

# Incidence and risk factors of hepatocellular carcinoma in patients with autoimmune hepatitis in Asia

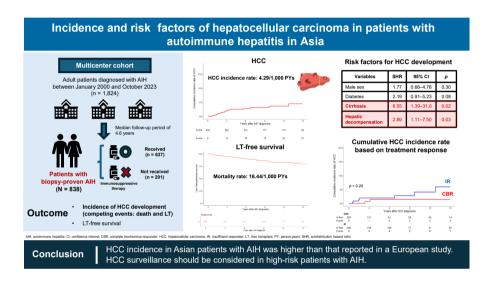
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# **Graphical abstract**



### **Highlights:**

- Asian patients with AIH have higher HCC incidence than Western patients.
- Asian patients with AIH have lower initial response than Western patients.
- Cirrhosis and hepatic decompensation are significant risk factors for HCC.
- IRs have high HCC risk and low liver transplantfree survival.
- Personalized HCC screening should be performed on highrisk patients with AIH and IRs.

## Impact and implications:

Autoimmune hepatitis (AIH) is rare, and the annual incidence of hepatocellular carcinoma (HCC) in patients with AIH is lower than that of other liver diseases, varying according to age, sex, and ethnicity, leading to an ongoing debate regarding the necessity for regular HCC surveillance in patients with AIH. However, most studies have focused on Western patients, and few have investigated HCC incidence in Asian populations, where the incidence of HCC is higher. Our multicenter study revealed that HCC incidence was higher in Asian populations than in Western populations. Regardless, this incidence did not meet the threshold for cost-effective surveillance. Our findings underscore the need for a nuanced approach to screening, balancing the low incidence of HCC with the presence of significant risk factors in Asian patients with AIH.



# Incidence and risk factors of hepatocellular carcinoma in patients with autoimmune hepatitis in Asia

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**Background & Aims:** A recent European multicenter study reported a low incidence of hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH), even after cirrhosis development. In this study, we evaluated the incidence and predictors of HCC in Asian patients with AIH.

**Methods:** We conducted a multicenter, retrospective study on adult patients diagnosed with AIH between January 2000 and October 2023 registered in the rare intractable disease registry of the Korean National Health Insurance Database. The primary outcome was HCC incidence by competing risk analysis, with death and liver transplantation (LT) considered as competing risk factors. The secondary outcome was LT-free survival. Therapeutic efficacy was also evaluated based on the International Autoimmune Hepatitis Group response criteria.

**Results:** We analyzed 838 patients with biopsy-proven AIH. The median age of patients was 57.7 years, and 709 (84.6%) patients were women. Cirrhosis was present upon diagnosis in 365 (43.6%) patients. During the median follow-up period of 4.6 years, 21 (2.5%) patients developed HCC, with an annual incidence of 4.29/1,000 person-years (PY). The annual incidence of LT-free mortality was 16.44/1,000 PYs. The risk factors for HCC included cirrhosis (subdistribution hazard ratio [HR] 6.55) and hepatic decompensation (subdistribution HR 2.89). Treatment status, diabetes, cirrhosis, hepatic decompensation, and variant syndrome (adjusted HR: 5.12, 2.00, 5.50, 3.05, and 2.01, respectively; all  $\rho$  <0.05) were significantly associated with poor LT-free survival. Insufficient responders had a higher incidence of HCC (4.45/1,000 PYs) and poorer LT-free survival (20.3/1,000 PYs) than complete biochemical responders.

**Conclusions:** The incidence of HCC in Asian patients with AIH was higher than that reported in a recent European study. The risk factors included cirrhosis and hepatic decompensation at diagnosis.

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### Introduction

Autoimmune hepatitis (AIH) is a rare disease characterized by hypergammaglobulinemia, autoantibodies, and interface hepatitis. 1–5 Due to its rarity and heterogeneity, there are no distinctive pathognomonic features or definitive diagnostic tools, making diagnosis difficult. Thus, most patients with AIH are only diagnosed after the exclusion of other liver diseases, consequently delaying diagnosis. However, in recent years, the incidence of AIH has increased across all age groups and ethnicities. 7–9

The probability of AIH progressing to cirrhosis and hepato-cellular carcinoma (HCC) is lower compared with that of other liver diseases. However, due to delayed initial diagnosis, approximately one-third of patients with AIH have progressed to cirrhosis at the time of diagnosis. <sup>10,11</sup> When cirrhosis is present at the time of the diagnosis, the pooled incidence of HCC significantly increases to 10.07/1,000 person-years (PYs), whereas in patients without cirrhosis at diagnosis, the pooled

HCC incidence is 1.14/1,000 PYs.<sup>10</sup> The guidelines of the American Association for the Study of Liver Diseases state that it is cost-effective to implement an HCC surveillance program for high-risk patients.<sup>12</sup> However, in most studies on patients with AIH, the annual risk of HCC does not meet this threshold and varies based on age, gender, ethnicity, and the presence of cirrhosis.<sup>9,10,13,14</sup> Therefore, implementing an HCC surveillance program in patients with AIH is not considered cost-effective.

A recent European study using data from the International Autoimmune Hepatitis Group (IAIHG) Retrospective Registry demonstrated that the annual incidence of HCC was as low as 1.44/1,000 PYs, despite a long observation period. Moreover, even when cirrhosis developed after AIH diagnosis, the HCC incidence still did not meet the cut-off for HCC surveillance. However, this study primarily focused on Western patients. Given that Asian patients have been shown to have a higher incidence of HCC and a poorer initial response to standard therapy compared with Western patients, 16,17

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research on Asian patients is warranted to determine the need for HCC surveillance in this patient population.

Therefore, we evaluated the incidence of HCC in patients with AIH in South Korea to identify the risk factors associated with HCC development and categorize high-risk patients. Based on our findings, we propose a personalized surveillance strategy for patients with AIH at high risk of developing HCC.

### Materials and methods

### Study design and patients

We performed a multicentric, retrospective cohort study on patients with AIH diagnosed from January 2000 to October 2023 at three academic teaching hospitals in South Korea (Asan Medical Center, Yonsei University Severance Hospital, and Korea University Hospital). A total of 1,824 consecutive patients with AIH were screened and analyzed. Patients were excluded if they met any of the following exclusion criteria: 1) aged <18 years, 2) other liver diseases etiologies at diagnosis, 3) concurrent malignancies, 4) finally diagnosed with primary biliary cholangitis by histopathology. 5) no rare intractable disease (RID) code for AIH (K75.4), 6) HCC diagnosis within 6 months after the initial AIH diagnosis (this criterion was applied because the participating institutions are tertiary referral centers specializing in HCC, increasing the likelihood that HCC was either detected concurrently during the diagnostic evaluation for AIH or was already present in a subclinical form and subsequently confirmed during follow-up assessments), 7) duration of follow-up period <6 months, and 8) patients who did not undergo liver biopsy or whose biopsy reports were unavailable for AIH diagnosis. Subsequently, 838 adult patients with biopsy-proven AIH in the RID registry were included (Fig. 1).

AIH diagnosis was based on simplified criteria and international guidelines<sup>2,4,5</sup> as well as RID registration in the Korean National Health Insurance Database. For RID registration, AIH must be clinically diagnosed according to serological tests (autoantibodies and IgG) or histological findings and differentially diagnosed from other liver diseases.<sup>18</sup>

#### Clinical assessment and data collection

Patient data were obtained from electronic medical records at each of the three centers. Demographic information, including age, sex, BMI, alcohol consumption, and comorbidities, along with data on concomitant autoimmune diseases at diagnosis, were collected. Laboratory tests were performed at the time of AIH diagnosis and every 6 months thereafter, including platelet count, creatinine, liver function test, and serological tests (antinuclear antibodies [ANAs], antimitochondrial antibodies, smooth muscle antibodies, and IgG). Liver function was estimated using the albumin–bilirubin index, while fibrosis was evaluated using both indirect and direct diagnostic tools, including the fibrosis-4 index. For the treatment data, we collected information on the administration of steroids and steroid-sparing agents, such as azathioprine and mycophenolate mofetil.

Cirrhosis was diagnosed on the basis of histopathologic finding, ultrasonographic findings (splenomegaly, coarse echogenicity of liver parenchyma, and irregular hepatic

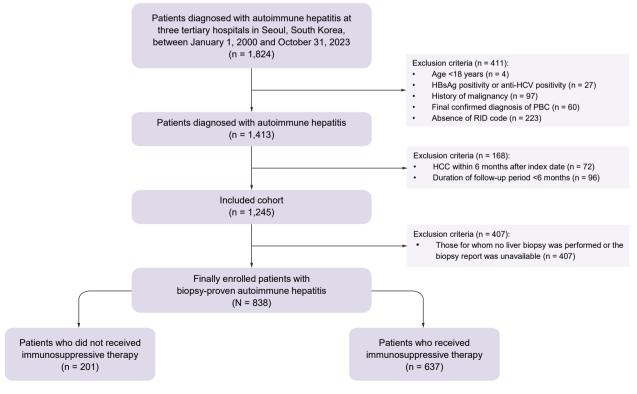


Fig. 1. Study flow. HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus C; HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis; RID, rare intractable disease.

margins), thrombocytopenia (<150  $\times$  10<sup>9</sup>/L), and radiological or clinical findings of hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy, and spontaneous bacterial peritonitis). The index date was defined as the date of the initial AIH diagnosis. The follow-up period extended from the index date to the occurrence of endpoints such as death, liver transplantation (LT), HCC diagnosis, or the last follow-up date (April 30, 2024), whichever occurred first.

This study received ethical approval from the Institutional Review Board (No.: 2023-1540). Informed consent was waived owing to the retrospective nature of the study. Our study also adhered to the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; Table S1).

# Definition of insufficient response and complete biochemical response in patients with AIH

The goal of AIH treatment is the normalization of serum alanine aminotransferase (ALT) and IgG levels and the resolution of histologic inflammation.<sup>2,5,20</sup> As defined by the IAIHG consensus statement, patients were categorized into two subgroups: complete biochemical response or insufficient response.<sup>20</sup> Complete biochemical response is defined as the normalization of serum aminotransferases and IgG levels (i.e. below the upper limit of normal) within 6 months of treatment. Insufficient response is defined as the failure to achieve a complete biochemical response within 6 months after treatment initiation. The normalization of aminotransferase and IqG levels was set according to the reference values of the treatment centers.<sup>21</sup> As per the IAIHG guideline, patients who achieved complete biochemical response were defined as complete biochemical responders (CBRs), and those with insufficient response were defined as insufficient responders (IRs).

# **Outcomes**

The primary outcome was the incidence of HCC development in patients with AlH. The follow-up period for the primary outcome was defined as the duration from the index date to endpoints including HCC diagnosis, LT, death, or last follow-up date, whichever came first. The secondary outcome was LT-free survival in patients with AlH. Furthermore, we analyzed predictive factors associated with an increased risk of HCC and poor LT-free survival in patients with AlH.

### Subgroup analysis

The cumulative incidence of HCC was assessed based on potential predictive factors, including immunosuppressant treatment status, age group, sex, diabetes, cirrhosis, and hepatic decompensation at baseline. Additionally, we compared the differences in the cumulative incidence of HCC and LT-free survival between IRs and CBRs to validate the IAIHG response criteria endpoint.

## Statistical analysis

Continuous and categorical variables were presented as median values with IQRs and numbers with proportions. The incidence rates of HCC and death were calculated per 1,000 PYs, and 95% CIs were estimated using Poisson distribution. The cumulative incidence of HCC after AIH diagnosis was estimated using the cumulative incidence function with death

and LT as competing events. Patients who were still alive on the date of the last follow-up were censored. The difference in HCC risk among subgroups was evaluated by Gray's test. The LT-free survival after AIH diagnosis was estimated using the Kaplan-Meier method. Univariate and multivariable Fine-Gray subdistribution proportion-hazard regression analyses were performed to identify risk factors associated with HCC development, accounting for competing risk.<sup>22</sup> Variables with a p value of <0.1 for the hazard ratio in the univariate analysis were included in the multivariable competing risk regression model. The risk factors associated with LT-free survival were identified through Cox regression analysis. Missing values constituted 0.1% (total bilirubin) to 6.6% (gamma-glutamyl transferase) of the baseline laboratory data and were imputed using linear interpolation and the mice package in R. Statistical analyses were performed using R software (http://cran.rprojec.org/). A p value <0.05 was considered statistically significant.

### Results

### Baseline characteristics of the study population

Following the exclusion criteria, 838 patients with biopsyproven AIH were subsequently included. Table 1 presents the baseline characteristics of the study population at AIH diagnosis. Among the cohort of 838 patients, 394 (47.0%) were from Asan Medical Center, 305 (36.4%) were from Severance University Hospital, and 139 (16.6%) were from Korea University Hospital (Table S2). The median age of the study cohort was 57.7 (IQR 48.1-65.4) years, and most patients were women (84.6%). At AIH diagnosis, cirrhosis was present in 365 (43.6%) patients, and 133 (15.9%) patients had hepatic decompensation such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding. The study cohort had a median fibrosis-4 index of 3.4 (1.9-6.3), with 432 patients (51.5%) classified at a high risk of fibrosis. Of the entire study cohort, 128 (15.3%) patients had variant syndrome, and 270 (32.2%) had other autoimmune diseases. Positivity for ANA, antimitochondrial antibodies, and smooth muscle antibodies was documented in 755 (90.1%), 93 (11.1%), and 134 (16.0%) patients, respectively. During the median follow-up of 4.6 (IQR, 4.2-4.9) years, patients underwent a median of eight (IQR, 4-14) imaging studies for HCC surveillance, including computed tomography, magnetic resonance imaging, or abdominal ultrasonography, with an estimated adherence rate of approximately 80%.

Of the 838 patients with biopsy-proven AIH, 201 (24.0%) patients did not receive immunosuppressive therapy. Compared to treated patients, those in the untreated group were older and exhibited a greater prevalence of concurrent autoimmune diseases and variant syndrome. Additionally, they demonstrated lower total bilirubin levels, baseline aspartate aminotransferase, alanine aminotransferase and IgG levels, and ANA titers, along with higher albumin and platelet counts, indicating better-preserved liver function. Although not statistically significant, the prevalence of cirrhosis and hepatic decompensation was lower in the patients in the untreated group (Table 1). Histologically, the treated group exhibited significantly increased levels of inflammation, lymphoplasmacytic infiltration, necrosis, and advanced fibrosis.

Table 1. Baseline characteristics of patients with biopsy-proven AIH based on their treatment status (N = 838).

Variables	Total (N = 838)	Untreated (n = 201)	Treated (n = 637)	p values
Demographic data				
Age, years	57.7 (48.1–65.4)	58.7 (50.9–67.3)	57.4 (47.1–64.3)	0.021
Age group				0.025
Age <50 years	251 (30.0)	47 (23.4)	204 (32.0)	
Age ≥50 years	587 (70.0)	154 (76.6)	433 (68.0)	
Female	709 (84.6)	174 (86.6)	535 (84.0)	0.440
Body mass index, kg/m <sup>2</sup>	23.5 (21.5–25.9)	23.6 (21.2–25.9)	23.5 (21.5–25.9)	0.879
Body mass index range				0.670
<25 kg/m <sup>2</sup>	571 (68.1)	134 (66.7)	437 (68.6)	
≥25 kg/m²	267 (31.9)	67 (33.3)	200 (31.4)	
Alcohol consumption <sup>a</sup>				0.707
Nondrinker	638 (76.1)	153 (76.1)	485 (76.1)	
Past drinker	93 (11.1)	19 (9.5)	74 (11.6)	
Current drinker	91 (10.9)	24 (11.9)	67 (10.5)	
Unavailable	16 (1.9)	5 (2.5)	11 (1.8)	
Diabetes	178 (21.2)	44 (21.9)	134 (21.0)	0.873
Hypertension	248 (29.6)	69 (34.3)	179 (28.1)	0.110
Concurrent autoimmune diseases	270 (32.2)	105 (52.2)	165 (25.9)	<0.001
Variant syndrome	128 (15.3)	42 (20.9)	86 (13.5)	0.015
AIH-PBC or AIC	109 (13.0)	35 (17.4)	74 (11.6)	0.039
AIH-PSC	3 (0.4)	2 (1.0)	1 (0.2)	
Undetermined	16 (1.9)	5 (2.5)	11 (1.7)	
Hepatic decompensation <sup>b</sup>	133 (15.9)	23 (11.4)	110 (17.3)	0.603
Hepatic encephalopathy	40 (4.8)	2 (1.0)	38 (6.0)	0.007
Ascites	108 (12.9)	20 (10.0)	88 (13.8)	0.192
Variceal bleeding	30 (3.6)	2 (1.0)	28 (4.4)	0.041
Spontaneous bacterial peritonitis	9 (1.1)	0 (0.0)	9 (1.4)	0.193
Cirrhosis <sup>c</sup>	365 (43.6)	77 (38.3)	288 (45.2)	0.101
Histologic findings	·	, ,	, ,	
Interface hepatitis	403 (48.1)	69 (34.3)	334 (52.4)	<0.001
Portal inflammation	432 (51.6)	62 (30.8)	370 (58.1)	<0.001
Lobular hepatitis	414 (49.4)	87 (43.3)	327 (51.3)	<0.001
Lymphoplasmacytic infiltration	394 (47.0)	72 (35.8)	322 (50.5)	0.004
Rosette/emperipolesis	163 (27.8)	72 (33.5)	206 (32.3)	<0.004
Centrilobular necrosis	391 (49.0)	11 (5.5)	156 (24.5)	<0.001
Fibrosis (METAVIR F3 or F4)	349 (41.6)	62 (30.8)	287 (45.1)	0.005
,	049 (41.0)	02 (50.0)	207 (43.1)	0.003
Laboratory findings	22/25 24	2.1.(.2.5	22 ( 2 ( 2 2)	
ALBI score	-0.3 (-0.5, -0.1)	-0.4 (-0.5, -0.3)	-0.3 (-0.4, 0.0)	<0.001
FIB-4 score	3.4 (1.9–6.3)	2.4 (1.5–4.5)	3.7 (2.0–7.3)	<0.001
FIB-4 risk				<0.001
Low group	139 (16.6)	43 (21.4)	96 (15.1)	
Intermediate group	267 (31.9)	82 (40.8)	185 (29.0)	
High group	432 (51.5)	76 (37.8)	356 (55.9)	
WBC, 10 <sup>6</sup> /L	5.4 (4.2–6.7)	5.5 (4.2–6.6)	5.3 (4.2–6.8)	0.785
Hb, g/dl	12.6 (11.6–13.4)	12.9 (12.0–13.6)	12.5 (11.4–13.3)	<0.001
Platelets, 10 <sup>9</sup> /L	184.0 (134.0–239.0)	203.0 (153.0–252.0)	177.0 (128.0–231.0)	<0.001
AST, U/L	76.0 (43.0–155.0)	59.0 (34.0–88.0)	86.0 (45.0–197.0)	<0.001
ALT, U/L	60.0 (27.0–140.0)	44.0 (23.0–82.0)	67.0 (28.0–164.0)	<0.001
ALP, U/L	116.0 (85.0–163.0)	107.0 (82.0–153.0)	118.0 (85.0–168.0)	0.092
GGT, U/L	94.0 (50.0–192.0)	86.0 (43.0–186.0)	96.0 (50.0–194.0)	0.163
PT, INR	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.1 (1.0–1.2)	<0.001
Total bilirubin, mg/dl	1.0 (0.6–2.1)	0.7 (0.6–1.1)	1.1 (0.7–2.6)	<0.001
Albumin, g/dl	3.8 (3.3–4.1)	4.1 (3.7–4.3)	3.7 (3.2–4.1)	<0.001
Creatinine, mg/dl	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.324
eGFR, ml/min/1.73 m <sup>2</sup>	92.0 (82.7–104.0)	92.0 (80.0–102.0)	92.4 (83.0–104.0)	0.119
ANA titer				0.019
<1:40	67 (8.0)	8 (4.0)	59 (9.3)	
1:40	107 (12.8)	19 (9.5)	88 (13.8)	
≥1:80	648 (77.3)	171 (85.0)	477 (74.9)	
Unavailable	16 (1.9)	3 (1.5)	13 (2.0)	
AMA		• •		0.084
Negative	712 (85.0)	161 (80.1)	551 (86.5)	
Positive	93 (11.1)	30 (14.9)	63 (9.9)	
Unavailable	33 (3.9)	10 (5.0)	23 (3.6)	
	()	()	()	

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Table 1. (continued)

Variables	Total (N = 838)	Untreated (n = 201)	Treated (n = 637)	p values
SMA				<0.001
Negative	638 (76.1)	145 (72.2)	493 (77.4)	
Positive	134 (16.0)	25 (12.4)	109 (17.1)	
Unavailable	66 (7.9)	31 (15.4)	35 (5.5)	
IgG range				<0.001
lgG ≥1,650 mg/dl	500 (59.7)	96 (47.8)	404 (63.4)	
Unavailable	128 (15.3)	43 (21.4)	85 (13.3)	

Data are presented as n (%) or median (interquartile range).

AIH, autoimmune hepatitis; AIC, autoimmune cholangitis; ALBI, albumin-bilirubin index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4; GGT, gamma-glutamyltransferase; Hb, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PT, prothrombin time; SMA, smooth muscle antibody; WBC, white blood cell.

<sup>a</sup>Past drinkers were defined as those who had abstained from alcohol for >1 year, whereas current drinkers were defined as those with a history of alcohol consumption within 1 year before AIH diagnosis.

bHepatic decompensation was defined as a composite of hepatic encephalopathy, ascites, variceal bleeding, and spontaneous bacterial peritonitis that occurred within 3 months before AIH diagnosis

°Cirrhosis was diagnosed by histopathologic findings, thrombocytopenia, radiological findings consistent with portal hypertension, or clinical history of hepatic decompensation.

# Incidence of HCC and LT-free survival in patients with biopsy-proven AIH

During the observational period, contributing to 4,900 PYs of observation, 21 (2.5%) patients developed HCC with an annual incidence rate of 4.29/1,000 PYs (95% CI 2.45–6.12), 37 (4.4%) died, and 48 (5.7%) underwent LT (Figs 2 and 3). The cumulative incidence rates of HCC development at 5, 10, and 15 years after AIH diagnosis were 2.5% (95% CI 1.5–4.0), 3.7% (95% CI 2.2–5.7), and 4.5% (95% CI 2.5–7.3), respectively (Fig. 2 and Table 2).

The median LT-free survival was not reached during the follow-up period. The annual LT-free mortality rate was 16.44/1,000 PYs (95% CI 12.86–20.03). The LT-free survival rates at 5, 10, and 15 years from AIH diagnosis were 92.1% (95% CI 90.0–94.3), 83.6% (95% CI 79.7–87.7), and 80.0% (95% CI 74.9–85.4), respectively (Fig. 3).

According to treatment status, only two (1.0%) untreated patients developed HCC, with an annual incidence rate of 2.02/1,000 PYs (95% CI 0.0–4.82). In addition, three (1.5%) patients died, and none underwent LT during the study period (Fig. S1). Among treated patients, 19 (3.0%) HCC cases were observed, corresponding to an annual incidence rate of 4.86/1,000 PYs (95% CI 2.67–7.05), 34 (5.3%) patients died, and 48 (7.5%) patients underwent LT. In the treated group, the cumulative incidence rates of HCC at 5, 10, and 15 years after AIH diagnosis were 3.1% (95% CI 1.9–4.9), 4.1% (95% CI 2.4–6.4), and 5.0% (95% CI 2.8–8.1), respectively (Table 2). Although the incidence of HCC was numerically higher in treated patients, the difference was not statistically significant (p = 0.20, Fig. S1A). Moreover, the LT-free survival rate was lower in treated patients than in untreated patients (p < 0.001, Fig. S1B).

# Risk factors associated with the development of HCC and LT-free survival in patients with AIH

In univariate Fine–Gray subdistribution proportion-hazard regression analyses, male sex, diabetes, cirrhosis, and hepatic decompensation at diagnosis were significantly associated with an increased risk of HCC (all p <0.05). Multivariable regression analysis revealed that cirrhosis (subdistribution hazard ratio [SHR] 6.55; 95% CI 1.39–31.0; p = 0.02) and hepatic decompensation (SHR 2.89; 95% CI 1.11–7.50; p = 0.03) were significant risk factors for HCC development (Table 3).

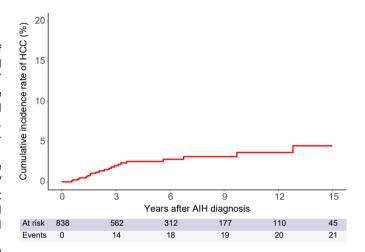


Fig. 2. Cumulative HCC incidence in the entire study cohort. The cumulative incidence of HCC after AIH diagnosis was estimated using the cumulative incidence function, with death and liver transplant as competing events. AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

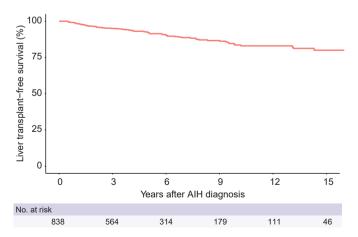


Fig. 3. Liver transplant-free survival in the entire study cohort. The liver transplant-free survival was estimated using the Kaplan-Meier method. AIH, autoimmune hepatitis.

Table 2. Cumulative incidence rate of HCC among patients with AIH and various risk factors.

	Cumulative	incidence rate of HCC after AIH diagnosis,	, % (95% CI)
Risk factors	5 years	10 years	15 years
All patients	2.5 (1.5–4.0)	3.7 (2.2–5.7)	4.5 (2.5–7.3)
Subgroups			
Treatment status			
Untreated patients	0.7 (0.1–3.6)	2.3 (0.4–7.9)	2.3 (0.4-7.9)
Treated patients	3.1 (1.9–4.9)	4.1 (2.4–6.4)	5.0 (2.8–8.1)
Age group			
<50 years	1.5 (0.4–4.1)	1.5 (0.4–4.1)	3.5 (0.8–9.5)
≥50 years	3.0 (1.7-4.8)	4.8 (2.6-8.0)	4.8 (2.6–8.0)
Sex			
Female	2.2 (1.2–3.7)	3.1 (1.6–5.2)	4.0 (2.0-7.0)
Male	4.6 (1.7–9.8)	7.9 (2.5–17.0)	7.9 (2.5–17.0)
Cirrhosis	5.5 (3.3-8.6)	8.2 (4.7-13.0)	8.2 (4.7-13.0)
Hepatic decompensation <sup>a</sup>	12.0 (6.4–19.0)	12.0 (6.4–19.0)	12.0 (6.4–19.0)
Diabetes	6.1 (3.0–11.0)	8.0 (3.7–14.0)	8.0 (3.7-14.0)

Statistical analysis: the cumulative incidence of HCC after AIH diagnosis was estimated using the cumulative incidence function, with death and liver transplant as competing events.

Multivariable regression analysis identified treatment status (adjusted HR [AHR] 5.12; 95% CI 1.60–16.3; p=0.006), diabetes (AHR 2.00; 95% CI 1.25–3.19; p=0.004), cirrhosis (AHR 5.50; 95% CI 2.75–11.0; p<0.001), hepatic decompensation (AHR 3.05; 95% CI 1.89–4.93; p<0.001), and presence of variant syndrome (AHR 2.01; 95% CI 1.17–3.45; p=0.01) at diagnosis as risk factors associated with poor LT-free survival (Table S3).

# Subgroup analysis of HCC development based on predictive factors

As age increased, the cumulative incidence rate of developing HCC became higher, with the highest incidence risk in the subgroup aged  $\geq$ 50 years (p=0.20; Fig. S2A and Table 2). Male patients had a higher risk of HCC compared with female patients (p=0.04; Fig. S2B). Moreover, patients with diabetes at the time of diagnosis exhibited a higher risk of developing HCC than those without diabetes (p=0.001; Fig. S2C).

The subgroup with cirrhosis at diagnosis showed a statistically significant association with an increased risk of HCC (p <0.001; Fig. S2D). The annual incidence rate of HCC in the subgroup with cirrhosis was 10.1/1,000 PYs (95% CI 5.58–14.7), which was higher than that of the subgroup without cirrhosis (0.66/1,000 PYs [95% CI 0.0–1.58]). The cumulative incidence rates of HCC in patients with cirrhosis were 5.5% (95% CI 3.3–8.6) at 5 years, 8.2% (95% CI 4.7–13.0) at 10 years, and 8.2% (95% CI 4.7–13.0) at 15 years (Table 2).

Notably, the subgroup with hepatic decompensation at diagnosis had a significantly higher risk of developing HCC than the subgroup without hepatic decompensation (p < 0.001, Fig. S2E). The cumulative incidence rates of HCC in this subgroup remained at 12.0% (95% CI 6.4–19.0) 5 years after AIH diagnosis (Table 2).

# Subgroup analysis of HCC development based on treatment response

Among the entire study population, 429 (51.2%) patients with sufficient follow-up data to evaluate biochemical response

were further divided into two subgroups: IRs (n = 226 [52.7%]) or CBRs (n = 203 [47.3%]) (Table S4). CBRs were older (58.3 [49.4–66.3] years vs. 53.9 [43.5–62.8] years) and had a lower prevalence of concurrent autoimmune diseases (19.7% vs. 22.6%) at the time of AIH diagnosis compared with IRs. The positivity rate of ANAs (80.3% vs. 89.0%; p = 0.015) and the proportion of patients with serum IgG  $\geq$ 1,650 mg/dl (62.1% vs. 77.9%; p < 0.001) were significantly lower in CBRs than in IRs. The prevalence of cirrhosis was significantly higher in IRs than in CBRs (49.1% vs. 37.9%; p = 0.026).

CBRs had a lower annual incidence rate of HCC (1.50/1,000 PYs [95% CI 0.0–3.58]) compared with IRs (4.45/1,000 PYs [95% CI 1.15–7.75]). The cumulative incidence rates of HCC in CBRs remained at 1.5% (95% CI 0.3–4.8) 5 years after AlH diagnosis, whereas those in IRs were 1.9% (95% CI 0.6–4.6) at 5 years, 4.1% (95% CI 1.5–8.8) at 10 years, and 5.9% (95% CI 2.2–12.0) at 15 years (Fig. S3 and Table S5). In the univariate Fine–Gray subdistribution hazard regression analysis of treated patients with sufficient follow-up data, IRs tended to have a higher risk of HCC development than CBRs (SHR, 2.89; 95% CI, 0.60–14.0; p = 0.20; Table S6). However, there were no significant factors associated with an increased risk of HCC after adjusting for covariates.

IRs had a higher annual incidence rate of LT-free mortality compared with CBRs (20.3/1,000 PYs [95% CI 13.3–27.3] vs. 7.39/1,000 PYs [95% CI 2.81–12.0]), with an HR of 2.74 (95% CI 1.35–5.58; p=0.005; Fig. S4). The LT-free survival rates were 97.2% (95% CI 94.5–100.0) at 5 years, 92.1% (95% CI 86.6–97.9) at 10 years, and 87.9% (95% CI 80.3–96.2) at 15 years in CBRs and 91.0% (95% CI 86.8–95.4) at 5 years, 78.6% (95% CI 71.5–86.4) at 10 years, and 76.1% (95% CI 67.8–85.3) at 15 years in IRs (Table S5). On multivariable analysis, IRs had worse LT-free survival than CBRs (AHR 3.66; 95% CI 1.33–10.0; p=0.01, Table S6). Moreover, diabetes (AHR 2.80; 95% CI 1.43–5.48; p=0.003), cirrhosis (AHR 4.29; 95% CI 1.67–11.0; p=0.002), and hepatic decompensation (AHR 4.17; 95% CI 2.05–8.46; p<0.001) were significantly associated with worse LT-free survival.

AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

<sup>&</sup>lt;sup>a</sup>Hepatic decompensation was defined as a composite of hepatic encephalopathy, ascites, variceal bleeding, and spontaneous bacterial peritonitis that occurred within 3 months before or after AIH diagnosis.

Table 3. Univariate and multivariable Fine-Gray regression models for risk factors of HCC development in patients with AIH.

		Univariate analysis		Multivariable analysis			
Variables	N	SHR	95% CI	p values	SHR	95% CI	p values
Entire cohort	838	-	-	-	-	_	_
Treatment status				0.20	_	-	_
Untreated	201	1	Reference				
Treated	637	2.79	0.64-12.2				
Female	709	1	Reference	0.04	1	Reference	0.30
Male	129	2.66	1.03-6.84		1.77	0.66-4.78	
Age group				0.20	-	-	-
<50 years	251	1	Reference				
≥50 years	587	2.04	0.69-6.00				
Body mass index range				0.50	_	_	-
<25 kg/m <sup>2</sup>	571	1	Reference				
≥25 kg/m²	267	1.36	0.56-3.29				
Diabetes, presence	178	3.71	1.59-8.65	0.002	2.19	0.91-5.23	0.08
Cirrhosis, presence	365	13.1	3.09-55.7	<0.001	6.55	1.39-31.0	0.02
Hepatic decompensation <sup>a</sup> , presence	133	7.97	3.38-18.8	<0.001	2.89	1.11-7.50	0.03
Concurrent autoimmune disease, presence	270	0.93	0.35-2.49	0.90	_	_	-
Variant syndrome, presence	128	0.27	0.04-2.03	0.20	-	-	-
ANA <sup>b</sup> , positive	755	2.35	0.31-17.8	0.40	_	-	_
AMA <sup>c</sup> , positive	93	0.38	0.05-2.81	0.30	=	=	-
SMA <sup>d</sup> , positive	134	0.26	0.03-1.94	0.20	-	-	_
Alcohol consumption <sup>e</sup> , presence	184	2.07	0.84–5.10	0.11	_	-	-

Statistical analysis: univariate and multivariable Fine-Gray regression models were fitted to identify potential risk factors for HCC, with p values less than 0.05, and SHRs were estimated.

AIH, autoimmune hepatitis; ANA, antinuclear antibody; AMA, antimitochondrial antibody; HCC, hepatocellular carcinoma; SHR, subdistribution hazard ratio; SMA, smooth muscle antibody.

### **Discussion**

In our multicentric cohort study, most patients with AIH had concurrent cirrhosis at diagnosis. The annual incidence of HCC was higher than that reported in a European study. 15 Among all patients, untreated patients were older and had a higher prevalence of other concurrent autoimmune disease than treated patients. Furthermore, they had lower aminotransferase levels, better-preserved liver function, and a lower prevalence of cirrhosis and hepatic decompensation. In contrast, treated patients more frequently showed histological findings of inflammation and advanced fibrosis. However, the risk of HCC did not differ significantly between both subgroups. Notably, patients with cirrhosis or hepatic decompensation at the time of AIH diagnosis had a significantly higher incidence of HCC and LT-free mortality compared to those without these conditions. Treatment efficacy varied based on the IAIHG response criteria endpoints, with IRs exhibiting a higher annual incidence rate of HCC and LT-free mortality compared with CBRs, particularly demonstrating statistical significance for LT-free mortality.

A surveillance strategy for HCC in patients with AlH is challenging to develop due to the rarity of AlH and its heterogeneity across age, sex, and ethnicity. Although international guidelines recommend surveillance for high-risk patients with an annual incidence of HCC risk ≥1.5%, the incidence of HCC in AlH is low and varies across studies. <sup>10,12</sup> Colapietro *et al.* reported that the incidence of HCC in European patients with AlH was extremely low, even after the development of

cirrhosis during the study period. 15 Given that cirrhosis is a crucial risk factor for HCC, the continued low incidence of HCC despite the development of cirrhosis during the study period indicates that strict HCC surveillance in patients with AIH cannot be made mandatory. Compared to the findings of Colapietro et al., the incidence of HCC in patients with AIH in our study was much higher (4.29/1,000 PYs vs. 1.44/1,000 PYs). We suspect that this difference may be due to heterogeneity among the study populations. Colapietro et al.'s study mainly focused on Western patients with AIH, and the incidence of HCC in Western populations is known to be lower compared to that in Asian populations. 10,15 The patients in our study had a higher prevalence of cirrhosis at diagnosis (43.6% vs. 20.5%) and a higher median age (57.7 years vs. 46 years) compared with those of Colapietro et al.'s study. Considering that cirrhosis and older age are independent risk factors for HCC, heterogeneity in baseline characteristics across ethnicities could influence variations in HCC incidence. 11,23

In line with previous studies, <sup>10,24</sup> cirrhosis emerged as the predominant risk factor for HCC in our study, with an annual incidence of 10.1/1,000 PYs. This is comparable to the pooled incidence reported in previous studies of patients with AlH and cirrhosis, which was 10.07/1,000 PYs. <sup>10</sup> Our finding suggests that strict HCC surveillance may not be essential for Asian patients with AlH, even in the presence of concurrent cirrhosis at the time of diagnosis. However, it is important to stratify risk categories and closely monitor patients with cirrhosis at the time of AlH diagnosis. As the number of LT donors is limited in Asian countries, HCC surveillance is recommended for this

<sup>&</sup>lt;sup>a</sup>Hepatic decompensation was defined as a composite of hepatic encephalopathy, ascites, variceal bleeding, and spontaneous bacterial peritonitis that occurred within 3 months before or after AIH diagnosis.

<sup>&</sup>lt;sup>b</sup>Of 83 patients with negativity of ANA, 16 with missing values were involved.

<sup>&</sup>lt;sup>c</sup>Of 745 patients with negativity of AMA, 33 with missing values were involved.

<sup>&</sup>lt;sup>d</sup>Of 704 patients with negativity of SMA, 66 with missing values were involved.

eOf 654 nondrinkers, 16 with missing values were involved.

category of patients. Compared with previous research, our study identified differences in the predictive factors associated with HCC risk. Although our results suggest a potential association between male sex and an increased risk of HCC, this association did not reach statistical significance. These results differ from studies conducted in the United States, the United Kingdom, and Italy, which reported a more pronounced gender-based risk difference for developing HCC.25-27 This discrepancy may be explained by the higher proportion of female patients compared with male patients in our study. Additionally, obesity was not identified as a significant risk factor for HCC development in AlH in our study. 15,25 In Asian populations, obesity is defined as a BMI of ≥25 kg/m<sup>2</sup>, which is lower than the threshold of ≥30 kg/m<sup>2</sup> used in Western populations.<sup>28</sup> The proportion of patients classified as obese based on the Asian criteria was relatively low (31.9%), and this remained markedly lower than that in previous Western studies even when applying Western criteria (6.3% vs. 13.7% in Colapietro et al.'s study). This suggests that the synergistic effect of steatotic liver disease on tumorigenesis in patients with AIH may be less pronounced in our study population.

Interestingly, consistent with previous external validation studies, our investigation showed that CBRs had a lower incidence of HCC and improved LT-free survival compared to IRs. <sup>21,29</sup> Therefore, more cautious surveillance is necessary for patients with AIH undergoing treatment, particularly those classified as IRs. However, in our study, the difference in HCC incidence between the two groups was not statistically significant, likely due to the shorter median follow-up period and the higher prevalence of cirrhosis at diagnosis compared with previous studies. <sup>21,29</sup>

Our biopsy-proven AIH cohort included 24.0% untreated patients; however, because it was a retrospective, multicenter study, the justifications for not administering immunosuppressive medication were not uniformly recorded. However, differences in clinical and histologic characteristics between the two groups may determine the rationale for treatment choices. At baseline, patients in the untreated group were typically older, more likely to exhibit concurrent autoimmune diseases and variant syndromes, had milder biochemical activity, and demonstrated better-preserved liver function. Additionally, they experienced reduced incidences of histological features such as inflammation and advanced fibrosis, indicating that several patients may have experienced a milder form of AIH, for whom clinicians might have opted for a more conservative approach with close monitoring rather than promptly initiating immunosuppressive therapy. This represents the diversity in real-world management strategies, particularly when histological or biochemical severity may not be obvious enough to necessitate treatment at presentation. Of note, their long-term outcomes, including HCC and LT-free survival, were not worse than those of treated patients, suggesting that their disease might have been less progressive at baseline. At present, the definition and treatment approach for mild AIH are not yet well established and require further investigation.

To the best of our knowledge, this is the first study to evaluate the incidence of HCC in patients with AIH in South Korea, using a large-sized multicentric cohort with a longer

duration of follow-up compared with other studies. The higher prevalence of HCC observed in our study may have contributed to increased statistical power. However, our study has several limitations. First, its retrospective design may introduce selection bias. We attempted to mitigate this by using a large multicentric cohort and employing multivariate Fine-Gray regression modeling. Second, incomplete medical records limited data on alcohol consumption, variant syndrome subtypes, and AIH relapses, preventing detailed analysis of their impact on HCC risk and LT-free survival. The small number of patients with variant syndrome, particularly AIH-primary sclerosing cholangitis, further restricted statistical evaluation. As a result, we analyzed variant syndrome as a single variable rather than stratifying by subtype. Despite these limitations, our findings align with prior epidemiologic studies on AIH-primary biliary cirrhosis and AIH-primary sclerosing cholangitis prevalence. 9,30 Contextually, the limited assessment of longitudinal changes in liver stiffness measurement (LSM at diagnosis and during follow-up) impeded us from thoroughly analyzing the relationship between clinically significant portal hypertension (CSPH) and HCC risk. Assessing the association between CSPH and HCC risk could have added valuable information. However, LSM, a key criterion for CSPH, was often unavailable or potentially overestimated at diagnosis due to hepatic inflammation. When excluding LSM, the definition of CSPH and cirrhosis applied in this study largely overlapped in our cohort, limiting separate analysis. This issue was further compounded by the lack of standardized guidelines for cirrhosis surveillance using FibroScan in patients with AIH. Further studies are needed to clarify this association in patients with AIH. Third, our study results showed that IRs tended to have a higher risk of HCC development compared to CBRs. However, because there were only seven HCC cases, it was difficult to observe a statistically significant difference between the two treatment response groups. Fourth, because our study centers are tertiary referral hospitals specializing in hepatology, our findings may not fully generalize to all patients with AIH. In South Korea, most AIH cases are diagnosed at tertiary hospitals due to limited availability of autoantibody testing and liver biopsy in primary care settings. Patients meeting AIH criteria are registered in the RID registry, with all diagnostic and treatment costs reimbursed. Despite this limitation, our results are consistent with prior nationwide studies supporting the validity of our findings. 10,18 Finally, we could not assess the impact of concomitant metabolic dysfunction-associated steatotic liver disease because of incomplete data on hepatic steatosis and key cardiometabolic risk factors (e.g. lipid profiles), which may influence long-term outcomes in AIH.

In conclusion, our study demonstrates that the incidence of HCC in patients with AIH in South Korea was higher than that recently reported in a European study. Although the incidence of HCC in patients with AIH is lower than in those with chronic hepatitis B or C, a personalized strategy to prevent development of HCC is recommended for high-risk patients, particularly with concomitant cirrhosis and hepatic decompensation. Furthermore, IRs should be closely monitored for HCC surveillance. Further prospective studies are warranted to better stratify the risk of HCC.

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#### **Abbreviations**

ANA, antinuclear antibody; AHR, adjusted hazard ratio; AlH, autoimmune hepatitis; CBR, complete biochemical responder; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HR, hazard ratio; IAIHG, International Autoimmune Hepatitis Group; IR, insufficient responders; LSM, liver stiffness measurement; LT, liver transplant(ation); PY, person-year; RID, rare intractable disease; SHR, subdistribution hazard ratio.

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#### Conflict of interest

J Choi has served as a speaker and an advisory committee member for Gilead Sciences and received research funding from Gilead Sciences. There are no other disclosures to declare

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

#### **Authors' contributions**

J Choi and HW Lee are the guarantors for this article. All authors had full access to the data used in this study and take responsibility for its integrity and the accuracy of the analyses. J Yang, SY Yim, K Kim, HW Lee, and J Choi were responsible for study conception and design; data acquisition, analysis, and interpretation; and drafting the manuscript. J Yang and J Choi performed the statistical analyses. J Yang, SY Yim, K Kim, HW Lee, and J Choi were responsible for critical revisions of the manuscript. All authors read and approved the final version of the manuscript.

### **Data availability**

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

### Ethics approval and patient consent

This study received ethical approval from the Institutional Review Board (No. 2023-1540). Informed consent was waived owing to the retrospective nature of the study.

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Not applicable.

### Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101524.

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Author names in bold designate shared co-first authorship

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