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

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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
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,\(^5\)–\(^7\)–\(^9\)–\(^12\)–\(^13\)–\(^15\)–\(^16\) 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. 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).

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. 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 continous 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. 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 motefil, mercaptapurine (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
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 \( p < 0.01 \) 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 (Figure 1).
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:

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

- **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 x \((e^{-\text{baseline hazard (t) \times Y}})\) with \(Y = \text{e}^{\text{prognostic index}}\).

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:

| 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 | Overall mortality |
|          | HR (95% CI)          | p-value | 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.
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% 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 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

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**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.
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. For liver-related mortality older age has also been reported as a risk factor. 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. 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. Recently a large study was published confirming these findings for patients with African or Caribbean ethnicity. 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 and has previously been identified as an important predictor for worse long-term survival, although not in all studies. 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. Patients with high aminotransferases had more often symptoms and less often decompensated cirrhosis. The reason for these relationships is not entirely clear, but an increased rate of symptoms could lead to earlier diagnosis and treatment. Alternatively, patients with high transaminases could have a better response to treatment.

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. 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
compared to AIH patients in general. 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 while multiple relapses were associated with a worse survival. 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. In 170 HLA‐DR4 positive patients in the Netherlands no LTs occurred. 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.

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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.

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

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