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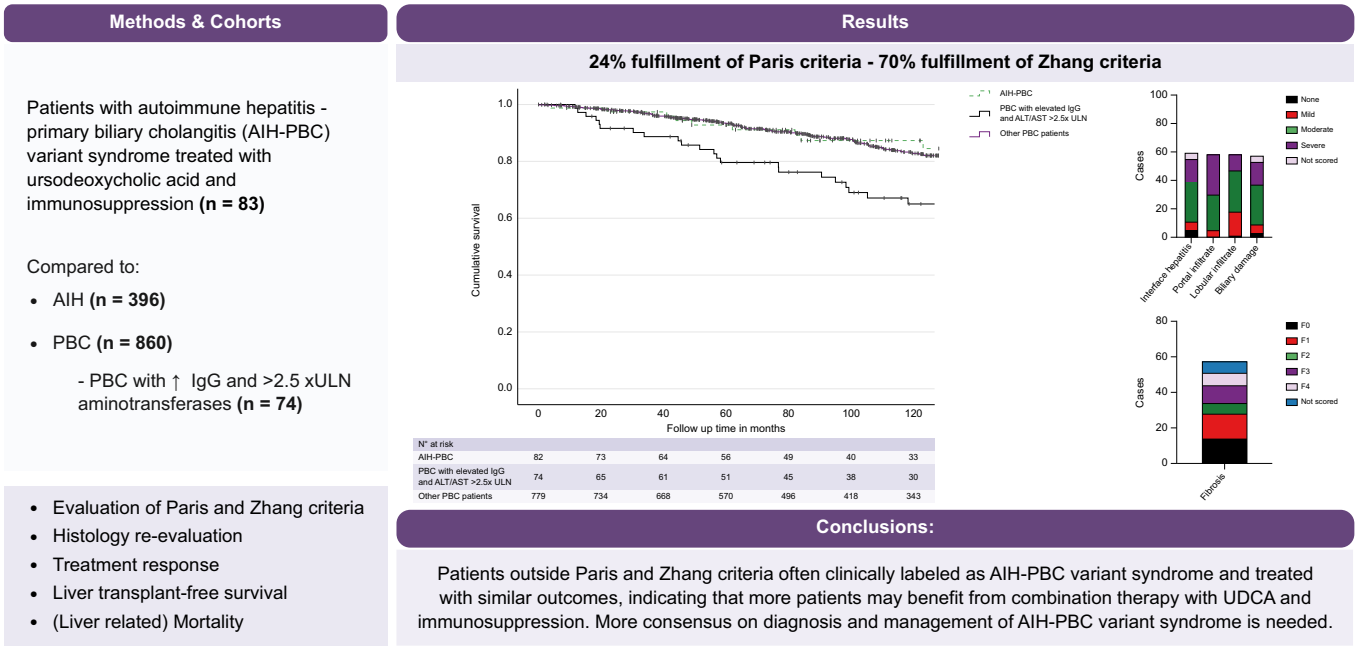
Graphical abstract



Highlights:

- In clinical practice patients outside of the Paris and Zhang criteria are frequently treated as having AIH-PBC variant syndrome.
- Treatment responses and long-term outcomes do not differ in patients in or outside the Paris or Zhang criteria.
- Patients outside the Paris or Zhang criteria for AIH-PBC variant syndrome might also benefit from combined treatment.
- Long-term outcomes for untreated suspected AIH-PBC variant syndrome are significantly worse compared to those of patients with PBC.
- Consensus on the diagnosis and management of AIH-PBC variant syndrome is necessary among experts in the field.

Impact and implications:

This study demonstrated that patients with AIH-PBC variant syndrome treated with combined therapy consisting of immunosuppressants and ursodeoxycholic acid often do not fulfill the Paris criteria. They do however have comparable response to therapy and long-term outcomes as patients who do fulfill the diagnostic criteria. Additionally, patients with PBC and additional signs of hepatic inflammation have poorer long-term outcomes compared to patients treated as having AIH-PBC. These results implicate that a larger group of patients with features of both AIH and PBC may benefit from combined treatment. With our results, we call for improved consensus among experts in the field on the diagnosis and management of AIH-PBC variant syndrome.

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Research article

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Diagnostic criteria and long-term outcomes in AIH-PBC variant syndrome under combination therapy

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Background & Aims: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) can co-exist in AIH-PBC, requiring combined treatment with immunosuppression and ursodeoxycholic acid (UDCA). The Paris criteria are commonly used to identify these patients; however, the optimal diagnostic criteria are unknown. We aimed to evaluate the use and clinical relevance of both Paris and Zhang criteria.

Methods: Eighty-three patients with a clinical suspicion of AIH-PBC who were treated with combination therapy were included. Histology was re-evaluated. Characteristics and long-term outcomes were retrospectively compared to patients with AIH and PBC.

Results: Seventeen (24%) patients treated with combination therapy fulfilled the Paris criteria. Fifty-two patients (70%) fulfilled the Zhang criteria. Patients who met Paris and Zhang criteria more often had inflammation and fibrosis on histology compared to patients only meeting the Zhang criteria. Ten-year liver transplant (LT)-free survival was 87.3% (95% CI 78.9–95.7%) in patients with AIH-PBC. This did not differ in patients in or outside the Paris or Zhang criteria (p = 0.46 and p = 0.40, respectively) or from AIH (p = 0.086). LT-free survival was significantly lower in patients with PBC and severe hepatic inflammation – not receiving immunosuppression – compared to those with AIH-PBC (65%; 95% CI 52.2–77.8% *vs*. 87%; 95% CI 83.2–90.8%; hazard ratio 0.52; p = 0.043).

Conclusions: In this study, patients with AIH-PBC outside Paris or Zhang criteria were frequently labeled as having AIH-PBC and were successfully treated with combination therapy with similar outcomes. LT-free survival was worse in patients with PBC and hepatic inflammation than in those treated as having AIH-PBC. More patients may benefit from combination therapy.

Introduction

Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are both autoimmune liver diseases predominantly affecting women. PBC is characterized by biliary damage and cholestasis, while inflammation and hepatocyte damage are typical in AIH. In classical PBC, minimal interface hepatitis may be present, whereas minimal biliary damage can be demonstrated in histological biopsy specimens of patients with AIH.[1] However, there is a spectrum between AIH and PBC in which overlap with varying degrees of cholangitis, interface hepatitis and lobular hepatitis may be present.[1] When biochemical and/or histological features of both diseases are clearly present, this is referred to as AIH-PBC variant syndrome, PBC with features of AIH or vice versa.[2]

In current practice and international guidelines, the Paris criteria are most commonly used to make the diagnosis of AIH-PBC. Patients have to fulfill two out of three PBC-related criteria and two out of three AIH-related criteria to meet the Paris criteria (Table S1).[3,4] The sensitivity of these criteria is a topic of debate, as they might underestimate the prevalence of AIH-PBC variant syndrome.[3,5–9] New criteria based on the revised AIH criteria were proposed by Zhang *et al.* and seemed to have a better sensitivity (Table S2).[10]

Of note, a diagnosis of AIH-PBC comes with treatment consequences for patients. In retrospective studies, combination therapy of glucocorticoids and ursodeoxycholic acid (UDCA) was more effective than UDCA monotherapy for reaching biochemical remission in patients with AIH-PBC.[3,11] The presence of interface hepatitis was an independent predictor of response to glucocorticoids.[11] Based on these retrospective studies, guidelines advise treatment with UDCA and immunosuppression for patients with AIH-PBC variant syndrome inside the Paris criteria.[8,12] Azathioprine can be used to decrease the use of glucocorticoids and related adverse effects, as glucocorticoids increase – among others – the risk of

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osteoporosis, cataract and diabetes mellitus.[13] It is difficult to determine in which patients the possible benefit of immunosuppressive therapy outweighs the side effects.

The primary aim of this study was to evaluate the proportion of clinically diagnosed patients with AIH-PBC treated with combination therapy with immunosuppression and UDCA who fulfilled the Paris criteria in a real-world cohort. The secondary aim was to compare the treatment response and long-term outcome of patients with AIH-PBC within and outside the Paris criteria to patients with AIH, PBC only, and patients with PBC and elevated immunoglobulin G (IgG) and aminotransferases but without immunosuppression. Characteristics and outcomes of patients inside Paris and/or Zhang criteria were compared. Liver histological biopsy specimens of patients labeled as having AIH-PBC variant syndrome were re-assessed.

Patients and methods

In a retrospective cohort study of patients with AIH in seven academic and three non-academic teaching hospitals in the Netherlands and Belgium, full chart review was performed and granular data, including treatment choice and response, were available. Within this cohort we identified a cohort of patients in whom there was a clinical suspicion of AIH-PBC variant syndrome and who were treated with a combination of immunosuppression and UDCA. These patients were considered as having AIH-PBC variant syndrome.

All clinical data regarding serology, histology, fulfillment of Paris and Zhang criteria, response to therapy, relapse, loss of remission and long-term outcome were retrospectively collected through medical chart review. In case of consecutive presentation of diagnosis and start of treatment, the date of initiating combination therapy was used as date of diagnosis and start of follow-up. Liver transplantation (LT)-free survival was defined as survival free of LT and mortality.

All ethical standards were followed according to the revised Helsinki declaration, ethical approval by Medical Ethical Committee of the Leiden University Medical Center was obtained (G18.067). If necessary ethical approval for the other participating hospitals was obtained separately. Informed consent was obtained if deemed necessary by the Medical Ethical Committee.

Reference cohorts

From the previously described cohorts from the Dutch Autoimmune Hepatitis Study group and the Dutch Cholestasis Research Group, patients with full details on treatment and response were used as reference cohorts of patients with AIH and PBC, respectively.[14,15] For the diagnosis of AIH, the revised AIH criteria were used.[16] The treatment goal for AIH was complete biochemical response, defined as normalization of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and IgG evaluated after 6 and 12 months of (combination) therapy.[12] Diagnosis of PBC was according to the EASL guidelines of 2009.[8] Patients with concomitant AIH (who fulfilled the diagnostic criteria for AIH) were excluded from the original PBC reference cohort.[15] Treatment response was determined after 12 months of treatment using the Paris-II criteria (alkaline phosphatase (AP) <1.5x upper limit of normal (ULN), AST <1.5x ULN and bilirubin <1x ULN).[17] Although the GLOBE score, consisting of age, bilirubin, albumin, AP and platelets, has not been validated in patients with AIH-PBC, it is frequently used in clinical care for these patients. We explored the use of the GLOBE score as a prognostic score in this cohort.[18]

As there is a spectrum between AIH and PBC in inflammation and biliary damage, a subgroup analysis was performed in patients with PBC with more inflammation than typical for PBC. These patients were clinically diagnosed with PBC, and not treated with combination therapy. Increased inflammation was defined as increased IgG and AST and/or ALT >2.5x ULN at diagnosis or after 12 months treatment with UDCA. A cut-off of 2.5x ULN was chosen to achieve a similar median ALT and AST value in these patients compared to patients with AIH-PBC. These cut-offs are more liberal than used by the Paris criteria with a cut-off of >2x ULN for IgG and >5x ULN for AST and/or ALT. None of these patients with PBC had been treated with immunosuppression.

Histology

Available liver biopsies were digitally scanned (InstelliSite Ultra-Fast Scanner, Philips) and re-evaluated simultaneously by three hepatobiliary pathologists in one session, thereby limiting interobserver variability. Disagreements were resolved by discussion and reaching consensus. For the re-evaluation, H&E staining and periodic acid Schiff reaction staining were used. Parameters assessed were severity of interface hepatitis (0 = no interface hepatitis; 1 = mild interface hepatitis; 2 = moderate interface hepatitis; 3 = severe interface hepatitis), portal inflammation (0 = no portal inflammation; 1 = mild portal inflammation; 2 = moderate portal inflammation; 3 = severe portal inflammation), lobular inflammation (0 = no lobular inflammation; 1 = mild lobular inflammation; 2 = moderate lobular inflammation; 3 = severe lobular inflammation), and bile duct injury (0 = no bile duct injury; 1 = mild bile duct injury; 2 = moderate bile duct injury; 3 = severe bile duct injury). Presence of florid duct lesions and granuloma was defined as severe bile duct injury. If no bile ducts could be scored due to ductopenia, bile duct injury was not scored. Fibrosis was scored from F0–F4 using the Metavir classification on fibrosis tissue staining.[19] The semiquantitative grading system used in this study was derived from the modified hepatitis activity index (mHAI). For interface hepatitis, the two scores for mild were combined into one score. For moderate and severe interface hepatitis the mHAI definitions were used. For portal inflammation, the two scores for moderate hepatitis used in the mHAI were combined into one score. In addition to the mHAI domains, cholestatic histopathological characteristics were scored, since florid duct lesions and granulomas may be present in AIH-PBC variant syndrome. If liver biopsies were not available for re-evaluation, pathology reports were used to determine the presence of cirrhosis, the modified Paris criteria and the recently published AIH-PBC criteria by Zhang *et al.*[3,4,10]

Statistical analysis

All data are presented as median (IQR) unless specified otherwise. Variables were corrected for the upper or lower limit of normal. For continuous variables, the Mann-Whitney *U* test was used. The Chi-square test was used for categorical variables. Kaplan Meier curves, log-rank test, and univariate Cox

regression analysis were used for analysis of survival and development of cirrhosis where appropriate. Multivariate Cox regression analysis was used to correct for known factors associated with survival in AIH and PBC, including age, cirrhosis and AP with a maximum of 1 variable per 10 events. *p* values of <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 25 or higher (Chicago IL, USA) and GraphPad Prism 6.0 (La Jolla, CA, USA).

Results

Patients

Out of 1,331 patients from the national Dutch prospective database, complemented by recruitment in seven academic and three non-academic teaching hospitals in Belgium and the Netherlands, a total of 86 patients with AIH-PBC variant syndrome under combination therapy, diagnosed between October 1989 and January 2019, were identified (Fig. 1). After exclusion of three patients with AIH-PBC because of missing treatment data, 83 patients with AIH-PBC were included in the present analyses. Diagnosis of AIH-PBC was made simultaneously in 56 patients (67%) and consecutively in 27 patients (33%) with a prior diagnosis of PBC in 22 patients and AIH in five patients. Median time between prior diagnosis and diagnosis of variant syndrome was 4 years (range: 7 months – 16 years).

Only 17 (24%) of the 72 patients with sufficient data to determine the Paris criteria fulfilled the Paris criteria. Of the 55 patients outside of the Paris criteria, 28 patients fulfilled the PBC items only, seven patients fulfilled the AIH items only and 20 patients did not fulfill either of the items (Table S3). The Zhang criteria could not be calculated in nine patients due to missing data, while 52 patients (70%) had probable or definite AIH-PBC according to these criteria (>19 points; Fig. 1). Thirty-five patients who did not fulfill the Paris criteria, did fulfill the Zhang criteria. No patients fulfilled only the Paris criteria, but not the Zhang criteria.

Nineteen patients (27%) presented with raised liver enzymes without clinical symptoms. The most prevalent symptoms at diagnosis were fatigue (n = 35; 52%), itching (n = 23; 34%) and jaundice (n = 17; 21%). Twenty-four extrahepatic autoimmune diseases were present in 22 patients (27% of all patients). Thyroid disease was the most prevalent extrahepatic autoimmune disease in seven patients, followed by rheumatic disease in six patients and skin disease in five patients. Twelve patients (14%) had cirrhosis of whom one patient presented with ascites. One patient presented with acute-severe AIH, accompanied by antimitochondrial antibody positivity and obvious bile duct injury on histology.

In line with the nature of the criteria, AST and ALT were numerically higher, and IgG at diagnosis was significantly higher inside the Paris criteria (Table 1) compared to patients outside Paris criteria. Characteristics at diagnosis of AIH-PBC were comparable between patients inside and outside the Zhang criteria except for higher platelets, IgG and higher AST among patients inside the Zhang criteria (Table S4).

No differences in baseline characteristics were found in patients who fulfilled both the Paris criteria and the Zhang criteria (n = 17) compared to patients who only fulfilled that Zhang criteria (Table 2).

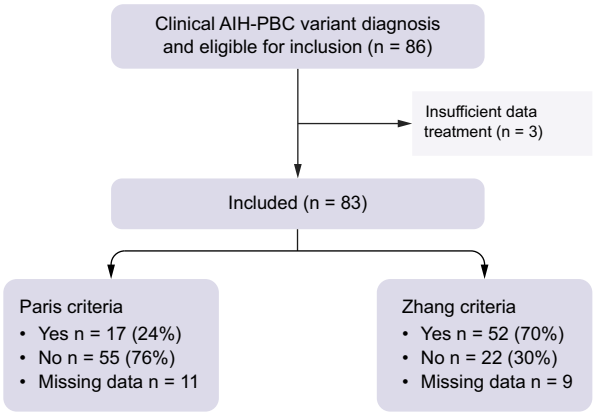


Fig. 1. Flowchart of included patients with AIH-PBC under combination therapy. AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome.

Liver histology

A liver biopsy had been performed in 80 patients (96%). For 59 patients, a liver biopsy specimen of good quality was available for re-evaluation (Fig. S1). Fig. 2A shows the individual scores in all patients with available material for interface hepatitis, portal inflammation, lobular inflammation and bile duct injury. The scores in each domain are independently categorized to demonstrate the distributions across the cohort.

Mild, moderate or severe interface hepatitis was present in 27 (46%), 11 (19%) and 16 (27%) patients, respectively. In five biopsies (9%), no interface hepatitis was identified. Severe portal inflammation was present in 29 biopsies (49%) and severe lobular inflammation in 12 biopsies (20%). Moderate and severe bile duct injury was present in 28 biopsies (48%) and 16 biopsies (27%), respectively. No bile duct injury was identified in three biopsies (5%). Bile duct injury could not be classified in five biopsies (9%). Fig. 2B demonstrates fibrosis scores in the available histopathology slides. Fibrosis could not be scored in seven of the available biopsies. A score of F0 and F1 was present in both 14 (26%) biopsies, F2 and F3 was scored in 6 (11%) and 10 (19%) biopsies and F4 was scored in 7 (13%) biopsies.

Liver histology within the Paris or Zhang criteria

For 12 of the 17 patients (71%) within the Paris criteria the liver biopsy was available for re-evaluation. Moderate and severe interface hepatitis was present in 3 (25%) and 9 (75%) patients, respectively. For 46 of the 55 patients (84%) outside the Paris criteria a liver biopsy was available for re-evaluation. Moderate and severe interface hepatitis was present in 8 (17%) and 7 (15%) biopsies, respectively. Patients within the Paris criteria more often had interface hepatitis (any severity), portal inflammation, lobular inflammation and fibrosis at presentation compared to patients outside the Paris criteria (p <0.001, p = 0.002, p = 0.001 and p = 0.003, respectively). The same differences were demonstrated when comparing patients who

Table 1. Comparison between patients inside and outside the Paris criteria at time of diagnosis and after 12 months of combination therapy.

	AIH-PBC inside Paris criteria	AIH-PBC outside Paris criteria	*p* value
N	17	55	
Female (%)	17 (100%)	45 (82%)	0.10
Median age at diagnosis (IQR)	55 (17)	53 (14)	0.96
ANA	8 (36%)	19 (35%)	0.64
SMA	9 (53%)	18 (33%)	0.22
AMA	15 (88%)	40 (73%)	0.46
Liver cirrhosis	1 (6%)	8 (15%)	0.67
At time of diagnosis, median (IQR)			
Bilirubin x ULN	0.8 (2.3)	0.9 (1.9)	0.86
Albumin x LLN	1.2 (0.2)	1.2 (0.2)	0.52
AST x ULN	4.2 (4.6)	2.8 (4.5)	0.11
ALT x ULN	5.4 (4.0)	3.5 (6.8)	0.22
AP x ULN	3.2 (2.5)	2.2 (2.8)	0.31
GGT x ULN	9.1 (9.9)	7.6 (14.2)	0.72
Platelets x LLN	2.0 (1.0)	1.7 (1.1)	0.32
IgG x ULN	1.6 (0.9)	1.0 (0.7)	0.026
GLOBE score	1.2 (2.7)	0.6 (3.2)	0.78
After 12 months, median (IQR)			
AST x ULN	1.4 (1.9)	1.0 (0.9)	0.26
ALT x ULN	1.0 (2.3)	1.0 (1.2)	0.72
AP x ULN	1.2 (1.0)	1.1 (0.7)	0.47
GGT x ULN	2.2 (6.7)	2.0 (4.8)	0.94
IgG x ULN	1.0 (0.4)	0.8 (0.4)	0.002
GLOBE score	0.4 (2.1)	-0.5 (1.4)	0.87

Level of significance: p <0.05 (Mann-Whitney U and Chi-square test where appropriate).
For 11 patients, it was not possible to determine the Paris criteria, since interface hepatitis could not be scored. It could not be scored because no liver biopsy was done at diagnosis (n = 3), no interface hepatitis was seen in the re-evaluated biopsy (n = 5) or the material for re-evaluation was not available and the pathology report did not mention the amount of interface hepatitis (n = 3).
AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, anti-nuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LLN, lower limit of normal; SMA, smooth muscle antibodies; ULN, upper limit of normal.

Table 2. Comparison between patients in- or ouside the Paris criteria and inside Zhang criteria at time of diagnosis and after 12 months of combination therapy.

	AIH-PBC patients inside Zhang criteria and inside Paris criteria	AIH-PBC patients inside Zhang criteria and outside Paris criteria	*p* value
N	17	35	
Female (%)	17 (100%)	30 (85.7%)	0.16
Median age at diagnosis (IQR)	55 (17)	54 (13)	0.74
ANA	8 (36%)	17 (49%)	0.80
SMA	9 (53%)	13 (37%)	0.32
AMA	15 (88%)	29 (83%)	1.00
Cirrhosis	1 (6%)	5 (14.3%)	0.66
At time of diagnosis, median (IQR)			
Bilirubin x ULN	0.8 (2.3)	0.9 (2.2)	0.66
Albumin x LLN	1.2 (0.2)	1.1 (0.3)	0.93
AST x ULN	4.2 (4.6)	3.0 (5..3)	0.27
ALT x ULN	5.4 (4.0)	3.5 (8.8)	0.28
AP x ULN	3.2 (2.5)	2.1 (3.4)	0.34
GGT x ULN	9.1 (9.9)	7.6 (12.3)	0.63
Platelets x LLN	2.0 (1.0)	1.7 (0.9)	0.49
IgG x ULN	1.6 (0.9)	1.2 (0.6)	0.14
GLOBE score	1.2 (2.7)	1.9 (1.4)	0.61
After 12 months, median (IQR)			
AST x ULN	1.4 (1.9)	1.0 (0.7)	0.17
ALT x ULN	1.0 (2.3)	0.9 (1.0)	0.42
AP x ULN	1.2 (1.0)	1.0 (0.9)	0.41
GGT x ULN	2.2 (6.7)	2.0 (7.9)	0.95
IgG x ULN	1.0 (0.4)	0.7 (0.4)	0.02
GLOBE score	0.4 (2.1)	-0.5 (1.0)	0.60

Level of significance: p <0.05 (Mann-Whitney U and Chi-square test where appropriate).
AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, anti-nuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LLN, lower limit of normal; SMA, smooth muscle antibodies; ULN, upper limit of normal.

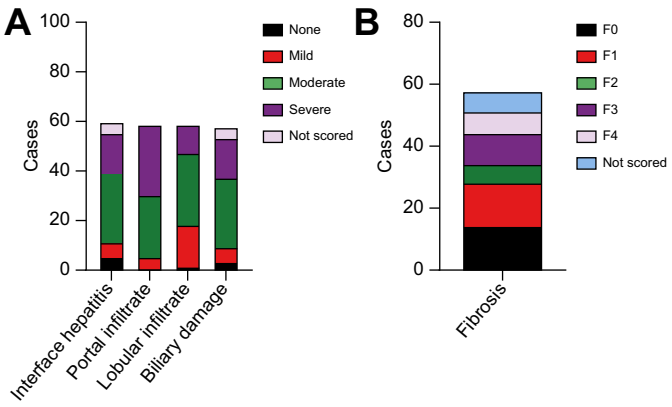


Fig. 2. Histology scores. (A) Interface hepatitis, portal infiltrate, lobular infiltrate, biliary damage and (B) fibrosis in available histopathology of patients with AIH-PBC under combination therapy. AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome.

fulfilled both the Paris criteria and the Zhang criteria (n = 24) to patients who only fulfilled the Zhang criteria (n = 28) (p = <0.001, p = 0.015, p = 0.002 and p = 0.002, respectively).

Treatment

All patients with AIH-PBC were treated with glucocorticoids and UDCA. Glucocorticoids consisted of prednisolone in 72 patients (87%; median 30 mg; IQR: 15-30 mg), budesonide in five patients (6%) and solumedrol in six patients (7.2%). Shortly after start of glucocorticoids, azathioprine was started in 65 (78%) patients, other thiopurines in four patients (5%), mycophenolate mofetil in three (4%) patients, tacrolimus in one patient and cyclosporine in one patient. Second-line immunosuppressive therapy was started in 19 (33%) patients during follow-up due to adverse effects of azathioprine in 10 patients, lack of effect of azathioprine in two patients and for unknown reasons in seven patients. Also, in seven patients with AIH-PBC, second-line PBC treatment with bezafibrate was started.

Twelve months after diagnosis, median ALT had decreased from 3.6 to 0.97x ULN and median AST from 2.8 to 1.0x ULN. At 12 months after diagnosis, AST and ALT were comparable between patients inside and outside the Paris criteria (p = 0.26 and p = 0.72, respectively; Table 2). Applying the Zhang criteria yielded similar results, no difference in AST and ALT, however, patients inside the Zhang criteria had higher IgG levels at 12 months (0.8x ULN *vs*. 0.5x ULN; p = 0.009) (Table S4).

Patients inside the Paris and inside the Zhang criteria had significantly higher IgG at 12 months compared to patients who only fulfilled the Zhang criteria (1.0x ULN *vs.* 0.7x ULN; p = 0.02) (Table 3). The treatment aim for the AIH component, complete biochemical response at 12 months, was reached by 23 patients with AIH-PBC (29% Paris *vs.* 51% non-Paris; p = 0.21). At 6 months, complete biochemical response was reached in 17 patients with AIH-PBC (35% Paris *vs.* 28% non-Paris; p = 0.55). The treatment aim for the PBC component, the Paris-II criteria, was reached in 25 patients (43% Paris *vs.* 64% non-Paris; p = 0.17).[20] Twenty-two (39%) patients reached the treatment aim for both AIH and PBC components after 12 months. Further details regarding response rates within the Paris and Zhang criteria can be found in Table S5.

In 18 (22%) patients, immunosuppressive therapy was stopped completely during follow-up. Reason for discontinuation was remission in 11 patients, doubt of variant diagnosis due to lack of effect of treatment in three patients, adverse effects in one patient, on patients own initiative in one patient and unknown in two patients. Fourteen patients (78%), including all three patients who stopped due to diagnostic doubt, developed a relapse or loss of remission. Immunosuppressive therapy was restarted in 11 of the 14 patients.

Long-term outcome

During a median follow-up of 92 months (IQR: 46-155 months), eight patients with AIH-PBC underwent a LT and eight patients died (liver-related causes in four, other causes in three, and unknown in one patient). None of the patients with liver-related mortality had cirrhosis at diagnosis. The cumulative 10-year LT-free survival estimate for AIH-PBC variant syndrome was 87.3% (95% CI 78.9–95.7%). LT-free survival was similar in patients in and outside the Paris criteria (log-rank p = 0.46). Comparable LT-free survival was also seen in patients inside and outside the Zhang criteria (log-rank p = 0.40) and no difference was seen between patients who fulfilled only Zhang criteria and not Paris criteria compared to patients who fulfilled both (log-rank p = 0.49).

Reference cohorts

The reference cohorts with full details on treatment and response included 396 patients with AIH with a median follow-up of 118 months (IQR: 71-206 months) and 860 patients with PBC with a median follow-up of 106 months (IQR: 57-170 months). Compared to those with AIH, patients with AIH-PBC had lower serum bilirubin, ALT, AST and IgG levels, higher AP and gamma glutamyltransferase (GGT), and less often cirrhosis. Compared to those with PBC, patients with AIH-PBC had higher bilirubin, ALT and AST, while AP and GGT were similar (Table 3).

Treatment response in patients with AIH-PBC was similar after 12 months of treatment compared to patients with AIH or PBC (biochemical remission 46% *vs.* 47%; p = 0.82; Paris-II criteria 56% *vs.* 55%; p = 0.87).

The cumulative 10-year LT-free survival estimate was similar: 87.3% (95% CI 78.9–95.7%) in patients with AIH-PBC, 87.0% (95% CI 83.2–90.8%) in AIH and 81.1% (95% CI 77.9–84.3%) in PBC (Fig. 3A,B; p = 0.086 for AIH and p = 0.67 for PBC). Corrected for age and cirrhosis at diagnosis for AIH and age and AP at diagnosis for PBC, risk of LT or mortality remained similar (hazard ratio [HR] 1.51; p = 0.15 for AIH; HR 1.31; p = 0.38 for PBC; Table S6).

PBC with elevated IgG and aminotransferases

In patients with PBC, 74 of 860 (8.6%) had IgG >ULN and aminotransferases of >2.5x ULN at diagnosis. In those 74 patients, age, bilirubin, AST and ALT at diagnosis did not differ compared to patients with AIH-PBC, but cirrhosis was more prevalent and AP, GGT and IgG were higher at diagnosis (Table 4). Only 20 (30%) patients with PBC with elevated IgG and aminotransferases reached sufficient treatment response (Paris-II criteria) compared to 32 (56%) patients with AIH-PBC (p = 0.003). Ten-year estimated LT-free survival in patients

Table 3. Characteristics of patients with AIH-PBC under combination therapy.

	AIH-PBC	AIH	*p* value [1]	PBC	*p* value [2]
N	83	396		860	
Female (%)	71 (86%)	303 (77%)	0.071	745 (87%)	0.78
Median age at diagnosis (IQR)	54 (15)	46 (32)	<0.001	57 (17)	0.005
ANA	41 (58%)	244 (69%)	0.073	—	—
SMA	28 (44%)	220 (64%)	0.003	—	—
AMA	58 (76%)	14 (4%)	<0.001	807 (94%)	<0.001
Cirrhosis	12 (14%)	124 (32%)	0.002	38 (9%)[3]	0.14
Bilirubin x ULN	0.8 (1.9)	2.2 (8.1)	<0.001	0.6 (0.48)	<0.001
Albumin x LLN	1.2 (0.21)	1.1 (0.2)	0.059	1.1 (0.19)	0.22
AST x ULN	2.8 (4.5)	14.5 (24.4)	<0.001	1.5 (1.2)	<0.001
ALT x ULN	3.6 (6.2)	11.3 (22.7)	<0.001	1.6 (1.7)	<0.001
AP x ULN	2.2 (2.9)	1.5 (1.2)	<0.001	2.1 (2.2)	0.47
GGT x ULN	7.6 (11.5)	3.6 (4.4)	<0.001	6.2 (6.9)	0.088
Platelets x LLN	1.7 (1.0)	1.3 (0.82)	<0.001	1.7 (0.71)	0.86
IgG x ULN	1.1 (0.79)	1.4 (0.9)	<0.001	—	—
GLOBE score at diagnosis	-0.36 (2.0)	—	—	-0.79 (1.4)	0.007
GLOBE score at 12 months	-0.35 (1.3)	—	—	0.06 (1.1)	0.27

Level of significance: p <0.05. (Mann-Whitney U and Chi-square test where appropriate).
AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, anti-nuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LLN, lower limit of normal; PBC, primary biliary cholangitis; SMA, smooth muscle antibodies; ULN, upper limit of normal.
[1]P value comparing AIH-PBC with AIH. Level of significance: p <0.05. (Mann-Whitney U and Chi-square test where appropriate).
[2]P value comparing AIH-PBC with PBC. Level of significance: p <0.05. (Mann-Whitney U and Chi-square test where appropriate).
[3]Liver biopsy results were only available in 418 patients with PBC.

with PBC and elevated IgG and aminotransferases at diagnosis – who did not receive immunosuppression – was lower (65%; 95% CI 52.2-77.8%) compared to patients with AIH-PBC (87%; 95% CI 83.2-90.8% HR 0.52; p = 0.043; Fig. 4). Corrected for age, the difference in LT-free survival was not significant anymore (HR 0.54; p = 0.057; Table S6).

After 12 months of UDCA treatment, 38 patients with PBC (4%) had IgG >ULN and aminotransferases of >2.5x ULN at diagnosis. Ten-year estimated LT-free survival was only 49% (95% CI 31.8-66.2%) in these patients with PBC compared to 87% in patients with AIH-PBC (p <0.001; Fig. S2).

Discussion

In this international, multicenter, cohort study, a discrepancy was found between the clinical diagnosis of AIH-PBC variant syndrome and the official Paris criteria: 24% of the clinically diagnosed and accordingly treated patients with AIH-PBC variant syndrome fulfilled the Paris criteria, endorsed by various international guidelines for the diagnosis of AIH-PBC.[8,12] To the best of our knowledge our present study has the largest reported representative reference cohorts of patients with AIH and PBC.

Although the Paris criteria are widely accepted, the sensitivity of these criteria remains a topic of debate.[2,6,21] Recently Zhang *et al.* proposed other AIH-PBC criteria modifying the revised AIH criteria such that features related to PBC receive positive points instead of negative points.[10] In our cohort more patients (70%) fulfilled these revised criteria than the Paris criteria, but still a large group of patients treated with combination therapy also did not fulfill these new criteria. The extent of patients with AIH-PBC variant syndrome may not be accurately assessed and a broader range of patients may benefit from combination therapy. It is crucial to discern who may benefit from combination therapy and which patients potentially can experience adverse effects of immunosuppression, such as risk of osteoporosis, cataract, and diabetes mellitus, without significant advantages as reported in AIH.[13]

Conversely, immunosuppressive treatment offers potential benefits, such as reducing liver inflammation and achieving biochemical remission, which are associated with decreased disease progression and improved long-term survival in AIH.[22,23] In this study, patients with a clinical diagnosis of AIH-PBC variant syndrome within and outside the Paris criteria demonstrated similar treatment responses after 12 months and long-term LT-free survival rates, which were also comparable to treatment responses and LT-free survival in patients with AIH and PBC. A relapse rate of 78% after discontinuation of immunosuppression suggests that the majority of patients clinically diagnosed with AIH-PBC benefitted from immunosuppression. A lower response rate at 12 months compared to at 6 months was found for the AIH component in the patients with AIH-PBC. Early tapering (within the first year) of immunosuppressive therapy may be associated with higher relapse risks. However, our study lacks granular data to assess whether this was the case. Interestingly, response rates found in our study are relatively low. International guidelines state that comparable response rates for the AIH component are found in patients with AIH-PBC.[8] In previously published studies, similar, considerably lower response rates for AIH were found.[24,25] Compared to patients with PBC with elevated IgG and aminotransferases before and during UDCA therapy without immunosuppression, signs of hepatic inflammation, treatment response and long-term survival were better in patients with AIH-PBC who received combination therapy. This suggests that with the current criteria, this subgroup of patients may have been wrongfully diagnosed as patients with PBC instead of AIH-PBC variant syndrome. Although the difference in LT-free survival was no longer significant after correction for age, the difference observed in patients with PBC and severe inflammation may be of clinical importance, since there may be

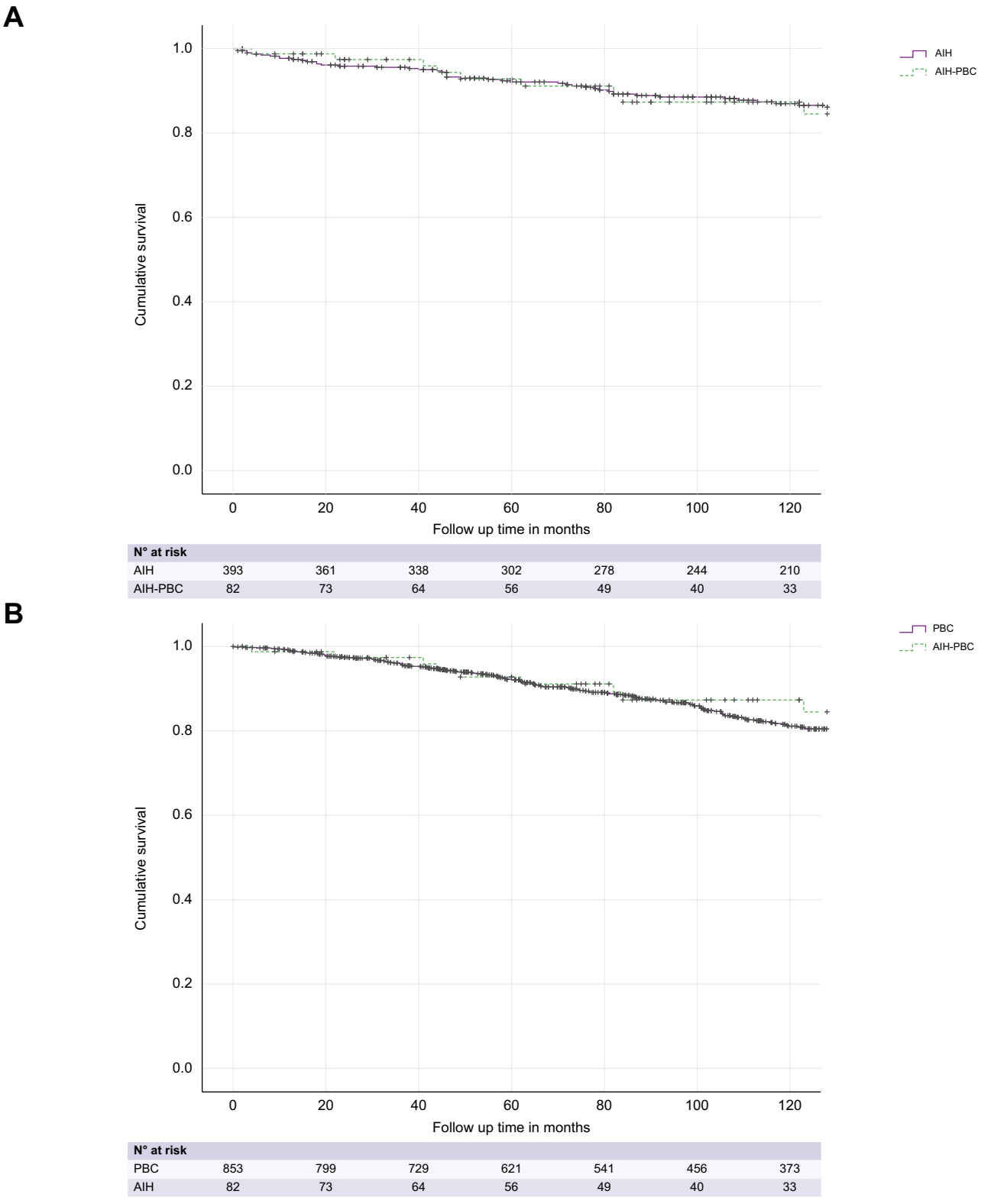


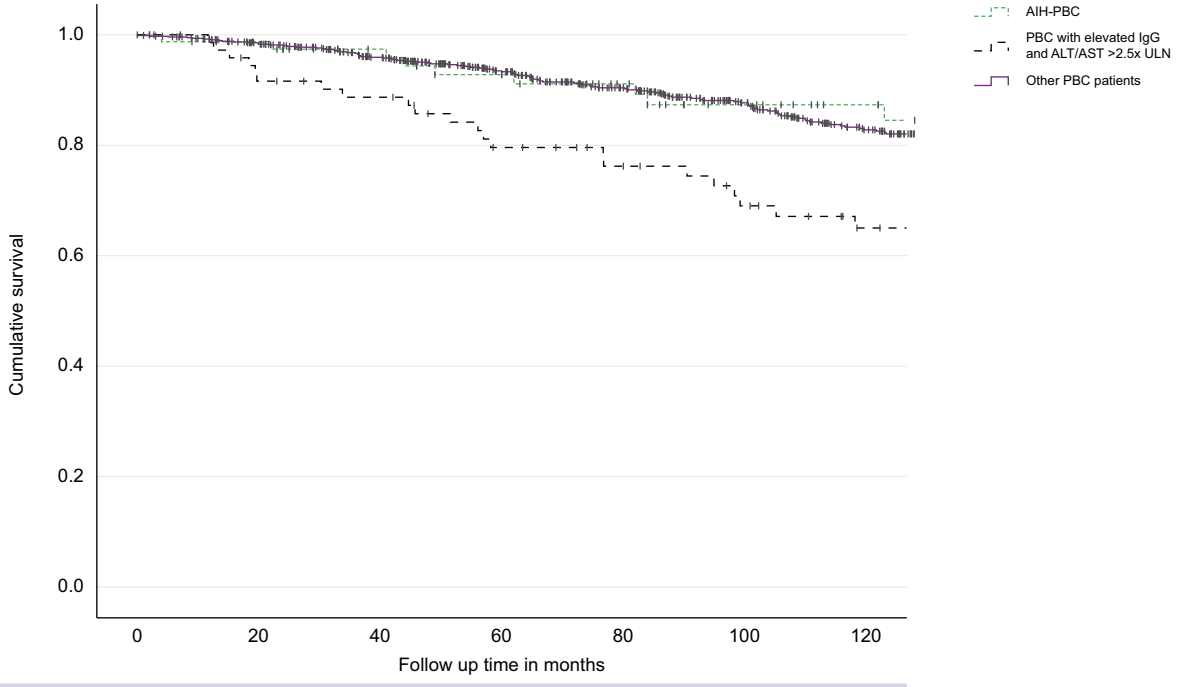
Fig. 3. Liver transplantation-free survival of patients with AIH-PBC under combination therapy. Compared to patients with (A) AIH and (B) PBC. AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; PBC, primary biliary cholangitis.

therapeutic consequences for this particular subset of patients. Due to the limited number of events, correction for the presence of cirrhosis was not possible. The possible effect of cirrhosis may be considered relevant when comparing these two subsets of patients. Indeed, commonly used guidelines recommend a liver biopsy to rule out AIH-PBC variant

Table 4. Baseline characteristics and treatment response of patients with AIH-PBC under combination therapy and patients with PBC with elevated IgG and aminotransferases.

	AIH-PBC	PBC with elevated IgG and aminotransferases[1]	*p* value
N	83	74	
Female (%)	71 (86%)	64 (86%)	0.86
Median age at diagnosis (IQR)	53.5 (15)	54.5 (17)	0.72
AMA	58 (76%)	71 (96%)	0.001
Liver cirrhosis	12 (14%)	15 (29%)	0.036
At time of diagnosis, median (IQR)			
Bilirubin x ULN	0.82 (1.94)	0.88 (0.77)	0.40
Albumin x LLN	1.18 (0.21)	1.09 (0.19)	0.021
AST x ULN	2.8 (4.5)	2.7 (0.95)	0.42
ALT x ULN	3.6 (6.2)	3.4 (2.0)	0.62
AP x ULN	2.2 (2.9)	4.2 (3.9)	<0.001
GGT x ULN	7.6 (11.5)	10.5 (12.1)	0.045
Platelets x LLN	1.75 (1.03)	1.74 (0.95)	0.93
IgG x ULN	1.13 (0.79)	1.39 (0.67)	<0.001
GLOBE score	-0.36 (2.0)	-0.62 (1.6)	0.36
After 12 months, median (IQR)			
AST x ULN	1.03 (1.34)	1.36 (1.17)	0.52
ALT x ULN	0.97 (1.87)	1.43 (1.23)	0.20
AP x ULN	1.11 (0.94)	1.86 (2.30)	<0.001
GGT x ULN	2.26 (4.82)	2.20 (4.14)	0.76
IgG x ULN	0.73 (0.55)	1.23 (0.59)	<0.001
GLOBE score	-0.35 (1.3)	-0.08 (1.27)	0.85

Level of significance: p <0.05. (Mann-Whitney U and Chi-square test where appropriate).
AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, anti-nuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LLN, lower limit of normal; PBC, primary biliary cholangitis; SMA, smooth muscle antibodies; ULN, upper limit of normal.
[1]PBC patients with IgG > ULN and AST and/or ALT > 2.5 × ULN at diagnosis.



N° at risk							
AIH-PBC	82	73	64	56	49	40	33
PBC with elevated IgG and ALT/AST >2.5x ULN	74	65	61	51	45	38	30
Other PBC patients	779	734	668	570	496	418	343

Fig. 4. Liver transplantation-free survival of patients with AIH-PBC under combination therapy is better than for patients with PBC and hepatic inflammation (logrank p = 0.045) and comparable to other patients with PBC. Patients with PBC and hepatic inflammation defined as those with elevated IgG and AST and/or ALT >2.5x ULN at diagnosis. AIH-PBC, autoimmune hepatitis – primary biliary cholangitis variant syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; ULN, upper limit of normal.

syndrome. Unfortunately, the retrospective design of this study did not allow us to obtain histological data from this subset of patients to compare and evaluate the possibility of missed AIH-PBC variant syndrome.

The retrospective study design means that only association and not causation can be inferred from the results. Note that all comparisons can only be made in an indirect manner. It is possible that associations may be the result of an effect of other variables that differ between exposed and non-exposed individuals. Additional data from before the variant syndrome diagnosis for patients with a consecutive AIH-PBC variant diagnosis might have strengthened this study. While a randomized-controlled trial would offer a more robust study design, it is unlikely to be conducted for patients with AIH-PBC in the foreseeable future. As an alternative, multicenter cohort studies emerge as the next best option for gaining a better understanding of the spectrum between AIH and PBC, as well as for improving treatment strategies and patient outcomes. More importantly, consensus on the diagnostic criteria and management of AIH-PBC should be established among experts in the field as this remains a controversial issue.

The efficacy of immunosuppression in patients with PBC has been assessed in randomized-controlled trials. Two studies with budesonide demonstrated improved liver biopsy outcomes compared to the control group.[26,27] Another study indicated a significant albeit minimal reduction in AP levels.[28] In a comparative study between UDCA monotherapy and a combination of UDCA, prednisolone, and azathioprine, symptomatic and laboratory improvements were observed.[29] More recently, a randomized-controlled trial in PBC revealed no significant histological differences with or without budesonide, but there was a notable improvement in AP levels among patients receiving budesonide.[30] These studies with immunosuppression in all patients with PBC leave the option open that a subset might have benefitted from immunosuppression. Additionally, it should be recognized that with the availability of second-line therapies for PBC, namely fibrates and obeticholic acid, treatment regimens have advanced significantly for PBC.[31–34]

In the study cohort, 96% of patients underwent a liver biopsy at diagnosis. Although required by the guidelines, the absence of liver histology (at diagnosis or at re-evaluation) may be considered a limitation of this study. In our study, we found that only 27 of 59 patients with a liver biopsy available for re-evaluation had moderate or severe interface hepatitis, a mandatory feature in the Paris criteria.[4,8,12] In five patients, no interface hepatitis was detected. However, these patients did show mild (n = 3) or moderate (n = 2) lobular inflammation. Despite not fulfilling the histological criteria, these patients do exhibit some form of hepatic inflammation, suggesting that a AIH-PBC variant syndrome should not be ruled out. Indeed, all patients fulfilling the Paris criteria had at least moderate interface hepatitis on liver histology. Research shows that patients with severe interface hepatitis in particular seem to benefit from combination therapy.[11] In a recent critical appraisal concerning the histological features of AIH, the presence of plasma cell clusters (defined as a collection of ≥5 plasma cells) in the lobule was the most sensitive diagnostic finding.[35] Additionally, a recent consensus regarding the uniformity of histological criteria in AIH described AIH to be histologically likely when a predominantly portal lymphoplasmacytic hepatitis is observed, along with more than mild interface activity.[36] Future studies should further investigate the role of the inflammatory infiltrate and other histological characteristics, using the mHAI.[37]

In patients with PBC who exhibit signs of hepatic inflammation, exemplified by elevated aminotransferases, a liver biopsy should initially be contemplated (as also recommended in the British PBC guidelines[38]). Second-line cholestasis therapy (*e.g.*, fibrates and obeticholic acid) should then be considered first, unless there is a clear suspicion of AIH (*i.e.*, presence of antibodies). Then, a trial of glucocorticoids may be initiated. If there is no improvement in liver biochemistry, discontinuation of glucocorticoid treatment should be considered to mitigate the risk of long-term side effects. Conversely, if liver biochemistry improves, the addition of thiopurines could be considered as a means to reduce the use of glucocorticoids. Addition of UDCA to immunosuppression in patients with AIH may be justified in case of significantly elevated cholestatic markers. It should be noted that in patients with acute-severe AIH, cholestatic markers may ameliorate after initiating immunosuppressive treatment, thereby rendering treatment with UDCA no longer necessary. Expert consensus on the optimal treatment strategy is still required.

In this cohort of patients with AIH-PBC under combination therapy, the clinical practice in the Netherlands and Belgium does not match the use of existing criteria. Patients with clinically diagnosed AIH-PBC variant syndrome are often treated with combination therapy, despite not fulfilling the diagnostic criteria, with similar long-term outcomes. Better expert consensus is needed since the prevalence of AIH-PBC variant syndrome may be underestimated. Patients with PBC and signs of hepatic inflammation and elevated IgG have a poorer clinical course compared to those with treated AIH-PBC variant syndrome and compared to other PBC patients when treated with UDCA monotherapy. This indicates that more patients than those who meet the existing criteria may benefit from combination therapy.

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Abbreviations

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; HR, hazard ratio; LT, liver transplantation; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

A.E.C.S.: data acquisition, data analysis and interpretation, writing – original draft preparation. M.B.: data acquisition, data analysis and interpretation, writing – editing. A.F.S., J.V., T.R., S.C.: re-evaluation of histopathology slides, critical revision of the manuscript. B. van H.: Study design, supervision, writing – editing. Remaining authors: data provision, critical revision of the manuscript. All authors have given approval to the final version of the manuscript.

Data availability statement

Data will be made available to other researchers upon any reasonable request and can be obtained through the principle investigator of the sponsor site.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to ensure adherence to British English standards and the guidelines of the journal. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Tiniakos DG, Brain JG, Bury YA. Role of histopathology in autoimmune hepatitis. Dig Dis 2015;33(Suppl 2):53–64.
[2] To U, Silveira M. Overlap syndrome of autoimmune hepatitis and primary biliary cholangitis. Clin Liver Dis 2018;22:603–611.
[3] Chazouillères O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28:296–301.
[4] European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–267.
[5] Liu F, Pan ZG, Ye J, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: simplified criteria may be effective in the diagnosis in Chinese patients. J Dig Dis 2014;15:660–668.
[6] Kuiper EM, Zondervan PE, van Buuren HR. Paris criteria are effective in diagnosis of primary biliary cirrhosis and autoimmune hepatitis overlap syndrome. Clin Gastroenterol Hepatol 2010;8:530–534.
[7] Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American association for the study of liver diseases. Hepatology 2020;72:671–722.
[8] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145–172.
[9] Boberg KM, Chapman RW, Hirschfield GM, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54:374–385.
[10] Zhang W, De D, Mohammed KA, et al. New scoring classification for primary biliary cholangitis-autoimmune hepatitis overlap syndrome. Hepatol Commun 2018;2:245–253.
[11] Ozaslan E, Efe C, Heurgue-Berlot A, et al. Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis. Clin Gastroenterol Hepatol 2014;12:863–869.
[12] European Association for the Study of the L. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 2015;63:971–1004.
[13] van den Brand FF, van der Veen KS, Lissenberg-Witte BI, et al. Adverse events related to low dose corticosteroids in autoimmune hepatitis. Aliment Pharmacol Ther 2019;50:1120–1126.
[14] Baven-Pronk M, Biewenga M, van Silfhout JJ, et al. Role of age in presentation, response to therapy and outcome of autoimmune hepatitis. Clin Transl Gastroenterol 2018;9:165.
[15] Lammers WJ, Leeman M, Ponsioen CI, et al. How the concept of biochemical response influenced the management of primary biliary cholangitis over time. Neth J Med 2016;74:240–246.
[16] Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929–938.
[17] Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol 2011;55:1361–1367.
[18] Lammers WJ, Hirschfield GM, Corpechot C, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804–1812 e4.
[19] Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15–20.
[20] Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology 2006;130:715–720.
[21] Wang Q, Selmi C, Zhou X, et al. Epigenetic considerations and the clinical reevaluation of the overlap syndrome between primary biliary cirrhosis and autoimmune hepatitis. J Autoimmun 2013;41:140–145.
[22] Hartl J, Ehlken H, Sebode M, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2018;68:754–763.
[23] Pape S, Gevers TJG, Vrolijk JM, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. Clin Gastroenterol Hepatol 2020;18:1609–1617 e4.
[24] **Snijders R**, **Stoelinga AEC**, Gevers TJG, et al. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. J Hepatol 2024;80:576–585.
[25] Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139:1198–1206.
[26] Leuschner M, Maier KP, Schlichting J, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double-blind trial. Gastroenterology 1999;117:918–925.
[27] Rautiainen H, Karkkainen P, Karvonen AL, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: a three-year randomized trial. Hepatology 2005;41:747–752.
[28] Angulo P, Jorgensen RA, Keach JC, et al. Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology 2000;31:318–323.
[29] Wolfhagen FH, van Hoogstraten HJ, van Buuren HR, et al. Triple therapy with ursodeoxycholic acid, prednisone and azathioprine in primary biliary

cirrhosis: a 1-year randomized, placebo-controlled study. J Hepatol 1998;29:736–742.
[30] Hirschfield GM, Beuers U, Kupcinskas L, et al. A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA. J Hepatol 2021;74:321–329.
[31] Grigorian AY, Mardini HE, Corpechot C, et al. Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: a meta-analysis. Clin Res Hepatol Gastroenterol 2015;39:296–306.
[32] Khakoo NS, Sultan S, Reynolds JM, et al. Efficacy and safety of bezafibrate alone or in combination with ursodeoxycholic acid in primary biliary cholangitis: systematic review and meta-analysis. Dig Dis Sci 2023;68:1559–1573.
[33] Trauner M, Nevens F, Shiffman ML, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet Gastroenterol Hepatol 2019;4:445–453.
[34] Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631–643.
[35] Gurung A, Assis DN, McCarty TR, et al. Histologic features of autoimmune hepatitis: a critical appraisal. Hum Pathol 2018;82:51–60.
[36] Lohse AW, Sebode M, Bhathal PS, et al. Consensus recommendations for histological criteria of autoimmune hepatitis from the international AIH pathology group: results of a workshop on AIH histology hosted by the European reference network on hepatological diseases and the European society of pathology: results of a workshop on AIH histology hosted by the European reference network on hepatological diseases and the European society of pathology. Liver Int 2022;42:1058–1069.
[37] Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696–699.
[38] Hirschfield GM, Dyson JK, Alexander GJM, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut 2018;67:1568–1594.

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