A nomogram for analyzing risk factors of poor treatment response in patients with autoimmune hepatitis

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Objective The objective of this study was to identify biochemical and clinical predictors of poor response (including incomplete response and non-response) to standard treatment in autoimmune hepatitis (AIH) patients.
Methods This study retrospectively collected clinical data from 297 patients who were first diagnosed with AIH in Beijing Ditan Hospital from 2010 to 2019. Finally, 149 patients were screened out. Risk factors were screened by univariate and multifactorial logistic regression. Then they were used to establish the nomogram. The ROC curve, calibration curve, decision curves analysis (DCA) and clinical impact curves (CIC) were used to evaluate the nomogram.
Results 149 patients were divided into two groups: the response group (n = 120, 80%) and the poor response group (n = 29, 20%). Multivariate logistic regression analysis found that IgG > 26.5 g/L (OR: 22.016; 95% CI: 4.677–103.640) in AIH patients increased the risk. In contrast, treatment response status was better in women (OR: 0.085; 95% CI: 0.015–0.497) aged >60 years (OR: 0.159; 95% CI: 0.045–0.564) with AST > 4.49 × ULN (OR: 0.066; 95% CI: 0.009–0.494). The C index (0.853) and the calibration curve show that the nomogram is well differentiated and calibrated; the DCA and CIC indicate that the model has good clinical benefits and implications.
Conclusion The study found that male patients aged ≤ 60 years with IgG > 26.5 g/L and elevated AST ≤ 4.49 × ULN were more likely to have a non-response/incomplete response to standard treatment. Eur J Gastroenterol Hepatol 36: 113–119

Introduction

Autoimmune hepatitis (AIH) is a rare chronic liver disease caused by an autoimmune regulation disorder, which is closely related to heredity and the external environment [1]. AIH can occur in all regions and age groups worldwide and is more prevalent in women, but the pathogenesis is still unclear [2]. Clinical studies in several countries have found that the incidence of AIH has been on the rise in recent years [3,4]. Therefore, paying more attention to patients with autoimmune liver disease is essential.

AIH is primarily diagnosed by clinical scores, and the International Health Organization has formulated a set of criteria [5,6]. However, the heterotopic disease phenotype often makes the diagnosis of the disease very challenging [7]. Corticosteroids and azathioprine are the first-line drugs for the treatment of AIH [8,9]. But there is a wide variation in the degree of response to treatment, with the majority of patients improving after treatment, however, a small percentage of patients still respond poorly to standard therapy [10,11]. There are few studies on the risk factors of treatment response in AIH patients [12,13]. Some clinical trial studies have shown that patients' age, genetic factors, serum transaminase levels, liver co-morbidities, methemoglobinemia, and so on are significant influencing factors in treatment response [14–16]. However, whether other clinical monitoring indicators have a suggestive effect on patients' treatment response still needs further study. In addition, there are no studies revealed the extent to which various risk factors influence the poor outcome of patients in response to treatment [17].

The nomogram is considered to be a mature, simple, intuitive, and reliable statistical prediction model for quantifying the risks of clinical events [14]. In this study, by collecting and screening risk factors associated with poor treatment response in clinical AIH patients, a nomogram was creatively used to screen risk factors attributed to the poor treatment response outcome in AIH patients. The quantitative scoring of each risk factor was used to assist in clinical decision-making.

Methods

Patients selection

Our study retrospectively collected 297 patients clinically diagnosed with AIH between 2010 and 2019 at Beijing Ditan Hospital affiliated with Capital Medical

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University. The diagnosis of all patients followed the simplified diagnostic criteria for AIH issued in 2008, which confirmed the diagnosis of patients as definite and probable AIH based on scores more than or equal to 7 and equal to 6 [6]. At the same time, patients with overlapping syndromes were identified and differentiated based on pathological sections and international AIH subgroups [18]. Disease history, medication history, and clinical features of all enrolled patients were thoroughly surveyed and recorded. Ultimately, a total of 149 patients with AIH were enrolled in the final study. The study was approved by the Ethics Committee of Beijing Ditan Hospital affiliated with Capital Medical University.

Inclusion and exclusion criteria

Patients who met the following criteria were included in the study: (a) Determined or probable AIH according to the 2008 Simplified Diagnostic Criteria for AIH; (b) Treatment for more than 6 months.

Patients with any of the following conditions were excluded: (a) Positive for hepatotropic viruses, such as, HBV HCV; (b) History of other chronic liver diseases, such as hereditary, metabolic liver diseases, and hepatocellular carcinoma; (c) Overlap syndromes (between AIH and primary biliary cholangitis, between AIH and primary sclerosing cholangitis); (d) History of hepatotoxic drug usage in the 3 months before diagnosis, such as antibiotics, non-steroidal anti-inflammatory drugs, and anti-cancer drugs; (e) Liver biopsy was not performed; (f) Treatment duration less than 6 months (Fig. 1).

Case-finding strategies

An exhaustive method was used to collect patients who were first diagnosed with AIH at Beijing Ditan Hospital of Capital Medical University from 2010 to 2019 and the clinical characteristics of the patients were recorded in detail. Specific embodiments include: (a) searching for the medical term 'AIH' in the electronic medical record system of the Beijing Ditan Hospital to collect data on patients who have been discharged from the hospital. (b) Retrieving paper case files of AIH patients with liver disease in Beijing Ditan Hospital to collect information on AIH patients as systematically and comprehensively as possible.

Treatment of autoimmune hepatitis

All patients were treated with first-line therapy, a combination of glucocorticoids and azathioprine. According to the American Association for the Study of Liver Diseases research guidelines [8], treatment was as follows: Initially, prednisone 30 mg/d for 1 week, then 20 mg/d for 2 weeks, 15 mg/d for 4 weeks, and finally prednisone was maintained at a dose of 10 mg/d; AZA 50 mg/d was then added daily throughout the treatment. Duration of treatment not less than 6 months.

Histopathological evaluation

The liver puncture biopsy was performed in all 149 patients. Interfacial hepatitis and lymphocytic infiltration were present in all patients with liver pathology, while the presence of hepatocellular rosette nodules and regenerative nodules represented severe histological activity [18].

Data collection and definition

Baseline data extracted from the hospital medical record system include demographic characteristics (sex, age at diagnosis, clinical comorbidities); laboratory tests: including routine biochemical parameters [white blood cells (WBC), red blood cells, platelets, alanine aminotransferase (ALT), portal aminotransferase (AST), etc.]; blood coagulation tests [prothrombin time (PT), prothrombin activity (PTA), international normalized ratio (INR)];

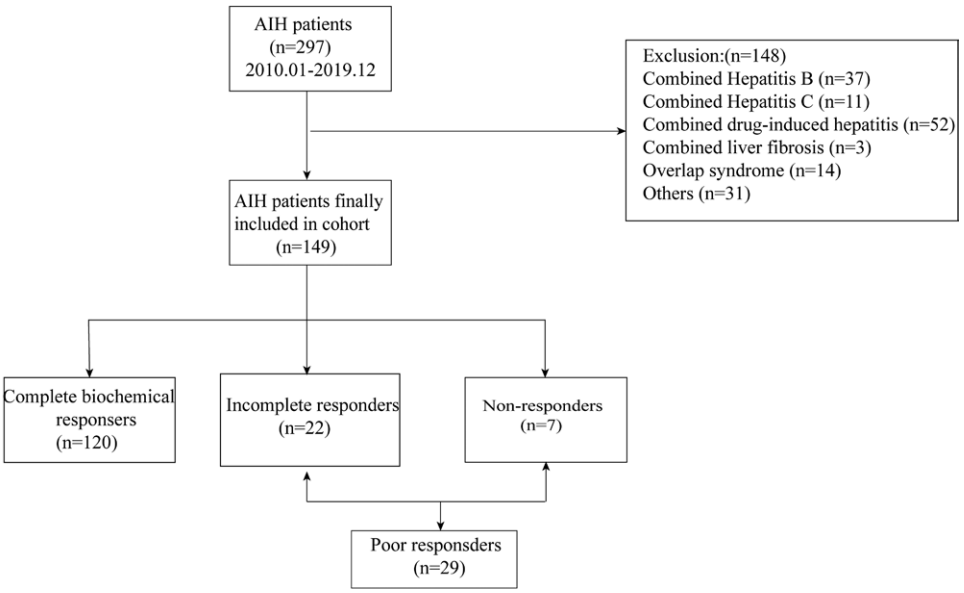

Fig. 1. Research workflow.

autoimmune disease-related antibodies (antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody); image and histological data.

Patients' response outcomes were divided into a response group and a poor response group, with the response group being the Complete biochemical response (CRB are patients whose serum transaminases decreased by ≥ 50% within 4 weeks of treatment and whose transaminases <ULN and IgG <ULN within 6 months of treatment). The poor response group included the non-responders (patients whose serum transaminases decreased by <50% within 4 weeks of treatment), and the incomplete responders (patients whose serum transaminases decreased ≥50% within 4 weeks of treatment, but whose transaminase and IgG levels remained >ULN after 6 months of treatment) [19].

Statistical analysis

Spss26.0 software (IBM, USA) and R4.2. 0 (R Core Team (2021), Vienna, Austria) was used to analyze the data and draw the chart, it is considered to be statistically significant when $P < 0.05$.

Baseline data from included patients with a continuous normal distribution (mean ± SD) for continuous variables were analyzed by t-test; categorical variables (values, percentages) were analyzed by chi-square test; and non-normally distributed data (median, interquartile spacing) were statistically analyzed by rank sum test. Univariate binary logistic regression analysis was used to assess the risk of poor response to treatment in AIH patients. Variables with $P < 0.2$ were input into a multivariate logistic regression analysis to identify risk factors for poor response. Based on the results of the last regression analysis, selected variables were included in the Nomogram.

Area Under the receiver operating characteristic curve was used to evaluate the discrimination of the Nomogram model. Calibration curves were used to calibrate the model and visualize the predicted probability of poor treatment response in AIH patients with the actual probability. Decision curves analysis (DCA) was used to assess whether the risk model helps us make better clinical decisions by quantifying the net benefit of a range of reasonable risk thresholds [20]. The clinical impact curve (CIC) was used to stratify the proportion of risk for each threshold probability in the model.

Results

Baseline characteristics of AIH patients with responding and poorly responding

This retrospective study included a total of 149 patients with AIH. Among them, 17 cases were male and 132 cases were female. The mean age of the patients was 61 years old. According to the biochemical indexes of the patients during treatment, patients were divided into two groups of biochemical responders and poor responders, in which there were 120 biochemical responders and 29 poor responders. Table 1 shows the baseline characteristics of the two cohorts of patients at admission. Including demographic characteristics, blood biochemical tests, and AIH-related antibody detection.

Table 1. The baseline characteristics of AIH patients with different response endpoints

	Response (n = 120)	Poor-Response (n = 29)	statistic	p-values
Age >60 years, n(%)	83 (69.2)	11 (37.9)	–2.890	**0.002**
Gender, n (%)				
Male	10 (8.3)	7 (24.1)		
Female	110 (91.7)	22 (75.9)	4.314	**0.038**
Type of AIH, n (%)				
Type 1	118 (98.4)	29 (100)		
Type 2	2 (1.6)	0 (0)	0.490	1.000
Associations, n (%)				
Hypertension	29 (24.2)	5 (17.2)	0.636	0.425
Diabetes	21 (17.5)	5 (17.2)	0.001	0.974
Heart diseases	8 (6.7)	4(13.8)	0.784	0.376
Ascites	13 (10.8)	2 (6.9)	0.083	0.773
Thyroid dysfunction	78 (65.0)	15 (51.7)	1.755	0.185
Laboratory				
IgG (g/L)	23.6 (20.4–29.4)	27.1 (21.6–32.4)	–1.824	0.068
IgM (g/L)	1.5 (0.95–2.5)	1.7 (0.73–2.6)	–0.151	0.880
C3 (g/L)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	–0.621	0.535
C4 (g/L)	0.1 (0.1–0.2)	0.1 ± 0.05	–0.788	0.431
WBC (10^9/L)	4.7 (3.4–6.0)	3.5 (2.6–4.2)	–2.752	**0.006**
Na (mmol/L)	139.8(137.1–141.8)	138.4 (136.5–140.6)	–1.786	0.074
ALT (U/L)	151.1 (52.1–389.6)	50.9 (29.3–114.4)	–3.450	**<0.001**
AST (U/L)	177.9 (68.4–328.7)	75.9 (48.1–119.4)	–3.711	**<0.001**
ALB (g/L)	33.1 ± 5.6	31.3 ± 6.0	–1.500	0.136
GGT (U/L)	143.4 (72.1–254.4)	118 (58.8–290.6)	–0.467	0.640
ALP (U/L)	132.4 (95.0–202.7)	144.9 (94.9–218.4)	–0.676	0.499
PT (s)	13.5 (12.2–16.1)	11.9 (11.4–14.5)	–2.285	**0.022**
PLT (10^9/L)	137.4 (93.3–196.3)	102.4 (64.6–207.0)	–1.086	0.277
PTA (%)	71.9 ± 23.1	82.7 ± 27.2	2.169	**0.032**
INR	1.2 (1.1–1.4)	1.1 (0.9–1.3)	–2.374	**0.018**
ANA+, n (%)	108 (90)	29 (100)	1.948	0.163
SMA+, n (%)	10 (8.3)	0 (0)	1.430	0.232
LKM-1, n (%)	2(1.7)	0(0)	0.490	1.000

The bolded *P*-value was considered to be statistically different between the two groups for this factor.

The study found that the proportion of males in the biochemically poor response group (24.1%) was significantly higher than that in the group of biochemically responsive patients (8.3%), and the group of biochemically poor responders was significantly younger than the responders. Analysis of the laboratory findings revealed that the levels of WBC, ALT, AST, and INR were significantly lower in treatment-poor responders than in biochemical responders, but the PTA and IgG were higher, and all were statistically significant ($P < 0.05$). However, there was no difference in autoimmune-related antibodies and type of AIH between the two groups. All indicators of differences were included in the following study.

Risk factors associated with poor biochemical response in AIH patients

Univariate and multifactorial binary logistic analyses were used to screen out possible risk factors affecting biochemical poor responses in AIH patients. The study found that a higher number of patients aged ≤60 years ($P = 0.004$), male ($P = 0.006$), with a higher IgG > 26.5g/L ($P < 0.0001$), and with elevated AST ≤ 4.49 × ULN($P = 0.008$) had a higher risk of poor response (Table 2).

Nomogram of the risk factors of poor response to treatment in AIH patients

Based on the results of multivariate binary Logistic regression analysis, the four variables of age, gender, IgG, and AST were included to construct a nomogram for the probability of poor treatment response in AIH patients after standard treatment. Each variable is assigned a score based on its projected value on the score axis, and the total score can be obtained by simply summing the scores of the four variables. The total score is used to predict the probability of poor treatment response in the AIH patients (Fig. 2).

Assessment of nomogram

The performance of the nomogram was evaluated by the calibration curve and ROC curve. Figure 3a and b shows the calibration curve of the nomogram and the ROC curve with an area under the receiver operating characteristic curve of 0.853 (95% CI: 0.777–0.928), indicating that the model has good discrimination. The true and corrected cohort curves in the calibration curve float up and down on the 45-degree line, indicating that the nomogram has a good model fit. DCA shows that patients will benefit greatly when using this clinical model for decision-making if the probability of a patient experiencing a poor treatment response is between 10% and 90% (Fig. 4a). The CIC shows the relationship between the number of people who have a poor response to treatment and the number of people at risk under different risk probabilities (Fig. 4b).

Discussion

In this retrospective study, 149 patients with AIH in Beijing Ditan Hospital affiliated with Capital Medical University were collected and screened, and the patients were divided into responders and poor responders according to the relevant biochemical indexes in the latest international consensus [19]. By constructing a nomogram with risk factors screened by logistic regression, we visually quantify the risk, which may provide help for clinicians in making treatment decisions for AIH patients. Finally, four factors as predictive risk factors for poor treatment response in patients with AIH were screened: namely, age ≤60 years, male, IgG > 26.5g/L, and AST ≤ 4.49 × ULN. The nomogram constructed in this study was validated by calibration curves, DCA, and CIC with high discrimination, calibration, and clinical benefit.

A systematic review revealed the close association of age with various liver diseases, including nonalcoholic liver disease, alcoholic liver disease, hepatitis, liver fibrosis, and cirrhosis [21]. Our study found that age seems to be an independent risk factor for poor response in AIH patients. A retrospective study from Italy found that younger AIH patients were more likely to have incomplete or non-responsive responses; and that younger patients had a greater tendency to develop liver fibrosis and cirrhosis [15]. The results of Ahmed Abdel-Razik *et al*. came to the same conclusion [22]. In our study, patients aged ≤60 years were 6.3 times more likely to have a poor treatment response than older patients, reinforcing these conclusions. However, one study found no difference in treatment response between younger patients and AIH patients over 70 years, which may be due to the different

Table 2. Factors associated with poor response in patients with AIH

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age >60 years	0.272	(0.117–0.634)	**0.003**	0.159	(0.045–0.564)	**0.004**
Female	0.286	(0.098–0.083)	**0.022**	0.085	(0.015–0.497)	**0.006**
Thyroid dysfunction	0.577	(0.254–1.309)	**0.188**			
IgG > 26.5 (g/L)	3.057	(1.329–7.032)	**0.009**	22.016	(4.677–103.640)	**<0.001**
WBC < 4 × 10^9/L	2.098	(0.923–4.768)	**0.077**			
ALT > 1.602 [×ULN]	0.198	(0.081–0.485)	**<0.001**			
AST > 4.49 [×ULN]	0.077	(0.017–0.337)	**0.001**	0.066	(0.009–0.494)	**0.008**
ALB < 40g/L	1.783	(0.382–8.323)	0.462			
PT (s)	0.973	(0.898–1.053)	0.492			
PTA < 70%	0.450	(0.185–1.096)	**0.079**			
INR > 1.2	0.421	(0.177–0.999)	**0.050**			

Factors with $P < 0.2$ in the univariate regression analysis were included in the multifactor regression analysis; factors with $P < 0.05$ in the multifactor regression analysis were considered independent risk factors for poor response. The *P*-value <0.2 in the univariate regression analysis was bolded, and the bold *P*-value in the multifactor regression analysis represented <0.05.

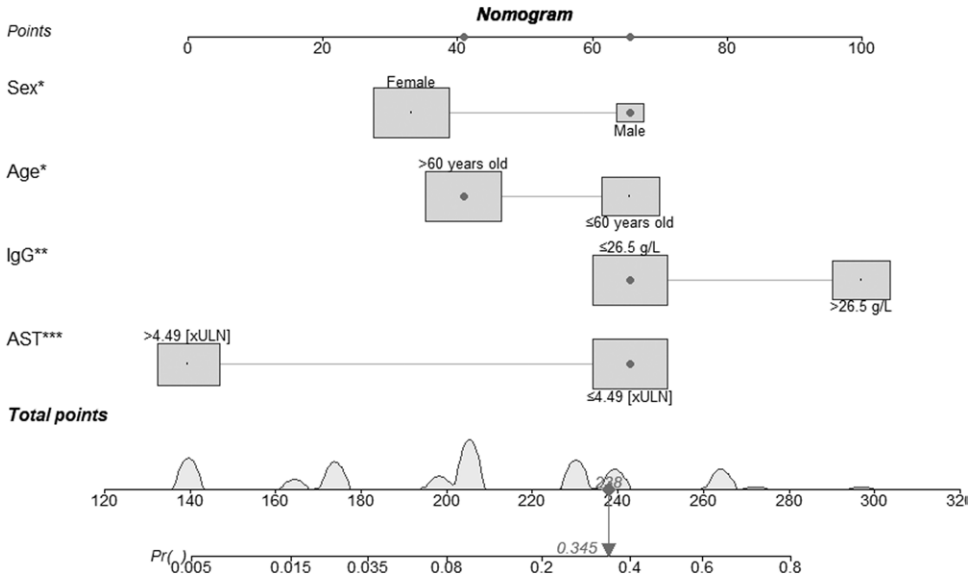

Fig. 2. The four variables screened by the multifactorial logistic regression are used to plot the nomogram. The bold dots represent the specific values of the four variables for a particular patient and each variable has a corresponding mapping on the score axis and the total score can be obtained by simple summation. The total score is used to predict the probability of poor response.

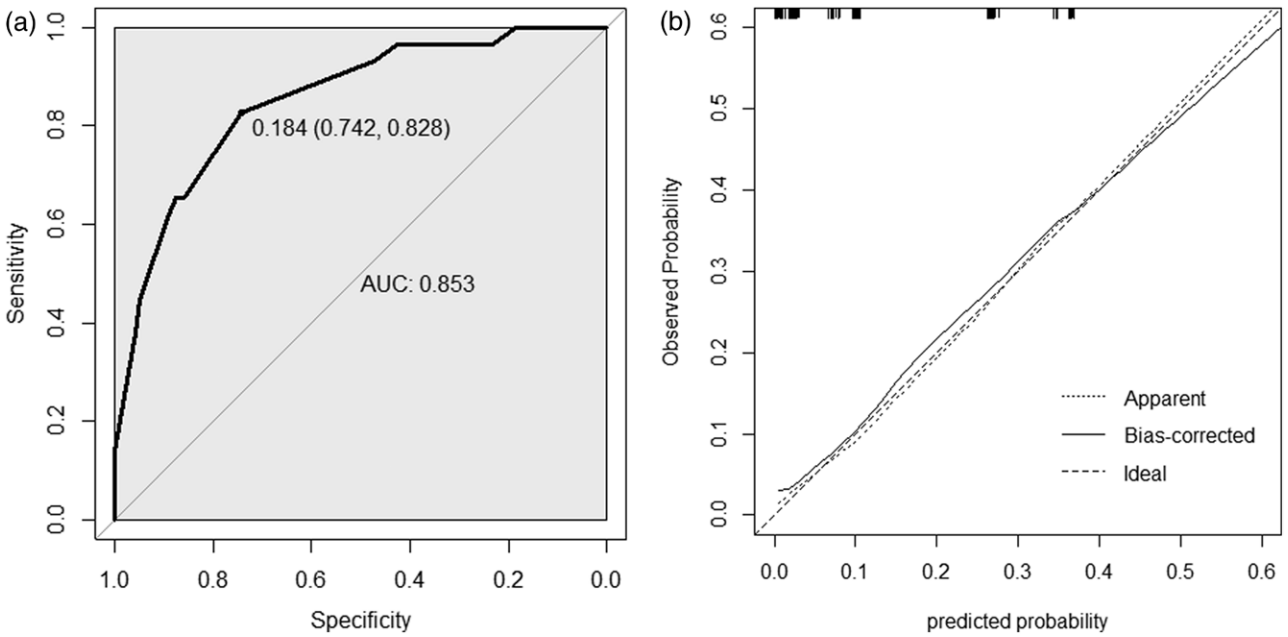

Fig. 3. (a) ROC curve for nomogram, the area under the curve (AUC) of 0.853. (b) Calibration curve for nomogram, the x-axis represents the predicted probability of nomogram, and the y-axis represents the actual probability of poor response. The 45-degree diagonal line represents the ideal prediction curve, the dashed curve represents the true cohort, solid line is the corrected curve.

geographic regions, ethnicity, and genetic factors of the study population [23].

Similar to other autoimmune diseases, AIH is also more common in female patients [24]. In our study, 89% of patients were female, which is consistent with the international consensus. Our study showed that male AIH patients were 11.7 times more likely to respond poorly to treatment than female patients, an independent risk factor. This is in agreement with the findings of Luis Téllez1 *et al* [14]. However, the exact mechanism has not been studied.

Elevated IgG is one of the important pieces of evidence for diagnosing AIH and judging patients' responses to treatment [19,25]. IgG levels are related to patient autoimmune regulation and immune hypersensitivity, resulting in differential responses in patients under standard therapy [26]. A prospective cohort study, also from China, found that among 569 AIH patients, those with lower IgG levels (17.8 g/L vs. 25 g/L) at diagnosis had better biochemical and histological remission, which coincides with our findings [27]. However, the minimum value of IgG that can cause an increased risk of poor treatment response

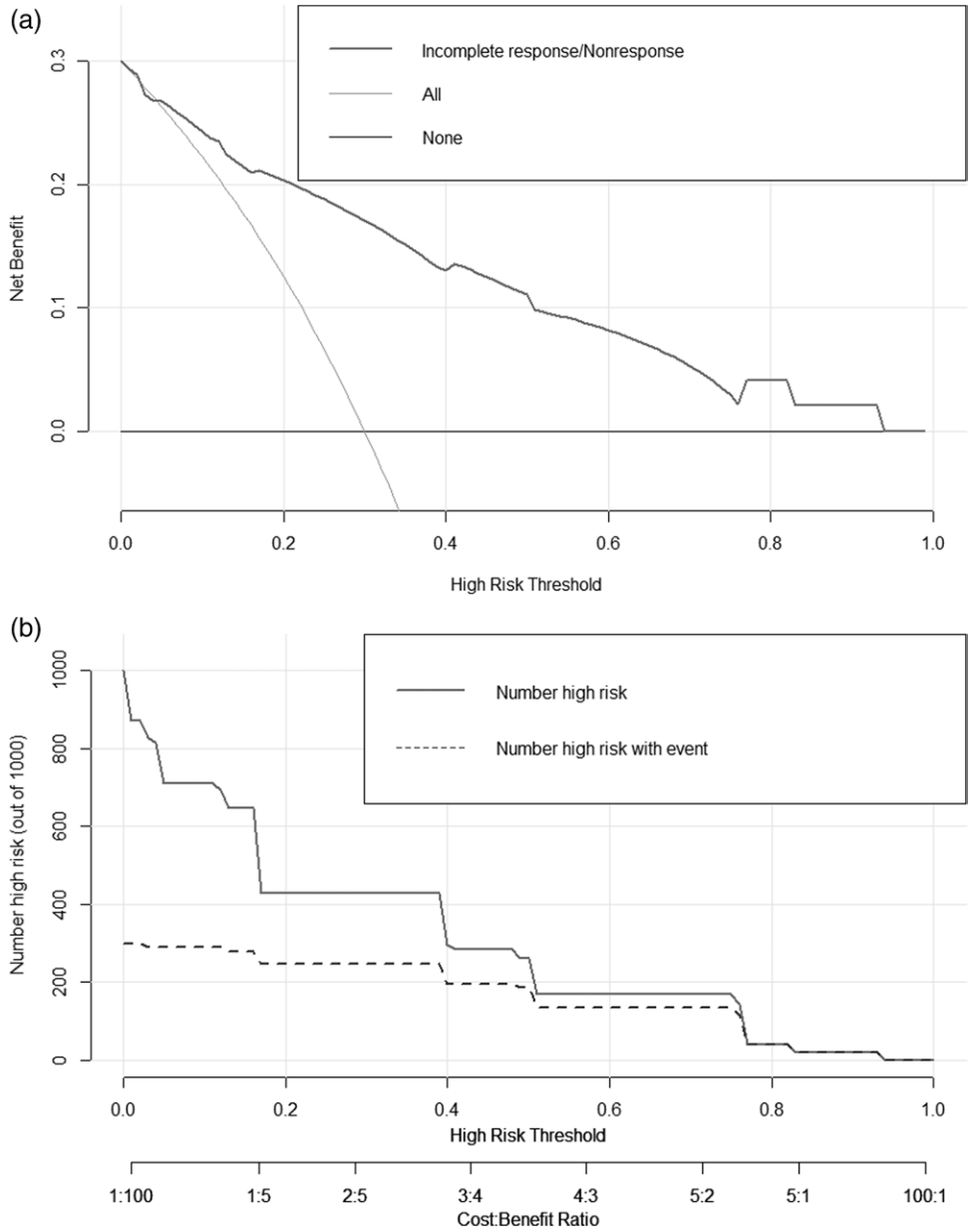

Fig. 4. (a) Nomogram's clinical Decision curves analysis (DCA) to predict the probability of occurrence of poor response. When the probability of occurrence is betweens 0.1 and 0.9, there is a good clinical benefit. (b) Clinical impact curve (CIC) of the nomogram. The solid line represents the number of poor responders predicted by the nomogram in the population, and the dashed line represents the number of true occurrences. When the nomogram predicted probability is greater than 0.75, the predicted number overlaps with the true number of occurrences.

remains unspecified. In this study, we assumed 26.5 g/L as the critical point based on the cutoff value of IgG data. Surprisingly, patients with IgG > 26.5 g/L had 22.016 times the poor treatment rate of the rest patients. which was adjacent to the predicted IgG value (1.5 ×ULN) of You Li *et al* [27]. Therefore, monitoring IgG levels at the patient's first visit helps physicians make better clinical decisions.

Aspartate aminotransferase (AST) is one of the important detectors in liver injury as a vital aid in the diagnosis of multiple liver diseases [28]. Elevated AST is present in most patients with AIH with liver injury [6]. In this study, we found that patients with AIH had better biochemical treatment responses when their elevated AST at diagnosis was greater than 4.49 × ULN. Both the Paolo Muratori and You Li teams similarly find that higher AST levels may contribute to the poor response to AIH, and Paolo Muratori *et al*. suggested that AST also played an inverse role in predicting histological remission of AIH [15,27]. Meanwhile, some past studies have not found significant differences in AST levels between the two different responding populations [14,16]. This may be related to the varying degrees of disease progression when the AIH patients were enrolled.

The response outcome of standard treatment in AIH patients is a key influencing factor for the clinician's next medical decision [9]. We creatively propose to use easily available influencing factors to assess the risk of under-response in patients. This is the first time to construct a nomogram to predict the probability of poor response to treatment in Chinese AIH patients.

There are still some limitations in this research. First, the current study is a single-center, small-scale study that is inevitably biased. Second, although the model has good discrimination and calibration, the universality of this alignment map still needs to be verified by external data sets, considering the influence of epidemiological characteristics and clinical manifestations of patients with different races, regions, and heredity. Due to the limitation of the number of AIH patients, further study and analysis are needed.

Conclusion

In summary, our study identified four risk factors associated with poor response outcomes in AIH patients by univariate and multifactorial logistic regression. Notably, we constructed a nomogram to assess the influence of each risk factor on treatment response. This will help clinicians to identify patients with poor treatment responses more precisely and carry out individualized treatment.

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WX is the first author of this study. Concept and design (LX, WX); data acquisition (WX, LH, WP, WYQ, YYY); statistical analysis (WX, LH), drafting of the manuscript (WX), critical revision of the manuscript for important intellectual content (LX); obtained funding: (LX). All authors read and approved the final manuscript.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University.

Conflicts of interest

There are no conflicts of interest.

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