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Spectrum of Autoimmune Liver Disease and Real-World Treatment Experience from a Tertiary Care Hospital

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Background and aims: **Autoimmune liver disease (AILD) comprises of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) with a spectrum of overlap amongst the three. We analyzed the spectrum and treatment outcomes of patients with AILD presenting to a tertiary care center in India.** ***Methods:*** **A retrospective analysis of AILD patients from June 2008 to April 2021 was performed. The diagnosis was based on clinical, biochemical, imaging, serological, and histological characteristics. Eligible patients received treatment depending on the disease stage. Biochemical response to treatment was defined as normalization of AST, ALT, bilirubin, and immunoglobulin G levels at 6 months in AIH, normalization of total bilirubin and/or albumin at 1 year in PBC and decrease in alkaline phosphatase (ALP) levels by 40% in PSC.** ***Results:*** **Two hundred seventy-five patients were analyzed. AIH (58.54%) was most common, followed by an overlap of AIH-PBC (24%) and AIH-PSC (6.54%), PSC (6.18%), and PBC (4.72%). Most patients presented in 3rd or 4th decade, except PBC which occurred predominantly in 5th decade. The majority of patients were females (72.72%). Jaundice was the most common presentation seen in 60% of patients. Cirrhosis was present in 57.47% of patients. Patients with overlap had more pruritus (54.76 vs 6.83%), fatigue (63.1% vs 49.7%), hepatomegaly (52.4% vs 25.5%), and higher ALP (80.9% vs 37.7%) than patients with AIH alone. Acute presentation was seen in 33 patients (13.5%) with most having AIH flare. Five patients had acute liver failure (ALF) and 9 had acute-on-chronic liver failure (ACLF). ALF was associated with 80% mortality while 55.56% of patients with ACLF had a complete biochemical response to immunosuppression. Among patients with AIH and/or overlap who received immunosuppression, a complete biochemical response to immunosuppression was seen in 60.69% of patients. High ALT (OR 1.001 [1.000–1.003], *P* = 0.034), high albumin (OR 1.91 [1.05–3.48], *P* = 0.034) and low fibrosis on biopsy (OR 0.54 [0.33–0.91], *P* = 0.020) predicted complete response.** ***Conclusion:*** **AIH is the most common AILD followed by overlap syndromes, PSC and PBC in our cohort. Biochemical response to immunosuppression is seen in 60% of patients with AIH & low fibrosis score on histopathology predicts a complete response. (J Clin Exp Hepatol xxxx;xxx:xxx)**

The spectrum of autoimmune liver disease (AILD) comprises of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap of the three disorders in varying presentations. AIH is the most common disorder among AILD and accounts for 15–200 cases per million in the west.[1] However, in India, the prevalence of AIH is low, comprising less than 5% of all patients with liver

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Abbreviations: ACLF: acute-on-chronic liver failure; AIH: autoimmune hepatitis; AILD: Autoimmune liver diseases; ALF: acute liver failure; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AMA: anti-mitochondrial antibody; ASMA: anti-smooth muscle antibody; AST: aspartate aminotransferase; ELISA: enzyme-linked immunosorbent assay; IBD: inflammatory bowel disease; IgG: immunoglobulin G; INR: international normalized ratio; LC-1: liver cytosol 1; LKM-1: liver kidney microsomal 1; LSM: liver stiffness measurement; LT: liver transplant; MMF: mycophenolate mofetil; MRCP: magnetic resonance cholangiopancreatography; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; SLA: soluble liver antigen; UDCA: ursodeoxycholic acid; ULN: upper limit of normal
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disease.[2–4] PBC and PSC are much rarer. AIH and PBC have effective therapies in the form of immunosuppression and ursodeoxycholic acid (UDCA) respectively, which can alter the natural history of the disease and slow its progression. Thus, early diagnosis is important so that effective therapy can be instituted before the development of cirrhosis. There is no effective treatment for PSC at present and management is focused on improving the cholestatic symptoms, treatment of cholangitis, endotherapy for dominant stricture, and early diagnosis and management of cholangiocarcinoma.[5] Liver transplantation (LT) remains the mainstay of therapy for decompensated cirrhosis, however, the nonavailability of donors and financial constraints have led to limited widespread availability of LT in India. This study was planned to study the spectrum of AILD at a tertiary referral center in North India and to assess the response to therapy in these patients.

PATIENTS & METHODS

A retrospective analysis of prospectively followed-up patients with confirmed AILD presenting to the Department of Hepatology from June 2008 to April 2021 at the Post Graduate Institute of Medical Education and Research, Chandigarh, India was performed. A detailed clinical history, biochemical parameters, serological studies, and histological characteristics using a precoded questionnaire were taken from the liver clinic file database. The study was approved by the Institutional Ethics Committee (IEC-INT/2022/Study-411) and informed consent was waived off as it was a retrospective analysis. The study has been reported in accordance with STROBE guidelines.

Clinical Assessment

A special emphasis was laid on precipitating events (including factors associated with immune-mediated hepatitis like drug history and history of vaccination), history of jaundice, extrahepatic features of autoimmune disease, and family history of autoimmune disease. The details of clinical examination to find out the presence of hepatomegaly, splenomegaly, ascites, pedal edema, jaundice, or skin rashes were noted.

Laboratory Assessment

Reports of hematological and biochemical tests including complete hemogram, liver function tests, kidney function tests, prothrombin time, and International Normalized Ratio (INR) were noted for all patients. Acute and chronic viral hepatitis was ruled out through serological tests (HBsAg, anti-HBc total for Hepatitis B; anti-HCV for Hepatitis C; anti-HAV IgM for Hepatitis A Virus and anti-HEV IgM for Hepatitis E Virus) done by ELISA (enzyme-linked immunosorbent assay).

Autoimmune screening was done by adult 1/40 screening sera dilutions, using rat composite tissues (stomach, liver, kidney). Positive sera for AMA (anti-mitochondrial antibody), LKM-1 (Liver kidney microsomal), LC-1 (liver cytosol 1) were run on immunoblots (AMA, LKM-1, LC-1, GP-210, SLA, SP100) and/or AMA, LKM-1 ELISAs.[6] From 2018, an in-house method was replaced by commercial biochips purchased from Euroimmune (Germany) carrying rat liver kidney, stomach, and Hep-2 cells. Immunoblots and ELISA were used as above. SLA ELISA was also put up in all negative sera. Magnetic resonance cholangiopancreatography (MRCP) was done in all patients with clinical or biochemical cholestasis. All patients suspected to have overlap syndromes or AIH also underwent testing for total serum immunoglobulin G (IgG) levels by nephelometry method. All patients with confirmed PSC or AIH with features of PSC underwent colonoscopy with segmental biopsies to screen for concomitant inflammatory bowel disease (IBD). As a protocol, 5-yearly screening colonoscopies with segmental biopsies were done in all patients with PSC (or AIH-PSC overlap) without evidence of colitis. All patients with sclerosing cholangitis were excluded for causes of secondary sclerosing cholangitis through history, serology (for HIV, ascariasis, etc.), biochemical tests (like serum IgG4), and imaging (MRCP).

Diagnosis

All patients with suspected AIH, suspected small duct PSC, and overlap of AIH with primary cholestatic disorders underwent liver biopsy. Patients who were suspected to have these entities clinically but did not undergo a liver biopsy were not included in this study.

1. **AIH:** Diagnosis of AIH was based on simplified diagnostic criteria of the International Autoimmune Hepatitis Group (IAIHG).[5] A score of ≥6 was suggestive of probable AIH and a score of ≥7 was suggestive of definite AIH.[5] Patients with positive ANA and/or SMA were classified as having type I AIH and those with positive LKM-1 antibodies (usually in the absence of ANA and/or SMA) were classified as having type 2 AIH.[7]
2. **PBC:** Diagnosis of PBC was made when 2 out of the following 3 criteria were met – elevation of alkaline phosphatase >1.5 times of upper limit of normal (ULN); AMA positivity; and presence of non-suppurative cholangitis in septal and interlobular bile ducts on liver biopsy.[8]
3. **PSC:** Diagnosis of PSC was based on the presence of cholestatic symptoms or cholestatic pattern of liver function tests with elevated alkaline phosphatase (ALP) and/or GGT in presence of typical features of PSC on cholangiography along with the exclusion of secondary causes of sclerosing cholangitis.[9] For patients without cholangiographic evidence of PSC, liver biopsy showing concentric periductal "onion skin" fibrosis was suggestive of small duct PSC.
4. **Overlap of AIH with PBC:** Diagnosis of overlap of AIH with PBC was based on Paris Criteria[10] which included 2 out of 3

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features of PBC (ALP >2 times ULN or GGT >5 times ULN; AMA positivity; or florid bile duct lesion on histology) and 2 out of 3 features of AIH (ALT >5 times of ULN; IgG >2 times of ULN or ASMA positivity, and moderate or severe interface hepatitis on histology).

5. **Overlap of AIH with PSC:** Diagnosis of overlap of AIH with PSC was based on the presence of probable or definite AIH according to IAIHG criteria (obligatory presence of interface hepatitis) along with cholangiographic evidence of multifocal bile duct strictures and absence of AMA.[10]

Disease Spectrum

The spectrum of disease was divided into acute hepatitis, chronic hepatitis, cirrhosis, and ACLF.

1. **Acute hepatitis** was defined by jaundice of ≤6 months in patients without clinical, biochemical, or imaging evidence of underlying chronic liver disease. These patients were further characterized into acute severe AIH (jaundice with coagulopathy i.e., INR ≥1.5 without encephalopathy) and acute liver failure (jaundice, coagulopathy, and encephalopathy).[7]
2. **Chronic hepatitis** was defined as the duration of disease >6 months or the presence of ≥ F2 fibrosis on liver biopsy.[7]
3. **Cirrhosis** - The diagnosis of cirrhosis was based on liver biopsy, or on a combination of clinical, imaging (altered liver size with heterogenous echotexture, irregular outline, portosystemic collaterals or ascites), laboratory (hypoalbuminemia, aspartate aminotransferase/alanine aminotransferase ratio >1) and endoscopic findings (presence of esophageal varices). The presence of ascites, gastrointestinal bleeding, or hepatic encephalopathy was defined as decompensations.[11]
4. **ACLF** was defined according to the Asia Pacific Association for Study of Liver (APASL) definition[12] as "acute hepatic insult manifesting as jaundice (Bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5) complicated within 4 weeks by clinical ascites and/or hepatic encephalopathy in a patient with known or unknown underlying chronic liver disease associated with high short-term mortality".

Treatment & Treatment Response

Autoimmune Hepatitis

Patients with Acute AIH were started on prednisolone 0.5–1 mg/kg, and azathioprine 0.5–1 mg/kg was added once serum bilirubin levels were less than 3 mg/dL.[7] Patients who presented with acute liver failure (ALF) received standard care and were counseled for liver transplantation. Those who did not agree to liver transplant were treated with plasmapheresis and/or prednisolone in a dose of 0.5–1 mg/kg after ruling out all contraindications. Patients with chronic hepatitis were started on prednisolone 30 mg and azathioprine 50 mg and doses were modified according to response.[7] For patients of cirrhosis with activity, prednisolone was initiated at a dose of 0.5 mg/kg. Azathioprine was added after 2 weeks in a dose of 0.5–1 mg/kg.[7] Patients of ACLF who were eligible for treatment received prednisolone in a dose of 0.5–1 mg/kg.[13] Azathioprine was only added once the bilirubin level was less than 3 mg/dL in a dose of 0.5–1 mg/kg.

Biochemical Response to Treatment

1. **Complete response** in AIH was defined as normalization of AST, alanine aminotransferase (ALT), bilirubin, and IgG levels at 6 months[7]
2. **Partial response** in AIH was defined as more than a 25% decrease in AST and/or ALT at 2 weeks and not meeting the criteria for complete response[14]
3. **Non-Response** in AIH was defined as less than a 25% decrease or increase in AST and/or ALT at 2 weeks.[14]

Patients who had a partial response and no response were classified as having a poor response for identifying predictors to complete response. Once biochemical remission was achieved with steroids, they were gradually tapered (2.5–5 mg every 2–4 weeks), to achieve the lowest possible dose to maintain biochemical remission. Simultaneously, azathioprine was increased to 1–2 mg/kg depending on the response and tolerance to azathioprine.[7] Patients who did not respond to corticosteroids and Azathioprine or those who were intolerant to azathioprine were treated with mycophenolate mofetil (MMF) or tacrolimus. Patients were followed up every 2–4 weeks after the initiation of steroids till biochemical remission was achieved. After the achievement of biochemical remission, patients were reviewed at 3-month intervals or earlier in case of any symptoms.

PBC and PSC

Patients of PBC and PSC were treated with 10–15 mg/kg/day of UDCA in 2–3 divided doses. Dominant stricture in PSC was managed endoscopically or through a percutaneous route by stricture dilatation ± stenting. Biochemical response to therapy in PBC was defined by the Rotterdam criteria i.e., normalization of total bilirubin and/or albumin at 1 year.[10] Biochemical response to therapy in PSC was defined as a decrease in ALP levels by 40%.[9]

Overlap of AIH with primary cholestatic disorders

Patients of AIH with features of PBC were treated with a combination of prednisolone, azathioprine, and UDCA in usual doses as used for AIH and PBC alone.[10]

Patients of AIH with features of PSC were also treated with a combination of prednisolone, azathioprine, and UDCA. In patients with a dominant biliary stricture, an endoscopic or percutaneous biliary intervention was done.[10]

Statistical Analysis

Data was compiled in a Microsoft excel sheet. Data was presented in the form of tables and graphs. Categorical data were expressed as percentages or proportions while continuous data were expressed as mean ± standard deviation (SD) or Median (Inter-Quartile Range; IQR) as appropriate. The normality of quantitative data was checked by the Shapiro–Wilk test of normality. Comparison between

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Table 1 Comparison of Baseline Characteristics and Treatment Response of AIH With Overlap Spectrum.

Characteristic	All AILD (n = 275)	AIH (n = 161)	Overlap of AIH with PSC or PBC (n = 84)	*P*-value (AIH vs overlap)
Age (years, mean ± SD)	40.48 ± 14.38	37.90 ± 15.15	43.70 ± 12.55	**0.014**
Females (n, %)	200 (72.73%)	117 (72.67%)	65 (77.38%)	0.423
Jaundice (n, %)	165 (60%)	95 (59.01%)	54 (64.29%)	0.421
Pruritus (n, %)	77 (28%)	11 (6.83%)	46 (54.76%)	**<0.001**
Fever (n, %)	38 (13.82%)	23 (14.29%)	15 (17.86%)	0.463
Fatigue (n, %)	147 (53.45%)	80 (49.69%)	53 (63.10%)	**0.045**
Hyperpigmentation (n, %)	21 (7.64%)	4 (2.48%)	9 (10.71%)	**0.006**
Abdominal pain (n, %)	54 (19.64%)	25 (15.53%)	19 (22.62%)	0.170
Hepatomegaly (n, %)	101 (36.73%)	41 (25.47%)	44 (52.38%)	**<0.001**
Splenomegaly (n, %)	81 (29.45%)	54 (33.54%)	21 (25%)	0.168
Concomitant AI disease (n, %)	89 (32.60%)	49 (30.82%)	33 (39.29%)	0.183
Bilirubin (mg/dL, Median [IQR])	2.23 [1.07–5.3]	2.5 [1.1–5.5]	2.3 [1.27–4.95]	0.300
AST (IU/L, Median [IQR])	135 [84–315]	166 [82–382]	130.5 [88.5–210]	**0.007**
ALT (IU/L, Median [IQR])	123 [74–271]	129 [79–336]	123.5 [77–227]	**<0.001**
ALP (IU/L, Median [IQR])	242 [157–464]	196 [123–257]	506.5 [16.5–742]	**<0.001**
Total Protein (g/dL, Median [IQR])	7.4 [6.7–8.1]	7.4 [6.5–8.07]	7.3 [6.8–8.15]	0.837
Serum Albumin (g/dL, Median [IQR])	3.4 [3–3.9]	3.4 [3–3.9]	3.53 [3.2–3.9]	0.725
Haemoglobin (gm/dL, Median [IQR])	11.5 [10.2–12.8]	11.4 [10.3–13]	11.3 [9.95–12.35]	0.459
Leukocyte count (x 10^3/cu. mm) (median [IQR])	6.8 [4.6–8.9]	6.1 [4.3–8.5]	7.7 [5.75–9.24]	**0.019**
Platelet Count (x 10^3/cu. mm) (median [IQR])	160 [110–234]	142 [107–218]	209 [133–282]	**0.004**
Total IgG (mg/dL, Median [IQR])	2200 [1835.4–2876]	2240 [1900–2930]	2240 [1700–2670]	0.211
Liver stiffness measurement (kPa, Median [IQR])	17.5 [9–27.7]	18.4 [8.8–27.4]	17.6 [9.9–28.4]	0.383
Cirrhosis (n, %)	158 (57.45%)	86 (53.41%)	46 (54.76%)	0.365
ANA positivity (n, %)	128 (46.72%)	76 (47.50%)	46 (54.76%)	0.280
SMA positivity (n, %)	91 (33.09%)	74 (45.96%)	15 (17.86%)	**<0.001**
LKM positivity (n, %)	8 (2.91%)	5 (3.11%)	3 (3.57%)	0.847
Response to treatment				
Complete (n, %)	154 (59.23%)	95 (62.09%)	44 (57.89%)	0.540
Partial (n, %)	76 (29.23%)	38 (24.84%)	29 (38.16%)	**0.037**
None (n, %)	24 (9.23%)	15 (9.80%)	2 (2.63%)	0.051
Flare (n, %)	6 (2.31%)	5 (3.27%)	1 (1.32%)	0.913

AI, autoimmune; AIH, autoimmune hepatitis; AILD, autoimmune liver diseases; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; IQR, inter-quartile range; LKM, liver kidney microsomal; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation; SMA, smooth muscle antibodies.

different groups was done by independent t-test (normality assumed) and Wilcoxon Rank sum test (non-normal data). For predicting the attainment of a complete response, ROC curves were drawn. Predictors of biochemical response to therapy were assessed by logistic regression analysis. All parameters with $P < 0.05$ on univariate analysis were further assessed on multivariate analysis. All statistical tests were two-sided and performed at a 5% level of significance ($\alpha = 0.05$). The analyses were performed using Stata/SE Version 16.1 for Mac (Stata Corp LLC).

RESULTS

A total of 275 patients of AILD were retrospectively studied. The most common AILD was AIH comprising 161 (58.54%) cases. Overlap presentation of AIH accounted for 84 (30.54%) cases (AIH-PBC – 66 cases (78%) and AIH-PSC – 18 (21.43%) cases). Thirteen patients (4.72%) were diagnosed with PBC, and 17 patients (6.18%) had PSC. All patients underwent liver biopsy, except 9 patients (3.27%) with cholangiographic evidence of PSC.

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Age Distribution in AILD

Patients of AIH presented predominantly in the 3rd and 4th decade of life (19.87% and 19.25% respectively). Overlap of AIH with PBC was most predominant in the 5th decade (34.85%) while the overlap of AIH with PSC was most common in the 3rd decade (33.33%). PBC was predominantly seen in the 5th decade (38.46%) while the majority of patients with PSC (9, 52.94%) presented in the 3rd and 4th decade of life.

Clinical Features of AILD (Table 1)

The mean age of presentation of AILD was 40.8 ± 14.38 years. The disease was predominantly seen in females (200, 72.73%). The most common clinical presentation was jaundice, seen in 165 (60%) patients followed by fatigue, seen in 147 (53.45%) patients. Eighty-nine (32%) patients with AILD had evidence of other autoimmune diseases. Antinuclear antibodies were present in 128 (46.72%) patients while smooth muscle antibodies (SMA) were seen in 91 (33.09%) patients. Sixty-three (23%) patients had negative autoantibodies and were labeled as seronegative AILD. Cirrhosis was present in 158 (57.45%) patients in our cohort.

Clinical Features of Autoimmune Hepatitis (Table 1)

The mean age of presentation of AIH in our cohort was 37.9 ± 15.15 years. The disease had a female preponderance (117, 72.67%). The most common presentation was jaundice (95, 59.01%), followed by fatigue (80, 49.69%). Extra-hepatic autoimmune diseases were present in 49 (30.82%) patients. Around 53% of patients (n = 86) had cirrhosis at initial presentation. Type I AIH was the predominant type seen in 156 (96.89%) patients, while type II AIH was seen in 5 patients (3.10%).

Table 2 Comparison of Baseline Characteristics and Treatment Response of Primary Cholestatic Disorders.

Characteristic	PBC (n = 13)	PSC (n = 17)	*P*-value
Age (years, mean ± SD)	50.69 ± 8.93	41.23 ± 12.84	**0.031**
Females (n, %)	13 (100%)	5 (29.41%)	**0.001**
Jaundice (n, %)	6 (46.15%)	10 (58.82%)	0.490
Pruritus (n, %)	8 (61.54%)	12 (70.59%)	0.602
Fatigue (n, %)	9 (69.23%)	5 (29.41%)	**0.030**
Hyperpigmentation (n, %)	5 (38.46%)	3 (17.65%)	0.201
Abdominal pain (n, %)	4 (30.77%)	6 (35.29%)	0.794
Hepatomegaly (n, %)	6 (46.15%)	10 (58.82)	0.490
Splenomegaly (n, %)	3 (23.08%)	3 (17.65%)	0.868
Concomitant AI disease (n, %)	5 (38.46%)	2 (11.76%)	0.712
Bilirubin (mg/dL, Median [IQR])	1.36 [0.9–1.8]	3.2 [1.1–5.7]	0.300
AST (IU/L, Median [IQR])	86 [60–108]	97 [80–128]	**0.007**
ALT (IU/L, Median [IQR])	70 [54–76]	97 [74–123]	**<0.001**
ALP (IU/L, Median [IQR])	432 [334–637]	359 [328–840]	**<0.001**
Total Protein (g/dL, Median [IQR])	7.4 [6.9–8]	7 [6.4–8]	0.837
Serum Albumin (g/dL, Median [IQR])	3.48 [3.1–3.8]	3.4 [2.9–3.95]	0.725
Haemoglobin (gm/dL, Median [IQR])	11.6 [10.7–12]	12.3 [11–13]	0.459
Leukocyte count (x 10^3/cu. mm) (median [IQR])	6.2 [3.64–7.5]	8 [6.3–8.9]	**0.019**
Platelet Count (x 10^3/cu. mm) (median [IQR])	183 [118–226]	201 [110–298]	**0.004**
Total IgG (mg/dL, Median [IQR])	1992 [1650–2490]	2007 [1520–2317]	0.211
Liver stiffness measurement (kPa, Median [IQR])	16.25 [7–50.5]	9.5 [7.8–17.8]	0.383
Cirrhosis (n, %)	6 (46.15%)	7 (41.18%)	0.127
Response to UDCA			
Complete (n, %)	8 (61.54%)	5 (29.41%)	0.259
Partial (n, %)	4 (30.77%)	4 (23.53%)	0.818
None (n, %)	1 (7.69%)	8 (47.06%)	**0.045**

AI, autoimmune; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; IQR, interquartile range; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid.

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Comparison of AIH & Overlap of AIH with Primary Cholestatic Disorders (Table 1)

Patients with AIH had a lower mean age as compared to patients in the overlapping spectrum. Pruritus, fatigue, hyperpigmentation, and hepatomegaly were more in patients presenting as an overlap when compared to AIH. There was no significant difference in presence of abdominal pain, splenomegaly, or concomitant autoimmune diseases among the two groups. Median AST [166 vs 130.5 IU/L; $P = 0.007$] and ALT [129 vs 123.5 IU/L; $P < 0.001$] levels were higher among patients with AIH while median ALP levels [506.5 vs 196 IU/L; $P < 0.001$] were higher among patients with overlap spectrum. ANA positivity was similar among the two groups while SMA positivity was more common in patients with AIH [45.96% vs 17.86%; $P = 0.043$]. The presence of cirrhosis and biochemical response to treatment was similar in both groups.

Comparison of Primary Cholestatic Disorders (Table 2)

PBC was predominantly seen in females while PSC was more common in males [100% females vs 29.41% females; $P = 0.001$]. PSC presented almost a decade earlier as compared to PBC [41.23 ± 12.84 vs 50.69 ± 8.93 years; $P = 0.031$]. Patients with PSC had a higher mean bilirubin level and a poor biochemical response to UDCA as compared to patients with PBC. AMA positivity was seen in 76.92% of patients with PBC (10/13) and 78.79% of patients (52/66) with AIH-PBC overlap. All patients with PBC were positive for AMA-M2. Fifty-six patients presenting as an overlap of AIH-PBC had results of AMA-M2 available, which was positive in 50 patients (89.29%). Dominant stricture was present in 3 patients (17.65%) of PSC and 4 patients (22.22%) with AIH-PSC spectrum. Concomitant IBD was seen in 2 patients of PSC (11.76%) and 1 patient (5.56%) with AIH-PSC overlap.

Presentation of Overlap of AIH with Primary Cholestatic Disorders (Supplementary Table 1)

Patients of AIH with PBC overlap were about a decade older as compared to overlap with PSC (45.51 ± 10.79 years vs 35.64 ± 14.97 years; $P = 0.002$). Females were predominantly affected (AIH-PBC vs AIH-PSC – 83.33% vs 55.56%, $P = 0.013$). Fatigue was more common in patients with AIH-PBC, while higher bilirubin levels were more common in patients with AIH-PSC. Biochemical response to therapy was similar in both groups.

Acute Presentation of AIH (Table 3)

Thirty-three patients had an acute presentation of AIH (13.47%). The majority were females (78.79%) with a mean age of 38.39 ± 12.75 years. Among the AILD presenting acutely, the majority had Type 1 AIH (28, 84.85%) while

Table 3 Baseline Characteristics and Treatment Response of Acute Presentation of AIH.

Characteristic	Acute AIH (n = 33)
Age (years, mean ± SD)	38.39 ± 12.75
Females (n, %)	26 (78.79%)
Etiology	
AIH (n, %)	28 (84.85%)
AIH-PBC overlap (n, %)	5 (15.15%)
AIH-PSC overlap (n, %)	0
Jaundice (n, %)	25 (75.76%)
Pruritus (n, %)	5 (15.15%)
Fever (n, %)	7 (21.21%)
Fatigue (n, %)	20 (60.61%)
Hyperpigmentation (n, %)	1 (3.03%)
Abdominal pain (n, %)	8 (24.24%)
Hepatomegaly (n, %)	10 (30.30%)
Splenomegaly (n, %)	4 (12.12%)
Concomitant AI disease (n, %)	8 (24.24%)
Bilirubin (mg/dL; Median [IQR])	6.4 [3.6–12]
AST (IU/L; Median [IQR])	342 [176–936]
ALT (IU/L; Median [IQR])	420 [152–902]
ALP (IU/L; Median [IQR])	198 [170–234]
Total Protein (g/dL; Median [IQR])	7.4 [6.5–8]
Serum Albumin (g/dL; Median [IQR])	3.3 [3.1–4]
INR (Median [IQR])	1.4 [1.19–1.7]
Haemoglobin (g/dL; Median [IQR])	11.9 [10.8–13.2]
Leukocyte count (x 10^3/cu. mm; Median [IQR])	7.9 [5.9–11]
Platelet Count (x 10^3/cu. mm; Median [IQR])	162 [136–233]
Total IgG (n = 30) (mg/dL; Median [IQR])	2165.45 [1837–3138]
Liver stiffness measurement (n = 21) (kPa; Median [IQR])	17.5 [8.3–27.7]
Cirrhosis (n, %)	11 (33.33%)
ANA positivity (n, %)	14 (42.42%)
SMA positivity (n, %)	15 (45.45%)
LKM positivity (n, %)	0
Seronegative (n, %)	9 (27.27%)
Response to treatment	
Complete (n, %)	21 (63.64%)
Partial (n, %)	5 (15.15%)
None (n, %)	5 (15.15%)
Flare (n, %)	2 (6.06%)

AI, autoimmune; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; INR, International Normalized Ratio; LKM, Liver kidney microsomal; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation; SMA, smooth muscle antibodies.

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5 (15.15%) patients had AIH-PBC. Seronegative disease was seen in 9 patients (27.27%). All patients underwent liver biopsy. On biopsy, acute hepatitis (lobular hepatitis with portal lymphoplasmacytic inflammatory infiltrate) was seen in 8 patients (24.24%), chronic active hepatitis with moderate–severe interface activity in 17 patients (51.51%), cirrhosis with moderate–severe interface activity in 8 patients (24.24%) and lobular hepatitis with central perivenulitis and necrosis (with portal plasmacytosis and/or interface hepatitis) in 22 patients (66.67%). Cholestasis was present in 19 patients (57.58%) and florid duct lesion was seen in 5 patients (15.15%). Five patients (17.24%) presented with ALF and was associated with high mortality (80%) despite 2 patients being treated with plasmapheresis and steroids.

AIH Presenting as ACLF

Nine patients (27.27%) presented with acute-on-chronic liver failure (ACLF), all of which received immunosuppression. On histology, interface hepatitis, rosetting, and lymphoplasmacytic infiltration were seen in all patients with ACLF. Lobular inflammation was seen in 4 (44.44%) patients, central perivenulitis in 5 (55.56%) patients, bile duct proliferation in 6 (66.67%) patients, and bile duct loss in 1 (11.11%) patient. Stage 2 fibrosis was seen in 2 (22.22%) patients, stage 3 fibrosis in 4 (44.44%) patients, and stage 4 fibrosis in 3 (33.33%) patients. Complete remission with immunosuppression was achieved in 5 patients (55.56%), partial remission in 2 patients (22.22%), and no response in 2 patients (22.22%). Two patients (22.22%) with ACLF succumbed to the disease.

Table 4 Predictors of Response to Immunosuppression (Complete vs Partial and No Response).

AIH/overlap treated with steroids (n = 229)	Complete response (n = 139)	Poor response (n = 90)	Odds Ratio (95% CI)	*P*-value
Age (years; Mean ± SD)	40.72 ± 14.43	37.27 ± 14.31	1.01 [0.99–1.03]	0.079
Presence of ascites (n, %)	27 (19.42%)	38 (42.22%)	0.32 [0.18–0.59]	**<0.001**
Presence of HE (n, %)	9 (6.47%)	11 (12.22%)	0.49 [0.19–1.27]	0.138
Presence of GI bleed (n, %)	5 (3.6%)	10 (11.11%)	0.29 [0.09–0.90]	**0.033**
Serum bilirubin (mg/dl; Median [IQR])	2.15 [0.98–5.6]	3.25 [1.5–5.5]	1.01 [0.96–1.06]	0.565
AST (IU/L; Median [IQR])	157 [86–389]	144 [101–237]	1.00 [0.99–1.00]	0.109
ALT (IU/L; Median [IQR])	151 [85–345]	125.5 [89–214]	1.00 [1.00–1.00]	**0.009**
ALP (IU/L; Median [IQR])	228 [56–402]	262.5 [160–552]	0.99 [0.99–1.00]	0.134
Albumin (g/dL; Median [IQR])	3.6 [3.1–3.9]	3.3 [2.9–3.7]	1.51 [1.00–2.30]	**0.049**
IgG (mg/dL; Median [IQR]	2267 [1836–2899]	2200 [1890–2641]	0.99 [0.99–1.00]	0.600
Liver Stiffness Measurement (kPa; Median [IQR])	14.8 [8–26.6]	22 [16–27.8]	0.97 [0.95–0.99]	**0.013**
Cirrhosis			0.16 [0.08–0.31]	**<0.001**
Yes (n = 127) (n; %)	55 (39.57%)	72 (80%)		
No (n = 102) (n; %)	84 (60.43%)	18 (20%)		
Seronegative AIH			0.76 [0.38–1.51]	0.442
Yes (n = 42) (n; %)	24 (17.27%)	18 (21.43%)		
No (n = 181) (n; %)	115 (82.73%)	66 (78.57%)		
Overlap			0.78 [0.44–1.37]	0.399
Yes (n = 74) (n; %)	42 (30.22%)	32 (35.56%)		
No (n = 155) (n; %)	97 (69.78%)	58 (64.44%)		
Fibrosis on biopsy (Median [IQR])	2 [1–4]	4 [4-4]	0.47 [0.36–0.60]	**<0.001**
Bile duct loss (n; %)	33 (24.09%)	33 (36.67%)	0.54 [0.30–0.97]	**0.042**
Histologic activity index (Median [IQR])	7 [6–8]	8 [7–8]	0.68 [0.54–0.86]	**0.001**
Acute presentation			1.15 [0.53–2.48]	0.709
Yes (n = 33) (n; %)	21 (15.11%)	12 (13.33%)		
No (n = 196) (n; %)	118 (84.89%)	78 (86.67%)		

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastro-intestinal; HE, hepatic encephalopathy; IgG, immunoglobulin G.

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Response to Therapy

Out of 161 patients with AIH, 151 (93.78%) received immunosuppression. All patients who were given immunosuppression received prednisolone while azathioprine could be given to 124 (82.11%) patients. Complete biochemical response was observed in 95 patients (62.09%) while partial response was seen in 38 patients (24.84%). Among 84 patients with an overlap of AIH-PBC and AIH-PSC, 76 (90.47%) were treated with a combination of immunosuppression and UDCA. All patients of AIH with cholestatic features who were given immunosuppression received prednisolone while azathioprine was received by 69 (90.78%) patients. Complete biochemical response was seen in 44 patients (57.89%) and partial response was seen in 29 patients (38.16%). Eight patients (61.54%) with PBC had a complete biochemical response to UDCA and a partial response was seen in 4 patients (30.77%). In patients with PSC, 5 patients (33.33%) had a complete biochemical response to UDCA, while a partial response was seen in 4 patients (26.67%). Five patients of AIH and one patient each of PSC, PBC, and AIH-PSC overlap underwent a liver transplant.

MMF or tacrolimus was used as rescue therapy in patients with no response. Four patients of AIH received MMF and one of them had a complete biochemical response (25%) while 2 patients (50%) had a partial response to MMF. Two patients with AIH received Tacrolimus, however, none of them achieved a partial or complete response. One patient each with AIH-PBC overlap and AIH-PSC overlap received MMF. Partial response was seen in the patient with AIH-PBC overlap while a patient with AIH-PSC overlap had no response. No patient with overlap syndrome received tacrolimus.

Predictors of Response to Therapy

On univariate analysis (Table 4), the presence of cirrhosis, high LSM, decompensation in the form of ascites and gastrointestinal bleeding, low albumin, low ALT, bile duct loss, high fibrosis, and high histologic activity index on biopsy predicted non-response to therapy. On multivariate analysis (Table 5), high ALT (Adjusted OR 1.001 [1.000–1.003], P = 0.034), high albumin (Adjusted OR 1.91 [1.05–3.48], P = 0.034) and low fibrosis on biopsy (Adjusted OR 0.54 [0.33–0.91], P = 0.020) were associated with good biochemical response to therapy. As ALT increases by 10, the odds of having a complete biochemical response increased by 1%. Fibrosis stage ≥4 predicted non-attainment of complete response with a sensitivity of 76.7% and specificity of 64.96% (AUROC – 0.736; Figure 1).

Table 5 Multivariate Analysis for Predictors of Complete Response to Steroids.

AIH/overlap treated with steroids (n = 229)	Adjusted Odds Ratio (95% CI)	*P*-value
ALT	1.001 [1.000–1.003]	**0.034**
Albumin	1.91 [1.05–3.48]	**0.034**
Fibrosis Stage on Histology	0.54 [0.33–0.91]	**0.020**

AIH, autoimmune hepatitis; ALT, alanine aminotransferase.

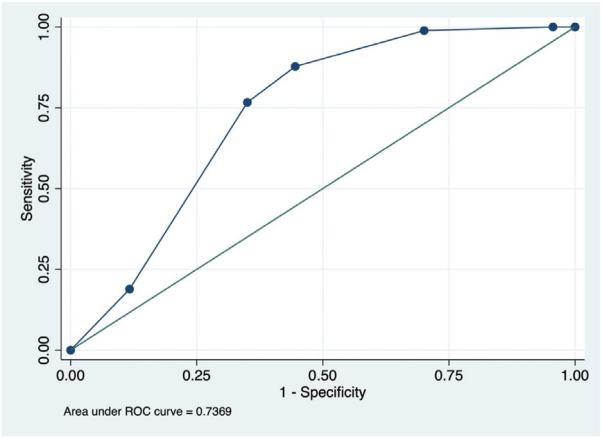

Figure 1 ROC curve analysis of fibrosis stage for predicting non-response to therapy.

Response to Therapy in Primary Cholestatic Syndromes (PBC and PSC)

In patients with PBC, biochemical response to UDCA was seen in 8 (61.53%) patients and no response was seen in 5 (38.46%) patients. Patients of PBC without biochemical response to UDCA had a significantly higher LSM on Fibroscan (Supplementary Table 2). Also, all patients without biochemical response had cirrhosis on histopathology. However, no factor could be identified as a predictor of response on log regression analysis.

In patients with PSC, biochemical response to UDCA was seen in 5 (29.41%) patients while no response was seen in 12 (70.59%) patients. Patients of PSC without biochemical response to UDCA had significantly lower serum albumin (Supplementary Table 3). Fifty percent of patients without response had cirrhosis on histopathology.

DISCUSSION

To the best of our knowledge, this is the largest cohort of AILD reported from India. AIH was the most common disorder observed in this study. PBC alone was seen in only 4.72% individuals. AIH, AIH with features of PSC, and PSC were common in the 3rd and 4th decades of life, while PBC and AIH with features of PBC were common in the 5th decade of life. The majority of patients were females (74.28%) in our cohort. Previous studies[2–4,15] reported AIH to be the most common AILD followed by PBC, which contrasts with the findings of our study. The explanation could

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be that since liver biopsy was done in the majority of our patients, many patients who had overlap were diagnosed which might be missed by using the clinical criteria alone. Majority of our patients (57.9%) had cirrhosis on initial presentation which is alarming and may be explained by the fact that early diagnosis of AILD is usually missed because of low suspicion and the high prevalence of viral hepatitis as a cause of jaundice in our country. Another reason could be a referral bias as being a tertiary care center, we tend to get patients who have advanced disease. Another explanation could be due to the impact of ethnicity on the natural history of AIH as previously described.[16]

Since the study included predominantly biopsy-proven patients, many patients (34.28%) who had an overlap of AIH with either PBC or PSC were diagnosed. They had more cholestasis (pruritus and raised ALP), hepatomegaly, hyperpigmentation, and fatigue than patients with AIH, while AST, ALT levels, and SMA positivity were more in patients with AIH alone. We did not find any difference in the biochemical response to treatment in patients with AIH or overlap, contrary to what has been previously reported.[17] This could be related to the high number of patients with cirrhosis in our cohort.

As had been reported previously,[2] a comparison of primary cholestatic disorders in our study revealed a female preponderance of PBC compared to patients with PSC. UDCA in a dose of 13–15 mg/kg/day has been shown to improve liver biochemistries, reduce disease progression and improve transplant-free survival in patients with PBC.[18,19] Previous studies have demonstrated the beneficial role of UDCA in improving liver biochemistry in patients with PSC.[20,21] A large prospective study by Wunsch *et al.*[22] reported that UDCA withdrawal for 3 months led to a significant worsening in fatigue, pruritus, overall general health, liver enzymes, and Mayo PSC risk score. We treated our patients of PSC with UDCA and demonstrated that approximately 53% of patients have some form of biochemical response to UDCA.

Patients with acute presentation of AIH encompass the complete spectrum of liver disease including acute hepatitis, chronic hepatitis, cirrhosis, and ACLF.[24,25,13] The majority of patients of AIH who presented acutely had underlying chronic hepatitis or cirrhosis on liver biopsy which is in concordance with the previous studies.[23,24] Almost 27% of patients in our cohort who presented acutely did not have positive serum autoantibodies suggesting that it is crucial to keep a high index of suspicion for AIH in patients of viral hepatitis who are not responding to treatment as delay in initiating therapy is associated with a poor outcome. Patients presenting with ALF or ACLF were associated with high mortality. However, once the diagnosis of AIH was established, 63.64% of patients had a complete biochemical response, and 15.15% of patients had a partial response, suggesting the role of early diagnosis and treatment in this sick group.

We demonstrate that in our cohort, very few patients with PSC had concomitant IBD. Although the prevalence of IBD among patients with PSC is lower in Asians when compared to the west,[25,26] the incidence of IBD among migrant PSC patients has not been studied previously to provide a head-to-head comparison between East and the West. However, in a migrant study by Benchimol *et al.*,[27] it was observed that the incidence of IBD was lowest in Asian immigrants as compared to the immigrants from Europe/USA and the native population of Canada, which further decreased as the age of the immigrant increased. Interestingly, children of immigrants had a similar prevalence of IBD as the native population signifying that early environmental exposure plays an important role in the development of IBD.

In our large cohort of 229 patients with AILD who were treated with immunosuppression, we demonstrated a high odd of complete biochemical treatment response in patients with a high ALT, high albumin, and low fibrosis on histology. Patients of AIH with cirrhosis usually have a lower ALT as compared to patients without cirrhosis.[28] Similarly, albumin being a marker of liver synthetic function, is decreased in patients with cirrhosis.[29] This is in line with the findings of previous studies which reported a poor response to steroids in patients with cirrhosis.[28,30]

Our study is the largest study from India of biopsy-proven patients with AIH and other AILDs and demonstrates real-world treatment experience across the whole spectrum of AILD. We have systematically compared the spectrum of AIH, PBC, PSC, and the overlap of AIH with PBC & PSC, correlated acute presentation of AIH with biopsy findings, and identified the predictors of response to immunosuppression in patients with AIH. However, our study is not free of limitations. The study was a retrospective analysis conducted at a tertiary referral center and hence selection bias cannot be completely ruled out. Secondly, many patients had cirrhosis on presentation. Third, we had very few patients with PBC or PSC because of which the analysis may not be a true representative of the population. Also, concomitant IBD was seen in a smaller number of patients as has been previously reported. Nevertheless, our study provides insight into the spectrum of AILD in India and the real-world biochemical treatment response in these patients.

AIH is a common AILD presenting to a tertiary care center. AIH and PSC present almost a decade earlier than PBC. Females are predominantly affected, except for PSC, which is more common in males. Cirrhosis is present in the majority of patients at presentation. Patients with acute onset AIH usually have evidence of fibrosis or cirrhosis on histology. The majority of patients with AIH or overlap of AIH with primary cholestatic disorders were treated with immunosuppression and high ALT, high albumin and low fibrosis score on histology predicted complete response to immunosuppression.

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CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Sunil Taneja – conceptualization, methodology, Writing-review and editing; **Rohit Mehtani** – draft writing, data collection, data analysis, review and editing; **Arka De** – Methodology, data collection, review and editing; **Suvradeep Mitra** – Investigation, Writing-review and editing; **Sahaj Rathi** - Writing-review and editing; **Nipun Verma** - Writing-review and editing; **Madhumita Premkumar** - Writing-review and editing; **Ranjana Minz** - Investigation, Writing-review and editing; **Ajay Duseja** - Writing-review and editing; **Ashim Das** - Investigation, Writing-review and editing; **Virendra Singh** - Supervision, Writing-review and editing; **Radha K. Dhiman** – Supervision, Writing-review and editing; **Yogesh K. Chawla** - Supervision, Writing-review and editing.

CONFLICTS OF INTEREST

None.

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APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.11.002.

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