Scientific Research Publishing

Open Journal of Gastroenterology, 2026, 16(6), 239-248
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Overlap Syndromes in Autoimmune Hepatitis: Experience from a Moroccan Tertiary Care Center

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How to cite this paper: El Kharrazi, A., Bouayad, A., Lahlali, M., Lamine, A., El Jim, R., Salih, A., Lahmidani, N., El Mekkaoui, A., El Yousfi, M., Benajeh, D.-A., El Abkari, M., Ibrahimi, S.A. and Abid, H. (2026) Overlap Syndromes in Autoimmune Hepatitis: Experience from a Moroccan Tertiary Care Center. *Open Journal of Gastroenterology*, **16**, 239-248.
https://doi.org/10.4236/ojgas.2026.166025

Received: May 26, 2026
Accepted: June 26, 2026
Published: June 29, 2026

Abstract

Introduction: Overlap syndromes associated with autoimmune hepatitis are rare and heterogeneous conditions that combine features of autoimmune hepatitis and autoimmune cholangiopathies, primarily primary biliary cholangitis or primary sclerosing cholangitis. Their diagnosis relies on a multidimensional approach integrating clinical, laboratory, immunological, radiological, and histological data. The objective of this study was to describe the characteristics of overlap syndromes observed in a Moroccan cohort of patients with autoimmune hepatitis and to compare them with forms of isolated autoimmune hepatitis. **Materials and Methods:** We conducted a retrospective descriptive and analytical study in the Hepatogastroenterology Department of Hassan II University Hospital, Fez, from January 2012 to December 2025. The full cohort included 78 AIH patients and the analysis compared 33 overlap cases with 45 isolated AIH cases. **Results:** Overlap syndromes represented 42.3% of AIH cases. AIH-primary biliary cholangitis overlap was predominant, occurring in 30 patients (90.9%), while AIH-primary sclerosing cholangitis overlap was observed in 3 patients (9.1%). The mean age at diagnosis was 47.3 years, with marked female predominance (91%). Cytolysis and cholestasis were frequent. Antinuclear antibodies were positive in 72% of cases and anti-mitochondrial antibodies in 66%. Liver biopsy showed fibrosis, inflammatory infiltrates, interface hepatitis, and biliary lesions. All patients received corticosteroids and ursodeoxycholic acid, and 90.9% received azathioprine. Complete biochemical remission at 12 months was achieved in 84.8% of patients. Compared with isolated AIH, overlap syndromes were significantly associated with cholestasis, anti-mitochondrial antibodies, and histological biliary lesions. **Conclusion:** Overlap syndromes account for a significant proportion of autoimmune

hepatitis cases in our setting, with a clear predominance of AIH-PBC forms. Their early recognition is essential for tailoring therapeutic management, particularly through the combination of immunosuppressive therapy and ursodeoxycholic acid. Prospective multicenter studies are needed to better define their long-term prognosis.

Keywords

Autoimmune Hepatitis, Overlap Syndrome, Primary Biliary Cholangitis, Primary Sclerosing Cholangitis, Ursodeoxycholic Acid

1. Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by a loss of immune tolerance toward hepatocytes [1]. They may be associated with other autoimmune liver diseases, notably primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), thereby defining overlap syndromes [1].

These conditions present a diagnostic and therapeutic challenge due to their clinical and biological heterogeneity. Diagnostic criteria are based on a combination of clinical, laboratory, immunological, and histological findings [2].

The objective of this study was to describe the frequency, clinical, biological, immunological, histological, therapeutic, and prognostic characteristics of overlap syndromes within a Moroccan cohort of patients with autoimmune hepatitis, and to compare them with isolated forms of AIH.

2. Materials and Methods

This is a retrospective descriptive and analytical study conducted in the Hepato-gastroenterology Department of the Hassan II University Hospital in Fez. The initial study included 78 patients followed for AIH over a 14-year period, from January 2012 to December 2025. For the present article, only patients presenting with an overlap syndrome were included, totaling 33 patients.

The diagnosis of AIH was made according to the criteria of the International Autoimmune Hepatitis Group and the simplified criteria of 2008, after Add rule out competing causes of liver disease, such as viral hepatitis, drug-induced liver injury, metabolic liver disease, and significant alcohol-related disease. The diagnosis of AIH-PBC was made based on Paris criteria with combination of evidence for AIH and at least two criteria supporting PBC, including biochemical cholestasis, positivity for anti-mitochondrial antibodies or PBC-specific antibodies, and/or compatible histological findings. The diagnosis of AIH-PSC was made based on cholestasis associated with characteristic biliary abnormalities on biliary MRI, after ruling out differential diagnoses.

The data collected included sociodemographic characteristics, mode of presentation, clinical manifestations, laboratory findings, immunal profile, radiological

and histological data, treatments received, therapeutic response, and disease progression. The analysis was performed using an Excel database and univariate.

analysis when sample sizes permitted. The significance threshold was set at $p < 0.05$.

3. Results

The mean age at diagnosis was 47.3 years, with a median age of 49.5 years and ages ranging from 21 to 76 years.

We divided the patients in our series into 3 age categories. Most patients belonged to the 40 - 59 age group (54.5%).

In our series, there was a clear predominance of females (91%, n = 30), with a male-to-female ratio of 1:10.

In our series, patients presenting with an overlap syndrome accounted for 42.3% of the cohort. Their clinical presentation was polymorphic, ranging from incidental findings to presentations of acute hepatitis, chronic hepatitis, or decompensated cirrhosis. In the overall cohort, the most common presentation was chronic hepatitis, observed in 35.89% of cases, followed by acute hepatitis in 28.2%, decompensated cirrhosis in 24.4%, and incidental discovery in 11.5%.

Clinical manifestations were dominated by asthenia, found in 67.9% of patients, and jaundice in 65.4%. Pruritus, a clinical feature suggestive of the cholestatic component of overlap syndrome, was observed in 35.9% of cases. Abdominal pain was reported in 20.51% of patients. Signs of cirrhosis or portal hypertension were also present in some patients, notably ascites in 16.66%, splenomegaly in 14.10%, and gastrointestinal bleeding in 5.12%.

Patients with overlap syndrome had a mixed laboratory profile, combining hepatic cytolysis and cholestasis. Cytolysis reflected the autoimmune hepatitis component, whereas elevated ALP and GGT levels reflected the associated cholangiopathy component. ALT were elevated in 93.9% of patients, ALP in 96.9%, and GGT in 93.9%, highlighting the frequency of the mixed biochemical profile in this series.

In the overlap syndrome subgroup, ANA was the most common, detected in 24 patients, followed by anti-mitochondrial antibodies, detected in 22 patients, antiSMA in 3 patients, and Anti-LC1 in 2 patients.

All sociodemographic, clinical and biological characteristics are shown in **Table 1**.

Liver biopsy was performed in 24 of the 33 patients followed for overlap syndrome. Histological analysis showed a heterogeneous pattern combining features of autoimmune hepatitis and autoimmune cholangiopathy (**Table 2**).

Hepatic fibrosis was observed in 15 patients. According to fibrosis stage, F2 fibrosis was found in 3 patients (12.5%), while F3 fibrosis was observed in 7 patients (29%). Advanced fibrosis corresponding to cirrhosis stage F4 was identified in 5 patients, representing 20.8% of liver biopsies.

Chronic active hepatitis was the most frequent histological finding, reported in 13 patients (54.1%). A lymphoplasmacytic inflammatory infiltrate was present in

8 patients, representing 33.3% of cases. Interface hepatitis was identified in 5 patients (20.8%).

Biliary lesions were also documented, supporting the diagnosis of overlap syndrome. Cholangitis was observed in 6 patients, corresponding to 25% of liver biopsies, while ductopenia was found in 4 patients, representing 16.6% of cases.

Table 1. Sociodemographic, clinical and biological characteristics.

Parameter	Number of cases	Percentage
Sociodemographic characteristics		
Women	30	90.9%
Men	3	9.1%
Age		
<20 years	1	3%
20 - 39 years	7	21.2%
40 - 59 years	18	54.5%
>60 years	7	21.2%
Clinical presentation		
Chronic hepatitis	12	36.3%
Acute hepatitis	10	30.3%
Decompensated cirrhosis	8	24.2%
Incidental diagnosis	4	12.1%
Biological presentation		
Cytolysis ALT	31 (5 - 33 × ULN)	93.9%
Cytolysis AST	31 (3 - 44 × ULN)	93.9%
Cholestasis GGT	31 (1.2 - 10 × ULN)	93.9%
Cholestasis ALP	32 (1.2 - 34 × ULN)	96.9%
Hypergammaglobulinemia	22	66.6%
Hypoalbuminemia < 35 g/L	9	27.7%
Prothrombin time/PT		
<50%	7	21.2%
>50%	26	78.7%
Autoantibodies		
ANA	24	72.7%
Anti-SMA	3	9%
Anti-LC1	2	6%
Anti-M2	22	66.6%
Anti-gp210 and anti-Sp100	2	6%

Table 2. Histological findings in our study.

Histological abnormality found	Number of patients	Percentage of liver biopsies performed, n = 24
Hepatic fibrosis		
F2	3	12.5
F3	7	29%
F4	5	20.80%
Nonspecific Chronic active hepatitis	13	54.10%
Lymphoplasmacytic infiltrate	8	33.30%
Interface hepatitis/focal necrosis	5	20.80%
Biliary lesions		
cholangitis	6	25%
ductopenia	4	16.60%

Overall, histological findings confirmed the mixed nature of overlap syndrome, with frequent hepatitic lesions such as chronic active hepatitis and lymphoplasmacytic infiltrates, associated in several cases with biliary abnormalities including cholangitis and ductopenia. These results highlight the importance of liver biopsy in the diagnostic assessment of overlap syndromes, particularly when clinical, biochemical, and immunological features are suggestive but not sufficient to fully characterize the disease phenotype.

The primary treatment for patients admitted for overlap syndrome was corticosteroids, prescribed in 100% of patients, followed by azathioprine in 90.9% of cases; 2 patients were started on mycophenolate mofetil (MMF) due to intolerance or after failure of azathioprine (Table 3).

UDCA was prescribed in patients with associated PBC or PSC, *i.e.*, 100% of cases (n = 33).

Table 3. Therapeutic approaches in our series.

Therapeutic approaches	Number of cases	Percentage of the 33 patients
Induction and maintenance treatment for AIH		
Oral corticosteroids+++, IV	33	100%
Azathioprine	30	90.9%
MMF	1	3.03%
Treatment of associated disease: PBC; PSC		
UDCA	33	100%
Symptomatic treatments		
Antihistamine, cholestyramine for pruritus	6	18.18%

Treatment indications were established according to the 2015 EASL guidelines plus recent updates and data from 2024/2025.

For PBC, indications were based on the 2017 EASL recommendations.

Among the 33 patients with overlap syndrome, complete biochemical remission at 12 months according to Paris II was achieved in 28 patients, or 84.8%. An incomplete response was observed in 5 patients, or 15.2%. Among patients for whom early biochemical data were available, biochemical improvement at 4 weeks was noted in 23/29 patients, while no significant improvement was observed in 5/29 patients and a mild response in 1 patient. No cases of treatment resistance were identified in the reported data.

Two deaths were observed in this subgroup, the results are shown in Table 4.

Table 4. Treatment response in our series.

Therapeutic response	Number of patients, n = 33	Percentage
Complete biochemical remission at 12 months	28	84.8%
Incomplete response at 12 months	5	15.2%
Early biological response at 4 weeks	23	79.3%
Early non-response at 4 weeks	5	17.2%
Therapeutic resistance	0	0%
Death during follow-up	2	7.1%

4. Comparison between Isolated AIH and Overlap Syndrome in Our Series

We conducted an analytical and comparative study between patients presenting with isolated AIH and those admitted for overlap syndrome.

Patients with overlap syndrome were significantly more likely to have a cholestatic profile, with elevated ALP and GGT levels, as well as more frequent positivity for M2 anti-mitochondrial antibodies. Histological biliary lesions were also significantly more common in the overlap group. In contrast, there were no significant differences regarding age, sex, cirrhosis, complete biochemical remission at 12 months, or treatment non-response (Table 5).

5. Discussion

Overlap syndromes may reflect a pathophysiological continuum among autoimmune liver diseases, involving both hepatocyte and cholangiocyte involvement. This complex immunological interaction suggests the existence of common mechanisms; notably aberrant activation of adaptive immunity directed against hepatic and biliary antigens.

Our study highlights a high prevalence of overlap syndromes (42.3%), higher than that typically reported in the literature, estimated at between 10% and 30%

[1] [2].

Table 5. Comparison of isolated AIH and overlap syndrome.

Variable	Isolated AIH n = 45	Overlap syndrome n = 33	p
Mean age at diagnosis, years	46.0	47.3	0.419
Female	41 (91.1%)	30 (90.9%)	1.000
High ALP	33/44 (75.0%)	32/33 (97.0%)	0.010
Elevated GGT	33/44 (75.0%)	31/32 (96.9%)	0.011
Anti-SLA	3 (6.7%)	1 (3.0%)	0.634
Cirrhosis	23 (51.1%)	22 (66.7%)	0.246
Complete biochemical remission at 12 months	36 (80.0%)	28 (84.8%)	0.767
Non-response to treatment	9 (20.0%)	8 (24.2%)	0.783

This difference could be explained by a recruitment bias inherent to a tertiary care center, as well as by a diagnostic delay favoring the identification of advanced and atypical forms. Indeed, several studies suggest the existence of a pathophysiological continuum between AIH, PBC, and PSC rather than strictly distinct entities [3] [4].

In our series, the AIH-PBC association was largely predominant, which is consistent with international data as shown in **Table 6** [2] [5]. Diagnosis is based on combined criteria, with the Paris criteria being the most widely used in practice due to their good diagnostic performance [6]. Their application in our cohort reinforces the validity of patient classification.

Phenotypically, our results confirm that patients with overlap syndrome have a more pronounced cholestatic profile, with elevated ALP and GGT levels and increased anti-mitochondrial antibody positivity. These features are classically described as markers of biliary involvement [7]. This association reflects a mixed immune-mediated process involving both hepatocytes and cholangiocytes [4].

The histological data from our study confirms this duality, with biliary lesions found in 16.7% of cases. Liver biopsy thus remains a central component of the diagnosis, as emphasized by international guidelines [8] [9].

A striking feature of our cohort is the high prevalence of cirrhosis (>66%). This rate, higher than that reported in some series [10], suggests a delayed diagnosis. Cirrhosis is a major prognostic factor influencing therapeutic response and disease progression, as reported in several studies [11] [12].

Regarding treatment response, our study shows a high rate of complete biological remission (84.8%), comparable to data in the literature [13]. However, several factors were associated with an incomplete response, notably anti-mitochondrial, anti-SLA, and anti-smooth muscle antibodies, as well as cirrhosis. These results confirm the role of certain immunological profiles as markers of disease severity

[14].

From a therapeutic standpoint, the management of overlapping syndromes relies on a combined approach that combines immunosuppressants and ursodeoxycholic acid (UDCA), particularly in cases of AIH-PBC [11] [12]. This strategy improves laboratory parameters and slows the progression of fibrosis.

Finally, in our cohort, an incomplete response was observed in 15.2% of patients. Due to the limited sample size, robust identification of independent predictors of non-response could not be performed. The high frequency of cirrhosis could, however, suggest late diagnosis and a population with a more unfavorable prognosis.

Nevertheless, this notion remains debated, as some studies report a prognosis comparable to that of isolated AIH when treatment is initiated early [5] [15].

Table 6. Comparison of overlap syndromes in literature.

Study	Overlap (%)	Dominant type
Our study	42.3%	AIH-PBC
Sohal *et al.* 2025 [9]	10% - 30%	AIH-PBC
Czaja 2013 [16]	Variable frequency	Mixed
Boberg *et al.* [5]	~20%	Mixed

6. Conclusions

In our Moroccan tertiary-care cohort, overlap syndromes accounted for a high proportion of autoimmune hepatitis cases, with a clear predominance of AIH-PBC overlap.

These patients showed a mixed hepatocellular and cholestatic profile, frequent anti-mitochondrial antibody positivity, histological biliary lesions, and a high rate of cirrhosis at diagnosis.

Despite this advanced disease profile, most patients achieved complete biochemical remission after combining therapy with immunosuppression and ursodeoxycholic acid. Our findings highlight the importance of actively screening for overlap features in patients with autoimmune hepatitis, particularly in the presence of cholestasis, and support the role of liver biopsy in difficult or atypical cases.

Prospective multicenter studies are required to better assess long-term prognosis and predictors of incomplete response.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Dalekos, G., Gatselis, N., Drenth, J.P., Heneghan, M., Jørgensen, M., Lohse, A.W., *et al.* (2025) EASL Clinical Practice Guidelines on the Management of Autoimmune Hepatitis. *Journal of Hepatology*, **83**, 453-501. https://doi.org/10.1016/j.jhep.2025.03.017

[2] Czaja, A.J. (1998) Frequency and Nature of the Variant Syndromes of Autoimmune Liver Disease. *Hepatology*, **28**, 360-365. https://doi.org/10.1002/hep.510280210

[3] Czaja, A.J. (2013) The Overlap Syndromes of Autoimmune Hepatitis. *Digestive Diseases and Sciences*, **58**, 326-343. https://doi.org/10.1007/s10620-012-2367-1

[4] Trivedi, P.J., Hirschfield, G.M., Adams, D.H. and Vierling, J.M. (2024) Immunopathogenesis of Primary Biliary Cholangitis, Primary Sclerosing Cholangitis and Autoimmune Hepatitis: Themes and Concepts. *Gastroenterology*, **166**, 995-1019. https://doi.org/10.1053/j.gastro.2024.01.049

[5] Boberg, K.M., Chapman, R.W., Hirschfield, G.M., Lohse, A.W., Manns, M.P. and Schrumpf, E. (2011) Overlap Syndromes: The International Autoimmune Hepatitis Group (IAIHG) Position Statement on a Controversial Issue. *Journal of Hepatology*, **54**, 374-385. https://doi.org/10.1016/j.jhep.2010.09.002

[6] Kuiper, E.M.M., Zondervan, P.E. and van Buuren, H.R. (2010) Paris Criteria Are Effective in Diagnosis of Primary Biliary Cirrhosis and Autoimmune Hepatitis Overlap Syndrome. *Clinical Gastroenterology and Hepatology*, **8**, 530-534. https://doi.org/10.1016/j.cgh.2010.03.004

[7] Czaja, A.J. (1999) Behavior and Significance of Autoantibodies in Type 1 Autoimmune Hepatitis. *Journal of Hepatology*, **30**, 394-401. https://doi.org/10.1016/s0168-8278(99)80096-8

[8] European Association for the Study of the Liver (2015) EASL Clinical Practice Guidelines: Autoimmune Hepatitis. *Journal of Hepatology*, **63**, 971-1004.

[9] Sohal, A., Nikzad, N. and Kowdley, K.V. (2025) Overlap Syndromes in Autoimmune Liver Disease: A Review. *Translational Gastroenterology and Hepatology*, **10**, Article 33. https://doi.org/10.21037/tgh-24-140

[10] Chazouillères, O., Wendum, D., Serfaty, L., Montembault, S., Rosmorduc, O. and Poupon, R. (1998) Primary Biliary Cirrhosis-Autoimmune Hepatitis Overlap Syndrome: Clinical Features and Response to Therapy. *Hepatology*, **28**, 296-301. https://doi.org/10.1002/hep.510280203

[11] Lindor, K.D., Bowlus, C.L., Boyer, J., Levy, C. and Mayo, M. (2022) Primary Biliary Cholangitis: 2021 Practice Guidance Update from the American Association for the Study of Liver Diseases. *Hepatology*, **75**, 1012-1013. https://doi.org/10.1002/hep.32117

[12] Czaja, A.J. (2002) Treatment Strategies in Autoimmune Hepatitis. *Clinics in Liver Disease*, **6**, 799-824. https://doi.org/10.1016/s1089-3261(02)00028-4

[13] Freedman, B.L., Danford, C.J., Patwardhan, V. and Bonder, A. (2020) Treatment of Overlap Syndromes in Autoimmune Liver Disease: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine*, **9**, Article 1449. https://doi.org/10.3390/jcm9051449

[14] Muratori, P., Lalanne, C., Bianchi, G., Lenzi, M. and Muratori, L. (2016) Predictive Factors of Poor Response to Therapy in Autoimmune Hepatitis. *Digestive and Liver Disease*, **48**, 1078-1081. https://doi.org/10.1016/j.dld.2016.06.018

[15] Al Alwan, A., Altraif, I., Alghamdi, H., Aljumah, A., Amer, M.O., Binjabal, D.O., *et al.* (2026) Autoimmune Hepatitis Overlap Syndrome: Clinical Presentation, Treatment Response, and Disease Evolution: Tertiary Centre Experience. *Saudi Journal of Gastroenterology*, **32**, 241-250. https://doi.org/10.4103/sjg.sjg_413_25

[16] Czaja, A.J. (2013) Diagnosis and Management of the Overlap Syndromes of Autoimmune Hepatitis. *Canadian Journal of Gastroenterology*, **27**, 417-423. https://doi.org/10.1155/2013/198070

Abbreviations

AIH	autoimmune hepatitis PBC: primary biliary cholangitis
PSC	primary sclerosing cholangitis GGT: gamma-glutamyl transferase ALP: alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies UDCA: ursodeoxycholic acid