# Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis

Colapietro, F.; Maisonneuve, P.; Lytvyak, E.; Beuers, U.; Verdonk, R.C.; Meer, A.J. van der; ... ; Int Autoimmune Hepatitis Grp

**Research Article**
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

# Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis

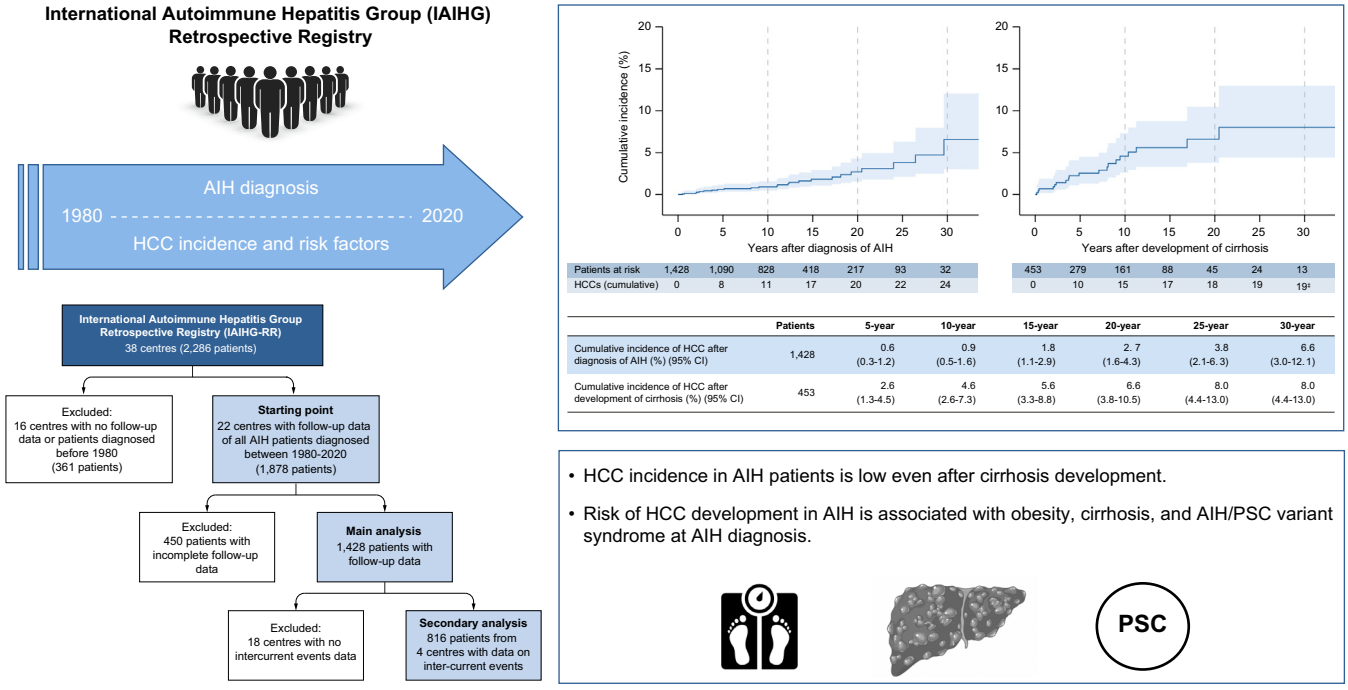
## Authors

Francesca Colapietro, Patrick Maisonneuve, Ellina Lytvyak, …, Rodrigo Liberal, Ynto S. de Boer, Ana Lleo

## Correspondence

ana.lleo@humanitas.it (A. Lleo).

## Graphical abstract




## Highlights

- This large multicentric cohort study shows that HCC incidence in patients with AIH is low even after cirrhosis development.
- The risk of HCC development in AIH is associated with obesity, cirrhosis, and AIH/PSC variant syndrome at AIH diagnosis.
- HCC surveillance programmes could be tailored according to risk factors.
- A sub-analysis showed that cirrhosis, HCC, and liver transplantation are significantly associated with increased mortality.

## Impact and implications

The risk of developing hepatocellular carcinoma (HCC) in individuals with autoimmune hepatitis (AIH) seems to be lower than for other aetiologies of chronic liver disease. Yet, solid data for this specific patient group remain elusive, given that most of the existing evidence comes from small, single-centre studies. In our study, we found that HCC incidence in patients with AIH is low even after the onset of cirrhosis. Additionally, factors such as advanced age, obesity, cirrhosis, alcohol consumption, and the presence of the AIH/PSC variant syndrome at the time of AIH diagnosis are linked to a higher risk of HCC. Based on these findings, there seems to be merit in adopting a specialized HCC monitoring programme for patients with AIH based on their individual risk factors.

https://doi.org/10.1016/j.jhep.2023.09.010
 

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

# Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis

Francesca Colapietro[1,2], Patrick Maisonneuve[3], Ellina Lytvyak[4], Ulrich Beuers[5], Robert C. Verdonk[6], Adriaan J. van der Meer[7], Bart van Hoek[8], Sjoerd D. Kuiken[9], Johannes T. Brouwer[10], Paolo Muratori[11,12], Alessio Aghemo[1,2], Francesco Carella[1,2], Ad P. van den Berg[13], Kalliopi Zachou[14], George N. Dalekos[14], Daniel E. Di Zeo-Sánchez[15], Mercedes Robles[15], Raul J. Andrade[15], Aldo J. Montano-Loza[16], Floris F. van den Brand[17], Charlotte D. Slooter[17], Guilherme Macedo[18], Rodrigo Liberal[18], Ynto S. de Boer[17], Ana Lleo[1,2,*], on behalf of the Dutch AIH Study Group[^], and the International Autoimmune Hepatitis Group[‡]

Journal of Hepatology **2024**. vol. 80 | 53–61

Check for updates

**See Editorial, pages 8–9**

**Background and Aims:** Autoimmune hepatitis (AIH) is a rare chronic liver disease of unknown aetiology; the risk of hepatocellular carcinoma (HCC) remains unclear and risk factors are not well-defined. We aimed to investigate the risk of HCC across a multicentre AIH cohort and to identify predictive factors.

**Methods:** We performed a retrospective, observational, multicentric study of patients included in the International Autoimmune Hepatitis Group Retrospective Registry. The assessed clinical outcomes were HCC development, liver transplantation, and death. Fine and Gray regression analysis stratified by centre was applied to determine the effects of individual covariates; the cumulative incidence of HCC was estimated using the competing risk method with death as a competing risk.

**Results:** A total of 1,428 patients diagnosed with AIH from 1980 to 2020 from 22 eligible centres across Europe and Canada were included, with a median follow-up of 11.1 years (interquartile range 5.2-15.9). Two hundred and ninety-three (20.5%) patients had cirrhosis at diagnosis. During follow-up, 24 patients developed HCC (1.7%), an incidence rate of 1.44 cases/1,000 patient-years; the cumulative incidence of HCC increased over time (0.6% at 5 years, 0.9% at 10 years, 2.7% at 20 years, and 6.6% at 30 years of follow-up). Patients who developed cirrhosis during follow-up had a significantly higher incidence of HCC. The cumulative incidence of HCC was 2.6%, 4.6%, 5.6% and 6.6% at 5, 10, 15, and 20 years after the development of cirrhosis, respectively. Obesity (hazard ratio [HR] 2.94, $p = 0.04$), cirrhosis (HR 3.17, $p = 0.01$), and AIH/PSC variant syndrome (HR 5.18, $p = 0.007$) at baseline were independent risk factors for HCC development.

**Conclusions:** HCC incidence in AIH is low even after cirrhosis development and is associated with risk factors including obesity, cirrhosis, and AIH/PSC variant syndrome.



## Introduction

Autoimmune hepatitis (AIH) is a rare and heterogeneous chronic liver disease characterized by circulating autoantibodies, hypergammaglobulinemia, and specific liver histological abnormalities.[1–3] The pathogenesis is largely unknown and, as there are no pathognomonic features, it remains a clinical diagnosis after the exclusion of other liver disorders.[4] Recent studies have reported a shift in AIH trends over the years, showing a rise across all age groups and ethnicities, and notably, an increased prevalence among males.[5–9] While the majority of patients with AIH respond well to immunosuppressive treatments, the disease can progress to cirrhosis, liver failure, and death if left untreated. The survival rate for patients with AIH is adversely affected by the presence of cirrhosis, either detected at diagnosis (in approximately 30% of cases) or later during follow-up, leading to an increased risk of liver-related complications.[8,10]

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, the sixth most common cancer, and the third leading cause of cancer-related death worldwide. In 2020, there were roughly 906,000 new HCC cases and 830,000 deaths globally.[11,12] Cirrhosis represents the main risk factor for the development of HCC, as it is present in more than 80%–90% of cases.[12] The average HCC incidence rate among patients with cirrhosis is 2-4 per 100 person-year.[13] When the anticipated risk of HCC surpasses 1.5% annually, surveillance is deemed cost-efficient for those with cirrhosis.[14,15] Accordingly, international guidelines recommend HCC surveillance for high-risk patient groups.[16,17]

Although the risk of HCC development in AIH seems to be lower than in other aetiologies of chronic liver disease, solid

Keywords: Autoimmune Hepatitis; Hepatocellular carcinoma; Liver cancer; Immunosuppressive therapy.
*Received 1 February 2023; received in revised form 28 August 2023; accepted 1 September 2023; available online 5 October 2023*
* Corresponding author. Address: Department of Biomedical Sciences, Humanitas University; Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Via A. Manzoni 56, Rozzano 20089, Italy; Tel.: +39-02-82247231, fax: +39-02-82242298.
*E-mail address*: ana.lleo@humanitas.it (A. Lleo).
[^] List of investigators provided in the supplementary file.
[‡] List of investigators provided the supplementary file.
https://doi.org/10.1016/j.jhep.2023.09.010

data in this subgroup of patients are missing as the current evidence stems from small single-centre studies.[18] Presently, only two large cohort studies[19,20] are available, both of which focused on Northern European cohorts. Both studies reported an elevated general cancer risk in patients with AIH compared with age- and sex-matched controls. Yet, the absolute HCC risk remained minimal. It is worth noting that patients with cirrhosis had the highest annual cancer risk, at 1.1%.[20] While surveillance recommendations have not been firmly established for patients with AIH and cirrhosis, HCC screening every 6 months is recommended by international societies.[3,21]

To address limitations in current knowledge and practice, we aimed to describe the incidence of HCC and identify risk factors and potential stratification indicators within a large international AIH cohort over long-term follow-up. Our goal is to furnish insights for tailored management of HCC surveillance in patients with AIH.

## Materials and methods

### Study setting and data collection

We conducted a multicentric, retrospective, observational study that included both adult and paediatric patients with an established diagnosis of AIH. These data were collected from the International Autoimmune Hepatitis Group Retrospective Registry (IAIHG-RR). The IAIHG-RR is a non-interventional international project that gathers retrospective data on patients clinically diagnosed with AIH by their physicians according to standardized directives.[2,3,21] Starting in 2018, 38 centres across seven countries began logging AIH cases in accordance with the Regulation (EU) 2016/679 (General Data Protection Regulation). However, 16 of these centres lacked the comprehensive data required for our analysis, making them ineligible for this study. To further ensure the accuracy and relevancy of our study, we limited our scope to patients diagnosed post-1980. Therefore, our study included well-documented patients diagnosed with AIH between 1980-2020 from 22 centres (9 general hospitals, 13 tertiary centres) across Europe and Canada (Fig. 1). These patients had clinical follow-ups extending to 2022. Of note, none of the patients in the study had been diagnosed with AIH prior to 1980.

AIH was diagnosed according to the simplified criteria in conjunction with the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines.[2,3,21] Additionally, patients with AIH/primary biliary cholangitis (PBC) and AIH/primary sclerosing cholangitis (PSC) variant syndromes were included in the study. Each centre reported these cases following international guidelines.[22–24]

Available data on sex, age at AIH diagnosis, liver histology, concomitant autoimmune diseases, documented risk factors (obesity, alcohol consumption), serological findings (antinuclear antibodies, smooth muscle antibodies, anti-liver kidney microsome type 1 antibodies), and serum IgG levels were extracted from the IAIHG-RR. Additional details collected covered AIH treatment specifics (type of immunosuppression, dosage, starting date, duration), laboratory results at AIH diagnosis and every 6 months thereafter, dates of HCC diagnosis and liver transplantation (LT), and survival status. The baseline was set as the timepoint of AIH diagnosis with the main outcomes being HCC development, LT, and mortality. Patient follow-up adhered to the standard practice of each centre. Importantly, given the study's retrospective nature, not all parameters were consistently available for every patient.

Where liver histology was available at the time of AIH diagnosis, fibrosis stages were categorized from F0 to F4, following the Metavir scoring system, with F4 corresponding to cirrhosis.[25] In cases lacking histological data, cirrhosis diagnoses relied on ultrasonography (coarse echo pattern of the liver parenchyma along with irregular hepatic margins, splenomegaly, or portal vein >16 mm), endoscopic evidence of cirrhosis (varices, portal gastropathy), and/or radiological or clinical findings of decompensation (ascites, variceal bleeding, encephalopathy). Complete biochemical response to therapy was defined according to international guidelines as the normalization of transaminases and IgG levels within 6 months of starting.[26]

Surveillance for HCC was conducted according to accepted international protocols.[21] HCC was diagnosed by histopathology or imaging criteria following the AASLD and EASL guidelines.[16,17] This included the convergence of two distinct imaging methods (CT, MRI, or contrast-enhanced ultrasonography) showing a focal hepatic lesion with arterial phase enhancement.

This study protocol was approved by the VU Medical Centre (VUmc) Institutional Review Committee, as the coordinating centre (VUmc, Amsterdam, the Netherlands). Additionally, each participating Centre obtained approval from their respective local ethics committees. Informed consent was either waived or obtained according to the local protocol at the individual centres.

### Quality control

Data were collected in a web-based, centralized, and anonymized format using the Castor Electronic Data Capture platform (https://data.castoredc.com/), which is hosted by Amsterdam UMC in Amsterdam, the Netherlands. Data inclusion was completed by physicians from each collaborating centre. Individuals were excluded from analysis if baseline or follow-up data relevant for analyses were incomplete or unavailable (follow-up shorter than 6 months or less than two visits recorded), the date of diagnosis or the exact date of major clinical events (*e.g.* HCC development) was unknown, and in the event of confirmed HBV/HCV infection, alcohol-related liver disease, or other hereditary or infectious liver diseases at the time of AIH diagnosis. Data export was performed in November 2022. Completed case report forms underwent quality control for completeness, validity, and accuracy of the data at the coordinating centre (by YDB, CDS and FFdB). Extensive efforts were undertaken to recover missing data.

### Statistical analysis

All statistical analyses were performed centrally in Milan using SAS software version 9.4 (Cary, NC). Patient characteristics are presented as categorical variables and the Chi-square test, Fisher's exact test or Mantel-Haenszel test for trend were used for comparisons between different groups. A $p$ value ≤0.05 was applied to determine statistical significance. Cumulative incidence of HCC after AIH diagnosis and after the diagnosis of cirrhosis was estimated using the cumulative incidence function with death considered as a competing risk event. Patients who were still alive were censored at the date of the last follow-up. The difference between groups was assessed by Gray's test. Overall survival after the AIH diagnosis was plotted using the Kaplan-Meier method. Univariate and multivariable Fine

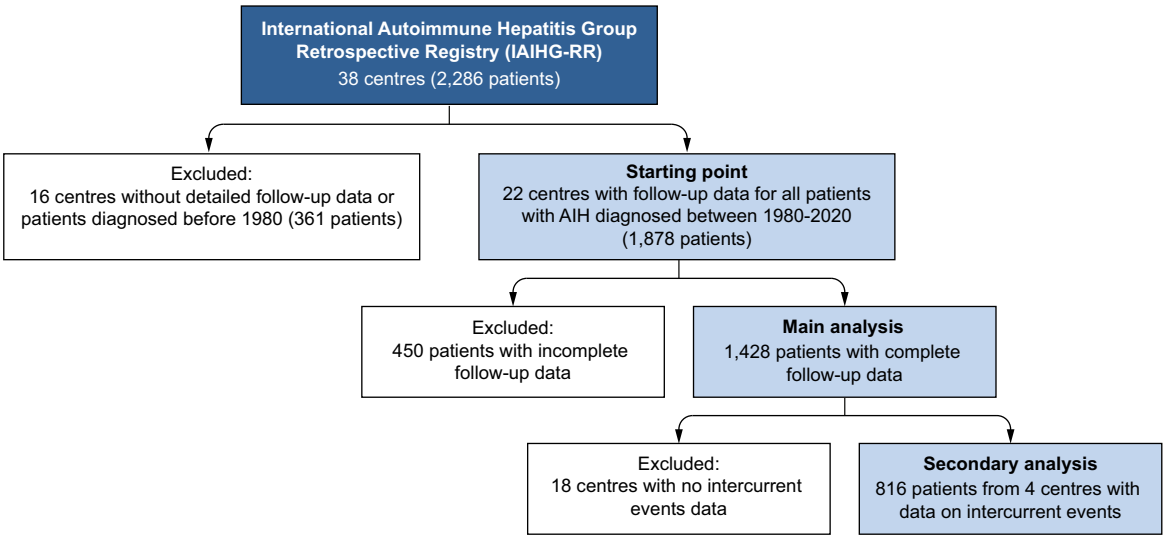



**Fig. 1. Study flowchart.** AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; IAIHG-RR, International Autoimmune Hepatitis Group Retrospective Registry.

and Gray subdistribution proportional-hazards regression analysis stratified by centre was conducted for relevant demographic and clinical variables to identify the factors associated with the development of HCC, accounting for competing risk.[27] In the regression models, the missing-indicator variable approach was utilized to denote missing values for certain variables, ensuring the inclusion of every patient in the analysis.[28] In a subset analysis limited to four centres with available data, cirrhosis development, HCC development and LT were treated as time-dependent covariates.

## Results

### Characteristics of the patient population and AIH features at diagnosis

At the time of data extraction, data on 1,878 patients with an initial diagnosis of AIH between 1980-2020 from 22 eligible centres, out of a total of 38 across Europe and Canada, had been retrieved from the IAIHG-RR. Of them, 450 patients (24.0%) were subsequently excluded from the analysis due to incomplete follow-up data, mainly consisting of missing date of last visit or missing dates of inter-current events (Fig. 1). Table 1 lists the baseline attributes of our final cohort of 1,428 patients, which were compared to the 450 excluded patients in Table S1. Importantly, centres with no follow-up data were excluded from the study and excluded individuals are a random subset of patients with AIH. Table S2 illustrates the distribution of included patients by centre. Missing values are indicated in tables and figures. The median age at AIH diagnosis was 46 years (interquartile range 28-58), with 600 (42.0%) patients being above 50 years of age, and 1,080 were female (75.6%). Among these females, 610 (56.5%) were under 50. Of the study population, 18.1% were overweight (BMI 25.0-29.9 kg/m$^2$, and 13.7% were obese (BMI ≥30.0 kg/m$^2$), with negligible gender-

**Table 1. Characteristics of patients with AIH at baseline.**

| Variable (n,%) | Total (N = 1,428) | Males (n = 348) | Females (n = 1,080) | *p* value |
|---|---|---|---|---|
| Age ≥50 years | 600 (42.0) | 130 (37.4) | 470 (43.5) | 0.04 |
| Overweight | 259 (18.1) | 77 (22.1) | 182 (16.9) | 0.35* |
| Obesity | 196 (13.7) | 41 (11.8) | 155 (14.4) | |
| Alcohol 25-60 g/day | 151 (10.6) | 56 (16.1) | 95 (8.8) | <0.0001* |
| Alcohol >60 g/day | 39 (2.7) | 17 (4.9) | 22 (2.0) | |
| Cirrhosis§ | 293 (20.5) | 90 (25.9) | 203 (18.8) | 0.008 |
| Splenomegaly† | 140 (9.8) | 46 (13.2) | 94 (8.7) | 0.08 |
| AIH-PBC | 125 (8.8) | 17 (4.9) | 108 (10.0) | 0.004 |
| AIH-PSC | 94 (6.6) | 49 (14.1) | 45 (4.2) | <0.0001 |
| Autoimmune diseases | 244 (17.1) | 33 (9.5) | 211 (19.5) | <0.0001 |
| IBD | 39 (2.7) | 14 (4.0) | 25 (2.3) | 0.05** |
| CD | 23 (1.6) | 5 (1.4) | 18 (1.7) | 1.00** |
| RA | 24 (1.7) | 3 (0.9) | 21 (1.9) | 0.32** |
| SLE | 22 (1.5) | 1 (0.3) | 21 (1.9) | 0.04** |
| DM | 14 (1.0) | 4 (1.1) | 10 (0.9) | 0.53** |
| THY | 120 (8.4) | 7 (2.0) | 113 (10.5) | <0.0001** |
| MS | 13 (0.9) | 4 (1.1) | 9 (0.8) | 0.51** |

AIH, autoimmune hepatitis; CD, coeliac disease; DM, diabetes mellitus; IBD, inflammatory bowel disease; MS, multiple sclerosis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; THY, thyroid disease. Data are missing for BMI (n = 625), alcohol (n = 68), cirrhosis (n = 56), splenomegaly (n = 600), PBC (n = 1), PSC (n = 1), autoimmune diseases (n = 474).

§Based on clinical, radiological, or histological evidence.

†Bipolar spleen length more than 12 cm.

*Mantel-Haenszel test for trend.

**Fisher's exact test.

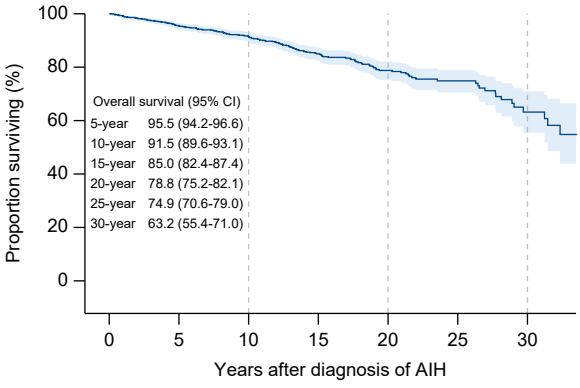
based disparities. The majority refrained from significant alcohol intake, but 2.7% reported consuming more than 60 g of alcohol daily. AIH variant syndromes with PBC and PSC were observed in 125 (8.8%) and 94 (6.6%) individuals, respectively. Definitive diagnosis of coexisting autoimmune diseases was made in 17.1% of the population, with thyroid diseases being the most common (8.4%) followed by inflammatory bowel disease (2.7%).

At the time of AIH diagnosis, 293 (20.5%) patients had cirrhosis, and 140 (9.8%) showed signs of splenomegaly, an indirect sign of portal hypertension, on radiological scans. During follow-up, an additional 169 patients developed cirrhosis, resulting in a total of 462 patients with cirrhosis participating in our study. AIH treatment after diagnosis was mainly predniso(lo)ne (n = 1,232, 86.3%) and/or azathioprine (n = 634, 44.4%). Only 2.3% (n = 33) were initially treated with budesonide, while 19.1% (n = 273) received ursodeoxycholic acid (UDCA).

### HCC incidence

During a median follow-up of 11.1 years (interquartile range 5.2-15.9) contributing to 16,550 person-years of observation, 24 patients developed HCC, at an incidence rate of 1.44 cases/1,000 patient-years, while 174 patients died (Fig. 2). The cumulative risk of HCC development increased over time from 0.9% (95% CI 0.5-1.6%) at the 10-year timepoint to 2.7% (95% CI 1.6-4.3) at 20 years and 6.6% (95% CI 3.0-12.1) at 30 years from AIH diagnosis (Fig. 3A, Table 2). As expected, the risk of HCC was higher in patients with AIH and cirrhosis (Fig. S1); the cumulative risk of HCC in patients with cirrhosis increased over time from 2.6% (95% CI 1.3-4.5) 5 years after the diagnosis of cirrhosis to 4.6% at 10-year (95% CI 2.6-7.3), 5.6% at 15-year (95% CI 3.3-8.8), 6.6% at 20-year (95% CI 3.8-10.5), and 8.0% (95% CI 4.4-13.0) at 30-year timepoints (Fig. 3B).

Among the 24 patients diagnosed with HCC, 15 were diagnosed by histology and nine by imaging techniques. Sixteen patients developed solitary HCC, eight had multifocal tumours, and two presented with extrahepatic metastases. Gender did not significantly correlate with tumour development. Thirteen patients had been diagnosed with AIH aged ≥50 years, while 10 patients with HCC already displayed signs of cirrhosis at baseline and six had splenomegaly (Table 3).




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patients at risk | 1,428 | 1,095 | 831 | 421 | 218 | 93 | 33 |
| Deaths (cumulative) | 0 | 51 | 88 | 130 | 152 | 160 | 170 |

**Fig. 2. Overall survival of patients with AIH.** Overall survival after the diagnosis of AIH was plotted using the Kaplan-Meier method. AIH, autoimmune hepatitis.

Given the retrospective nature of the IAIHG-R registry and considering few recorded deaths (n = 3) between 1980 and 1999, it is plausible that patients with long-standing AIH were identified during active follow-ups after centre-specific electronic databases or registries were established (Table S3 includes the distribution of deaths by calendar year of diagnosis of AIH and calendar year of death). We executed a sensitivity analysis focusing on patients diagnosed from 2000 to 2020 (Table S3) to reduce potential bias, revealing consistent HCC incidence trends (Table S4). The cumulative incidence of HCC following AIH diagnosis and subsequent development of cirrhosis remained consistent at 5, 10, 15, and 20-year intervals, indicating no distinct temporal trends throughout the study period.

### HCC-associated risk factors and survival

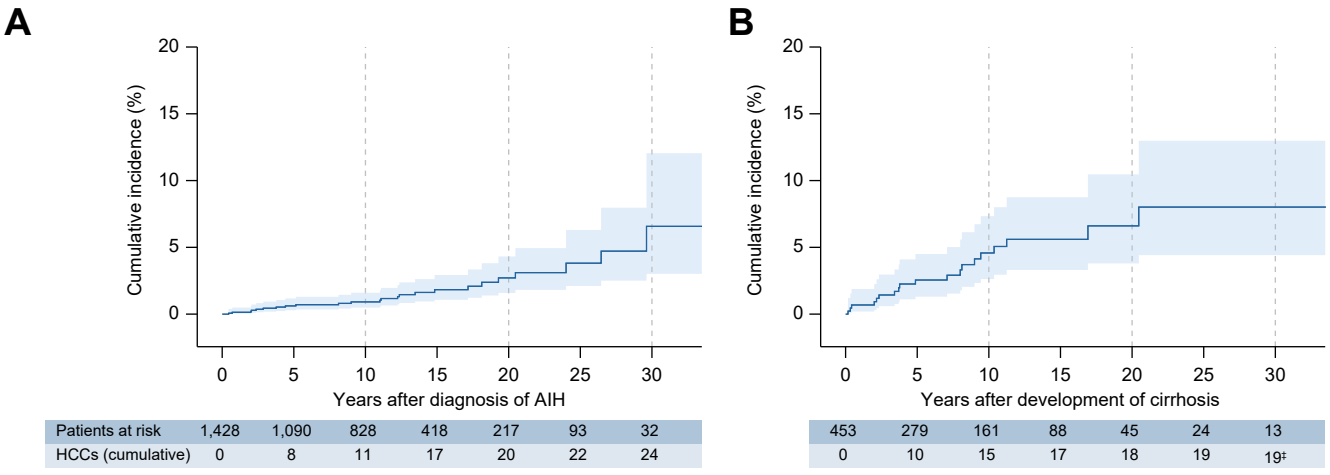
The multivariable analysis showed significant correlations between the development of HCC and factors such as age (≥50 years), obesity (BMI of ≥30 kg/m$^2$), an alcohol intake of ≥25 g/day, the AIH/PSC variant, and the presence of cirrhosis at baseline (Table 3). Specifically, obesity (BMI ≥30 kg/m$^2$) emerged as independently associated with HCC development, posing a risk nearly 3-fold greater than that seen in patients of normal weight or those who are overweight (hazard ratio [HR] 2.94, 95% CI 1.04-8.33, $p$ = 0.04). Cirrhosis at baseline was associated with a significantly increased risk of tumour development (HR 3.17, 95% CI 1.28-7.82, $p$ = 0.01). Notably, individuals with the AIH/PSC variant faced a 5-fold increased risk of developing HCC compared to those with just AIH (HR 5.18, 95% CI 1.56-17.2, $p$ = 0.007). Among the six HCC cases identified in patients with the AIH/PSC variant, three (or 50%) were histologically confirmed.

As expected, cirrhosis emerged as a time-dependent factor associated with HCC diagnosis (Table 4). It is noteworthy that there was no observed association between HCC and the type of treatment received, or the activity level of the disease as indicated by liver histology. Furthermore, the cumulative incidence of HCC was not associated with response to immunosuppressive therapy in our cohort (Fig. 4, Table S5).

To assess the impact of time-dependent factors on the development of HCC, LT, and death in patients with AIH, a multivariable regression model was built. This model was restricted to data from four centres that had the necessary information. Development of cirrhosis and LT were significantly associated with increased mortality after adjustment for age and centre (Table 4). One-hundred and twenty-six patients required LT during the follow-up period. Notably, the rate of LT was significantly higher in patients with HCC (43.5% *vs.* 9.7% among patients without HCC, $p$ <0.0001).

## Discussion

In this study, we report on the largest multicentric AIH cohort assembled to date. Our primary goal was to determine the cumulative incidence and identify risk factors for HCC development. Given the rarity of AIH, epidemiological and prognostic analyses are often limited to small retrospective cohorts and, frequently, monocentric or population-based studies. Notably, there remain unresolved challenges in AIH management, such as the effective categorization of high-risk patients, cost-effective surveillance for HCC development, and the decision




C

| | Patients | 5-year | 10-year | 15-year | 20-year | 25-year | 30-year |
|---|---|---|---|---|---|---|---|
| Cumulative incidence of HCC after diagnosis of AIH (%) (95% CI) | 1,428 | 0.6 (0.3-1.2) | 0.9 (0.5-1.6) | 1.8 (1.1-2.9) | 2. 7 (1.6-4.3) | 3.8 (2.1-6. 3) | 6.6 (3.0-12. 1) |
| Cumulative incidence of HCC after development of cirrhosis (%) (95% CI) | 453 | 2.6 (1.3-4.5) | 4.6 (2.6-7.3) | 5.6 (3.3-8.8) | 6.6 (3.8-10.5) | 8.0 (4.4-13.0) | 8.0 (4.4-13.0) |

**Fig. 3. Development of HCC after diagnosis of AIH and after cirrhosis development in patients with AIH.** Cumulative incidence of HCC after (A) AIH diagnosis and (B) after the diagnosis of cirrhosis was estimated using the cumulative incidence function with death considered as a competing risk event. Patients still alive were censored at the date of last follow-up. ‡Four patients developed HCC in the absence of established cirrhosis and for one patient with HCC the date of cirrhosis was missing. Nine patients diagnosed with cirrhosis during follow-up were excluded from this analysis due to a missing date of diagnosis. AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

**Table 2. Cumulative incidence of HCC in patients with AIH and selected risk groups.**

| | Cumulative incidence of HCC after AIH diagnosis, % (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| **Baseline characteristics** | **5-year** | **10-year** | **15-year** | **20-year** | **25-year** | **30-year** |
| All patients | 0.6 (0.3-1.2) | 0.9 (0.5-1.6) | 1.8 (1.1-2.9) | 2.7 (1.6-4.3) | 3.8 (2.1-6.3) | 6.6 (3.0-12.1) |
| ≥50 years-old | 1.5 (0.7-2.8) | 2.0 (1.0-3.6) | 3.2 (1.5-5.8) | 4.1 (2.0-7.6) | 4.1 (2.0-7.6) | 4.1 (2.0-7.6) |
| Obesity | 1.6 (0.4-4.2) | 1.6 (0.4-4.2) | 3.0 (0.8-7.6) | 4.9 (1.5-11.6) | 4.9 (1.5-11.6) | 17.5 (4.2-38.3) |
| Cirrhosis | 1.8 (0.7-4.0) | 2.8 (1.2-5.4) | 4.1 (2.0-7.5) | 4.1 (2.0-7.5) | 5.9 (2.5-11.5) | 5.9 (2.5-11.5) |
| AIH-PSC variant | 2.2 (0.4-6.9) | 2.2 (0.4-6.9) | 2.2 (0.4-6.9) | 8.0 (2.2-18.9) | 8.0 (2.2-18.9) | 8.0 (2.2-18.9) |

AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis. Cumulative incidence of HCC after AIH diagnosis and after the diagnosis of cirrhosis was estimated using the cumulative incidence function with death considered as a competing risk event. Patients still alive were censored at the date of last follow-up.

**Table 3. Univariate and multivariable Fine and Gray regression models for the assessment of baseline factors associated with HCC development in patients with AIH.**

| | HCC, n (%) | Univariate HR (95% CI) | *p* value | Multivariable HR* (95% CI) | *p* value |
|---|---|---|---|---|---|
| **All** | 24 | | | | |
| Female | 16 | 0.52 (0.22-1.22) | 0.13 | | |
| Age ≥50 years | 13 | 2.02 (0.86-4.75) | 0.11 | 2.25 (0.89-5.70) | 0.09 |
| Obesity | 7 | 2.52 (0.96-6.63) | 0.06 | 2.94 (1.04-8.33) | 0.04 |
| Alcohol ≥25 g/day | 7 | 3.71 (0.86-16.1) | 0.08 | 4.12 (0.93-18.3) | 0.06 |
| Cirrhosis§ | 10 | 2.77 (1.20-6.41) | 0.02 | 3.17 (1.28-7.82) | 0.01 |
| Splenomegaly† | 6 | 2.30 (0.83-6.35) | 0.11 | | |
| PBC | 4 | 2.44 (0.82-7.20) | 0.11 | | |
| PSC | 4 | 2.82 (0.94-8.45) | 0.06 | 5.18 (1.56-17.2) | 0.007 |
| Autoimmune disease | 4 | 0.91 (0.27-3.08) | 0.88 | | |
| IBD | 0 | — | | | |
| CD | 0 | — | | | |
| RA | 0 | — | | | |
| SLE | 1 | 2.77 (0.32-24.2) | 0.36 | | |
| DM | 0 | — | | | |
| THY | 2 | 0.71 (0.15-3.50) | 0.68 | | |
| MS | 0 | — | | | |

AIH, autoimmune hepatitis; CD, coeliac disease; DM, diabetes mellitus; IBD, inflammatory bowel disease; MS, multiple sclerosis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; THY, thyroid disease.
*Variables retaining a *p* value below 0.10 using backward stepwise selection.
§Presence of cirrhosis (at baseline) based on clinical, radiological, or histological evidence.
†Bipolar spleen length ≥12 cm.

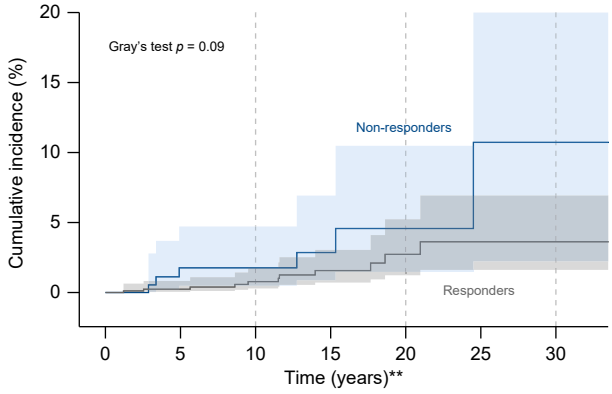
**Table 4. Multivariable regression models for the assessment of time-dependent factors associated with HCC development, LT, and death.**

| | HCC | | LT | | Deaths | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| **Baseline factors** | | | | | | |
| Age 50-59 | | | Age 60 or more | | 2.49 (1.41-4.37) | 0.001 |
| Age 60-69 | | | 0.21 (0.09-0.49) | 0.0003 | 2.42 (1.26-4.66) | 0.006 |
| Age 70-79 | | | | | 4.08 (1.77-9.44) | 0.0004 |
| Obesity | 5.82 (1.46-23.3) | 0.01 | 0.54 (0.31-0.94) | 0.03 | | |
| AIH-PSC | 6.79 (1.81-25.4) | 0.005 | | | | |
| **Time-dependent factors** | | | | | | |
| Cirrhosis | 17.3 (1.96-152) | 0.01 | 29.5 (14.3-60.9) | <0.0001 | 6.04 (3.51-10.4) | <0.0001 |
| HCC | | | 4.92 (1.47-16.4) | 0.01 | 2.98 (1.03-8.61) | 0.09 |

HCC, hepatocellular carcinoma; HR, hazard ratio; LT, liver transplantation.
HR and 95% CI were obtained from multivariable Fine and Gray regression models stratified by centre.
Analysis limited to four centres with complete follow-up data and based on 11 HCC cases in 791 patients; 106 LT procedures in 591 patients; and 88 deaths in 589 patients.

to discontinue immunosuppressive treatments to mitigate the side effects of long-term therapy.

Our findings highlight that the risk of developing HCC in patients with AIH is lower than in other aetiologies of liver disease. Throughout an 11.1-year follow-up, the overall HCC prevalence was 1.7% (24 HCC cases among 1,428 patients). The annual HCC incidence rate in our cohort varied from 0.09/100 patient-years over the first decade for all patients with AIH to 0.5/100 patient-years within the same timeframe for patients with AIH and cirrhosis. This rate is extremely low considering that cirrhosis is a well-known precursor of HCC reported in over 90% of HCC cases.[12] Similar results emerged from two large population-based studies using Danish healthcare registries.[5,19] However, a more recent prospective cohort study, drawing from UK Biobank data, indicated a significantly higher risk of hepatobiliary cancer in patients with AIH.[29] It is worth mentioning that this UK study only comprised 203 patients with AIH, who were generally older than participants in our study.




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Non-responders | | | | | | | |
| Patients at risk* | 200 | 141 | 111 | 50 | 26 | 11 | 6 |
| Cirrhosis* | 0 | 3 | 3 | 5 | 5 | 6 | 6 |
| Responders | | | | | | | |
| Patients at risk* | 864 | 668 | 472 | 247 | 113 | 42 | 16 |
| Cirrhosis* | 0 | 2 | 5 | 8 | 10 | 11 | 11 |

**Fig. 4. Development of HCC in patients with AIH based on response to immunosuppressive therapy.** Cumulative incidence of HCC was estimated using the cumulative incidence function. Difference between groups was assessed by the Gray's test. ^Data on response to immunosuppressive therapy missing for 359 patients. *Patients with signs of cirrhosis at baseline visit were excluded. **Follow-up was initiated 6 months after the diagnosis of AIH to include information about response to therapy. AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

Furthermore, just three hepatobiliary cancer cases were observed, with no distinction between HCC and biliary tract cancers provided. Additionally, a meta-analysis including 6,528 patients with AIH, with a median follow-up of 8 years, reported a pooled HCC incidence rate of 3.06 per 1,000 patient-years and 10.07 per 1,000 patient-years in patients without and with cirrhosis, respectively.[18]

In agreement with previous reports, our findings strongly validate advanced liver disease as a significant risk factor and showed that cirrhosis, HCC, and LT were significantly associated with increased mortality. Indeed, advanced disease at baseline was associated with the development of HCC in our cohort, and the development of cirrhosis over time was significantly associated with HCC and death. Those who developed cirrhosis during follow-up had a significantly higher incidence of HCC, with the cumulative risk increasing from 2.6% at 5 years to 8% at 30 years post-AIH diagnosis (Fig. 3B). Previous research had already identified older age as a risk factor associated with HCC development in AIH,[18,30,31] as well as alcohol abuse. However, male gender was not identified as a significant predictor in our study, a finding that contrasts with certain other reports.[5,7,32] Moreover, patients with a BMI ≥30 kg/m$^2$ had a significantly higher risk of HCC development. The fact that obesity is a well-known risk factor for cancer development and that the concurrent presence of non-alcoholic fatty liver disease can synergistically increase tumour formation risk[33] might explain the 4-fold increase in the risk of HCC development in patients with obesity in our cohort. Importantly, in our cohort, the risk of HCC in patients with obesity seemed similar to the risk in patients with cirrhosis, highlighting the relevance of the risk associated with obesity.

In the present study, the AIH-PSC variant emerged as a positive determinant of HCC development. This contrasts with the findings of Tansel *et al.*[18] and previous research on patients with PSC alone.[34] Importantly, only 50% of the HCC diagnoses in patients with AIH-PSC variant syndrome were confirmed via biopsy, while the remainder were identified through radiological diagnosis. Given that the radiological enhancement patterns of intrahepatic cholangiocarcinoma (iCCA) can often be mistaken for HCC, resulting in misdiagnosis in 4% of cases (up to 9% in patients with cirrhosis),[35] there is a possibility that some patients with AIH-PSC variant syndrome with either iCCA or a mixed HCC-iCCA form might have been misdiagnosed as having HCC.

Moreover, long-term immunosuppression has been associated with hepatic or extrahepatic malignancies. Jensen *et al.*[19]

reported that long-term use of immunosuppressive drugs in the setting of AIH exerts a protective effect against HCC development. In contrast, another study on a small Asian cohort identified the lack of remission as an independent risk factor for HCC development.[31] The majority of patients in our cohort received immunosuppressive therapy, mostly predniso(lo)ne based. Although treatment non-responders were at a significantly higher risk of cirrhosis in our study (data not presented), there was no observed difference in HCC development. Of note, the small number of tumours in our cohort might account for these findings. Furthermore, we observed a significant association between UDCA treatment and HCC development, which was likely due to the increased HCC risk associated with the PSC-AIH variant. It is worth noting that some patients on UDCA did not exhibit the PBC/PSC variant syndrome and were possibly taking this drug off-label for other conditions.

International guidelines consider surveillance for HCC to be cost-effective when the expected risk of HCC development is higher than 1.5% annually.[21,36] A recent nation-wide population-based study showed a large variation in the absolute risk of HCC among aetiologies of cirrhosis, supporting individualized decision-making on HCC surveillance.[37] Albeit the cumulative incidence in our cohort was below the proposed cut-off for surveillance, HCC was significantly associated with LT and death. Indeed, while almost all patients who developed HCC had progressed to cirrhosis during their follow-up period, they also had specific characteristics, including older age, portal hypertension, AIH-PSC variant, and obesity. All things considered, our data support the evaluation of patients for HCC screening based on risk factors present at the time of AIH diagnosis. Moreover, it is essential to remember that patients with advanced liver conditions should undergo radiological tests to detect early-stage complications of cirrhosis, such as portal hypertension, ascites, or portal vein thrombosis. The precise frequency for these ultrasonography sessions remains a subject for future prospective validation studies. A prospective registry coordinated by the ERN-RARE LIVER (https://rare-liver.eu/registry) has been developed to address these challenging issues.

Notably, our data indicates that the cumulative incidence of HCC in patients aged under 50 without cirrhosis is low. Therefore, monitoring in this demographic might be deemed unnecessary. Considering that a large proportion of patients with AIH develop the disease at a young age, these findings could greatly influence both clinical practice and resource allocation. Economic studies and cost-effectiveness assessments are required to support the optimal surveillance approach. A dedicated study using data from the IAIHG-RR is currently attempting to resolve lingering questions about cost analysis.

The present study has some limitations that need to be considered. First, its retrospective nature, multicentric design, and exclusion of a substantial proportion of patients due to a lack of essential information might introduce immortal time bias and selection bias. We endeavoured to mitigate this by ensuring rigorous quality control and consulting all participating centres about data collection and patient inclusion. To further diminish the risk of immortal time bias, we concentrated our analysis on post-1980 diagnoses and performed a sensitivity analysis limited to patients diagnosed during more recent decades (2000-2020), which intimated a minimal impact from such biases. About a quarter of the patients initially selected were excluded from the analysis due to the absence of a last follow-up date. The characteristics of these excluded individuals varied from those included in the evaluation. For instance, a smaller percentage of patients with cirrhosis were excluded compared to those without cirrhosis. While this might slightly affect the overall HCC cumulative incidence rates, it does not influence the rates post the onset of cirrhosis (Table S1). Second, histology and treatment strategy data were frequently missing. Third, we could not determine the number of patients who strictly adhered to the recommended ultrasonography surveillance protocol for HCC, and surveillance methodologies might have differed between centres. Finally, there was no centralized assessment of HCC diagnosis. However, a major strength of our study lies in its extensive geographic reach, encompassing both specialty centres and general hospitals, and the inclusion of a large number of patients affected by a rare condition, coupled with the availability of long-term follow-up data.

In conclusion, our analysis reveals that the incidence of HCC in AIH is lower than that in chronic liver disease due to other aetiologies. Although patients developing AIH-related cirrhosis have an increased risk for HCC, it remains below the cut-off suggested for surveillance programmes. Moreover, the risk of HCC development in patients with no advanced liver diseases is so low that routine surveillance for this subgroup might be unwarranted, reinforcing previously established findings. Factors like older age, obesity, the AIH-PSC variant, alcohol intake, and the presence of cirrhosis at the time of diagnosis emerged as independent risk factors for HCC development. Conversely, biochemical markers, initial histological characteristics, or treatment strategy did not demonstrate a predictive value for HCC development. Although general HCC surveillance may not be cost-effective in this population, personalized strategies should be adopted for patients with distinct risk factors. Finally, further prospective studies are needed to identify at-risk populations and tailor both therapeutic and surveillance strategies.

**Affiliations**

*[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [2]Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [3]Division of Epidemiology and Biostatistics, IEO European Institute of Oncology IRCCS, Milan, Italy; [4]Department of Medicine, Division of Preventive Medicine, University of Alberta, Edmonton, Alberta, Canada; [5]Department of Gastroenterology and Hepatology, Amsterdam UMC, Location AMC, Amsterdam, the Netherlands; [6]Department of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, Netherlands; [7]Department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, the Netherlands; [8]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands; [9]Department of Gastroenterology and Hepatology, OLVG, Amsterdam, the Netherlands; [10]Reinier de Graaf Medical Center, Delft, The Netherlands; [11]Division of Internal Medicine, Morgagni-Pierantoni Hospital, Forlì 47100, Italy; [12]Department of Science for the Quality of Life, University of Bologna, Bologna, Italy; [13]University Medical Center Groningen, University of Groningen, the Netherlands; [14]Department of Medicine and Research, Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, 41110, Larissa, Greece; [15]Liver Unit, Virgen de Victoria University Hospital-IBIMA, University of Málaga, CIBERehd, Malaga, Spain; [16]Department of Medicine, Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton, Alberta, Canada; [17]Department of Gastroenterology and Hepatology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [18]Department of Gastroenterology and Hepatology, Centro Hospitalar São João, Porto, Portugal*

## Abbreviations

AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; HR, hazard ratio; IAIHG, International Autoimmune Hepatitis Group; IAIHG-RR, International Autoimmune Hepatitis Group Retrospective Registry; iCCA, intrahepatic cholangiocarcinoma; LT, liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

## Financial support

The authors did not receive any financial support to complete the study or write the manuscript. The International Autoimmune Hepatitis Group (IAIHG) Retrospective Registry was funded by the United European Gastroenterology LINK award (2015). AL was supported by the Italian Association for Cancer Research (AIRC) grant IG-2019-23408 and the Italian Ministry of Health Grant NET-2019-12370049. This work was partially supported by the Italian Ministry of Health (Ricerca Corrente and 5x1000 funds to PM).

## Conflict of interest

All the authors have given substantial contribution to the completion of this work and have seen and approved the text in the current version. The authors report no conflict of interest with respect to this manuscript.

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

## Authors' contributions

Conceptualization and design of study (FC, PM, CDS, YdB, AL). Patient selection and data collection (all authors). Data analysis and interpretation (FC, PM, CDS, FFdB, YdB, AL). Manuscript preparation (FC, PM, CDS, YdB, AL). Critical review and editing (all authors). Funding (RL, YdB, AL, PM).

## Data availability statement

Data are available upon request to the corresponding author.

## Acknowledgements

The authors thank Dana Shiffer, MD for proofreading this article.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.09.010.

## References

*Author names in bold designate shared co-first authorship*

[1] **Lohse AW**, **Sebode M**, Bhathal PS, Clouston AD, Dienes HP, Jain D, 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 May;42(5):1058–1069.

[2] **Galaski J**, **Weiler-Normann C**, Schakat M, Zachou K, Muratori P, Lampalzer S, et al. Update of the simplified criteria for autoimmune hepatitis: evaluation of the methodology for immunoserological testing. J Hepatol 2021;74:312–320.

[3] Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, 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.

[4] Herkel J, Carambia A, Lohse AW. Autoimmune hepatitis: possible triggers, potential treatments. J Hepatol 2020;73:446–448.

[5] Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol 2014;60:612–617.

[6] Ngu JH, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. Hepatology 2012;55:522–529.

[7] Puustinen L, Barner-Rasmussen N, Pukkala E, Farkkila M. Incidence, prevalence, and causes of death of patients with autoimmune hepatitis: a nationwide register-based cohort study in Finland. Dig Liver Dis 2019;51:1294–1299.

[8] van den Brand FF, van der Veen KS, de Boer YS, van Gerven NM, Lissenberg-Witte BI, Beuers U, et al. Increased mortality among patients with vs without cirrhosis and autoimmune hepatitis. Clin Gastroenterol Hepatol 2019;17:940–947 e942.

[9] Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. Gut 2021;70:1989–2003.

[10] Hoeroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, et al. Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology 2011;140:1980–1989.

[11] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249.

[12] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–1314.

[13] Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450–1462.

[14] Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harms. Am J Gastroenterol 2020;115:1642–1649.

[15] Lin OS, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. Aliment Pharmacol Ther 2004;19:1159–1172.

[16] European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

[17] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.

[18] Tansel A, Katz LH, El-Serag HB, Thrift AP, Parepally M, Shakhatreh MH, et al. Incidence and determinants of hepatocellular carcinoma in autoimmune hepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15:1207–1217 e1204.

[19] Jensen MD, Jepsen P, Vilstrup H, Gronbaek L. Increased cancer risk in autoimmune hepatitis: a Danish nationwide cohort study. Am J Gastroenterol 2022;117:129–137.

[20] Sharma R, Verna EC, Simon TG, Soderling J, Hagstrom H, Green PHR, et al. Cancer risk in patients with autoimmune hepatitis: a nationwide population-based cohort study with histopathology. Am J Epidemiol 2022;191:298–319.

[21] European Association for the Study of the L. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 2015;63:971–1004.

[22] Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut 2019;68:1356–1378.

[23] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology 2022;75:1012–1013.

[24] 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.

[25] 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.

[26] **Pape S**, **Snijders R**, Gevers TJG, Chazouilleres O, Dalekos GN, Hirschfield GM, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76:841–849.

[27] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

[28] Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255–1264.

[29] He MM, Lo CH, Wang K, Polychronidis G, Wang L, Zhong R, et al. Immune-mediated diseases associated with cancer risks. JAMA Oncol 2022;8:209–219.

[30] Dakhoul L, Jones KR, Gawrieh S, Ghabril M, McShane C, Vuppalanchi R, et al. Older age and disease duration are highly associated with hepatocellular carcinoma in patients with autoimmune hepatitis. Dig Dis Sci 2019;64:1705–1710.

[31] Choi J, Choi GH, Lee D, Shim JH, Lim YS, Lee HC, et al. Long-term clinical outcomes in patients with autoimmune hepatitis according to treatment response in Asian country. Liver Int 2019;39:985–994.
[32] Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. Hepatology 2008;48:863–870.
[33] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
[34] Zenouzi R, Weismuller TJ, Hubener P, Schulze K, Bubenheim M, Pannicke N, et al. Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. Clin Gastroenterol Hepatol 2014;12:1733–1738.
[35] Vigano L, Lleo A, Muglia R, Gennaro N, Sama L, Colapietro F, et al. Intrahepatic cholangiocellular carcinoma with radiological enhancement patterns mimicking hepatocellular carcinoma. Updates Surg 2020;72:413–421.
[36] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 2018;68:723–750.
[37] Bengtsson B, Widman L, Wahlin S, Stal P, Bjorkstrom NK, Hagstrom H. The risk of hepatocellular carcinoma in cirrhosis differs by etiology, age and sex: a Swedish nationwide population-based cohort study. United Eur Gastroenterol J 2022 Jun;10(5):465–476.