

University of Groningen

Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1

Dutch Autoimmune Hepatitis Study G; Biewenga, Maaïke; Verhelst, Xavier P. D. M. J.; Baven-Pronk, Martine A. M. C.; Putter, Hein; van den Berg, Aad P.; van Nieuwkerk, Karin C. M. J.; van Buuren, Henk R.; Bouma, Gerd; de Boer, Ynte S.

Published in:
United European Gastroenterology Journal

DOI:
[10.1002/ueg2.12112](https://doi.org/10.1002/ueg2.12112)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Dutch Autoimmune Hepatitis Study G, Biewenga, M., Verhelst, X. P. D. M. J., Baven-Pronk, M. A. M. C., Putter, H., van den Berg, A. P., van Nieuwkerk, K. C. M. J., van Buuren, H. R., Bouma, G., de Boer, Y. S., Simoen, C., Colle, I., Schouten, J., Sermon, F., van Steenkiste, C., van Vlierberghe, H., van der Meer, A. J., Nevens, F., & van Hoek, B. (2021). Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1. *United European Gastroenterology Journal*, 9(6), 662-671. <https://doi.org/10.1002/ueg2.12112>

Copyright




Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1

Maaïke Biewenga¹  | Xavier P.D.M.J. Verhelst²  | Martine A.M.C. Baven-Prong³ | Hein Putter⁴ | Aad P. van den Berg⁵ | Karin C.M.J. van Nieuwkerk⁶ | Henk R. van Buuren⁷ | Gerd Bouma⁶ | Ynte S. de Boer⁶ | Cedric Simoen² | Isabelle Colle⁸ | Jeffrey Schouten⁹ | Filip Sermon¹⁰ | Christophe van Steenkiste^{11,12} | Hans van Vlierberghe² | Adriaan J. van der Meer⁷ | Frederik Nevens¹³ | Bart van Hoek¹  | Dutch Autoimmune Hepatitis Study Group

¹Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

²Department of Gastroenterology and Hepatology, UZ Ghent, Ghent, Belgium

³Department of Gastroenterology and Hepatology, Green Heart Hospital, Gouda, the Netherlands

⁴Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands

⁵Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, the Netherlands

⁶Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands

⁷Department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, the Netherlands

⁸Department of Gastroenterology and Hepatology, ASZ Aalst, Aalst, Belgium

⁹Department of Gastroenterology and Hepatology, AZ Nikolaas, Sint-Niklaas, Belgium

¹⁰Department of Gastroenterology and Hepatology, OLV Aalst, Aalst, Belgium

¹¹Department of Gastroenterology and Hepatology, AZ Maria Middelaes Ghent, Ghent, Belgium

¹²Department of Gastroenterology and Hepatology, University Hospital Antwerp, Antwerp, Belgium

¹³Department of Gastroenterology and Hepatology, UZ Leuven, Leuven, Belgium

Correspondence

Bart van Hoek, Department of Gastroenterology and Hepatology, C4-P Leiden University Medical Center PO Box 9600, 2300 RC Leiden, the Netherlands. Email: B.van_Hoek@lumc.nl

Funding information

Zambon Pharma, Grant/Award Number: Unrestricted grant

Abstract

Background: No prognostic score is currently available for long-term survival in autoimmune hepatitis (AIH) patients.

Objective: The aim of this study was to develop and validate such a prognostic score for AIH patients at diagnosis.

Methods: The prognostic score was developed using uni- & multivariate Cox regression in a 4-center Dutch cohort and validated in an independent 6-center Belgian cohort.

Results: In the derivation cohort of 396 patients 19 liver transplantations (LTs) and 51 deaths occurred (median follow-up 118 months; interquartile range 60–202 months). In multivariate analysis age (hazard ratio [HR] 1.045; $p < 0.001$), non-caucasian ethnicity (HR 1.897; $p = 0.045$), cirrhosis (HR 3.266; $p < 0.001$) and

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. UEG Journal published by Wiley Periodicals LLC. on behalf of United European Gastroenterology.

alanine aminotransferase level (HR 0.725; $p = 0.003$) were significant independent predictors for mortality or LT (C-statistic 0.827; 95% CI 0.790–0.864). In the validation cohort of 408 patients death or LT occurred in 78 patients during a median follow-up of 74 months (interquartile range: 25–142 months). Predicted 5-year event rate did not differ from observed event rate (high risk group 21.5% vs. 15.7% (95% CI: 6.3%–24.2%); moderate risk group 5.8% versus 4.3% (95% CI: 0.0%–9.1%); low risk group 1.9% versus 5.4% (95% CI: 0.0%–11.4%); C-statistic 0.744 [95% CI 0.644–0.844]).

Conclusions: A Dutch-Belgian prognostic score for long-term transplant-free survival in AIH patients at diagnosis was developed and validated.

KEYWORDS

AIH, autoimmune hepatitis, autoimmune liver disease, liver transplantation, long-term survival, mortality, prognostic score, risk stratification, transplant-free survival, validation

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver characterized by interface hepatitis, presence of serum autoantibodies and raised serum immunoglobulin G (IgG).¹ Introduction of corticosteroid treatment in the 70's has greatly improved prognosis.^{2–4} With corticosteroid and thiopurine treatment 10 year liver transplantation (LT) free survival is 80–96%.^{5–8}

Older age has been identified as an important risk factor for LT, liver related mortality and overall mortality by several,^{5,9–12} but not all studies.¹³ The severity and prognosis of AIH also differs between ethnic populations as decreased survival has been reported in patients with Asian, African or Caribbean ethnicity as compared to Caucasian patients.^{14–16} In 20%–30% of the patients cirrhosis is present at diagnosis.^{10,16} Cirrhosis at diagnosis is associated with worse survival in most,^{5,7,9,12,13,16,17} but not in all studies.^{18–20} In a Dutch study, in treated, non-cirrhotic AIH patients life expectancy was comparable to the general population.²¹

Although these risk factors have been reported with univariate analysis, no multivariate risk score predicting long-term survival is currently available for AIH. Risk scores predicting long-term survival are useful tools for risk stratification in the context of clinical trials, to personalize treatment and to determine risk of LT and mortality in individual patients to aid with timely referral to transplant centers.^{22,23} The aim of this study was to develop and validate a risk score for long-term LT-free survival at diagnosis of AIH.

Key Summary

What is known?

- Cirrhosis, ethnicity and age have been univariately associated with worse survival in patients with autoimmune hepatitis (AIH).
- No prognostic models are available for patients with AIH.

What is new here?

- A prognostic model consisting of age, ethnicity, alanine aminotransferase and cirrhosis at diagnosis was developed.
- This model can predict survival free of liver transplantation accurately in an independent cohort.
- This model can be used for risk stratification in clinical trials and aid in timely referral to a transplant center if necessary.

METHODS

All patients with probable or definite AIH type 1 according to the revised pre-treatment International AIH Group (IAIHG) criteria from four academic centers in the Netherlands were eligible for inclusion in the derivation cohort.²⁴ Since August 2006 all previously known patients were retrospectively and new patients are prospectively included in the national database of the Dutch

Autoimmune Hepatitis Study Group. The study protocol was in accordance with the ethical standards of the medical ethical committee of the Leiden University Medical Center and with the 1975 Declaration of Helsinki as revised in 2008. Informed consent was obtained from each patient at outpatient clinic visit. All patients were above 18 years of age at time of informed consent. Data regarding laboratory values before treatment, AIH revised score, initial treatment and occurrence of LT and death during follow-up were obtained from the national database and chart review. Patients with AIH type 2, defined by the presence of anti liver kidney microsomal type 1 antibodies, patients with AIH-primary biliary cholangitis (AIH-PBC) and AIH-primary sclerosing cholangitis (AIH-PSC) variant syndromes were excluded. AIH-PBC was defined as clinical diagnosis—consisting of antimitochondrial antibodies, cholestasis or PBC features on liver biopsy—in combination with ursodeoxycholic acid treatment. AIH-PSC was defined as clinical diagnosis in combination with features of PSC on bile duct imaging or onion ring fibrosis.

AIH patients from two academic centers and four general hospitals in Belgium were included in the validation cohort; variables needed for the validation analyses were collected in this cohort.

Response to treatment was defined according to the European Association for the Study of the Liver guidelines: complete biochemical remission was defined as normalization of aminotransferases and IgG and partial remission as improvement of aminotransferases and IgG without normalization.²⁵

Presence of cirrhosis at diagnosis was based on liver histology. If no liver biopsy was performed, presence of cirrhosis was determined with ultrasound, CT or MRI scan. Decompensated cirrhosis was defined as cirrhosis with presence of ascites, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome or hepatocellular carcinoma (HCC).²⁶

Follow-up time was defined as the time from diagnosis until last visit to the outpatient clinic, LT or death. LT-free survival was chosen as primary outcome parameter and was defined as survival free of LT. Liver-related survival was defined as survival free of LT and liver-related death. Liver-related death included death related to acute liver failure, complications of (decompensated) cirrhosis and HCC. In liver-related survival analysis patients who died from other causes were censored.

As treatment response is associated with a better survival, a landmark analysis at 6 and 12 months was performed to analyze the correlation of the baseline predictors corrected for the effect of treatment response.²⁷ In a landmark analysis follow-up starts at the landmark and all patients with an event or end of follow-up before the landmark are excluded. First complete biochemical remission within 6 or 12 months was used to evaluate treatment response.

STATISTICAL ANALYSIS

Statistical analysis were performed in IBM SPSS 25.0 and R. For statistical analysis ANOVA, Fisher's exact test, Chi square test, Mann Whitney *U* test and independent samples *T* test were used where appropriate. Missing data were imputed in the derivation cohort using fully conditional specification, creating 10 imputed data sets. Imputation was used for continuous biochemical variables and outcomes were included in the imputation model.

Biochemical parameters with different upper or lower limits of normal in the participating centers, were corrected according to the upper or lower limit of normal. Logarithmic transformation was used in case of not normal distribution. Predictors of survival were analyzed by Kaplan Meier (KM) survival analysis with log-rank test, univariate and multivariate Cox regression analysis. Variables with $p < 0.10$ were included in multivariate analysis with a maximum of one variable per 10 events. As co-linearity was expected between cirrhosis, platelets, international normalized ratio (INR), PT and albumin, it was decided to only include cirrhosis in the multivariate analysis. Between aspartate aminotransferase (AST) and alanine aminotransferase (ALT) also co-linearity was expected, it was decided to include the most significant variable in univariate analysis in the multivariate analysis. Discrimination of the model was assessed by the calculated C-statistic value. Multivariate analysis were repeated after excluding patients with decompensated cirrhosis and patients with acute severe AIH (INR >1.5 and bilirubine >45 $\mu\text{mol/L}$ at diagnosis).²⁸ Calibration of the model was assessed by comparing predicted and observed survival. Patients were divided in three risk groups of equal size (high, moderate and low risk) based on the prognostic index. Discrimination and calibration was done in an independent validation cohort. p -value <0.05 was considered significant.

RESULTS

Baseline characteristics of the 396 AIH patients included in the derivation cohort are shown in Table 1. Median follow-up was 118 months (interquartile range [IQR]: 60–202). Liver biopsy was performed in 354 (89%) patients at diagnosis. Cirrhosis was present in 124 (31%) patients at diagnosis and was classified as compensated in 87 (22%) patients and decompensated in 37 (9%) patients. Treatment was started in all but 12 (3%) patients. First-line treatment consisted of prednisolone in 359 (91%) patients, budesonide in 17 (4%) patients and azathioprine in 318 (80%) patients. Mycophenolate mofetil, mercaptopurine (6-MP) and thioguanine (6-TG) were given as first-line treatment to three, three and one patient respectively.

During follow-up 314 (80%) patients reached complete biochemical remission in a median of 10 months (IQR: 4–24 months).

During follow-up 19 patients received LT, 18 patients died from liver-related causes, 30 patients died from other causes and in three

TABLE 1 Baseline characteristics of derivation and validation cohort

	Derivation cohort	n = 396	Validation cohort	n = 408
Female (%)	303 (77%)	396	303 (74%)	408
Median age in years (range)	46 (5–84)	396	51 (5–86)	401
Caucasian (%)	352 (89%)	396	387 (95%)	406
Cirrhosis status at diagnosis		394		333
No cirrhosis (%)	270 (69%)		256 (77%)	
Cirrhosis	124 (31%)		77 (23%)	
Compensated (%)	87 (22%)			
Decompensated (%)	37 (9%)			
Concurrent autoimmune disease (%)	93 (24%)	396	-	
Alcohol use > 60 g/day (%)	6 (1.5%)	396	-	
HLA-DR3 positive (%)	103 (61%)	168	-	
HLA-DR4 positive (%)	43 (26%)	168	-	
Median AIH revised score (range)	16 (10–23)	385	-	
Blood tests (median [range])				
Serum IgG level in g/l	22 (6.7–92)	371	-	
Anti-SMA positive (%)	220 (64%)	346	-	
ANA positive (%)	244 (69%)	355	-	
Anti-SLA positive (%)	21 (6%)	332	-	
Bilirubin in $\mu\text{mol/L}$	38 (3–596)	244	29 (3–787)	273
ALT in IU/l	404 (13–3478)	359	359 (11–4524)	294
AST in IU/l	462 (19–4388)	253	294 (19–4977)	294
AP in IU/l	150 (27–2197)	355	-	
GGT in IU/l	152 (2–1317)	245	-	
Albumin in g/l	38 (13–53)	298	-	
Creatinine in $\mu\text{mol/L}$	71 (27–561)	302	-	
Platelets in $\times 10^9/l$	192 (37–649)	229	-	
PT in seconds	14.6 (9.7–35.2)	217	-	
INR	1.1 (0.9–4.3)	154	-	

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-SLA, anti soluble liver antigen; anti-SMA, anti smooth muscle antigen; AST, aspartate aminotransferase; IgG, immunoglobulin G; INR, international normalized ratio.

patients the cause of death was unknown. The 10 year liver-related survival rate was 91% (95% CI 88%–94%), the LT-free survival rate was 86% (95% CI 82%–90%).

Univariate analysis of baseline predictors

In univariate analysis older age (hazard ratio [HR] 1.02; $p = 0.018$ and HR 1.05; $p < 0.001$), non-caucasian ethnicity (HR 2.83; $p < 0.001$ and HR 2.18; $p = 0.012$) and cirrhosis (HR 11.20; $p < 0.001$ and HR 3.31; $p < 0.001$) were significantly associated with decreased liver-related survival and LT-free survival respectively. Higher ALT (HR 0.57; $p < 0.001$ and HR 0.61; $p < 0.001$), AST (HR 0.66; $p = 0.022$ and HR 0.72; $p = 0.016$), albumin (HR

0.86; $p < 0.001$ and HR 0.92; $p < 0.001$) and platelets (HR 0.99; $p < 0.001$ and HR 0.99; $p = 0.001$) at diagnosis were associated with increased liver-related survival and LT-free survival respectively. In addition to these variables, revised AIH score (HR 0.88; $p = 0.014$) and INR (HR 2.11; $p = 0.048$) were associated with liver-related mortality or LT but not with overall mortality or LT (Table 2).

As no events occurred in patients positive for anti-SLA and in patients positive for HLA-DR4, further statistical analysis of these factors was not possible.

Median 10 year LT-free survival was 94% (95% CI 90%–97%), 79% (95% CI 69%–88%) and 44% (95% CI 26%–63%) in patients without cirrhosis, compensated cirrhosis and decompensated cirrhosis respectively ($p < 0.001$; Figure 1).

TABLE 2 Univariate Cox regression of prognostic factors for liver-related mortality and liver transplantation and overall mortality and liver transplantation in the derivation cohort

	Liver-related mortality HR (95% CI)	p-value	Overall mortality HR (95% CI)	p-value
Female gender	1.02 (0.47–2.24)	0.96	0.85 (0.49–1.48)	0.57
Age at diagnosis (years)	1.02 (1.00–1.04)	0.018	1.05 (1.03–1.07)	<0.001
Non-caucasian	2.83 (1.33–6.01)	0.007	2.18 (1.19–3.99)	0.012
Cirrhosis	11.20 (4.93–25.47)	<0.001	3.31 (2.07–5.29)	<0.001
Compensated cirrhosis	11.07 (4.08–30.03)	<0.001	2.42 (1.39–4.23)	0.002
Decompensated cirrhosis	31.72 (11.47–87.75)	<0.001	8.14 (4.57–14.52)	<0.001
Concurrent autoimmune disease	1.26 (0.56–2.88)	0.58	1.40 (0.83–2.35)	0.20
HLA-DR3	0.91 (0.16–5.25)	0.53	0.84 (0.32–2.19)	0.72
Revised AIH score	0.88 (0.79–0.98)	0.014	0.95 (0.88–1.02)	0.14
Anti-SMA	0.83 (0.39–1.74)	0.62	0.93 (0.55–1.56)	0.78
ANA	1.25 (0.60–2.57)	0.55	0.89 (0.51–1.55)	0.69
IgG	1.01 (0.98–1.03)	0.61	1.00 (0.98–1.02)	0.84
Ln bilirubin	1.38 (0.97–1.96)	0.070	0.93 (0.72–1.21)	0.61
Ln ALT/ULN	0.57 (0.43–0.76)	<0.001	0.61 (0.49–0.75)	<0.001
Ln AST/ULN	0.66 (0.46–0.94)	0.022	0.72 (0.55–0.94)	0.016
AP/ULN	1.01 (0.80–1.28)	0.91	0.95 (0.77–1.16)	0.60
GGT/ULN	0.99 (0.89–1.1)	0.83	1.02 (0.95–1.10)	0.53
Albumin	0.86 (0.82–0.91)	<0.001	0.92 (0.89–0.96)	<0.001
Creatinin	0.99 (0.98–1.01)	0.76	1.00 (0.99–1.01)	0.96
Platelets	0.99 (0.98–0.99)	<0.001	0.99 (0.99–1.00)	0.001
INR	2.11 (1.01–4.42)	0.048	1.39 (0.65–2.95)	0.39

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-SMA, smooth muscle antibody; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HLA, human leukocyte antigen; HR, hazard ratio; IgG, immunoglobulin G; INR, international normalized ratio; ULN, upper limit of normal.

Multivariate analysis of baseline predictors

Age at diagnosis, ethnicity, cirrhosis and ALT level at diagnosis were included in the multivariate analysis of liver-related survival and LT-free survival. Because of expected co-linearity albumin, platelets and AST were not included. All included variables remained significantly associated with liver-related and LT-free survival (Table 3).

The C-statistic for LT-free survival of the final model was 0.827 (95% CI 0.790–0.864). After exclusion of patients with decompensated cirrhosis the C-statistic for LT-free survival was 0.823 (95% CI 0.773–0.873). Exclusion of 19 patients with acute severe AIH resulted in similar results (Table S1).

The following formula can be used to calculate the prognostic index for LT-free survival:

$$\text{Prognostic index} = 0.044 \times \text{Age} + 0.640 \times \text{Ethnicity} + 1.184 \times \text{Cirrhosis} - 0.322 \times \ln(\text{ALT/upper limit of normal [ULN]})$$

- Age: age in years at diagnosis of AIH
- Ethnicity: non-caucasian = 1; caucasian = 0;

- Cirrhosis: cirrhosis = 1, no cirrhosis = 0
- ALT/ULN: ALT level at diagnosis divided by the upper reference limit of ALT in IU/L

The baseline hazard (prognostic index = 0) for LT or mortality was 0.002468, 0.01030 and 0.01953 for 1, 5 and 10 year survival respectively.

Figure 2 illustrates the link between the prognostic index and the predicted 5-year survival. The predicted 1, 5 and 10 year survival for individual patients can be calculated with the following formula: survival probability (t) = 100 × (e^{-baseline hazard (t) × Y}) with Y = e^{prognostic index}.

Model validation

Baseline characteristics of the 408 patients included in the validation cohort are shown in Table 1. In 20 patients LT and in 58 patients death occurred in a median follow-up time of 74 months (IQR:

25–142 months). Discrimination of the prognostic index as calculated with the C-statistic was 0.744 (95% CI 0.644–0.844). Based on prognostic index patients were divided in three equal sized groups: high risk with a prognostic index >2.18, medium risk with a prognostic index 1.24–2.18 and low risk with a prognostic index of <1.24.

In the high risk group 1 year survival rate was 91.5%, 5 year survival rate was 84.3%, 10 year survival rate was 58.6% and median survival was 152 months. In the moderate risk group the one, five and 10 year survival rate were 98.9%, 95.7% and 93% and median survival was more than 250 months. In the low risk group the 1, 5 and 10 year survival was 98.8%, 94.6% and 90.6% and median survival was more

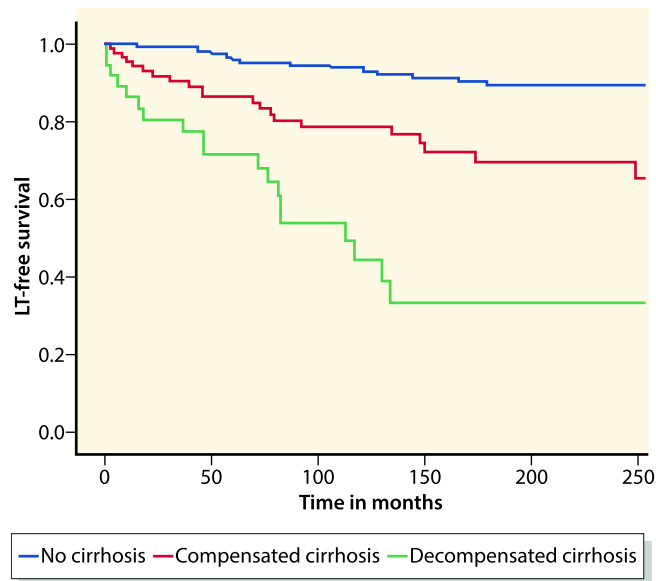


FIGURE 1 Autoimmune hepatitis patients without cirrhosis had a significantly better survival than patients with compensated or decompensated cirrhosis at diagnosis ($p < 0.001$ for both). Patients with decompensated cirrhosis had a worse survival compared to patients with compensated cirrhosis ($p < 0.001$)

TABLE 3 Multivariate Cox Regression of prognostic factors for liver-related mortality and liver transplantation and overall mortality and liver transplantation in the derivation cohort

	Hazard ratio (CI 95%)	Ln hazard ratio	p-value
Liver-related mortality			
Age	1.02 (1.01–1.04)	0.023	0.008
Non-caucasian	2.63 (1.23–5.67)	0.968	0.013
Cirrhosis	10.57 (4.61–24.22)	2.358	<0.001
Ln ALT corrected for ULN	0.67 (0.49–0.91)	–0.404	0.010
Overall mortality			
Age	1.05 (1.03–1.06)	0.044	<0.001
Non-caucasian	1.90 (1.02–3.54)	0.640	0.045
Cirrhosis	3.27 (2.02–5.27)	1.184	<0.001
Ln ALT corrected for ULN	0.73 (0.59–0.90)	–0.322	0.003

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; ULN, upper limit of normal.

than 250 months. Predicted and observed survival for all risk groups is shown in Figure 3 and the calibration plot is shown in Figure S1.

Predicted 5-year event rate was not significantly different from observed event rate in all three risk groups (high risk group 21.5% vs. 15.7% [CI: 6.3%–24.2%]; moderate risk group 5.8% versus 4.3% [CI: 0.0%–9.1%]; low risk group 1.9% versus 5.4% [CI: 0.0%–11.4%]).

Treatment response

In the landmark analysis, performed in the derivation cohort, 21 patients were excluded due to LT in five patients, mortality in four patients and follow-up less than 12 months in 12 patients. Complete biochemical remission within 12 months was added to the baseline predictors in multivariate analysis (Table 4). Complete biochemical remission within 12 months was associated with a better LT-free survival (HR 0.33; $p = 0.002$). Corrected for treatment response, ethnicity was not significantly associated with decreased LT-free survival anymore although the HR remained quite similar (HR 1.66; $p = 0.145$ vs. HR 1.90; $p = 0.045$ in the baseline model). This difference in HR would change the factor for ethnicity in the model slightly from 0.64 to 0.51. All other baseline variables remained significant when corrected for treatment response. Analysis at 6 months resulted in similar results (Table S2).

DISCUSSION

In this study the first risk score for prediction of long-term LT-free survival was developed and validated in large multicenter cohorts of patients with AIH type 1 at diagnosis.

Using univariate analysis, four simple, readily available clinical variables were identified: age, ethnicity, cirrhosis and ALT levels. These variables have all been associated with mortality or LT in univariate analysis in previous studies, but no multivariate analysis had been

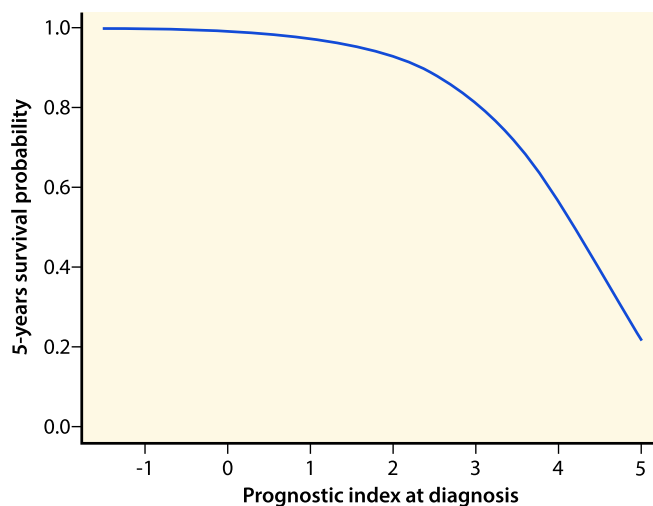


FIGURE 2 Five-year survival probability based on the prognostic index at diagnosis

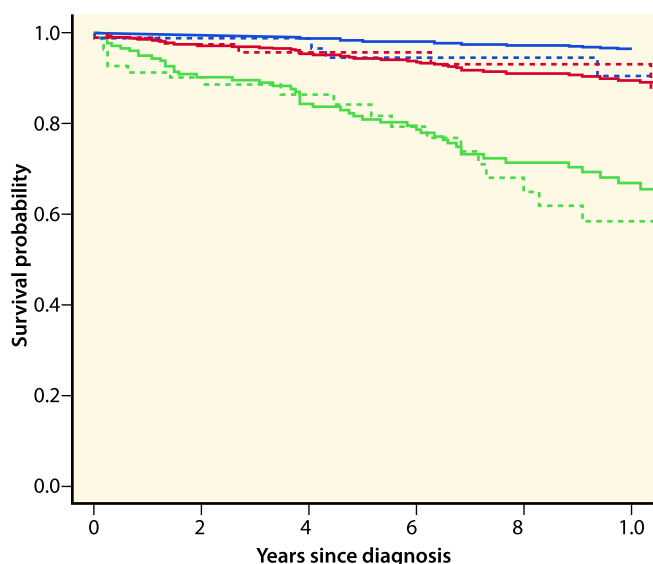


FIGURE 3 Survival probability in the validation cohort of the high risk (green), medium risk (red) and low risk (black). The solid line is the calculated survival based on the prognostic index at diagnosis, the dashed line is the observed survival

performed previously. In multivariate analysis all of these factors were independent predictors of mortality or LT. The predictive value of the score was satisfactory, as reflected by a C-statistic of 0.827. After excluding patients with decompensated cirrhosis or acute severe AIH the performance of the risk score remained similar. Next, the risk score was validated in an independent large cohort with good discrimination (C-statistic of 0.744) and good calibration. Finally the effect of treatment response in relation to the score was analyzed.

This risk score can be used for risk stratification in clinical trials and may be useful in the management and counseling of patients. The risk score seems especially valuable for identification of high risk patients at diagnosis. The score predicts the risk of overall mortality and LT. This outcome parameter was chosen for the model since non-

liver related mortality can still be related to AIH. For instance, long-term immunosuppressive therapy increases the risk of infections and cancer, while steroid treatment can cause diabetes mellitus and weight gain which are risk factors for cardiovascular disease. Also in some cases, it can be difficult to determine if mortality is related to the liver. Moreover, the higher event-rate for overall mortality and LT increased the robustness of the model.

All variables included in the score have previously been associated with mortality or LT in univariate analysis in other studies. Age at diagnosis of AIH has been identified previously as an important risk factor for overall mortality.^{5,9} For liver-related mortality older age has also been reported as a risk factor.¹⁰⁻¹² One study did not find a significant effect of age on liver-related mortality, but the HR was comparable with the HR found in the current study.¹³ Elderly patients can have more frailty which could increase the risk of overall or even liver-related death.

In this study non-caucasian patients had a higher risk of LT and death. Previous small studies showed that AIH patients with Asian or African ethnicity have a worse prognosis.^{14,15} Recently a large study was published confirming these findings for patients with African or Caribbean ethnicity.¹⁶ This could relate to genetic factors influencing severity of AIH or response to treatment, but could also relate to socio-economic, environmental or cultural factors, for instance influencing access or adherence to treatment. More research into this important finding is needed.

Cirrhosis is present in 20%–30% of AIH patients at diagnosis^{9,10,16,29} and has previously been identified as an important predictor for worse long-term survival,^{5,7,9,12,13,16,17} although not in all studies.¹⁸⁻²⁰ This study confirms the important prognostic significance of cirrhosis for long-term survival in AIH patients.

High levels of aminotransferases at diagnosis have previously been associated in univariate analysis with better survival of AIH patients.^{9,30} Patients with high aminotransferases had more often symptoms and less often decompensated cirrhosis.³⁰ The reason for these relationships is not entirely clear, but an increased rate of symptoms could lead to earlier diagnosis and treatment.³⁰ Alternatively, patients with high transaminases could have a better response to treatment.⁹

Sensitivity analysis were performed by excluding patients with decompensated cirrhosis and acute severe AIH. In this study a different impact of compensated versus decompensated cirrhosis was shown for patients with AIH: the 10 year survival rate of AIH patients with decompensated cirrhosis was 44% as compared to 79% for patients with compensated cirrhosis. In a cohort of cirrhotic patients with mixed aetiologies -mainly hepatitis B, C and alcohol induced cirrhosis- 10 year survival rates of 50% and 35% were reported for compensated and decompensated cirrhosis.³¹ The long term prognosis of AIH patients with (decompensated) cirrhosis is remarkably better than for patients with other causes of cirrhosis. Immunosuppressive medication reduces liver inflammation and prevents further damage and progression of liver disease, resulting in a better survival rate. After excluding patients with decompensated cirrhosis, the predictive value of the model remained similar (C-statistic of 0.823). Patients presenting with acute severe AIH have also a decreased survival

TABLE 4 Multivariate Cox Regression of baseline prognostic factors for treatment response using a landmark-analysis at 12 months in the derivation cohort

	Hazard ratio (CI 95%)	Ln hazard ratio	p-value
Liver related mortality			
Age	1.02 (0.99–1.04)	0.020	0.061
Non-caucasian	2.66 (1.13–6.27)	0.977	0.026
Cirrhosis	7.44 (2.86–19.37)	2.006	<0.001
Ln ALT corrected for ULN	0.52 (0.37–0.75)	−0.646	<0.001
Biochemical remission	0.28 (0.08–0.95)	−1.286	0.040
Overall mortality			
Age	1.05 (1.03–1.06)	0.045	<0.001
Non-caucasian	1.66 (0.84–3.29)	0.507	0.145
Cirrhosis	2.30 (1.33–3.99)	0.833	0.003
Ln ALT corrected for ULN	0.69 (0.55–0.88)	−0.365	0.003
Biochemical remission	0.33 (0.16–0.67)	−1.125	0.002

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; ULN, upper limit of normal.

compared to AIH patients in general.³² After excluding patients with acute severe AIH, the HR's remained similar.

Besides baseline characteristics, treatment response and biochemical remission have also been associated with a better long term survival^{11–13,33,34} while multiple relapses were associated with a worse survival.¹³ When corrected for treatment response, all variables in the baseline model except ethnicity remained significantly associated with survival. Although ethnicity was not significantly correlated to survival anymore, this might be a power problem as the HR remained quite similar. This shows that the prognostic score at diagnosis is predictive of long-term survival in AIH independent of treatment response which is an additional independent predictor.

HLA-DR 4 has been associated with better survival while HLA-DR3 and anti-SLA were associated with worse outcomes.^{29,35,36} In 170 HLA-DR4 positive patients in the Netherlands no LTs occurred.³⁷ A subset of those 170 patients was included in the current study and with longer follow-up still no events occurred. Although no further statistics could be performed, this confirms the impression that presence of HLA-DR4 is beneficial.

This study had a few limitations: although large cohorts of AIH patients were included, due to the relatively good prognosis of the disease with treatment only a relatively low number of events occurred, limiting the number of variables that could be included in multivariate analysis. Retrospective collection of the data resulted in missing data. Multiple imputation was used to limit the influence of missing data but prospective data collection is better. As patients with AIH type 2 and variant syndromes were excluded, the developed score is only validated in AIH type 1.

In conclusion, this novel Dutch-Belgian AIH survival model consisting of age, ethnicity, cirrhosis and ALT at diagnosis can accurately predict the long-term LT-free survival in AIH patients. This model can be used for early identification of high risk patients at diagnosis, for

risk stratification in clinical trials and for more personalized treatment in the future.

ACKNOWLEDGEMENTS

We thank the other members of the Dutch Auto-Immune Hepatitis Study Group for fruitful discussions regarding the manuscript: J.P.H. Drenth (Radboud UMC Nijmegen); N.M. van Gerven (Rode Kruis ziekenhuis; Beverwijk); U. Beuers (AMC Amsterdam); K.J. van Erpecum (UMCU Utrecht); J.W. den Ouden and A. Bhalla (Hagaziekenhuis den Haag); J.T. Brouwer (Reinier de Graaf Gasthuis Delft); J.M. Vrolijk (Rijnstate hospital Arnhem); G.H. Koek (MUMC, Maastricht); M.M.J. Guichelaar (Medisch Spectrum Twente, Enschede); E.J. van der Wouden (Isala hospital Zwolle); J.J.M van Meyel and L.C. Baak (OLVG, Amsterdam); R.C. Verdonk (St. Antonius Hospital Nieuwegein); M. Klemt-Kropp (Noordwest Ziekenhuisgroep Alkmaar); M.A.M.T. Verhagen (Diakonessenhuis, Utrecht); J. Ph. Kuijvenhoven (Spaarne Gasthuis Haarlem); H.M. de Jonge (Jeroen Bosch ziekenhuis den Bosch); MB was supported by unrestricted grants from Zambon Pharma. No other financial support received for this study.

CONFLICT OF INTEREST

All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Maaïke Biewenga  <https://orcid.org/0000-0002-2797-6164>

Xavier P.D.M.J. Verhelst  <https://orcid.org/0000-0002-2798-5415>

Bart van Hoek  <https://orcid.org/0000-0001-6527-764X>

REFERENCES

- van Gerven NM, de Boer YS, Mulder CJ, van Nieuwkerk CM, Bouma G. Auto immune hepatitis. *World J Gastroenterol.* 2016; 22:4651–61.
- Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med.* 1971;40:159–85.
- Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology.* 1972; 63:820–33.
- Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet.* 1973;1:735–7.
- Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology.* 2005;42:53–62.
- Kanzler S, Lohr H, Gerken G, Galle PR, Lohse AW. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. *Z Gastroenterol.* 2001;39:339–41, 344–8.
- Migita K, Watanabe Y, Jiuchi Y, Nakamura Y, Saito A, Yagura M, et al. Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization-autoimmune hepatitis prospective study). *Liver Int.* 2012;32:837–44.
- Czaja AJ. Global disparities and their implications in the occurrence and outcome of autoimmune hepatitis. *Dig Dis Sci.* 2017; 62:2277–92.
- Werner M, Wallerstedt S, Lindgren S, Almer S, Björnsson E, Bergquist A, et al. Characteristics and long-term outcome of patients with autoimmune hepatitis related to the initial treatment response. *Scand J Gastroenterol.* 2010;45:457–67.
- Baven-Pronk M, Biewenga M, van Silfhout JJ, van den Berg AP, van Buuren HR, Verwer BJ, et al. Role of age in presentation, response to therapy and outcome of autoimmune hepatitis. *Clin Transl Gastroenterol.* 2018;9:165.
- Ngu JH, Geary RB, Frampton CM, Stedman CA. Predictors of poor outcome in patients with ith autoimmune hepatitis: a population-based study. *Hepatology.* 2013;57:2399–406.
- 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;39:985–94.
- 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;140:1980–9.
- Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. *Hepatology.* 2007; 46:1828–35.
- Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. *J Clin Gastroenterol.* 2012;46:155–61.
- deBoer YS, Gerussi A, van den Brand FF, Wong GW, Halliday N, Liberal R, et al. Association between black race and presentation and liver-related outcomes of patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol.* 2019;17(8):1616–1624.
- Ladeira G, Morise S, Fassio E, Ramonet M, Alvarez E, Caglio P, et al. Effect of cirrhosis at baseline on the outcome of type 1 autoimmune hepatitis. *Ann Hepatol.* 2012;11:100–6.
- Floreani A, Niro G, Rosa Rizzotto E, Antoniazzi S, Ferrara F, Carderi I, et al. Type I autoimmune hepatitis: clinical course and outcome in an Italian multicentre study. *Aliment Pharmacol Ther.* 2006;24:1051–7.
- Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology.* 1996; 110:848–57.
- Yoshizawa K, Matsumoto A, Ichijo T, Umemura T, Joshita S, Komatsu M, et al. Long-term outcome of Japanese patients with type 1 autoimmune hepatitis. *Hepatology.* 2012;56:668–76.
- 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(5):940–947.
- de Vries EM, Wang J, Williamson KD, Leeflang MM, Boonstra K, Weersma RK, et al. A novel prognostic model for transplant-free survival in primary sclerosing cholangitis. *Gut.* 2018;67:1864–9.
- Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. *Gastroenterology.* 2015;149:1804–12.
- Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol.* 1999;31:929–38.
- European association for the study of the L. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol.* 2015;63:971–1004.
- D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. *J Hepatol.* 2018;68:563–76.
- Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transpl Int.* 2018;31:125–30.
- Rahim MN, Liberal R, Miquel R, Heaton ND, Heneghan MA. Acute severe autoimmune hepatitis: corticosteroids or liver transplantation? *Liver Transplant.* 2019;25:946–59.
- Kirstein MM, Metzler F, Geiger E, Heinrich E, Hallensleben M, Manns MP, et al. Prediction of short- and long-term outcome in patients with autoimmune hepatitis. *Hepatology.* 2015; 62:1524–35.
- Al-Chalabi T, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Effects of serum aspartate aminotransferase levels in patients with autoimmune hepatitis influence disease course and outcome. *Clin Gastroenterol Hepatol.* 2008;6:1389–95.
- Samonakis DN, Koulentaki M, Coucoutsi C, Augoustaki A, Baritaki C, Digenakis E, et al. Clinical outcomes of compensated and decompensated cirrhosis: a long term study. *World J Hepatol.* 2014;6:504–12.
- Biewenga M, Inderson A, Tushuizen ME, Crobach A, van Hoek B. Early predictors of short-term prognosis in acute and acute severe autoimmune hepatitis. *Liver Transplant.* 2020;26:1573–81.
- Pape S, Gevers TJG, Vrolijk JM, van Hoek B, Bouma G, van Nieuwkerk CMJ, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. *Clin Gastroenterol Hepatol.* 2020;18:1609–17.
- Verma S, Gunuwan B, Mendler M, Govindrajana S, Redeker A. Factors predicting relapse and poor outcome in type I autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission and plasma cell activity in the liver biopsy. *Am J Gastroenterol.* 2004;99:1510–6.
- Sanchez-Urdazpal L, Czaja AJ, van Hoek B, Krom RA, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. *Hepatology.* 1992;15:215–21.
- Donaldson PT, Czaja AJ. Genetic effects on susceptibility, clinical expression, and treatment outcome of type 1 autoimmune hepatitis. *Clin Liver Dis.* 2002;6:707–25.

37. van Gerven NM, de Boer YS, Zwiers A, Verwer BJ, Drenth JP, van Hoek B, et al. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1. *Gene Immun.* 2015;16:247–52.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Biewenga M, Verhelst XPDMJ, Baven-Pronk MAMC, Putter H, van den Berg AP, van Nieuwkerk KCMJ, et al. Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1. *United European Gastroenterol J.* 2021;9(6):662–71. <https://doi.org/10.1002/ueg2.12112>