Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: First report of the IAIHG retrospective registry

Lack of complete biochemical response (normal ALT/AST and IgG) at 6 months is associated with liver-related adverse outcome in autoimmune hepatitis

Study design

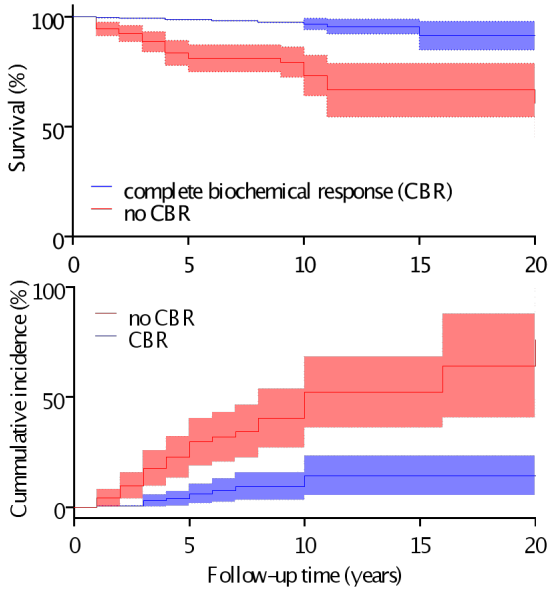
IAIHG-Retrospective Registry cohort study

2559 AIH patients
38 centers
7 countries

Quality control

Clinical characteristics, treatment response and follow-up

Survival analysis



Key findings

The IAIHG-RR registry is a suitable platform for patient selection in future studies

Lack of complete biochemical response to treatment, non-white ethnicity, cirrhosis and PSC-AIH are associated with liver-related death and liver transplantation

Lack of complete biochemical response to treatment is associated with cirrhosis development

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HEPATOLOGY

Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: first report of the IAIHG Retrospective Registry

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Conflict of interest

All the authors report no conflict of interest concerning this manuscript.

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Authors contributions

All the authors have given substantial contributions to the completion of this work and have seen and approved the manuscript in the current version.

Abbreviations:

AIH, Autoimmune hepatitis; AMA, Anti-Mitochondrial Antibody; ANA, Anti-Nuclear Antibodies; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard ratio; HCC, Hepatocellular carcinoma; IAIHG-RR, International Autoimmune hepatitis Group retrospective registry; ICD, International Classification of Diseases; IgG, Immunoglobulin G; INR, International Normalized Ratio; IQR, Interquartile range; LT, Liver transplantation; MELD, Model for End-stage Liver Disease; METAVIR, Meta-analysis of histological data in Viral hepatitis; LKM, anti-Liver-Kidney Microsomal antibody; PBC, Primary biliary cholangitis; PSC, Primary sclerosing cholangitis; SMA, anti–Smooth Muscle Antibodies; UDCA, Ursodeoxycholic acid; UEG, United European Gastroenterology; VU, Vrije Universiteit

ABSTRACT (word count: 240)

Background and Aim: The International Autoimmune hepatitis (AIH) Group retrospective registry (IAIHG-RR) is a web-based platform with subjects enrolled with a clinical diagnosis of AIH. As prognostic factor studies with enough power are scarce, this study aimed to ascertain data quality and identify prognostic factors in the IAIHG-RR cohort.

Methods: This retrospective, observational, multicenter study included all patients with a clinical diagnosis of AIH from the IAIHG-RR. Quality assessment consisted of external validation of completeness and consistency for 29 pre-defined variables. Cox regression was used to identify risk factors for liver-related death and liver transplantation (LT).

Results: This analysis included 2559 patients across 7 countries. In 1700 patients, follow-up was available, with a completeness of individual data of 90% (range 30-100). During a median follow-up period of 10 (range 0-49) years, there were 229 deaths, of which 116 were liver-related and 143 patients underwent LT. Non-white ethnicity (HR 4.1 95% CI 2.3-7.1), cirrhosis (HR 3.5 95% CI 2.3-5.5), variant syndrome with primary sclerosing cholangitis (PSC) (HR 3.1 95% CI 1.6-6.2), and lack of complete biochemical response within 6 months (HR 5.7 95% CI 3.4-9.6) were independent prognostic factors.

Conclusion: The IAIHG-RR represents the world's largest AIH cohort with moderate-to-good data quality and a relevant number of liver-related events. The registry is a suitable platform for patient selection in future studies. Lack of complete biochemical response to treatment, non-white ethnicity, cirrhosis and PSC-AIH were associated with liver-related death and liver transplantation.

Lay summary: The International Autoimmune hepatitis Group retrospective registry is a suitable platform for patient selection in future studies. Non-white ethnicity, cirrhosis, PSC, and incomplete

treatment response are associated with liver-related death and liver transplantation. Patients with these characteristics may warrant closer follow-up.

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare chronic liver disease characterized by elevated serum aminotransferases, elevated immunoglobulin G (IgG) or gamma globulins, presence of autoimmune markers and interface hepatitis on liver histology. Treatment is immunosuppression and commonly includes a combination of prednisone and azathioprine (1). The aim of treatment is the achievement of complete biochemical response defined as normalization of aminotransferases and IgG in order to prevent further progression of the disease and development of complications (2). Although prognosis in AIH is relatively good with 10-year overall survival rates between 68% and 90% (3-8), for some patients it is still a progressive and sometimes severe life-threatening condition that may require liver transplantation (LT). It is important to identify these patients so that tailored management strategies can be developed, studied, and implemented.

Cirrhosis is associated with reduced survival in most (9-14), but not all studies (15-17). Other risk factors described include no normalisation of aminotransferases, low serum albumin concentration at diagnosis, age, and ethnicity (9, 15, 18-20). To date, risk assessment remains a challenge as available data mainly derives from small cohort, single-center studies. Also due to a relatively good prognosis, studies have been limited to a low number of events, which restricts the number of parameters that can be included in multivariate analysis. For these reasons and because serum IgG levels are often not routinely monitored, the independent prognostic effect of insufficient response as determined by a lack of complete biochemical response has never been assessed.

To facilitate studies aiming to provide further insight into disease characteristics and prognostic factors, the international AIH group (IAIHG) developed a registry to generate a web-based platform with a large number of clinically well-phenotyped AIH cases. However, the data quality of this registry

has not yet been ascertained. This international multicenter study aimed to check the quality of the data in the IAIHG-retrospective registry and to identify prognostic factors for adverse liver-related outcomes.

MATERIALS AND METHODS

Study setting and data collection

This study is an observational analysis of retrospectively collected data from the IAIHG-RR. To access data for this research, the participating centers were informed according to the rules of the Regulation (EU) 2016/679 (General Data Protection Regulation). This study protocol was in accordance with the ethical standards of the medical ethical committee of the Vrije Universiteit (VU) medical center, as the coordinating center. Approval of each participating center was obtained from the local ethical committee.

The IAIHG-RR is designed to include all patients with a clinical diagnosis of AIH, as determined by the treating physician. This analysis included all patients captured in the registry between December 2018 and December 2022. Informed consent was obtained according to the local protocol from each patient at the individual centers. Patient characteristics retrieved from the IAIHG-RR include demographics, clinical course, prescribed treatment, biochemical markers, immunological laboratory, histology results, and imaging reports. Outcomes were recorded at the last follow-up and included cirrhosis development, hepatocellular carcinoma (HCC), LT, and death.

Definitions of variables

AIH diagnosis was classified according to the simplified AIH diagnostic criteria (21). Patients with the variant syndromes primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) were included in this study. PBC and PSC were defined by a clinical diagnosis according to international guidelines (22, 23). Cirrhosis was determined by the presence of one of the following; cirrhosis on histology as defined by Ishak stage 6 or METAVIR stage 4 (24), liver imaging consistent

with cirrhosis, or when clinical signs of cirrhosis (splenomegaly, ascites, oesophageal or gastric varices) were reported. Complete biochemical response was defined by normalization of aminotransferases and IgG serum levels within 6 months. As the upper limit of normal for ALT and AST ranged from 35-80 IU/L among centers and changed through time, normalization of ALT/AST and IgG within was based on either reported normalization or when laboratory values were normalized according to local protocol. Biochemical relapse was defined according to international guidelines (25) by an increase in serum ALT levels above three times the upper limit of normal (ULN) and/or an increase in serum IgG levels to more than 20 g/L. Follow-up time was determined as the time from diagnosis until the last visit to the outpatient clinic, LT, or death. The primary endpoint of this study was liver-related death and LT. Secondary endpoints were overall mortality and LT, cirrhosis development, and insufficient response defined as lack of complete biochemical response according to the recent response criteria and endpoints by the IAIHG (2).

Quality control assessment

The registry captures a total of 689 variables. For quality purposes, a subset of 29 relevant baseline and outcome variables was assessed based on the following domains: completeness, consistency, and validity (Supplementary table 1). The participating centers were informed about the completeness and any inconsistencies in the provided data and were asked to clarify and/or update these data entries. Analysis was performed after all centers updated their data accordingly.

Statistical analysis

Variables were noted as median (range) or frequency (percentage). For descriptive analysis, the Chi-square test or Mann-Whitney U-test were used as appropriate. Logistic regression analysis was performed to identify factors associated with lack of complete biochemical response. Predictors of survival and cirrhosis development were analysed by Kaplan-Meier curves with log-rank test and univariate and multivariate cox survival regression. A cut-off of p-value of < 0.05 was used in backward selection. In order to optimize the power of the multivariate model, variables with more than

25% missing data were not included. A separate model with lack of complete biochemical response was provided. Patients were censored at 20 years of follow-up and at the date of death or LT. Statistical analyses were performed with IBM SPSS 26.0 (IBM Corp, Armonk, NY). Kaplan-Meier curves were computed with Graph Pad Prism 9.1.0 (Graph Pad Software, La Jolla, CA). The significance level (a) was set at 0.05.

RESULTS

Quality assessment

In December 2022, the registry captured a total of 2559 patients from 38 institutes in seven countries. Patients were recruited from general hospitals (28%) and tertiary referral centers (72%). Forty-five percent of the patients were treated at a transplantation centers (Supplementary table 2). Center-specific characteristics are presented in Supplementary table 3. Patients were diagnosed between 1965 and 2022, characteristics of the patients per decade of diagnosis can be found in Supplementary table 4.

Follow-up data were reported for 1700 patients. Median completeness of the subset of variables per patient was 83% (range 17-100). In patients with follow-up data, this was 90% (range 30-100). Completeness of the data per variable in the subset is presented in Supplementary figure 1. Patients with follow-up data presented with cirrhosis more often (Supplementary table 5). With the inclusion criteria being a clinical diagnosis, all patients were eligible for inclusion. There were no clinically impossible values, and all outliers were supported by the literature. Only for the body mass index (BMI) variable, and in one case follow-up time, inconsistencies were identified and adjusted.

Characteristics of the study cohort

There was a strong female predominance (75%), and the median age was 48 (range 2-88) (Table 1). 1547 (73%) patients had a probable or definite diagnosis by the simplified IAIHG score. In 2139 (84%) patients, a liver biopsy at diagnosis was performed and cirrhosis on histology was reported in 448

(20.9%). Characteristics of patients with and without reported liver biopsy are reported in Supplementary table 6. Another 48 patients were regarded as having cirrhosis at diagnosis as either clinical signs (splenomegaly, ascites, oesophageal or gastric varices) were present or liver imaging was consistent with cirrhosis. Patients were white (n=1728), Asian (n=53), Black (n=37), Hispanic (n=12) or of other (n=64) descent (Supplementary table 7). A clinical diagnosis of PBC and PSC variants was reported in 263 (11%) and 183 (7%) patients, respectively. No normalization of aminotransferases and IgG within 6 months after treatment initiation was observed in 418 (32%) and 153 (22%) patients, respectively. Information on both normalization of aminotransferases and IgG was available for 706 patients. Of these patients, 224 (32%) patients did not achieve complete biochemical response at 6 months after treatment initiation. For 151 patients of the patients that did not achieve complete response, information on response at 12 months was available, this was the case for 25 (17%) patients. After a median follow-up of 10 (range 0-49) years, 229 deaths were registered, of which 116 were due to liver-related causes. During follow-up, 143 patients received LT. The 5-, 10-, and 20-year survival for liver-related death and LT in this cohort were 93% (95% confidence interval (CI) 92-94), 88% (95% CI 86-90), and 77% (95% CI 73-80) respectively. Survival rates were lower at liver transplant centers compared to non-liver transplant centers (Supplementary figure 2). When the patients were divided into quartiles based on their date of diagnosis, no significant difference was observed in the 5-year survival between groups (log-rank 0.122).

Liver-related death and liver transplantation.

Characteristics of patients who reached the composite endpoint (n=238, 14%) are summarized in Table 2. Factors significantly associated with liver-related death and LT in univariate analysis were sex, non-white ethnicity, simplified AIH score, cirrhosis at diagnosis, PBC, PSC, MELD score, AMA, ALT, ALP, γ-GT, bilirubin, INR, albumin and lack of complete biochemical response at 6 months. Lack of a liver biopsy was also associated with liver-related outcome (Supplementary table 6, Supplementary figure 3). Independent predictors in multivariate analysis were non-white ethnicity (hazard ratio (HR)

3.6 95% CI 2.1-6.2), cirrhosis at diagnosis (HR 3.9 95% CI 2.6-5.9), PSC (HR 2.8 95% CI 1.6-5.1), and no normalization of aminotransferases within 6 months (HR 2.9 95% CI 1.9-4.4) (Table 3). In the multivariate model including 706 cases with available data on biochemical response, lack of complete biochemical response at 6 months (HR 5.7 95% CI 3.4-9.6) was an independent predictive factor liver-related death and LT. Including complete biochemical response at 6 or 12 months as a prognostic factor resulted in the same model (Supplementary table 8). Incorporation of normalization of aminotransferases at 6 months only instead of complete biochemical response in the multivariate model produced a similar model, but this was a less strong predictor (HR 4.4 95% CI 2.5-7.8). Survival curves for cirrhosis, variant syndromes, normalisation of aminotransferases≤6 months of follow-up, and complete biochemical response are presented in Figure 1.

Overall survival and liver transplantation

Of the prognostic factors in the multivariate model for liver-related death and LT, cirrhosis at diagnosis (HR 2.3 95% CI 1.4-3.1), non-white ethnicity (HR 3.1 95% CI 1.8-5.8), no normalization of aminotransferases ≤6 months (HR 2.5 95% CI 1.7-3.7) and lack of complete biochemical response (HR 5.7 95% CI 3.4-9.6) were also independent predictors of overall mortality and LT. Other factors that were associated in multivariate analysis were age (HR1.0 95% CI 1.0-1.1), female sex (HR 0.6 95% CI 0.3-0.8), ALT at first evaluation (HR 1.0 95% CI 1.0-1.0), and bilirubin (HR 1.0 95% CI 1.0-1.0) (Supplementary table 9).

Cirrhosis development

In an analysis restricted to the centers (N = 638) that recorded a date of cirrhosis development, the following baseline independent risk factors for cirrhosis development were observed; variant syndromes with PBC (HR 2.0 95% CI 1.0-3.9) and PSC (HR 6.7 95% CI 2.6-17.6), as well as no normalisation of aminotransferases ≤6 months (HR 3.6 95% CI 2.1-6.4) and lack of complete biochemical response (HR 4.2 95% CI 2.2-8.2) (table 4). The cumulative incidence of cirrhosis was higher in patients without complete biochemical response (Figure 2).

Complete biochemical response.

Factors independently associated with lack of complete biochemical response in logistic regression were cirrhosis at diagnosis (HR 2.6 95% CI 1.7-3.9), presence of SMA (HR 0.5 95% CI 0.3-0.7), and the laboratory values ALP (1.0 95% CI 1.0-1.0) and IgG (HR 1.1 95% CI 1.0-1.1) at first evaluation (Table 5). Of the 205 patients with cirrhosis at diagnosis and available follow-up data, 111 (54%) achieved complete biochemical response within 6 months. Survival was impaired in patients with cirrhosis at diagnosis who did not achieve complete biochemical response compared to patients with cirrhosis who did (Supplementary figure 4).

DISCUSSION

This international registry comprises the largest international cohort of AIH patients who were followed for a long period. Quality of the data as observed in this analysis is moderate-to-good, making the IAIHG-RR a suitable platform for patient selection in future AIH studies. Prior studies investigating multiple predictive factors in multivariate analysis for liver-related outcomes were hampered by a lack of power (7, 15, 26-28) and complete biochemical response, which is the aim of treatment in AIH, was never assessed as prognostic factor. In this analysis, both the large number of included patients affected by this rare disease, together with the high number of events have translated this into a study with relatively high power. Prognostic factors for liver-related death and LT were lack of complete biochemical response within 6 months after treatment initiation, non-white ethnicity, cirrhosis at diagnosis, PSC and no normalization of aminotransferases and failure to achieve complete biochemical response was associated with development of cirrhosis during follow-up.

In concordance with several previous studies (9-12, 26, 29, 30) but with the exception of a few studies (15-17), we found that cirrhosis at diagnosis adversely influences long-term outcomes. The finding in this report that cirrhosis is a risk factor for insufficient response is in line with earlier studies indicating that in AIH patients with cirrhosis, complete biochemical response is more difficult to achieve,

requiring more prolonged therapy with a higher risk of relapse (30, 31). In 54% of the patients with cirrhosis at diagnosis, complete biochemical response was achieved within 6 months, and response also conferred a survival benefit in this group. These data suggest that striving for complete biochemical response should be pursued in patients with cirrhosis.

Lack of complete biochemical response within 6 months of treatment initiation was an independent prognostic factor for LT and liver-related death and cirrhosis development. Eighty percent of patients that reached the composite endpoint did not achieve complete biochemical response. On the other hand, survival was good and the cumulative incidence of cirrhosis development was low in patients with complete biochemical response. This finding supports IAIHG statement that treatment of AIH should aim at complete biochemical response within 6 months, as defined by normalization of both liver enzymes and IgG (2). However, 17% of the patients who did not attain complete biochemical response at 6 months achieved it at the 12-month mark, and this observation also holds prognostic significance. This implies that initiated induction and maintenance treatment can still provide benefits even after 6 months. These data suggest that lack of complete biochemical response at 6 months mandates careful follow-up, but do not mandate immediate therapeutic change in case of an improving biochemical trend.

Survival was reduced in patients with an AIH-PSC variant syndrome. Also, the risk to develop cirrhosis was higher in this subgroup. Currently, there is no established specific treatment for patients with AIH-PSC variant syndromes. Although it is conceivable that this partly explains the adverse long-term outcomes, in this study, both variant syndromes were not independently associated with lack of complete biochemical response.

The last identified risk factor for adverse outcome was non-white ethnicity. Our finding that ethnicity is associated with long-term outcomes is in line with some studies (20, 32, 33). Among other factors, ethnic-specific differences in drug metabolism may contribute to variations in disease course. In other liver diseases, such as hepatitis C and HCC, disparities in response to treatment have been described

(34, 35). It is conceivable that, also in AIH, this may underlie some of the discrepancies in long-term outcomes. A study comparing African Americans and whites found that more immunosuppression was required to control the disease in African Americans, which may have reflected more aggressive disease or resistance to immunosuppressants (32). In our analysis, ethnicity was not associated with treatment response. It should be noted that studies investigating ethnic background as a risk factor for liver-related outcomes are inherently hampered by differences in terminology (ethnicity, race, etc.) as well as definitions and often do not reliably control for confounders such as access to healthcare and socio-economic factors. Due to this and the varying endpoints that are used in literature, results cannot readily be compared.

Characterisation of this cohort showed that in up to 16% of cases there was no report of a liver biopsy at diagnosis. These patients were younger, tested more often LKM-1 positive and were followed in higher proportion at transplant centers. Although liver biopsy is considered as an essential part of the diagnostic work-up of AIH, these real world data show that a significant proportion of patients is nonetheless diagnosed with AIH and may suffer from adverse outcome. This underlines the importance of performing an initial liver biopsy to establish the diagnosis, as diagnostic uncertainty may be difficult to address after immunosuppressive induction therapy has already been initiated.

The current study has strengths and limitations that need to be addressed. First, we cannot ascertain that all consecutive patients from the centers were included, with the potential risk of selection bias. A substantial number of the patients in this study are treated at tertiary centers with expertise in AIH. Because of this attrition and referral bias, survival rates as reported in this paper are likely an overestimate of reflect liver-related mortality on AIH population level. This bias, however, would have affected all patients (cirrhotic vs. non-cirrhotic, white vs. non-white, variant syndrome vs. AIH alone) and thus would be an unlikely explanation for poorer outcomes. This fact, together with the expected boundaries of a retrospective registry, such as missing data are limitations of this study. Lastly, as several of the cases included in this analysis have been described in previous studies (9, 12, 20), this

report is not entirely independent. However, the long follow-up period, the large multicenter AIH cohort in both transplant, non-transplant and general referral hospitals, and the high number of liver-related events, represent the key strengths of our study.

In conclusion, the IAIHG-RR represents the world's largest patient cohort with moderate-to-good quality of baseline and follow-up data with a relevant number of liver-related adverse events. As such, this registry is a suitable platform for patient selection for future etiological and therapeutic studies. In this analysis, we showed that lack of complete biochemical response within 6 months of treatment initiation, non-white ethnicity, cirrhosis at diagnosis and AIH-PSC variant syndrome were associated with liver-related death and LT. Recognition and close follow-up of these patients is warranted.

TABLE LEGENDS

Table 1. Characteristics at diagnosis and outcome of the IAIHG-RR cohort.

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; IBD, inflammatory bowel disease; SLE. Systemic lupus erythematosus; DM T1, diabetes mellitus type 1; UDCA, ursodeoxycholic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; INR international normalized ratio; MELD, model for end-stage liver disease; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; HCC, hepatocellular carcinoma.

Table 2. Characteristics at diagnosis for AIH patients with and without liver-related death or liver transplantation.

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, anti-smooth muscle antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease; INR, international normalized ratio; HCC, hepatocellular carcinoma.
* Median, number (range, %)
*a p-value <0.05 was considered statistically significant.

Table 3. Univariate and multivariate cox regression models for the assessment of baseline factors associated with liver-related death and liver transplantation in patients with AIH.

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, anti-smooth muscle antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease; INR, international normalized ratio; HCC, hepatocellular carcinoma.
*a p-value <0.05 was considered statistically significant.

Table 4. Univariate and multivariate cox regression models for the assessment of baseline factors associated with development of cirrhosis in patients with AIH. *Analysis limited to centers with recorded date of cirrhosis development

Abbreviations: OR, odds ratio; BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease: INR, interational normalized ratio.
*a p-value <0.05 was considered statistically significant.

Table 5. Univariate and multivariate logistic regression models for the assessment of baseline factors associated with lack of complete biochemical response within 6 months in patients with AIH.

Abbreviations: OR, odds ratio; BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease: INR, interational normalized ratio.
*a p-value <0.05 was considered statistically significant.

FIGURE LEGENDS

Fig. 1. Survival curves for liver-related death and liver transplantation in patients with AIH. **(**A) Cirrhosis at diagnosis ($p < 0.001$ log-rank) (B) Variant syndromes ($p < 0.001$ log-rank) (C) Normalization of aminotransferases ($p < 0.001$ log-rank) (D) Lack of complete biochemical response ($p < 0.001$ log-rank).

Fig. 2. Cumulative incidence of cirrhosis development according to response to treatment in patient with AIH (P < 0.001 log-rank).

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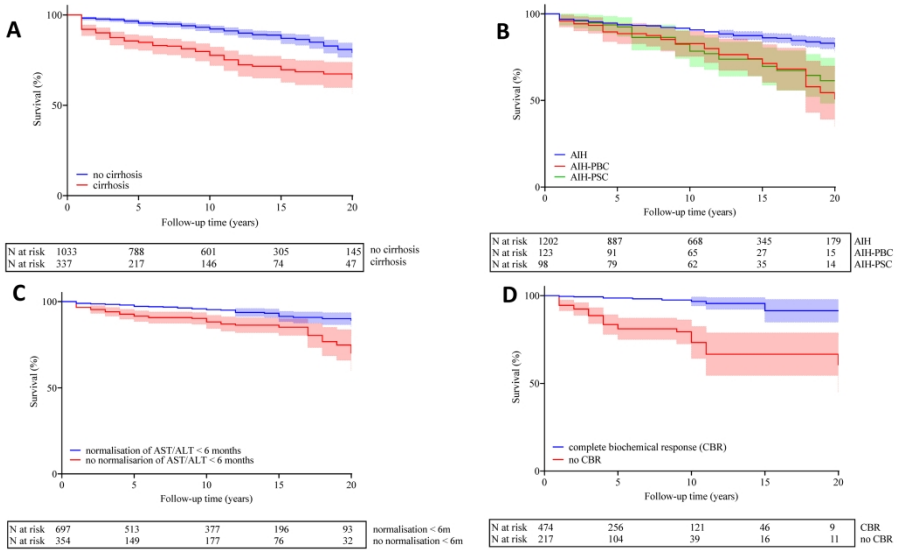

Fig. 1. Survival curves for liver-related death and liver transplantation in patients with AIH. (A) Cirrhosis at diagnosis ($p < 0.001$ log-rank) (B) Variant syndromes ($p < 0.001$ log-rank) (C) Normalization of aminotransferases ($p < 0.001$ log-rank) (D) Lack of complete biochemical response ($p < 0.001$ log-rank).

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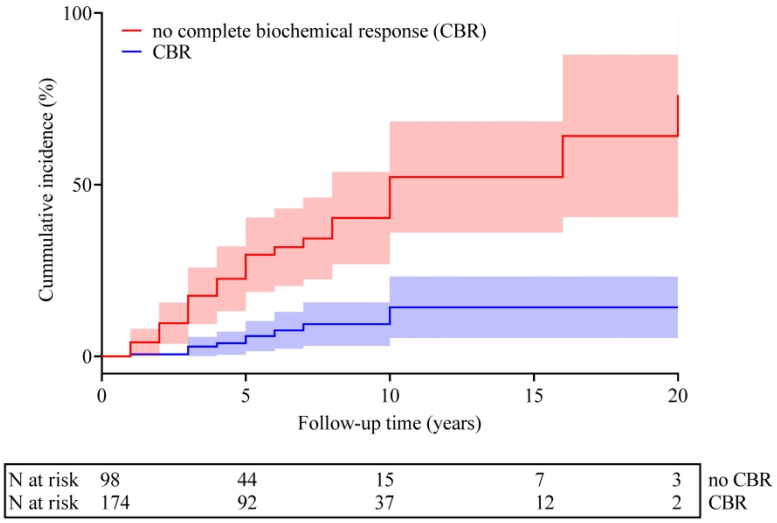

Fig. 2. Cumulative incidence of cirrhosis development according to response to treatment in patient with AIH ($P < 0.001$ log-rank).

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TABLES

Table 1. Characteristics at diagnosis and outcome of the IAIHG-RR cohort.

	Median (range), N (percentage)	N
Patient characteristics		
Age (years)	48 (2-88)	2557
BMI (kg/m^2)	26 (11-69)	1396
Sex (female)	1924 (75.2)	2559
Ethnicity (white)	1728 (91.2)	1894
Disease characteristics		
Simplified AIH score		2125
≤5	578 (27.2)	
Probable	555 (26.1)	
Definite	992 (46.7)	
Cirrhosis	536 (22.8)	2354
PBC	263 (10.6)	2483
PSC	183 (7.2)	2555
Other associated diseases	694 (27.2)	2555
IBD	135 (5.3)	
Celiac disease	29 (2.3)	
Rheumatoid arthritis	70 (2.7)	
SLE	49 (1.9)	
DM T1	30 (1.2)	
Thyroid disease	237 (9.3)	
Multiple sclerosis	24 (0.9)	
Initial treatment		
Prednisone	2180 (88.2)	2472
Azathioprine	1152 (47)	2451
Budesonide	34 (1.4)	2460
UDCA	524 (21.2)	2468
Other immunosuppression	217 (10.8)	2009
Laboratory values		
AST (U/L)	301 (9-4404)	1507
ALT (U/L)	337 (7-5200)	2292
ALP (U/L)	152 (2-227)	2186
γ-GT (U/L)	175 (2-227)	1649
IgG (g/L)	21 (1-94)	1945
Albumin (g/L)	37 (15-62)	1222
MELD score	10 (6-47)	978
Bilirubin (μmol/L)	28 (2-723)	1379
Creatinine (μmol/L)	70 (14-1035)	1167
INR	1.1 (0.4-11.5)	1106
Auto-antibody testing		
ANA	1431 (63.1)	2267
AMA	282 (12.9)	2194
SMA	1433 (65.7)	2181
LKM	61 (7.1)	858
SLA/LP	57 (4.5)	1269
Outcome		
Follow-up time (years)	10 (0-49)	1700
Normalization of ALT/AST <6m	908 (68.5)	1326
Normalization of IgG <6m	554 (78.4)	707
Lack of complete biochemical response <6m	224 (31.5)	706
Relapse (number)	1 (0-8)	607
Cirrhosis	472 (38.3)	1233
HCC	32 (1.9)	1697
Liver transplantation	143 (8.4)	1697
Death	229 (13.5)	1697
Liver related death	116 (51.6)	225

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; IBD, inflammatory bowel disease; SLE. Systemic lupus erythematosus; DM T1, diabetes mellitus type 1; UDCA, ursodeoxycholic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT,

gamma-glutamyltransferase; IgG, immunoglobulin G; INR international normalized ratio; MELD, model for end-stage liver disease; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; HCC, hepatocellular carcinoma.

Table 2. Characteristics at diagnosis for AIH patients with and without liver-related death or liver transplantation.

	Survival (N=1462)*	Liver-related death or liver transplantation (N=238)*	p-value**
Patient characteristics			
Age (years)	47 (2-88)	41 (5-82)	**0.002**
Sex (female)	1132 (75)	165 (69)	**0.028**
Ethnicity (non-white)	88 (7)	32 (14)	**<0.001**
Disease characteristics			
Simplified AIH score			**0.007**
≤5	233 (20)	26 (15)	
Probable	327 (28)	39 (22)	
Definite	603 (52)	115 (64)	
Cirrhosis	334 (23)	103 (44)	**<0.001**
PBC	117 (8)	31 (13)	**0.005**
PSC	92 (6)	39 (16)	**<0.001**
Other associated diseases	420 (28)	64 (27)	0.531
Laboratory values			
ANA	886 (65)	118 (61)	0.329
AMA	167 (13)	35 (19)	0.016
SMA	932 (70)	135 (72)	0.456
LKM	53 (7)	4 (5)	0.609
SLA/LP	45 (6)	2 (3)	0.263
AST (U/L)	312 (9-4404)	166 (26-3831)	0.070
ALT (U/L)	397 (7-4926)	200 (22-3098)	**<0.001**
ALP (U/L)	150 (18-1626)	175 (17-1665)	**0.006**
γ-GT (U/L)	149 (7-2227)	160 (14-1694)	0.100
IgG (g/L)	21 (1-94)	24 (6-90)	**<0.001**
MELD score	10 (6-34)	13 (6-47)	**<0.001**
Bilirubin (µmol/L)	26 (2-719)	49 (6-723)	**<0.001**
Creatinine (µmol/L)	71 (23-1035)	67 (14-195)	0.072
INR	1.1 (0.4-11.4)	1.3 (1.0-11.5)	**<0.001**
Albumin (g/L)	38 (16-62)	33 (15-48)	**<0.001**
Outcome			
Follow-up time (years)	10 (0-49)	11 (0-49)	**<0.001**
No normalization of ALT/AST <6m	350 (29)	68 (57)	**<0.001**
No normalization of IgG <6m	124 (19)	29 (53)	**<0.001**
Lack of complete biochemical response <6m	181 (28)	43 (80)	**<0.001**
Relapse (number)	1 (0-7)	1 (0-8)	0.659
Cirrhosis	285 (28)	187 (94)	**<0.001**
HCC	5 (0.3)	27 (11)	**<0.001**

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, anti-smooth muscle antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease; INR, international normalized ratio; HCC, hepatocellular carcinoma.
* Median, number (range, %)
**a p-value <0.05 was considered statistical significant.

Table 3. Univariate and multivariate cox regression models for the assessment of baseline factors associated with liver-related death and liver transplantation in patients with AIH.

	Univariate		Multivariate (N= 1700)		Multivariate (N= 706)	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*	HR (95% CI)	p-value*

Patient characteristics						
Age (years)	1.002 (0.954-1.009)	0.546				
Sex (female)	0.684 (0.520-0.899)	**0.006**	-	-	-	
Ethnicity (non-white)	2.340 (1.608-3.404)	**<0.001**	3.580 (2.075-6.175)	**<0.001**	-	
Disease characteristics						
Simplified AIH score						
≤5	0.424 (0.254-0.706)	**<0.001**	-	-	-	
Probable	0.034 (0.457-0.971)	**0.034**	-	-	-	
Definite	-	-	-	-	-	
Cirrhosis	2.633 (2.032-3.411)	**<0.001**	3.948 (2.607-5.981)	**<0.001**	8.542 (1.255-8.074)	**<0.001**
PBC	1.733 (1.188-2.529)	**0.004**	-	-	-	
PSC	2.142 (1.514-3.030)	**<0.001**	2.838 (1.575-5.115)	**<0.001**	3.183 (1.255-8.074)	**0.015**
Other associated diseases	0.878 (0.656-1.175)	0.381				
Laboratory values						
ANA	0.765 (0.572-1.023)	0.071				
AMA	1.905 (1.313-2.764)	**0.001**	-	-	-	
SMA	1.244 (0.901-1.718)	0.184				
LKM	0.859 (0.313-2.357)	0.768				
SLA/LP	0.971 (0.236-4.002)	0.968				
AST (U/L)	1.000 (1.000-1.000)	0.243				
ALT (U/L)	1.000 (0.999-1.000)	**0.014**	-	-	-	
ALP (U/L)	1.001 (1.000-1.002)	**0.018**	-	-	-	
γ-GT (U/L)	1.001 (1.000-1.001)	**0.023**	-	-	-	
IgG (g/L)	1.006 (0.994-1.018)	0.316				
MELD score	1.094 (1.066-1.123)	**<0.001**				
Bilirubin (µmol/L)	1.002 (1.001-1.003)	**<0.001**	-	-	-	
Creatinine (µmol/L)	0.997 (0.986-1.007)	0.504				
INR	2.047 (1.791-2.341)	**<0.001**				
Albumin (g/L)	0.908 (0.887-0.930)	**<0.001**				
Outcome						
No normalization of ALT/AST <6m	2.844 (1.945-4.160)	**<0.001**	2.926 (1.933-4.430)	**<0.001**		
No normalization of IgG <6m	8.823 (4.360-17.855)	**<0.001**				
Lack of complete biochemical response <6m	9.318 (4.790-18.127)	**<0.001**			5.736 (3.432-9.586)	**<0.001**
Relapse (number)	0.974 (0.827-1.146)	0.751				

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, anti-smooth muscle antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease; INR, international normalized ratio; HCC, hepatocellular carcinoma.
*a p-value <0.05 was considered statistical significant.

Table 4. Univariate and multivariate cox regression models for the assessment of baseline factors associated with development of cirrhosis in patients with AIH. *Analysis limited to centres with recorded date of cirrhosis development

	Univariate		Multivariate		Multivariate	
	HR (95% CI)	**p-value***	**HR (95% CI)**	**p-value***	**HR (95% CI)**	**p-value***
Patient characteristics						
Age at diagnosis (y)	1.000 (0.992-1.009)	0.925				
Sex (female)	1.103 (0.777-1.566)	0.585				
Ethnicity (non-white)	1.399 (0867-2.258)	0.169				
Disease characteristics						
Simplified AIH score						
≤5	-	-				
Probable	1.032 (0.550-1.614)	0.831				
Definite	1.453 (0.867-2.039)	0.769				
PBC	2.325 (1.559-3.467)	**<0.001**	2.032 (1.044-3.954)	**0.037**	2.373 (1.090-5.167)	**0.029**
PSC	1.776 (1.183-2.667)	**0.006**	6.741 (2.581-17.609)	**<0.001**	6.384 (1.886-21.610)	**0.003**
Other associated diseases	0.981 (0.706-1.364)	0.909				
Laboratory values						
ANA	0.806 (0.573-1.134)	0.215				
AMA	1.740 (1.196-2.533)	**0.004**	-	-	-	-
SMA	0.973 (0.688-1.377)	0.879				
LKM	0.624 (0.251-1.549)	0.309				
SLA/LP	0.782 (0.176-3.472)	0.782				
AST (U/L)	1.000 (1.000-1.000)	0.903				

ALT (U/L)	1.000 (1.000-1.000)	0.211				
ALP (U/L)	1.001 (1.000-1.001)	0.062				
y-GT (U/L)	1.001 (1.000-1.001)	0.090				
IgG (g/L)	1.016 (1.001-1.032)	**0.037**				
MELD score	1.003(0.994-1.073)	0.097				
Bilirubin (μmol/L)	1.001 (1.000-1.003)	0.166				
Creatinine (μmol/L)	0.990 (0.976-1.004)	0.177				
INR	1.323 (1.035-1.692)	**0.025**				
Albumin (g/L)	0.916 (0.887-0.946)	**<0.001**				
No normalization of ALT/AST <6m	3.967 (2.357-6.677)	**<0.001**	3.641 (2.080-6.373)	**<0.001**		
No normalization of IgG <6m	3.576 (1.996-6.408)	**<0.001**				
Lack of complete biochemical response <6m	4.922 (2.590-9.353)	**<0.001**			4.205 (2.162-8.178)	**<0.001**
Relapse (number)	0.839 (0.534-1.319)	0.448				

Abbreviations: OR, odds ratio; BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease: INR, interational normalized ratio.

*a p-value <0.05 was considered statistical significant.

Table 5. Univariate and multivariate logistic regression models for the assessment of baseline factors associated with lack of complete biochemical response within 6 months in patients with AIH.

	Univariate		Multivariate	
	OR (95% CI)	**p-value***	**OR (95% CI)**	**p-value***
Patient characteristics				
Age at diagnosis (y)	0.992 (0.983-1.000)	0.052		
Sex (female)	0.876 (0.612-1.253)	0.468		
Ethnicity (non-white)	2.085 (0.973-4.465)	0.059		
Disease characteristics				
Simplified AIH score				
≤5	-	-		
Probable	1.064 (0.550-2.059)	0.853		
Definite	2.441 (1.364-4.369)	**0.003**	-	-
Cirrhosis	2.417 (1.721-3.394)	**<0.001**	2.592 (1.697-3.960)	**<0.001**
PBC	1.910 (1.057-3.451)	**0.032**	-	-
PSC	1.762 (0.811-3.830)	0.153	-	-
Other associated diseases	0.651 (0.454-0.934)	0.020		
Laboratory values				
ANA	1.169 (0.842-1.624)	0.352		
AMA	1.877 (1.163-3.027)	**0.010**	-	-
SMA	0.628 (0.434-0.909)	**0.014**	0.452 (0.277-0.737)	**0.001**
LKM	1.273 (0.672-2.412)	0.459		
SLA/LP	0.460 (0.175-1.210)	0.116		
AST (U/L)	1.000 (1.000-1.000)	0.877		
ALT (U/L)	1.000 (1.000-1.000)	0.637		
ALP (U/L)	1.002 (1.001-1.003)	**<0.001**	1.003 (1.001-1.004)	**<0.001**
y-GT (U/L)	1.001 (1.000-1.002)	**0.006**	-	-
IgG (g/L)	1.057 (1.037-1.079)	**<0.001**	1.053 (1.031-1.075)	**<0.001**
MELD score	1.087 (1.047-1.129)	**<0.001**		
Bilirubin (μmol/L)	1.001 (1.000-1.003)	0.087		
Creatinine (μmol/L)	1.002 (0.998-1.006)	0.375		
INR	5.271 (2.491-11.156)	**<0.001**		
Albumin (g/L)	0.922 (0.899-0.947)	**<0.001**		

Abbreviations: OR, odds ratio; BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease: INR, interational normalized ratio.

*a p-value <0.05 was considered statistical significant.

SUPPLEMENTARY MATERIALS

SUPPLEMENTARY FIGURES

Fig. 1. Completeness of data in a subset of variables from the IAIHG-RR.

Abbreviations: BMI, body mass index; AIH, ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; HCC, hepatocellular carcinoma.

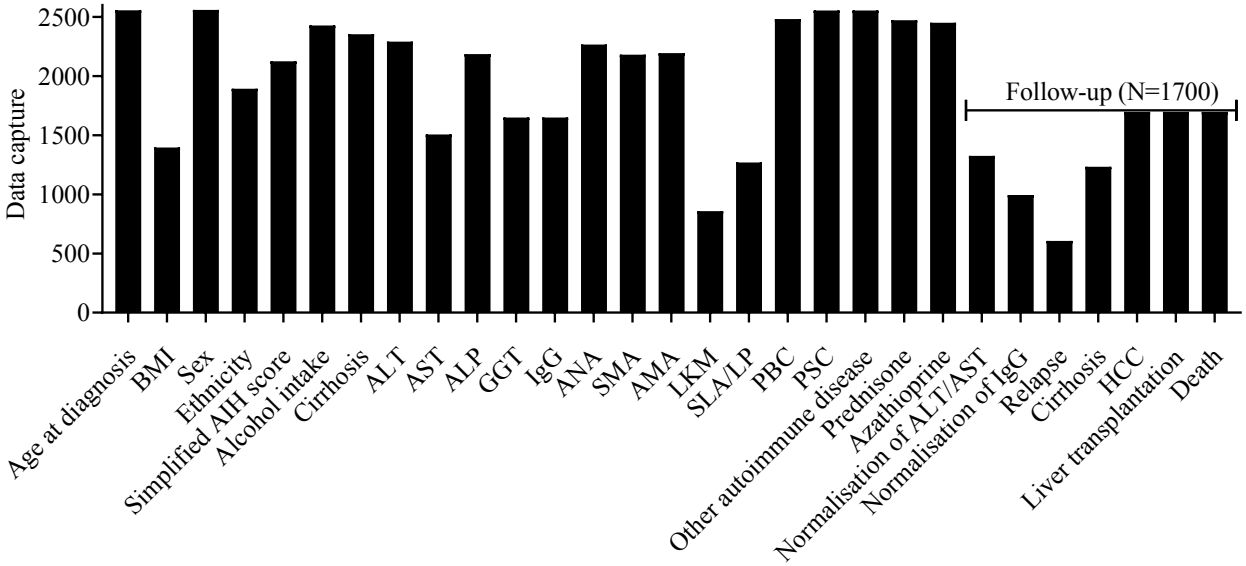
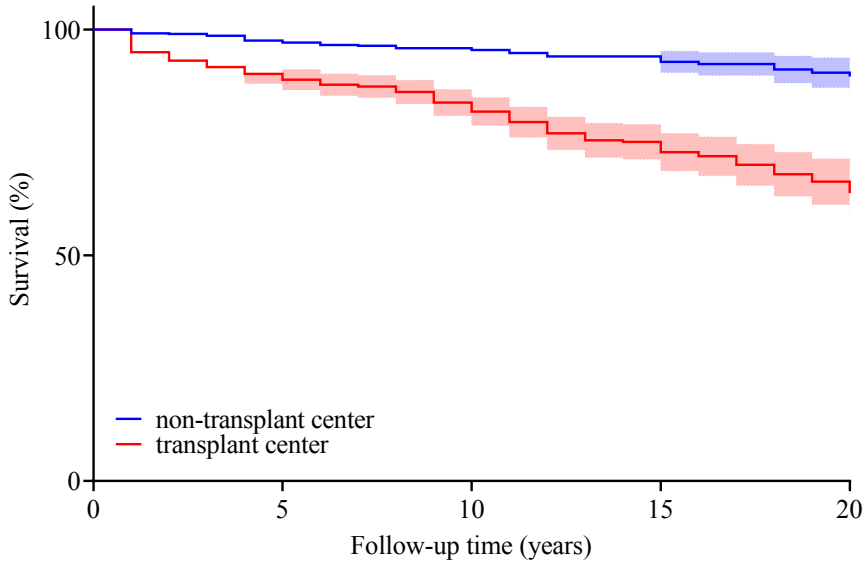


Fig. 2. Survival of patients with AIH treated at transplant or non-transplant centres. (P < 0.001 log-rank).



N at risk	836	612	479	235	106	non-transplant center
N at risk	833	559	378	197	105	transplant center

Fig. 3. Survival of AIH patients with and without biopsy at diagnosis (P < 0.001 log-rank).

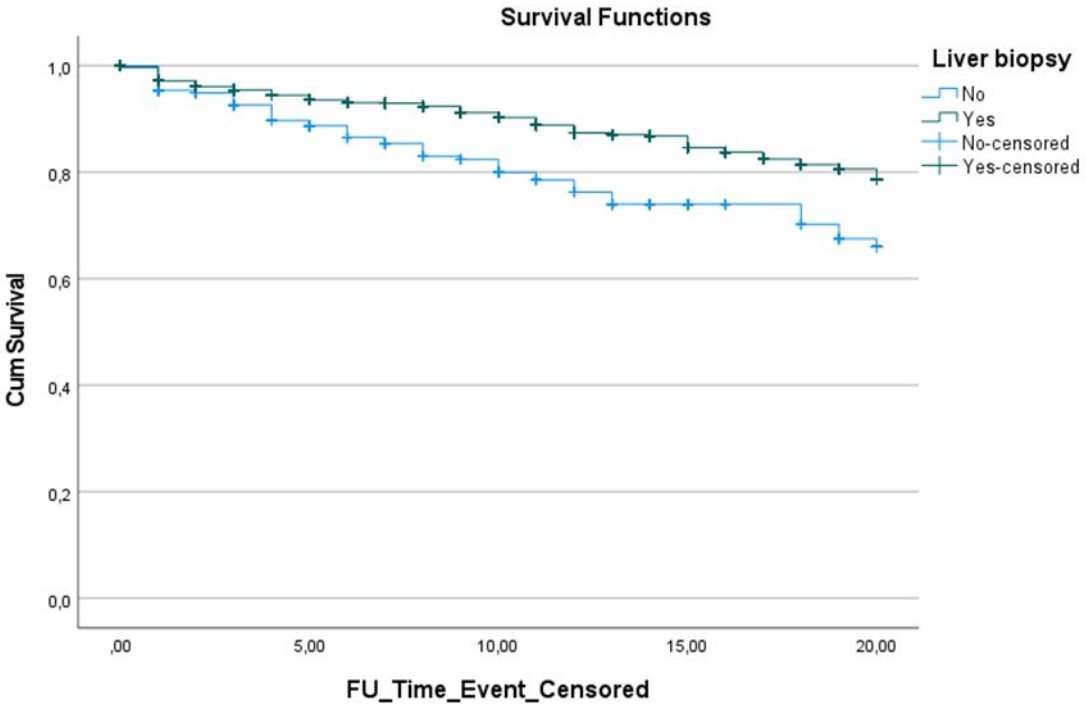
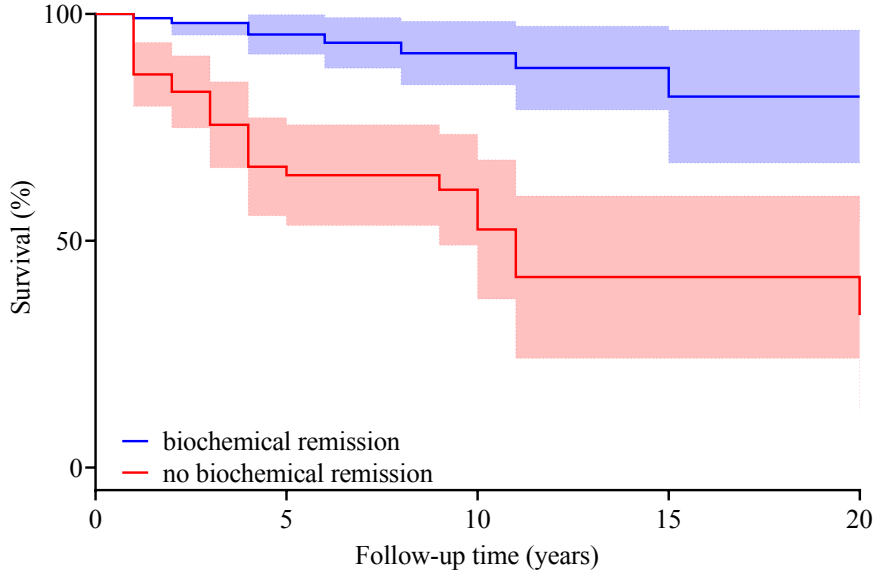


Fig. 4. Survival of patients with AIH and cirrhosis at diagnosis according to complete biochemical response (P < 0.001 log-rank).



N at risk	110	61	31	14	5	biochemical remission
N at risk	90	36	14	7	5	no biochemical remission

SUPPLEMENTARY TABLES

Supplementary table 1. Domains of quality assessment

Quality domain	**Completeness**	**Consistency**	**Validity**
Level of assessment	Cohort	Registry	External
Domain objective	Assess the capture for variables and individuals	Assess the accuracy of placement of patients in the registry; identify issues with data capture and errors (e.g. transcription errors).	Assess the reliability of data against benchmarks determined from evidence-based literature.
Method of assessment	Ratio of data captured for a variable was calculated by dividing the number of patients with data available, by the total number of patients. assessed for a pre-defined set of variables*. Individual data capture was calculated by dividing the number of variables with data entered by the total number of variables from the predefined set.	For all records diagnosis was checked against inclusion criteria. Outlier analysis utilizing quartiles method was performed on baseline characteristics including age, BMI, and laboratory values. If outliers were not supported by literature the corresponding centre was asked to double-check patient records. For each variable, the 15 highest and lowest values were checked.	The highest quality evidence of appropriate patient outcomes was used to benchmark aggregated cohort data. Assessed for a pre-defined set of variables*.

*Pre-defined set of variables: age, BMI, sex, ethnicity, simplified AIH score, alcohol intake, cirrhosis, ALT, AST, ALP, γ-GT, IgG, ANA, AMA, SMA, LKM, SLA/LP, PBC, PSC, other autoimmune diseases, prednisone use, azathioprine use, cirrhosis at last follow-up, HCC, liver transplantation, death.

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis, ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; HCC, hepatocellular carcinoma.

Supplementary table 2. Characteristics at diagnosis and final outcome data of patients treated for AIH at transplant centres vs non-transplant centres.

	Transplant centers (N=1089)	**Non-transplant centers (N=1470)**	**p-value****
Patient characteristics			
Age (years)	42 (2-87)	51 (2-88)	**<0.001**
Sex (female)	807 (74)	1117 (76)	0.276
Ethnicity (white)	781 (88)	947 (94)	**<0.001**
Disease characteristics			
Simplified AIH score			**<0.001**
≤5	120 (14)	458 (35)	
Probable	171 (21)	384 (30)	
Definite	542 (65)	450 (35)	
Cirrhosis	225 (22)	311 (24)	0.225
PBC	112 (11)	151 (11)	0.984
PSC	97 (9)	86 (6)	**0.003**
Other associated diseases	285 (26)	409 (28)	0.331
Laboratory values			
AST (U/L)	432 (9-4388)	186 (9-4404)	**<0.001**
ALT (U/L)	417 (11-5200)	287 (7-4919)	**<0.001**
IgG (g/L)	23.3 (6-90)	19.8 (1-94)	**<0.001**
Outcome			
Follow-up time (years)	10 (0-49)	11 (0-49)	**<0.001**
No normalization of ALT/AST <6m	214 (42)	204 (25)	**<0.001**
No normalization of IgG <6m	120 (35)	33 (9)	**<0.001**
Lack of complete biochemical response <6m	154 (45)	70 (19)	**<0.001**
Relapse (number)	1 (0-7)	1 (0-8)	0.981
Cirrhosis	320 (43)	152 (31)	**<0.001**
HCC	17 (2)	16 (2)	0.773

Liver transplantation	132 (16)	11 (1)	**<0.001**
Death	140 (17)	89 (10)	**<0.001**
Liver related death	77 (56)	39 (44)	0.082

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G; HCC, hepatocellular carcinoma.
* Median, number (range, %).
** a p-value of <0.05 was considered statistical significant.

Supplementary table 3. Center specific characteristics.

Centre	Country	Period diagnosis	Type	Transplant center	Number of annual transplantations last 5 years	N	N (follow-up)	Follow-up time (y)
AMC	Netherlands	1967-2010	Tertiary referral centre	no	-	65	45	17 (4-49)
AZB	Netherlands	1982-2010	General hospital	no	-	31	-	-
AZU	Netherlands	1985-2011	General hospital	no	-	30	12	14 (10-20)
CHSJ	Portugal	2003-2018	Tertiary referral centre	no	-	33	33	8 (1-16)
DKU	Netherlands	1977-2010	General hospital	no	-	36	18	13 (4-39)
EMC	Netherlands	1974-2010	Tertiary referral centre*	yes	~90	114	22	18 (6-34)
ETZ	Netherlands	1984-2010	General hospital	no	-	9	-	-
HAGA	Netherlands	1980-2010	General hospital	no	-	23	10	13 (5-27)
HMCB	Netherlands	1995-2010	General hospital	no	-	13	-	-
HRHM	Italy	1989-2022	Tertiary referral centre	no	-	120	98	3 (0-32)
IsZ	Netherlands	1982-2010	General hospital	no	-	61	32	15 (9-34)
LUMC	Netherlands	1970-2010	Tertiary referral centre*	yes	~60	112	66	15 (0-42)
MCL	Netherlands	1972-2010	General hospital	no	-	41	-	-
MMCA	Netherlands	1969-2010	General hospital	no	-	10	-	-
MST	Netherlands	1982-2010	General hospital	no	-	38	-	-
MUMC	Netherlands	1992-2010	Tertiary referral centre	no	-	42	-	-
NZA	Netherlands	1980-2010	General hospital	no	-	44	17	13 (1-34)
OLVGo	Netherlands	1980-2009	General hospital	no	-	19	11	14 (5-36)
OLVGw	Netherlands	1985-2009	General hospital	no	-	20	10	14 (10-29)
RdGMC	Netherlands	1992-2010	General hospital	no	-	36	21	12 (1-24)
RKZ	Netherlands	1985-2010	General hospital	no	-	7	-	-
RUMC	Netherlands	1967-2009	Tertiary referral centre*	no	-	91	-	-
RZA	Netherlands	1979-2010	General hospital	no	-	38	22	15 (10-37)
SAZ	Netherlands	1996-2008	General hospital	no	-	7	-	-
SFG	Netherlands	1988-2009	General hospital	no	-	35	-	-
SGH	Netherlands	1986-2011	General hospital	no	-	16	9	13 (10-24)
SLZ	Netherlands	1981-2010	General hospital	no	-	24	-	-
TGZ	Netherlands	1994-2010	General hospital	no	-	5	-	-
UMCG	Netherlands	1972-2010	General hospital	yes	~70	128	88	15 (0-40)
UMCU	Netherlands	1981-2010	Tertiary referral centre	no	-	55	43	18 (10-35)
UoAE	Canada	1965-2021	Tertiary referral centre*	yes	~100	535	535	10 (0-49)

UOB	Italy	1974-2014	Tertiary referral centre*	yes	~120	212	211	5 (0-26)
UoTL	Greece	1999-2020	Tertiary referral centre	no	-	309	309	5 (0-21)
URMC	United States	2012-2021	Tertiary referral centre*	yes	~80	16 -		-
VUMC	Netherlands	1980-2010	Tertiary referral centre	no	-	123	36	14 (0-27)
VVHM	Spain	1992-2020	General hospital	no	-	51	46	2 (0-27)
ZhA	Netherlands	2009-2009	General hospital	no	-	1 -		-
ZMC	Netherlands	1993-2010	General hospital	no	-	9 -		-
Total: 38		**1965-2022**				**2559**	**1700**	**10 (0-49)**

* liver transplant centre

Supplementary table 4. Characteristics at diagnosis and final outcome data of patients with AIH stratified for year of diagnosis.

-	1965-1999 (N=624)	2000-2004 (N=507)	2005-2009 (N=703)	2010-2014 (N=355)	2015-2022 (N=368)
Patient characteristics					
Age (years)	36 (2-80)	47 (3-84)	51 (5-88)	53 (3-81)	53 (2-86)
Sex (female)	492 (79)	380 (75)	523 (74)	266 (75)	261 (71)
Ethnicity (white)	408 (95)	355 (92)	404 (91)	273 (91)	187 (88)
Transsplant center	334 (54)	191 (38)	252 (36)	167 (47)	144 (39)
Disease characteristics					
Simplified AIH score					
≤5	165 (31)	164 (36)	174 (28)	45 (16)	30 (14)
Probable	127 (24)	113 (25)	171 (27)	81 (29)	63 (28)
Definite	243 (45)	181 (40)	287 (45)	151 (55)	129 (58)
Cirrhosis	109 (20)	91 (21)	119 (18)	91 (27)	126 (34)
PBC	63 (11)	48 (10)	86 (13)	31 (9)	34 (9)
PSC	43 (7)	41 (8)	51 (7)	26 (7)	22 (6)
Other associated diseases	177 (28)	130 (26)	181 (26)	98 (28)	108 (29)
Outcome					
Follow-up time (years)	20 (1-49)	13 (0-21)	10 (0-16)	7 (0-11)	3 (0-7)
No normalization of ALT/AST <6m	88 (33)	86 (29)	65 (30)	81 (36)	98 (31)
No normalization of IgG <6m	36 (55)	21 (18)	22 (18)	47 (28)	27 (12)
Lack of complete biochemical response <6m	37 (56)	26 (23)	33 (26)	62 (37)	66 (28)
Relapse (number)	1 (0-7)	1 (0-8)	1 (0-8)	1 (0-5)	0 (0-4)
Cirrhosis	110 (58)	69 (38)	91 (36)	99 (37)	103 (30)
HCC	14 (4)	7 (2)	3 (1)	3 (1)	6 (2)
Liver transplantation	65 (16)	22 (6)	27 (8)	20 (8)	9 (3)
Death	82 (21)	60 (16)	44 (14)	26 (10)	17 (5)
Liver related death	40 (49)	32 (54)	23 (52)	13 (57)	8 (47)

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G; HCC, hepatocellular carcinoma.

* Median, number (range, %)

Supplementary table 5. Characteristics at diagnosis of patients with follow-up data and without follow-up data.

	No follow-up (N=859)	Follow-up (N=1700)	p-value
Patient characteristics			
Age (years)	50 (2-88)	46 (2-88)	**<0.001**
BMI	25 (15-55)	26 (11-69)	**0.001**
Sex (female)	661 (77)	1263 (74)	0.146
Ethnicity (white)	320 (87)	1408 (92)	**0.005**
Disease characteristics			
Cirrhosis	107 (15)	429 (26)	**<0.001**
PBC	121 (15)	142 (8)	**<0.001**
PSC	58 (7)	125 (7)	0.626
Other associated diseases	224 (26)	470 (28)	0.423
Prednisone	711 (84)	1469 (91)	**<0.001**

Azathioprine	468 (55)	684 (43)	**<0.001**
Laboratory values			
ANA	448 (60)	983 (65)	**0.037**
SMA	385 (56)	1048 (70)	**<0.001**
AST (U/L)	348 (9-3104)	298 (9-4404)	0.491
ALT (U/L)	268 (10-5200)	378 (7-4926)	**<0.001**
ALP (U/L)	150 (16-7106)	154 (17-1665)	0.893
γ-GT (U/L)	207 (2-1341)	149 (7-2227)	**<0.001**
IgG (g/L)	21 (6-74)	21 (1-94)	**<0.001**
MELD score	10 (6-22)	10 (6-47)	0.503

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, anti-smooth muscle antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease.
*a p-value <0.05 was considered statistical significant.

Supplemtentary table 6. Characteristics at diagnosis and final outcome for patients with AIH diagnosed with or without liver biopsy.

	Biopsy (n=2139)	No biopsy (n=420)	p-value*
Age (years)	48 (2-88)	46 (3-88)	**<0.001**
Sex (female)	1602 (75)	319 (77)	0.488
Ethnicity (Caucasian)	1454 (91)	272 (94)	0.093
AST	312 (9-4404)	252 (16-3422)	0.853
ALT	352 (10-5200)	237 (7-3789)	0.188
INR	1.1 (0.4-11.5)	1.22 (0.7-3.2)	0.837
ANA	1204 (62)	226 (67)	0.103
AMA	248 (13)	34 (11)	0.204
SMA	1227 (66)	205 (66)	0.995
LKM	46 (6)	15 (11)	**0.049**
SLA/LP	52 (5)	5 (3)	0.209
PBC	234 (11)	28 (7)	0.030
PSC	153 (7)	30 (7)	0.970
Cirrhosis	478 (22)	57 (27)	0.171
Transplant centre	883 (41)	205 (49)	**0.003**
Follow-up time (years)	10 (0-49)	10 (0-44)	**<0.001**
Lack of CBR <6m	225 (35)	40 (37)	0.578

* Median, number (range, %)

Supplementary table 7. Characteristics at diagnosis and final outcome data of patients with AIH stratified for ethnicity.

	White (N=1728)	Black (N=37)	Asian (N=53)	Hispanic (N=12)	Other (N=64)
Patient characteristics					
Age (years)	47 (2-87)	40 (6-82)	52 (13-73)	52 (3-66)	40 (5-66)
Sex (female)	1299 (76)	28 (76)	38 (73)	10 (83)	52 (81)
Disease characteristics					
Simplified AIH score					
≤5	316 (23)	8 (24)	6 (12)	0 (0)	11 (21)
Probable	370 (27)	11 (33)	8 (16)	2 (29)	9 (17)
Definite	697 (50)	14 (42)	36 (72)	5 (71)	32 (62)
Cirrhosis	404 (25)	9 (26)	7 (14)	4 (33)	19 (32)
PBC	153 (9)	1 (3)	7 (13)	2 (17)	13 (21)
PSC	122 (7)	4 (11)	2 (4)	1 (8)	2 (3)
Other associated diseases	457 (27)	13 (35)	8 (15)	4 (33)	17 (27)
Laboratory values					
AST (U/L)	285 (9-4404)	447 (37-1585)	722 (91-2600)	687 (27-1883)	387 (41-2600)
ALT (U/L)	352 (7-4926)	355 (47-2087)	513 (11-2264)	553 (31-1894	303 (35-2637
IgG (g/L)	21 (1-94)	23 (11-92)	22 (9-61)	24 (13-76)	24 (10-57)
Outcome					
Follow-up time (years)	10 (0-49)	14 (2-39)	6 (0-27)	4 (2-11)	8 (0-27)
No normalization of ALT/AST <6m	318 (29)	5 (29)	12 (50)	2 (29)	12 (46)
No normalization of IgG <6m	134 (21)	0 (0)	6 (46)	1 (33)	3 (30)
Lack of complete biochemical response <6m	190 (29)	0 (0)	9 (70)	1 (33)	3 (30)
Relapse (number)	1 (0-8)	2 (0-7)	2 (1-2)	-	2 (0-6)
Cirrhosis	406 (38)	3 (60)	13 (33)	3 (33)	25 (60)
HCC	29 (2)	0 (0)	1 (2)	1 (11)	0 (0)
Liver transplantation	115 (8)	2 (10)	7 (17)	1 (11)	12 (27)
Death	182 (13)	3 (15)	8 (19)	1 (11)	11 (22)
Liver related death	90 (51)	2 (67)	5 (63)	1 (100)	7 (64)

Abbreviations: BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G; HCC, hepatocellular carcinoma.
* Median, number (range, %)

Supplementary table 8. Multivariate cox regression model for liver related death and liver transplantation in patients with AIH with complete biochemical response at 6 or 12 months.

	HR (95% CI)	p-value*
Cirrhosis	6.861 (3.621-13.000)	0.052
PSC	3.699 (1.731-7.901)	0.468
Complete biochemical response at 6 or 12 months	7.356 (3.871-13.979)	0.059

Supplementary table 9. Univariate and multivariate cox regression models for the assessment of baseline factors associated with overall mortality and liver transplantation in patients with AIH.

	Univariate		Multivariate (N= 1700)		Multivariate (N= 706)	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Patient characteristics						
Age (years)	1.024 (1.017-1.031)	**<0.001**	1.043 (1.022-1.053)	**<0.001**		
Sex (female)	0.666 (0.522-0.849)	**0.001**	0.576 (0.326 -0.812)	**0.002**	-	
Ethnicity (white)	1.960 (1.367-2.808)	**<0.001**	3.068 (1.761-5.808)	**<0.001**	-	
Disease characteristics						
Simplified AIH score						
≤5	0.563 (0.382-0.830)	**0.004**	-	-	-	

Probable	0.763 (0.561-1.038)	0.085	-	-	-	
Definite	-	-	-	-	-	
Cirrhosis	2.710 (2.149-3.417)	**<0.001**	2.315 (1.436-3.104)	**<0.001**	8.542 (1.255-8.074)	**<0.001**
PBC	1.531 (1.076-2.179)	**0.018**	-	-	-	
PSC	1.562 (1.107-2.204)	**0.011**	-	-	3.183 (1.255-8.074)	**0.015**
Other associated diseases	0.856 (0.658-1.113)	0.245				
Laboratory values						
ANA	0.897 (0.691-1.165)	0.415				
AMA	1.576 (1.123-2.211)	**0.008**	-	-	-	
SMA	1.456 (1.083-1.956)	**0.013**	-	-		
LKM	0.596 (0.219-1.622)	0.311				
SLA/LP	0.907 (0.286-2.882)	0.869				
AST (U/L)	0.999 (0.999-0.999)	**0.037**	-	-		
ALT (U/L)	0.999 (0.999-0.999)	**0.001**	0.999 (0.999-1.000)	**<0.001**	-	
ALP (U/L)	1.001 (1.000-1.001)	0.050			-	
γ-GT (U/L)	1.001 (1.000-1.001)	**0.015**			-	
IgG (g/L)	1.006 (0.996-1.017)	0.227				
MELD score	1.077 (1.053-1.100)	**<0.001**				
Bilirubin (µmol/L)	1.002 (1.001-1.003)	**0.001**	1.003 (1.001-1.004)	**<0.001**	-	
Creatinine (µmol/L)	1.004 (1.002-1.005)	**<0.001**				
INR	1.914 (1.697-2.159)	**<0.001**				
Albumin (g/L)	0.918 (0.900-0.936)	**<0.001**				
Outcome						
No normalization of ALT/AST <6m	2.175 (1.593-2.971)	**<0.001**	2.487 (1.726-3.667)	**<0.001**		
No normalization of IgG <6m	6.529 (3.770-11.304)	**<0.001**				
Lack of complete biochemical response <6m	6.269 (3.828-10.267)	**<0.001**			5.736 (3.432-9.586)	**<0.001**
Relapse (number)	0.897 (0.774-1.039)	0.897				

Abbreviations: HR, hazard ratio; BMI, body mass index; AIH, autoimmune hepatitis; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; SMA, anti-smooth muscle antigen; LKM, anti-liver-kidney microsomal antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyltransferase; IgG, immunoglobulin G; MELD, model for end-stage liver disease; INR, international normalized ratio.

* a p-value of <0.05 was considered statistical significant.