0.69–0.77) • **PBC:** ◦ Chen et al. 2023 [77]: – Advanced fibrosis: summary AUROC 0.74 (95% CI 0.70–0.78); Sn 0.54; Sp 0.73; PLR 2.15; NLR 0.63 (cut-off: 0.81–1.01) – Cirrhosis: summary AUROC 0.88 (95% CI: 0.84–0.90); Sn 0.81; Sp 0.77; PLR 4.55; NLR 0.28 (cut-off: 1.00–1.10)
GPR	$\text{GPR} = \left(\frac{\text{GGT}}{\text{GGT}_{\text{ULN}}}\right) \times \frac{100}{\text{PLT}}$ • GGT (U/L) • PLT (10^9/L)	• **PBC:** ◦ Avcioğlu et al. 2022 [79]: – Advanced fibrosis: AUROC 0.84 (95% CI 0.71–0.97); Sn 0.41; Sp 0.96 (cut-off: 4.81)

(Continues)

TABLE 2 | (Continued)

Liver fibrosis biomarkers and scores	Calculation or description	Performance in AILD
ELF score	ELF score = 2.494 + 0.846 ln (HA) + 0.735 ln (PIIINP) + 0.391 ln (TIMP − 1) • HA (ng/mL) • PIIINP (ng/mL) • TIMP-1 (ng/mL)	• **AIH:** ◦ Gungoven et al. 2018 [80]: – Significant fibrosis: AUROC 0.88 (95% CI 0.75–1.00); Sn 0.92; Sp 0.78; PPV 0.70; NPV 0.94 • **PBC:** ◦ Fujinaga et al. 2021 [81]: – Advanced fibrosis: AUROC 0.81 (95% CI 0.67–0.92)
ALBI grade	$\text{ALBI} = (\log_{10}\text{bilirubin} \times 0.66) + (\text{albumin} \times -0.0852)$ • Bilirubin (μmol/L) • Albumin (g/L)	• **AIH:** ◦ Fujita et al. 2021 [82]: – Cirrhosis: AUROC 0.86 (95% CI 0.77–0.94; $p = 0.0004$); Sn 1.00; Sp 0.71; PLR 3.39 (cut-off: −1.994)
FibroQ	$\text{FibroQ} = \frac{10 \times \text{age} \times \text{AST} \times \text{INR}}{\text{PLT} \times \text{ALT}}$ • Age (years) • AST (U/L) • ALT (U/L) • INR • PLT (10^9/L)	• **AIH:** ◦ Anastasiou et al. 2016 [83]: – F1 versus significant fibrosis to cirrhosis: AUROC 0.68 ($p = 0.08$); Sn 0.67; Sp 0.73; PPV 0.92; NPV 0.34 (cut-off: 1.34) – F1 to significant fibrosis versus advanced fibrosis to cirrhosis: AUROC 0.77 ($p = 0.08$); Sn 0.59; Sp 0.92; PPV 0.90; NPV 0.65 (cut-off: 2.70) – F1 to advanced fibrosis versus cirrhosis: AUROC 0.92 ($p = 0.08$); Sn 0.82; Sp 0.93; PPV 0.76; NPV 0.95 (cut-off: 4.00)
Fibrometer	Patented formula, please refer to Table 1 for the included parameters	• **AIH:** ◦ Zachou et al. 2021 [84]: – Advanced fibrosis: AUROC 0.87 ($p = 0.004$)
Hepascore	$\text{Hepascore} = \frac{y}{1+y}$ $y = \exp[-4.185818 - (0.0249 \times \text{age}) + (0.7464 \times \text{sex}) + (1.0039 \times \alpha 2 - \text{macroglobulin}) + (0.0302 \times \text{HA}) + (0.0691 \times \text{bilirubin}) - (0.0012 \times \text{GGT})]$ • Age (years) • Sex (female = 0, male = 1) • α-2 macroglobulin (g/L) • HA (μg/L) • Bilirubin (μmol/L) • GGT (U/L)	• **PSC:** ◦ Cylwik et al. 2023 [85]: – Significant fibrosis: AUROC 1.00; Sn 0.97; Sp 1.00; PPV 1.00; NPV 0.95 (cut-off: 0.52) – Cirrhosis: AUROC 1.00; Sn 0.95; Sp 1.00; PPV 1.00; NPV 0.97 (cut-off: 0.80)
RPR	$\text{RPR} = \frac{\text{RDW}}{\text{PLT}}$ • RDW (%) • PLT (10^9/L)	• **PBC:** ◦ Chen et al. 2023 [77]: – Advanced fibrosis: summary AUROC 0.53 (95% CI 0.49–0.58); Sn 0.49; Sp 0.89; PLR 4.27; NLR 0.59 (cut-off: 0.10–0.14)
TGF-β	Cytokine involved in inflammation, fibrosis and regulatory activity	• Under exploration
TGF-β1	Part of the TGF-β family of proteins and plays a role in fibrosis	• Under exploration
LOXL2	An enzyme which catalyses the formation of collagen fibres	• **PSC:** ◦ Muir et al. 2016 [86]: – Cirrhosis: AUROC 0.78 (95% CI 0.67–0.89); Sn 0.64; Sp 0.86; PPV 0.35; NPV 0.95

(Continues)

TABLE 2 | (Continued)

Liver fibrosis biomarkers and scores	Calculation or description	Performance in AILD
PRO-C3	N-terminal pro-peptide of type III collagen	• **AIH:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.77 (95% CI 0.64–0.90; $p < 0.001$) • **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.83 (95% CI 0.72–0.94; $p < 0.001$) • **PSC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.86 (95% CI 0.77–0.94; $p < 0.001$)
PRO-C5	C-terminal pro-peptide of type V collagen	• **AIH:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.68 (95% CI 0.53–0.82; $p = 0.02$) • **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.64 (95% CI 0.51–0.78; $p = 0.04$)
PRO-C3M	Biomarker of MP-degraded type III collagen	• **AIH:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.71 (95% CI 0.57–0.85; $p = 0.004$) • **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.67 (95% CI 0.54–0.81; $p = 0.01$)
PRO-C4M	Biomarker of MP-degraded type IV collagen	• **AIH:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.71 (95% CI 0.56–0.86; $p = 0.01$) • **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.67 (95% CI 0.53–0.80; $p = 0.02$)
PRO-C3/C3M	Ratio of PRO-C3 to PRO-C3M	• **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.77 (95% CI 0.64–0.89; $p < 0.001$) • **PSC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.59 (95% CI 0.42–0.76; $p < 0.001$)
BGM	Neo-epitope of MMP-9	• **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.64 (95% CI 0.51–0.78; $p = 0.04$)
VICM	Citrullinated type III intermediate filament	• **AIH:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.34 (95% CI 0.17–0.51; $p = 0.06$) • **PBC:** ◦ Vesterhus et al. 2021 [87]: – Advanced fibrosis: AUROC 0.28 (95% CI 0.15–0.41; $p = 0.001$)
M2BP	Glycoprotein in the extracellular matrix involved in cell adhesion	• **AIH:** ◦ Chen et al. 2023 [77]: – Advanced fibrosis: summary AUROC 0.86 (95% CI 0.82–0.88); Sn 0.68; Sp 0.80; PLR 4.26; NLR 0.32 (cutoff: 1.00–1.40)

Abbreviations: AAR, AST/ALT ratio; Acc, accuracy; advanced fibrosis, F ≥ 3; AIH, autoimmune hepatitis; AILD, autoimmune liver diseases; ALBI grade, Albumin-Bilirubin grade; ALT, alanine aminotransferase; APRI, AST/platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BGM, biglycan; CI, confidence interval; ELF score, Enhanced Liver Fibrosis score; FIB-4 score, Fibrosis-4 score; GGT, gamma-glutamyl transferase; GPR, GGT to platelet ratio; HA, hyaluronic acid; INR, international normalised ratio; LOXL2, lysyl oxidase like-2; M2BP, mac-2 binding protein; NLR, negative likelihood ratio; NPV, negative predictive value; PBC, primary biliary cholangitis; PIIINP, pro-collagen type III levels; PLR, positive likelihood ratio; PLT, platelet count; PPV, positive predictive value; PSC, primary sclerosing cholangitis; RDW, red cell distribution width; RPR, RDW to PLT ratio; significant fibrosis, F ≥ 2; Sn, sensitivity; Sp, specificity; TGF-β, transforming growth factor beta; TIMP-1, tissue inhibitor of matrix metalloproteinase type 1; ULN, upper limit of normal; VICM, citrullinated vimentin; α-2-macroglobulin, alpha-2-macroglobulin.

TABLE 3 | Non-invasive radiological tools for assessing fibrosis in AILD.

Method	Nature	Performance in AILD
VCTE	Ultrasound and low-frequency waves induce transient vibrations and propagation velocities reflect liver stiffness [94]	• **AIH:** ◦ Chen et al. 2023 [77]: – Significant fibrosis: summary AUROC 0.84 (95% CI 0.80–0.87) – Advanced fibrosis: summary AUROC 0.88 (95% CI 0.85–0.90) – Cirrhosis: summary AUROC 0.90 (95% CI: 0.87–0.92) • **PBC:** ◦ Chen et al. 2023 [77]: – Significant fibrosis: summary AUROC 0.93 (95% CI 0.91–0.95) – Advanced fibrosis: summary AUROC 0.93 (95% CI 0.90–0.95) – Cirrhosis: summary AUROC 0.91 (95% CI: 0.88–0.93) • **PSC:** ◦ Chen et al. 2023 [77]: – Cirrhosis: summary AUROC 0.95 (95% CI: 0.93–0.97); Sn 0.82; Sp 0.89; PLR 7.46; NLR 0.25 (cut-off: 13.70–14.40)
SWE	Radiation force is used to generate shear waves that are captured and used to calculate liver elasticity [97]	• **AIH:** ◦ Chen et al. 2023 [77]: – Cirrhosis: summary AUROC 0.91 (95% CI 0.89–0.94); Sn 0.83; Sp 0.86; PLR 5.85; NLR 0.21 (cut-off: 14.30–19.30) ◦ Park et al. 2019 [98]: – Significant fibrosis: AUROC 0.70 (95% CI 0.56–0.83); Sn 0.94; Sp 0.44; PPV 0.74; NPV 0.80; PLR 1.68; NLR 0.15 (cut-off: 4.47 kPa) – Advanced fibrosis: AUROC 0.76 (95% CI 0.62–0.87); Sn 0.67; Sp 0.79; PPV 0.70; NPV 0.76; PLR 3.11; NLR 0.42 (cut-off: 7.11 kPa) – Cirrhosis: AUROC 0.75 (95% CI 0.61–0.87); Sn 0.64; Sp 0.87; PPV 0.58; NPV 0.89; PLR 4.84; NLR 0.42 (cut-off: 9.28 kPa) • **PBC:** ◦ Manesis et al. 2021 [99]: – ≥F1: AUROC 0.95 (95% CI 0.87–1.00; $p < 0.001$); Sn 0.89; Sp 1.00; Acc 0.90 (for cut-off 6.6 kPa) – Significant fibrosis: AUROC 0.87 (95% CI 0.78–0.97; $p < 0.001$); Sn 0.84; Sp 0.87; Acc 0.85 (for cut-off 7.8 kPa) – Advanced fibrosis: AUROC 0.85 (95% CI 0.77–0.95; $p < 0.001$); Sn 0.81; Sp 0.81; Acc 0.81 (for cut-off 10.0 kPa) – Cirrhosis: AUROC 0.90 (95% CI 0.81–0.99; $p < 0.001$); Sn 0.90; Sp 0.83; Acc 0.87 (for cut-off 11.9 kPa) ◦ Park et al. 2019 [98]: – Significant fibrosis: AUROC 0.81 (95% CI 0.65–0.91); Sn 0.82; Sp 0.73; PPV 0.53; NPV 0.92; PLR 3.07; NLR 0.25 (for cut-off 5.56 kPa) – Advanced fibrosis: AUROC 0.91 (95% CI 0.78–0.98); Sn 1.00; Sp 0.82; PPV 0.30; NPV 1.00; PLR 5.43; NLR 0 (for cut-off 6.04 kPa) • **PSC:** ◦ Roccarina et al. 2023 [100]: – ≥F1: AUROC 0.96 (95% CI 0.91–0.98); Sn 0.91; Sp 0.92; PPV 0.94; NPV 0.88; PLR 11.4; NLR 0.10 (cut-off: 7.4 kPa) – Significant fibrosis: AUROC 0.97 (95% CI 0.93–0.99); Sn 0.95; Sp 0.88; PPV 0.89; NPV 0.94; PLR 7.9; NLR 0.06 (cut-off: 8.5 kPa) – Advanced fibrosis: AUROC 0.97 (95% CI 0.93–0.99); Sn 0.89; Sp 0.94; PPV 0.92; NPV 0.92; PLR 14.8; NLR 0.12 (cut-off: 10.5 kPa) – Cirrhosis: AUROC 0.99 (95% CI 0.95–0.99); Sn 1.0; Sp 0.89; PPV 0.80; NPV 1.0; PLR 9.1; NLR 0 (cut-off: 12.1 kPa)

(Continues)

TABLE 3 | (Continued)

Method	Nature	Performance in AILD
ARFI imaging	Measures changes in wave propagation speed without external compression [101]	• **PBC:** ◦ Zhang et al. 2014 [102]: – Significant fibrosis: AUROC 0.83 (95% CI 0.72–0.94); Sn 0.80; Sp 0.77; PPV 0.89; NPV 0.62 (cut-off: 1.51 m/s) – Advanced fibrosis: AUROC 0.93 (95% CI 0.86–0.99); Sn 0.91; Sp 0.82; PPV 0.77; NPV 0.93 (cut-off: 1.79 m/s) – Cirrhosis: AUROC 0.91 (95% CI 0.83–0.99); Sn 1.00; Sp 0.79; PPV 0.47; NPV 1.00 (cut-off: 2.01 m/s)
MRE	Acoustic vibrations produce propagating shear waves within the liver that are imaged by the scanner [103]	• **AIH:** ◦ Wang et al. 2017 [104]: – Advanced fibrosis: AUROC 0.97 (95% CI 0.85–1.0); Sn 0.90; Sp 1.0; PPV 1.0; NPV 0.90; Acc 0.97 (cut-off: 4.1 kPa) – Cirrhosis: AUROC 0.98 (95% CI 0.87–1.00); Sn 0.92; Sp 0.96; PPV 0.92; NPV 0.88; Acc 0.98 (cut-off: 4.5 kPa) • **PBC:** ◦ Osman et al. 2021 [105]: – ≥F1: AUROC 0.50 (95% CI 0.40–0.60); Sn 0.46; Sp 0.88; PPV 0.96; NPV 0.11 (cut-off: 3.80 kPa) – Significant fibrosis: AUROC 0.60 (95% CI 0.50–0.70); Sn 0.51; Sp 0.90; PPV 0.93; NPV 0.32 (cut-off: 3.80 kPa) – Advanced fibrosis: AUROC 0.71 (95% CI 0.61–0.80); Sn 0.75; Sp 0.76; PPV 0.66; NPV 0.77 (cut-off: 3.70 kPa) – Cirrhosis: AUROC 0.82 (95% CI 0.73–0.89); Sn 0.80; Sp 0.83; PPV 0.33; NPV 0.97 (cut-off: 4.60 kPa) • **PSC:** ◦ Jhaveri et al. 2019 [106]: – ≥F1: AUROC 0.76 (95% CI 0.65–0.87); Sn 0.69; Sp 0.83; PPV 0.79; NPV 0.74; Acc 0.76 (cut-off: ≥3.33) – Significant fibrosis: AUROC 0.82 (95% CI 0.72–0.92); Sn 0.74; Sp 0.90; PPV 0.83; NPV 0.83; Acc 0.84 (cut-off: ≥3.61) – Cirrhosis: AUROC 0.92 (95% CI 0.83–1.00); Sn 0.88; Sp 0.96; PPV 0.88; NPV 0.96; Acc 0.94 (cut-off: ≥4.02) ◦ Eaton et al. 2016 [107]: – ≥F1: AUROC 0.97; Sn 0.94; Sp 1.00; PPV 1.00; NPV 0.80 (cut-off: ≥2.41 kPa) – Significant fibrosis: AUROC 0.97; Sn 0.85; Sp 1.00; PPV 1.00; NPV 0.78 (cut-off: ≥3.26 kPa) – Cirrhosis: AUROC 0.99; Sn 1.00; Sp 0.94; PPV 0.80; NPV 1.00 (cut-off: ≥4.93 kPa)
RTE	Ultrasound probe used to deform the underlying liver tissue to estimate liver elasticity [97]	• **PBC:** ◦ Koizumi et al. 2017 [108]: – Significant fibrosis: AUROC 0.92 (95% CI 0.79–0.97); Sn 0.94; Sp 0.89 – Advanced fibrosis: AUROC 0.95 (95% CI 0.81–0.99); Sn 0.92; Sp 0.83 – Cirrhosis: AUROC 0.97 (95% CI 0.87–0.99); Sn 0.95; Sp 0.89

Abbreviations: Acc, accuracy; advanced fibrosis, F≥3; AIH, autoimmune hepatitis; AILD, autoimmune liver diseases; ARFI imaging, acoustic radiation force impulse imaging; AUROC area under the receiver operating characteristic curve; CI, confidence interval; MRE, magnetic resonance elastography; NLR, negative likelihood ratio; NPV, negative predictive value; PBC, primary biliary cholangitis; PLR, positive likelihood ratio; PPV, positive predictive value; PSC, primary sclerosing cholangitis; RTE, real-time tissue elastography; significant fibrosis, F≥2; Sn, sensitivity; Sp, specificity; SWE, shear wave elastography; VCTE, Vibration-Controlled Transient Elastography.

3.7 | Vibration-Controlled Transient Elastography (VCTE)

The VCTE technique was introduced in 2003 and provides LSM, a surrogate of liver fibrosis, by assessing liver elasticity using low-frequency waves to bring transient vibrations in the liver and calculating spread speeds [94].

In a prospective study of AIH patients, LSM strongly correlated with the histological fibrosis stage [95]. The VCTE performance was impaired in patients in their first 3 months since diagnosis, most likely, due to extensive hepatic inflammation. However, when VCTE was performed after 6 months of AIH treatment, it had excellent accuracy in discriminating severe from non-severe fibrosis [95, 96]. Overall, the diagnostic accuracy for the

detection of cirrhosis in AIH was excellent (AUROC 0.96 for a cut-off of 16 kPa), and for patients treated for over 6 months the AUROC for the same cut-off reached 1.00 (Table 3). Furthermore, LSM by VCTE was shown to be a strong independent predictor for adverse liver outcomes when considering other risk factors and biochemical treatment response [109, 110]. In addition, LSM also correlated with histological improvement following AIH treatment, indicating that VCTE may potentially play a role in disease monitoring; however, the optimal threshold remains to be identified [111].

In PBC patients, significant correlations were observed between LSM values and fibrosis stage measured using Ludwig's ($r_S = 0.81$) and METAVIR ($r_S = 0.86$) scoring systems [112]. Similar results were found in other studies involving PBC patients with a significant correlation between histological fibrosis stages and LSM, and the values obtained from AUROC were 0.89 for $F > 2$ and 0.96 for cirrhosis [113]. Analysing the VCTE performance prospectively, diagnostic thresholds of liver stiffness in discriminating fibrosis stages were established as follows: 7.1 kPa for ≥F1, 8.8 kPa for significant fibrosis, 10.7 kPa for advanced fibrosis, and 16.9 kPa for cirrhosis [114]. VCTE displayed high performance and was significantly superior to biochemical markers (APRI, FIB-4, HA and AAR) in diagnosing significant fibrosis, advanced fibrosis and cirrhosis. Moreover, LSM by VCTE is independently associated with adverse clinical outcomes [115].

In patients with PSC, both the baseline values and changes in liver stiffness measured by VCTE are associated with both the severity of fibrosis and clinical outcomes [116]. In a cohort of 28 patients with PSC, LSM revealed significant correlations with fibrosis stage ($r_S = 0.75$ when assessed using Ludwig's classification and $r_S = 0.79$ when METAVIR scoring was used) [112]. In a retrospective study of German PSC patients, VCTE showed excellent performance in identifying cirrhosis in PSC patients (AUROC 0.98) [117]. A VCTE cut-off of 14.4 kPa corresponds to histological evidence of liver cirrhosis.

In a recent meta-analysis with over 5000 AILD patients, VCTE exerted better diagnostic accuracy compared to APRI, AAR and FIB-4 scores (Table 3) [77]. These results support the major role of LSM in clinical trials as a risk-stratifying tool and potential surrogate endpoint [118]. Given that the data in AILD is limited, based on the Baveno-VII consensus, it is recommended to repeat VCTE every one to 2 years for patients without advanced stages of disease (LSM 7-10 kPa), whereas in patients with compensated advanced chronic liver disease (LSM > 10 kPa), it is recommended to repeat VCTE on an annual basis to monitor fibrosis progression [119].

VCTE has limitations, as it only captures approximately 1% of hepatic volume and therefore is subject to the "sampling" error [94]. It also has considerable limitations in patients with obesity and steatotic liver disease, with a substantial failure rate that increases with an increase in body mass index (BMI) and hepatic fat content [120]. Characterised by significant fluctuations in inflammatory activity that could potentially be misinterpreted as fibrosis, LSM by VCTE may overestimate the fibrosis stage in AIH patients [95, 121].

3.8 | Shear Wave Elastography (SWE)

SWE involves the use of an ultrasound probe to send a localised radiation force to the liver and capture the resulting shear waves to estimate elasticity [97]. The performance of SWE in assessing fibrosis in AILD patients is described in Table 3. SWE has higher AUROC than FIB-4 and APRI for distinguishing between stages of hepatic fibrosis in AILD, except for identifying significant fibrosis, while accounting for other factors such as steatosis and histological activity.

3.9 | Acoustic Radiation Force Impulse (ARFI) Imaging

A preliminary study evaluated the performance of ARFI in discriminating hepatic fibrosis stages in 61 patients with PBC [102]. The results showed an AUROC of 0.83 with a cut-off of 1.51 m/s for significant fibrosis, an AUROC of 0.93 with a cut-off of 1.79 m/s for advanced fibrosis, and an AUROC of 0.91 with a cut-off of 2.01 m/s for cirrhosis [102]. However, some limitations of ARFI include a small measurement region and that the elasticity measurement and standard deviation are not provided [97].

3.10 | Real-Time Tissue Elastography (RTE)

The RTE technique creates a colour map in which elasticity is measured to be inversely proportional to the deformation of the liver tissue [97]. In patients with PBC, RTE resulted in AUROC of 0.92, 0.95 and 0.97 for significant fibrosis and advanced fibrosis and cirrhosis respectively [108]. Limitations of this technique include the lack of standardisation, operator bias for manual systems and the qualitative nature of the technique [97].

3.11 | Magnetic Resonance Elastography (MRE)

MRE constitutes one of the most precise non-invasive methods for the recognition and staging of fibrosis [103]. While MRE is limited by the ease of access and cost when compared to VCTE, it has the advantage of capturing a larger liver volume and providing liver stiffness (LS) maps that can encompass a major portion of the liver, having better sensitivity without being influenced by BMI, and being able to be performed in conjunction with magnetic resonance cholangiography, which is pivotal in the diagnosis and disease progression assessment in PSC [106, 122].

Studies using MRE in other liver diseases have demonstrated excellent diagnostic performance for advanced fibrosis and cirrhosis. In addition, results are better than those of non-invasive laboratory markers for fibrosis. These attributes of MRE await confirmation in AIH and PBC [122]. In contrast, MRE was validated for the staging of fibrosis in PSC and recently published data suggest that MRE can accurately detect the presence of cirrhosis (Table 3) [106, 107, 123]. Furthermore, in PSC there was a significant correlation between SWE and APRI [123].

4 | Anti-Fibrotic Treatment in AILD

4.1 | Corticosteroids

Predniso(lo)ne reduces inflammation and impairs the activation of TGF-β1, decreases ROS production and arrests liver fibrosis [4]. In AIH, studies have demonstrated over 50% regression in histological fibrosis in sequential liver biopsies after 5 years of treatment [124–126]. This extensive fibrosis regression was mainly present in patients who achieved and maintained biochemical remission and/or had a reduction in necro-inflammatory scores; moreover, some of the studies demonstrated complete reversal in cirrhosis [124–126]. Corticosteroid treatment can help stabilise or improve liver fibrosis in up to 80% of patients [125]. Nevertheless, predniso(lo)ne or any other corticosteroids are not recognised as direct anti-fibrotic medications, as they lack sustainable effects and, unfortunately, carry a substantial risk of significant side effects. The mechanisms of action and experience in AILD for corticosteroids and other anti-fibrotic interventions is summarised in Table 4.

4.2 | Immunomodulators

In a retrospective study of 120 AIH patients, fibrosis regression occurred in 32%–60% of those with biochemical remission after 6 months of immunosuppressive therapy with prednisone and azathioprine [127]. Similar findings were observed in another study with paired liver biopsy following immunosuppressive treatment. After 28 months of treatment, fibrosis regression was found in 41% of AIH patients [149].

4.3 | Ursodeoxycholic Acid (UDCA)

UDCA has a well-established use in chronic liver conditions and exerts a wide spectrum of positive actions, including liver cytoprotection, immunomodulation, stimulation of anti-apoptotic pathways, improvement of hepatobiliary bile acid secretion, and inhibition of ROS generation [128].

One of the randomised controlled trials (RCTs) in AIH revealed no difference in a fibrosis score before and after UDCA treatment and no difference in comparison to the placebo group [129]. In PBC, UDCA was studied extensively and several large RCTs across the world demonstrated the effectiveness of UDCA in preventing/delaying histological stage progression [131–134]. UDCA therapy was associated with a five-fold lower progression rate from early-stage disease to extensive fibrosis or cirrhosis (7% per year with UDCA vs. 34% per year with placebo); however, treatment with UDCA was not associated with a significant difference in fibrosis regression rates (3% per year for both UDCA and placebo) [10]. From the long-term perspective, 59% and 40% of UDCA-treated patients are predicted to remain at an early stage of liver fibrosis after 10 and 20 years of follow-up, respectively [150]. Lastly, in PBC patients with histological evidence of interface hepatitis, the combination of UDCA and immunosuppressive therapy has been shown to significantly improve the fibrosis regression rate (6.3% vs. 52.4%) [151]. Interestingly, UDCA treatment in PBC was found to be associated with the partial alleviation of microbial dysbiosis, which might be one of the fibrotic pathways to be altered [152].

While UDCA has been undoubtedly shown to reduce the rate of fibrosis progression in PBC patients, the evidence surrounding its benefits in PSC is less robust. In a randomised, double-blind study comparing UDCA at a regular dose of 13–15 mg/kg/day with a placebo, UDCA treatment was not associated with significant changes in histologic findings in the liver after 2 years [130]. In another long-term double-blind RCT of high-dose UDCA (28–30 mg/kg/day), the difference between the two groups in histologic stage change was not significant [153].

4.4 | Obeticholic Acid (OCA)

OCA is a selective farnesoid X receptor (FXR) agonist that is derived from the bile acid chenodeoxycholic acid, the endogenous FXR ligand. It activates FXR exhibiting hepatoprotective effects against bile acid toxicity through impairing bile acid synthesis and stimulating choleresis along with direct anti-inflammatory and antifibrotic effects [135]. In a double-blind, placebo-controlled, phase 3 RCT in PBC patients with inadequate response to UDCA, OCA showed greater biochemical improvement (ALP reduction) without any meaningful changes in non-invasive measures of liver fibrosis (LSM or ELF) at 12 months between treatment and placebo groups [154]. However, when exploring the long-term effects of OCA after 3 years of treatment, 71% of PBC patients had improvements or stabilisation in the fibrosis stage [136]. Notably, as of June 2024, the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) has recommended that the conditional marketing authorization of OCA be revoked in the European Union (EU). After review of data shared by the company marketing OCA, health care professionals and patient associations for people living with PBC, the CHMP concluded that the benefits of OCA do not outweigh the risks. Particularly, the COBALT Study Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT), a phase 4, double-blind, multicenter study evaluating the safety and efficacy of OCA for patients with PBC who are intolerant or unresponsive to UDCA did not find any differences between OCA and placebo for the primary composite endpoint of death, liver transplant, or hepatic decompensation [155].

4.5 | Peroxisome Proliferator-Activated Receptor Agonist

Fibrates are agonists of peroxisome proliferator-activated receptors (PPARs). Bezafibrate, a pan-PPAR agonist, has been shown to improve liver fibrosis in up to 41% of PBC patients based on paired liver biopsies over a median of 60 months [139]. In a 24-month, double-blind, placebo-controlled, phase 3 trial involving PBC patients with an inadequate response to UDCA, no significant difference was observed between treatment and placebo groups in changes in histological fibrosis stage; however, LSM by VCTE decreased by 15% from baseline in the bezafibrate group and increased by 22% in the placebo group at 24 months. In parallel with these findings, there was a significant reduction in PIIINP and a downward trend in TIMP-1 levels resulting in a significant reduction in ELF score [156].

TABLE 4 | Anti-fibrotic interventions in AILD.

Intervention	Actions	Experience in AILD
Corticosteroids • Predniso(lo)ne	Decreases ROS production [4] Arrests liver fibrosis [4]	• **AIH:** ◦ Predniso(lo)ne: – 50% reduction in histological fibrosis after 5 years [124–126]
Immunomodulators • Azathioprine	Impair activation of HSCs [14] Increase ECM degradation [14]	• **AIH:** ◦ Azathioprine: – Fibrosis regression in 32%–60% of patients with biochemical remission after 6 months [127]
Bile acids • UDCA	Stimulation of anti-apoptotic pathways [128] Inhibition of ROS generation [128]	• **AIH & PSC:** ◦ UDCA: – The placebo-controlled trial showed no difference in fibrosis score [129, 130] • **PBC:** ◦ UDCA: – Several RCTs show it prevents or delays the progression of fibrosis [131–134]
FXR agonists • OCA • Cilofexor	Activates FXR [135] Anti-inflammatory and anti-fibrotic effects [135]	• **PBC:** ◦ OCA: – 71% of patients showed improvements or stabilisation in fibrosis after 3 years [136] • **PSC:** ◦ Cilofexor: – Phase 3 trial terminated after medical futility [137]
PPAR agonists • Bezafibrate • Seladelpar • Elafibranor	Decreases inflammation and bile acid toxicity [138]	• **PBC:** ◦ Bezafibrate: – Improves liver fibrosis in up to 41% of patients over a median of 60 months [139] ◦ Seladelpar & elafibranor: – No meaningful changes in liver stiffness or ELF were observed at month 12 [141,142]
Lysyl oxidase inhibitors • Simtuzumab	Inhibits lysyl oxidase and collagen cross-linkage [140]	• **PSC:** ◦ Simutzumab: – Phase 2 trial discontinued after lack of efficacy [140]
Chemokine inhibitors • CVC	CVC inhibits CCR2 and CCR5 [141]	• **PSC:** ◦ CVC: – Variable changes in liver fibrosis indices after 24 weeks of treatment [141]
$\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins inhibitors • Bexotegrast	Blocks activation of TGF-β [142]	• **PSC:** ◦ Bexotegrast: – Phase 2 trial resulted in lower ELF score and PRO-C3 [142]
Adhesion protein inhibitors • Timolumab	Blocks VAP-1 [143]	• **PSC:** ◦ Timolumab: – Phase 2 trial discontinued after lack of efficacy [143]
FGF19 analogue • Aldafermin	Inhibits bile acid synthesis via CYP7A1 activity [144]	• **PSC:** ◦ Aldafermin: – Improved non-invasive markers of fibrosis such as the ELF score and Pro-C3 [144]

(Continues)

TABLE 4 | (Continued)

Intervention	Actions	Experience in AILD
Calcineurin inhibitors • Tacrolimus	Inhibits the activity of calcineurin in the immune system [145]	• **AIH:** ◦ Tacrolimus – Lowered liver inflammation and fibrosis in steroid-refractory AIH patients [145]
BAFF inhibitors • Belimumab • Ianalumab	Blocks BAFF activity by targeting BAFF or BAFF-R [146]	• **AIH:** ◦ Belimumab: – Improved liver stiffness in refractory AIH [146] ◦ Ianalumab: – Ongoing phase 2/3 trials [147]
Microbiome-targeted therapy	Gut-liver axis [12, 16]	• **Paediatric PSC:** ◦ Oral vancomycin: – A retrospective study showed a lack of efficacy in improving fibrosis and outcomes [148]
Zinc supplementation	Increases MMP-2/−9 and MMP-9/TIMP-1	• **AIH:** ◦ Zinc supplementation: – Improved fibrosis indices in AIH [58]

Abbreviations: AIH, autoimmune hepatitis; AILD, autoimmune liver diseases; BAFF, B-cell activating factor; BAFF-R, BAFF receptor; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; CVC, cenicriviroc; ECM, extracellular matrix; ELF, Enhanced Liver Fibrosis test; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; HSC, hepatic stellate cells; MMP-2/−9, matrix metalloproteinase-2/−9; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; RCT, randomised controlled trial; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitor of matrix metalloproteinase type 1; UDCA, ursodeoxycholic acid; VAP-1, vascular adhesion protein-1.

4.6 | Simtuzumab

Simtuzumab, a monoclonal antibody directed against LOXL2, has been trialled in patients with PSC. However, treatment for 96 weeks in a phase 2 RCT did not provide clinical benefit including hepatic fibrosis [140].

4.7 | Cenicriviroc (CVC)

One study evaluated the efficacy and safety of CVC, a dual antagonist of chemokine receptors, CCR2 and CCR5, for the treatment of PSC. After 24 weeks of CVC treatment, participants receiving CVC achieved a modest reduction of 18% in the surrogate endpoint of ALP [141]. However, fibrosis indices showed variable results with an increase in LSM by VCTE, but a decrease in APRI and FIB-4 scores.

4.8 | Cilofexor

Cilofexor is a nonsteroidal FXR agonist tested successfully in a 12-week, phase 2 RCT in which it induced a 21% reduction in ALP level and fibrosis markers, such as TIMP-I [157]. However, the phase 3 study (PRIMIS), consisting of 96 weeks of therapy with paired biopsy specimens for patients with noncirrhotic large-duct PSC, was terminated after the first 160 patients completed treatment as a result of futility [137].

4.9 | Bexotegrast

A new molecule, bexotegrast, a dual-selective inhibitor of the $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, has been developed for the treatment of PSC [142]. The $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins are expressed at very low levels in normal tissues but are up-regulated in the liver tissues of PSC patients and serve as activators of TGF-β. A phase 2 trial after 12 weeks demonstrated that the ELF score for patients treated with bexotegrast 160 mg was 84% lower compared to placebo, with similar findings for PRO-C3 [142].

4.10 | Seladelpar

Seladelpar, a selective PPARδ agonist, was recently evaluated in a phase 3, 12-month, double-blind, placebo-controlled trial for patients with PBC with LSM and the ELF score set as secondary endpoints [158]. While changes in LSM over 12 months appeared to be greater with seladelpar than with placebo, there was no significant difference between the two groups [158].

4.11 | Elafibranor

ELATIVE is a phase 3, double-blind, placebo-controlled, 12-month trial that tested the safety and efficacy of elafibranor, a medication which decreases inflammation and bile acid toxicity through its effects as a dual peroxisome proliferator-activated receptor alpha (PPARα) and δ agonist in 161 patients with PBC [138]. Elafibranor did not result in significant changes in fibrosis as measured through LSM and the ELF score.

4.12 | Timolumab

A phase 2, multicenter, single-arm, two-stage trial investigated the efficacy of timolumab, a monoclonal antibody that targets

VAP-1, a protein found in hepatic endothelium, in treating patients with PSC in which changes in liver fibrosis were a secondary endpoint [143]. After 120 days of treatment, fibrosis Multiscan scores, serum biomarkers and scores of fibrosis and LSM by VCTE were unchanged [143].

4.13 | Aldafermin

Aldafermin or NGM282 is a fibroblast growth factor 19 (FGF19) endocrine hormone analogue that controls bile acid synthesis and was tested in a phase 2, multicenter RCT for PSC [144]. Treatment with aldafermin improved non-invasive markers of fibrosis such as the ELF score and Pro-C3.

4.14 | Tacrolimus

Tacrolimus is a calcineurin inhibitor with wide-ranging downstream effects on the immune system through the inhibition of $CD4^+$ T helper cells [156]. A small retrospective study of nine patients with steroid-refractory AIH treated on tacrolimus with a median dose of 2 mg/day for a median of 18 months reported an improvement in histologically assessed liver inflammation and fibrosis [145].

4.15 | B-Cell Activating Factor (BAFF) Inhibitors

BAFF inhibitors such as belimumab and ianalumab, block BAFF activity by targeting BAFF or the receptor for BAFF (BAFF-R) [146]. BAFF is a cytokine released by T-cells and dendritic cells, involved in B-cell proliferation. A monoclonal antibody targeting BAFF, belimumab, has been shown to improve LSM by VCTE and achieve complete response as a third-line treatment in two patients with refractory AIH [146]. Similarly, ianalumab is a monoclonal antibody against BAFF-R and is being evaluated for treating AIH in phase 2/3 RCTs [147].

4.16 | Microbiome-Targeted Therapy

No clinical trials to date investigated the impact of microbiome-based therapies on liver fibrosis in AILD; however, it was shown that non-absorbable antibiotics could improve fibrosis [12, 16]. Additionally, a retrospective study examined the use of oral vancomycin in the paediatric PSC population, with the results showing a lack of efficacy in improving either fibrosis or clinical outcomes [148]. Nevertheless, the critical importance of the gut-liver axis homeostasis is undoubted, warranting further investigation and potential application in AILD.

4.17 | Zinc Supplementation

Zinc supplementation was shown to be associated with reduced serum concentration of direct hepatic fibrosis biomarkers, such as HA, TIMP-1, and type IV collagen in chronic liver diseases [159]. In a retrospective study that included 31 patients with AIH and PBC, a serum zinc concentration of $\geq 70\,\mu g/dL$ was revealed to be effective in inhibiting HCC development, and fibrosis suppression is hypothesized to play a crucial role in this beneficial effect [160]. Furthermore, in AIH patients, zinc supplementation has been demonstrated to safely improve serum fibrosis indices through increases in MMP-2/−9 and MMP-9/TIMP-1 [58].

5 | Conclusion

Liver injury in autoimmune liver diseases (AILD) could result in fibrosis progression, leading to cirrhosis and liver-related morbidity and mortality. While evidence suggests fibrosis progression carries prognostic value in patients with AILD, the performance of conventional blood-based fibrosis markers needs to be further validated in this population. VCTE demonstrates excellent performance in evaluating fibrosis and identifying cirrhosis in AILD patients. Predniso(lo)ne and immunomodulators were shown to regress fibrosis and reverse cirrhosis in AIH patients. In PBC, treatment with either UDCA, OCA or fibrates leads to the improvement or stabilisation in the fibrosis stage. Patients with AIH and insufficient response to treatment despite appropriate adjustment of first-line treatment should be considered for off-label therapies aiming to prevent or slow the progression of fibrosis. In the same line, patients with PBC and incomplete response to UDCA, who do not respond to OCA should be considered for off-label therapies aiming to prevent or slow the progression of fibrosis. There is an urgent need for effective medical treatments, including anti-fibrotics in PSC. The emerging landscape of newly introduced anti-fibrotic agents may provide hope for the much-needed cure for people living with AILD.

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All authors made contributions to the conception and design, compilation and interpretation of data; took part in drafting the article and/or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

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Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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