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Liver inflammation activity in patients with autoimmune hepatitis with normal alanine aminotransferase and immunoglobulin G levels

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ABSTRACT

Background and aims: Normal serum transaminases and immunoglobulin G (IgG) levels are surrogate markers for hepatic histologic disease activity in autoimmune hepatitis (AIH). This study aimed to evaluate liver inflammation in patients with AIH with normal serum alanine aminotransferase (ALT) and IgG levels.
Methods: Two hundred and five AIH patients who underwent liver biopsy in four medical centers were included. Logistic regression analysis was used to identify risk factors associated with advanced inflammation.
Results: One hundred and thirty-one (63.9 %) AIH patients had advanced liver inflammation, and 108 (52.7 %) patients had advanced liver fibrosis. 60.0 % of patients with normal ALT and 51.7 % of patients with normal ALT and IgG had advanced inflammation. However, 76.7 % and 35.0 % of patients with or without advanced fibrosis with normal ALT had advanced inflammation, while the corresponding proportions of advanced inflammation were 78.6 % and 26.7 % in patients with normal ALT and IgG, respectively. Moreover, 81.0 % and 44.8 % of patients with and without cirrhosis with normal ALT had advanced inflammation, while the corresponding proportions were 83.3 % and 29.4 % in patients with normal ALT and IgG, respectively. Red cell distribution width (OR = 1.325, 95%CI 1.045–1.681, P = 0.020) and PT (OR = 1.514, 95%CI 1.138–2.014, P = 0.004) were independent factors associated with advanced inflammation.
Conclusions: High proportion of advanced inflammation was found in AIH patients with normal ALT and IgG levels despite without advanced fibrosis. Although using non-invasive methods may contribute to rule out liver fibrosis in AIH patients with normal ALT and IgG levels, liver biopsy is encouraged to assess liver inflammation.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of the normal range; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; Tbil, total bilirubin; ALP, alkaline phosphatase; ALB, albumin; GLB, globulin; Hb, hemoglobin; PLT, platelet; RDW, red cell distribution width; IgG, immunoglobulin G; INR, international normalized ratio; PT, prothrombin time; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis index based on the four factors; ANA, antinuclear antibody; IQR, interquartile range; CI, confidence interval; OR, odds ratio; AUROC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic curve; LB, liver biopsy; AIH, autoimmune hepatitis.

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1. Introduction

Autoimmune hepatitis (AIH) is a chronic and progressive disease, with an increasing prevalence trend worldwide [1], which is characterized with elevated transaminases, hypergrammaglobulinemia, the presence of autoantibodies, and histological interface hepatitis, and could progress to cirrhosis [2].

Due to the lack of special diagnostic markers, liver biopsy (LB) is essential for diagnosis of AIH [2,3] and for the assessment of inflammatory and fibrosis activity. It is also recommended to perform LB in non-response or incomplete response patients during treatment and before treatment withdrawal [2]. In patients with type 1 AIH, liver histologic confluent necrosis has been demonstrated to be a predictor for the development of liver cirrhosis [4]. Although liver biopsy is a golden standard for evaluation of hepatic histologic inflammation and fibrosis [2], it is not a repeated routine practicable method in the disease course.

Serum aminotransferases levels and immunoglobulin G (IgG) levels were associated with hepatic histologic disease activity in patients with AIH [5]. However, the association between normalization of the biochemical parameters and histological activity is controversial in AIH patients. Although normalization of both serum parameters indicated histologic remission and at a low risk of fibrosis progression in patients with AIH, about half of those patients still showed residual histologic activity [5]. A study suggested that as high as 46 % of patients had persisting histological activity despite of normal serum alanine aminotransferase (ALT) and globulin in AIH patients and the persisting histological activity was associated with lower fibrosis regression and long-term survival [6]. Another study demonstrated that normalization of both serum ALT level and IgG level in patients with AIH with cirrhosis was a poor surrogate marker of histological remission while have good performance in predicting efficacy in AIH patients without cirrhosis [7]. Our previous study also found that the performance of ALT and IgG in predicting significant liver inflammation is not satisfactory in AIH patients, with the area under the receiver operating characteristic curve (AUROC) of 0.496 and 0.594, respectively [8].

There is increased availability of non-invasive tests as an alternative of biopsy in diagnosing of hepatic advanced fibrosis and determining of prognosis in patients with chronic liver disease [9]. Recently, Sonneveld et al. found that low probability of significant liver inflammation in patients with chronic hepatitis B (CHB) with low ALT levels without fibrosis [10]. They demonstrated that using non-invasive methods may rule out fibrosis in CHB patients and liver biopsy solely to evaluate inflammatory activity is discouraged [10]. However, the distributions of liver inflammation activity in AIH patients without advanced fibrosis/cirrhosis with normal ALT and IgG levels were not investigated.

In this study, we assessed the liver inflammation activity in patients with AIH depending on serum ALT and IgG levels, especially in patients with different fibrosis stages.

2. Methods

2.1. Patient population

AIH patients who underwent LB from July 2011 to November 2020 in four medical centers (The Fifth People's Hospital of Wuxi, The Affiliated Infectious Diseases Hospital of Soochow University, Nanjing Second Hospital and Nanjing Drum Tower Hospital) were retrospectively collected. The inclusion criteria were patients fulfilled AIH diagnostic criteria of relevant guidelines [11], and the diagnostic time of AIH was made within 2 weeks after liver biopsy in all patients. The exclusion criteria were the overlap syndrome, co-existence with hepatitis virus, or Epstein-Barr virus infection. Patients with drug induced liver disease, fatty liver, or insufficient data were also excluded. The study was approved by the ethics committees of local hospitals and was conducted according to the ethical principles of the Declaration of Helsinki.

2.2. Clinical and biochemical parameters

The clinical and biochemical parameters were collected. Completed blood count was evaluated using automated hematology analyzers. Biochemical markers were determined using automated biochemical analyzers. Prothrombin time (PT) and international normalized ratio (INR) were tested by automated blood coagulation analyzers. Immunoglobulin G (IgG) levels was measured by immune scatter turbidity method. Antinuclear antibodies (ANA) was evaluated by indirect immunofluorescence. APRI and FIB-4 were calculated as: APRI = (AST (U/L)/upper limit of normal AST(U/L)) × 100/platelet counts (10^9/L) [12]; FIB-4 = [age(years) × AST(U/L)]/[(platelet counts (10^9/L) × (ALT [U/L]$^{1/2}$)] [13].

2.3. Liver histology

The liver biopsy was performed under ultrasound guided. Liver histopathology was evaluated according to Scheuer's scoring system by two pathologists [14]. Histological inflammation grades were classified into G0-G4, while the fibrosis stages were classified into S0–S4. Advanced inflammation was defined as ≥ G3, whereas advanced fibrosis was defined as ≥ S3. Liver cirrhosis was defined as S4.

2.4. Statistical analysis

Statistical Package for the Social Sciences version 27.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Continuous data were expressed as the medians (inter-quartile range, IQR). Categorical data were presented as percentages. To test difference between groups, the T-test, Mann-Whitney *U* test, one-way ANOVA, Kruskal-wallis one-way ANOVA, chi-squares test or Fisher's exact test was used when appropriate. Logistic regression analysis was used to identify the predictors for evaluating advanced liver inflammation. In the univariate analysis, parameters with P values less than 0.1 were input multivariate logistic regression analysis. P value less than 0.05 was considered as statistical significance.

3. Results

3.1. Patient characteristics

Of these 489 patients screened, 205 patients with AIH were eligible in this study (Fig. 1). The clinical characteristics of AIH patients were

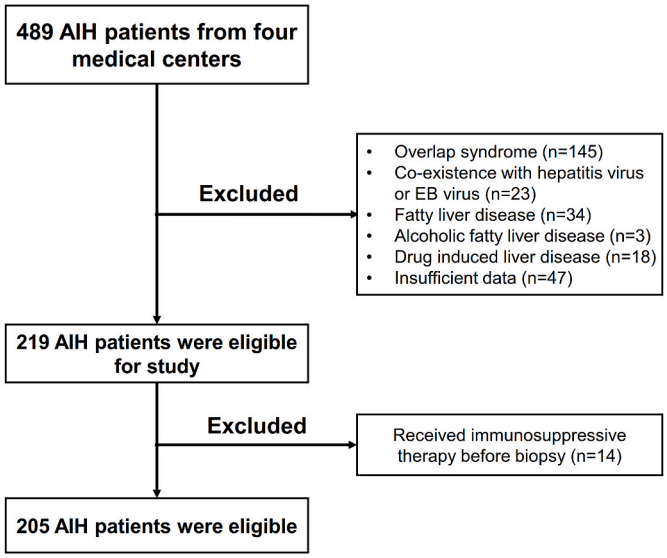

Fig. 1. Flow chart of patient selection.

presented in Table 1. The majority (83.9 %) of patients were female and the median age of patients were 54.00 (IQR 46.00, 63.00) years. The median levels of ALT and IgG were 2.15 (IQR 1.00, 5.17) × ULN and 1.01 (IQR 0.81, 1.27) × ULN, respectively. One hundred and twenty-five patients (62.8 %) were positive for autoantibody.

Table 1
Comparison of biochemical and clinical features of patients with autoimmune hepatitis with and without advanced fibrosis.

Variables (n % or median IQR)	Total (n = 205)	AIH without advanced fibrosis (n = 97)	AIH with advanced fibrosis (n = 108)	P value
Age (years)	54.00 (46.00, 63.00)	53.00 (46.00, 59.50)	57.50 (47.00, 66.00)	0.020
Female (%)	172 (83.9)	79 (81.4)	93 (86.1)	0.364
ALT/ULN	2.15 (1.00, 5.17)	2.62 (1.21, 5.58)	1.71 (0.93, 4.93)	0.085
AST/ULN	1.83 (1.03, 4.41)	2.00 (1.00, 5.04)	1.73 (1.05, 3.82)	0.522
GGT (U/L)	137.00 (64.05, 229.00)	145.00 (52.95, 222.65)	127.50 (72.83, 232.50)	0.930
Tbil (μmol/L)	22.00 (13.25, 43.05)	18.60 (11.95, 36.65)	25.45 (16.08, 46.30)	0.018
ALP (U/L)	123.00 (92.50, 189.45)	123.00 (92.60, 182.90)	125.00 (92.25, 207.50)	0.441
ALB (g/L)	37.70 (33.90, 40.20)	38.90 (35.60, 41.30)	36.10 (32.73, 39.08)	0.001
GLB (g/L)	31.20 (26.80, 36.30)	29.20 (26.20, 33.65)	33.15 (28.18, 38.28)	<0.001
Hb (g/L)	123.00 (112.50, 133.00)	126.00 (113.00, 133.00)	121.50 (112.00, 132.50)	0.197
PLT (× 10^9/L)	148.00 (106.00, 188.00)	172.00 (121.50, 210.50)	129.00 (99.75, 164.25)	<0.001
RDW (%)	13.90 (13.00, 15.40)	13.40 (12.70, 14.95)	14.00 (13.20, 15.70)	0.005
IgG/ULN	1.01 (0.81, 1.27)	0.90 (0.77, 1.15)	1.11 (0.90, 1.33)	<0.001
INR	1.06 (1.00, 1.17)	1.05 (1.00, 1.14)	1.09 (1.01, 1.22)	0.022
PT (s)	13.20 (12.20, 14.15)	12.50 (11.70, 13.45)	13.75 (12.93, 14.70)	<0.001
APRI	1.43 (0.71, 2.96)	1.42 (0.59, 2.96)	1.45 (0.78, 3.22)	0.427
FIB-4	3.19 (1.86, 5.90)	2.65 (1.38, 4.87)	3.92 (2.26, 6.65)	0.003
ANA positive	125 (62.8)[a]	63 (67.7)[‡]	62 (58.5)[§]	0.178
Inflammation activity (%)				<0.001
G1	12 (5.9)	12 (12.4)	0 (0.0)	
G2	62 (30.2)	41 (42.3)	21 (19.4)	
G3	112 (54.6)	36 (37.1)	76 (70.4)	
G4	19 (9.3)	8 (8.2)	11 (10.2)	
Fibrosis stage (%)				
S0	2 (1.0)	–	–	
S1	37 (18.0)	–	–	
S2	58 (28.3)	–	–	
S3	50 (24.4)	–	–	
S4	58 (28.3)	–	–	

[a] n = 199, ‡: n = 93, §: n = 106. ALT, alanine aminotransferase; ULN, upper limit of the normal range; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; Tbil, total bilirubin; ALP, alkaline phosphatase; ALB, albumin; GLB, globulin; Hb, hemoglobin; PLT, platelet; RDW, red cell distribution width; IgG, immunoglobulin; INR, international normalized ratio; PT, prothrombin time; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis index based on the four factors; ANA, antinuclear antibody; IQR, interquartile range.

The distributions of liver histological inflammation and fibrosis were showed in Fig. 2. As high as 63.9 % of patients with AIH had advanced inflammation and 52.7 % of patients had advanced fibrosis. The distributions of liver inflammation and fibrosis in patients with different gender and age were presented in Fig. S1.

The clinical features of AIH patients with and without advanced fibrosis subgroups were compared (Table 1). The median levels of age, total bilirubin (Tbil), globulin (GLB), red cell distribution width (RDW), IgG, INR, PT and FIB-4 were significantly lower in AIH patients without advanced fibrosis, compared to those patients with advanced fibrosis. While, the median levels of ALB and PLT were significantly higher in AIH patients without advanced fibrosis. The clinical features were also compared between AIH patients with and without cirrhosis (Table S1). Similar trends were also found except the differences in Tbil, GLB, RDW and IgG without statistical significance.

3.2. Histological disease activity depending on ALT and IgG levels

The proportion of advanced inflammation with elevated ALT and IgG was 69.0 % (60/87). However, the proportions of advanced inflammation in patients with normal ALT level and patients with normal IgG level were 60.0 % (30/50) and 57.7 % (56/97) respectively, while the corresponding proportions were 51.7 % (15/29) in patients with normal ALT and normal IgG levels (Fig. 3A, 3B, 3C).

There were 61.0 % (53/87) of patients with elevated ALT and IgG had advanced fibrosis. The proportions of advanced fibrosis were 60.0 % (30/50), 40.2 % (39/97) and 48.3 % (14/29) in patients with normal ALT, normal IgG, both normal ALT and IgG levels, respectively (Fig. 3D, 3E, 3F).

3.3. Histological inflammation activity and biochemical features depending on ALT and IgG levels in AIH patients with and without advanced fibrosis

We compared the histological inflammatory activity according to ALT level and IgG level in patients with and without advanced fibrosis. The biochemical features of patients despite advanced fibrosis with normal or elevated ALT levels were compared (Table S2). One hundred and eight (52.7 %) patients had advanced fibrosis, and these patients were classified into elevated and normal ALT subgroups. Of these patients, the median levels of AST, gamma-glutamyl transpeptidase (GGT), Tbil and APRI were significantly higher in elevated ALT subgroup. Similar findings were observed in AIH patients without advanced fibrosis subgroups except the difference in Tbil with no statistical significance. In patients with normal ALT levels, the median levels of PT in patients with advanced fibrosis was significantly higher than in patients without advanced fibrosis, while the median levels of PLT and ALB were significantly lower.

The liver inflammation of patients with AIH with and without advanced fibrosis according to ALT level and IgG level were shown in Fig. S2 and Fig. S3. The proportions of advanced inflammation of AIH patients with and without advanced fibrosis with normal ALT were 76.7 % (23/30) and 35.0 % (7/20), while the corresponding proportions of patients with normal IgG levels were 82.1 % (32/39) and 41.4 % (24/58). As high as 26.7 % (4/15) of patients had advanced inflammation in patients with AIH with normal ALT level and normal IgG level in absence of advanced fibrosis, while 78.6 % (11/14) of patients with normal ALT level and IgG level and advanced fibrosis had advanced inflammation.

3.4. Histological disease activity and biochemical features depending on ALT and IgG levels in AIH patients with and without cirrhosis

The biochemical, histological and clinical features in patients with AIH despite with or without cirrhosis, were presented in Table S3. In

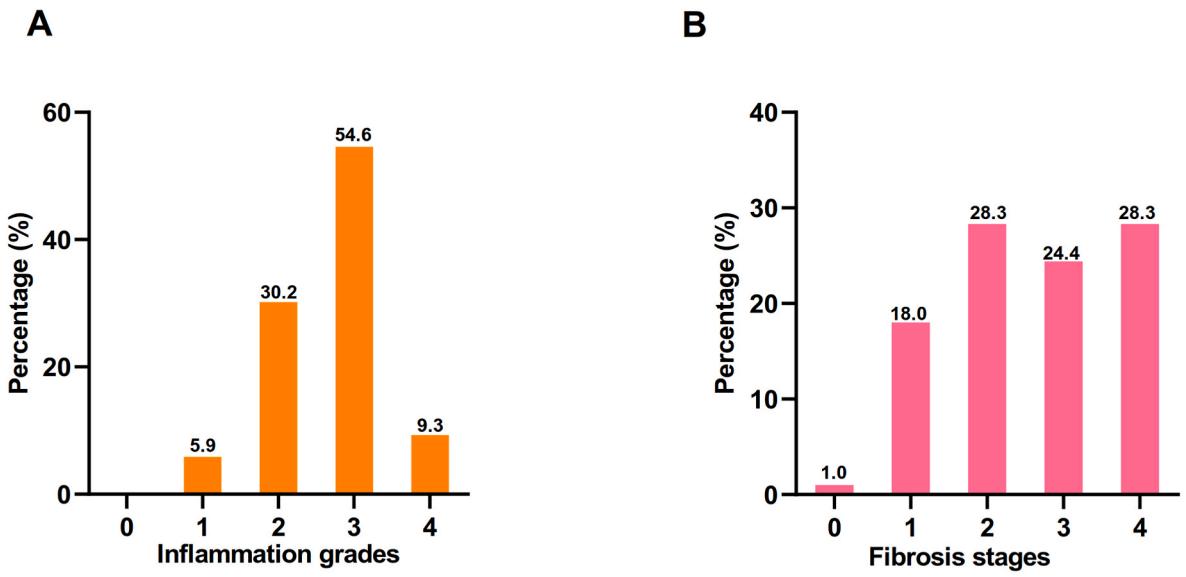

Fig. 2. Distribution of liver inflammation and fibrosis in patients with autoimmune hepatitis.

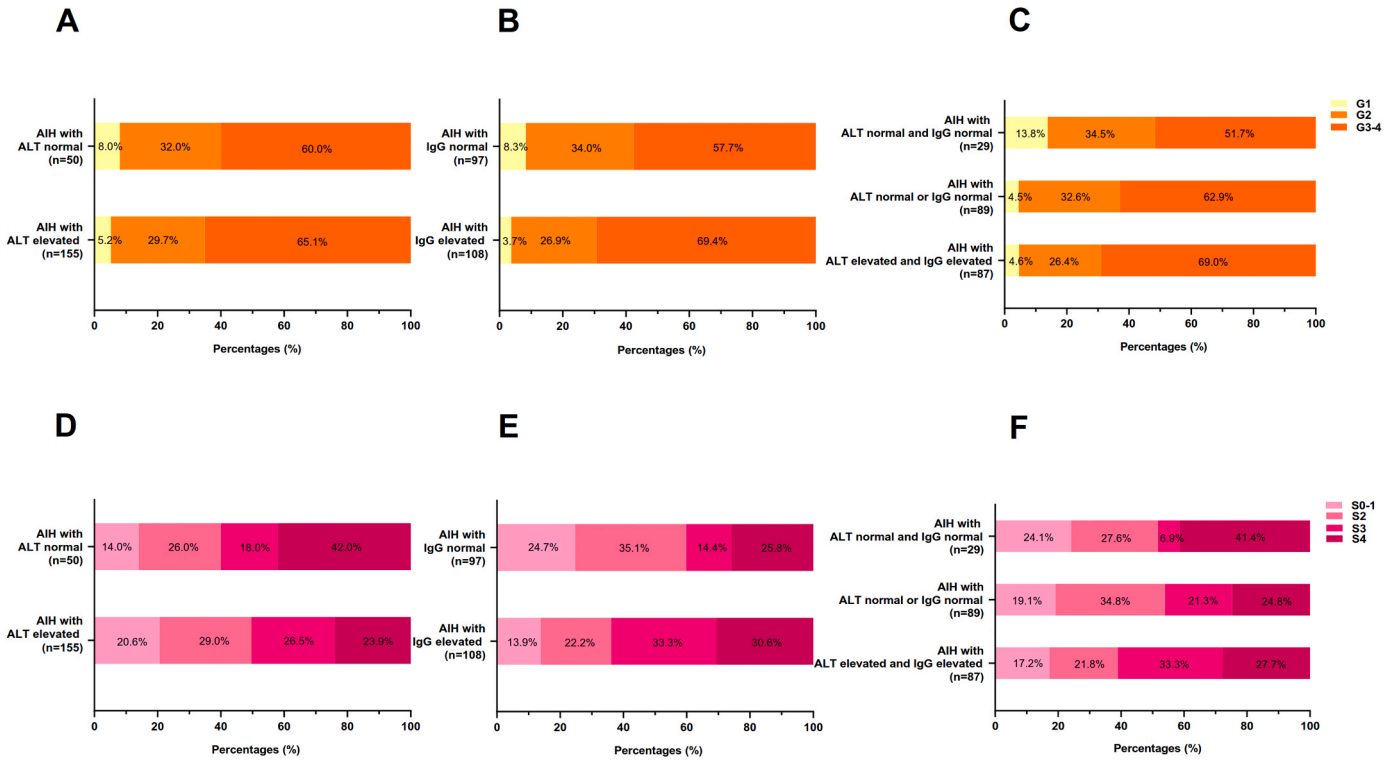

Fig. 3. Liver inflammation and fibrosis of patients with AIH depending on ALT and IgG levels.

patients with AIH with cirrhosis, the median levels of AST, GGT, Tbil and APRI were significantly lower in the normal ALT level subgroup than the elevated ALT subgroup. Similar findings were observed in patients without cirrhosis. In patients with normal ALT, the median levels of PLT and ALB in patients without cirrhosis subgroup were significantly higher than patients with cirrhosis, while the median levels of PT was significantly lower.

The proportions of liver inflammation in patients with and without cirrhosis according to ALT and IgG levels were presented in Fig. S4 and Fig. S5. The proportions of advanced inflammation in patients with and without cirrhosis with normal ALT were 81.0 % (17/21) and 44.8 % (13/29), while the corresponding proportions with normal IgG were 84.0 % (21/25) and 48.6 % (35/72). The proportions of advance inflammation were 87.5 % (21/24) and 62.0 % (39/63) in patients with elevated ALT and IgG levels with and without cirrhosis. However, there were as high as 29.4 % (5/17) of patients had advanced inflammation in non-cirrhosis patients with normal ALT and IgG, compared to 83.3 % (10/12) of cirrhosis patients with normal ALT and IgG levels (Fig. S5).

We analyzed the histological disease activity of patients with and without advanced fibrosis according to AST level (Fig. S6). The proportions of advanced inflammation in patients with and without advanced fibrosis with normal AST were 70.8 % (17/24) and 29.1 % (7/24), while the proportions with elevated AST in these groups were 83.3 % (70/84) and 50.7 % (37/73). Similar trends in patients with and

without cirrhosis were found (Fig. S7). The proportions of advanced inflammation in patients with and without cirrhosis with normal AST were 68.7 % (11/16) and 40.6 % (13/32) respectively, while the corresponding proportions were 90.5 % (38/42) and 60.0 % (69/115) in patients with elevated AST.

3.5. Factors of advanced liver histological inflammation

The logistic regression was used to identify the factors of advanced histological inflammation of AIH patients (Table 2). In univariate logistic regression, GGT, Tbil, alkaline phosphatase (ALP), albumin (ALB), globulin (GLB), platelet (PLT), RDW, PT were factors of advanced inflammation ($P < 0.05$). However, The RDW (OR = 1.325, 95 % CI: 1.045–1.681, $P = 0.020$), and PT (OR = 1.514, 95 % CI: 1.138–2.014, $P = 0.004$) were independent factors for advanced liver inflammation by multivariate regression analysis. AUROC was used to compare the performances of RDW, PT, ALT and IgG in predicting advanced inflammation (Fig. 4). The RDW (0.710, 95%CI: 0.634–0.786) and PT (0.703, 95%CI: 0.631–0.774) showed relatively high AUROCs in predicting advanced inflammation. We next examined the factors of advanced inflammation in patients without advanced fibrosis (Table 3). The age (OR = 1.052, 95 % CI: 1.007–1.100, $P = 0.024$) and RDW (OR = 1.506, 95 % CI: 1.012–2.241, $P = 0.044$) were risk factors for advanced liver histological inflammation by multivariate analysis. We further evaluate the performance of age, RDW, ALT and IgG in predicting advanced inflammation in these patients (Fig. S8A) and the AUROC of RDW (0.759, 95%CI: 0.663–0.856) was highest. In addition, the risk factors of advanced inflammation in the AIH patients without cirrhosis were also analyzed. As shown in Table S4, male (OR = 0.228, 95 % CI: 0.060–0.870, $P = 0.030$), RDW (OR = 1.437, 95 % CI: 1.049–1.969, $P =$

Table 2
Risk factors of advanced inflammation in patients with autoimmune hepatitis.

Variable	Univariate		Multivariate	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Age (years)	1.019 (0.998, 1.042)	0.081	1.019 (0.991, 1.047)	0.180
Sex				
Female	Reference			
Male	0.541 (0.255, 1.147)	0.109		
ALT/ULN	1.019 (0.961, 1.080)	0.538		
AST/ULN	1.052 (0.965, 1.146)	0.251		
GGT (U/L)	1.003 (1.000, 1.005)	0.033	1.002 (0.998, 1.005)	0.332
Tbil (μmol/L)	1.026 (1.011, 1.042)	0.001	1.010 (0.994, 1.025)	0.219
ALP (U/L)	1.004 (1.000, 1.007)	0.028	1.000 (0.996, 1.005)	0.814
ALB (g/L)	0.878 (0.823, 0.936)	<0.001	0.982 (0.904, 1.066)	0.662
GLB (g/L)	1.046 (1.003, 1.090)	0.035	1.085 (0.988, 1.191)	0.089
Hb (g/L)	0.985 (0.968, 1.003)	0.102		
PLT ($\times 10^9$/L)	0.993 (0.988, 0.998)	0.005	0.996 (0.990, 1.002)	0.180
RDW (%)	1.533 (1.248, 1.885)	<0.001	1.325 (1.045, 1.681)	0.020
IgG/ULN	2.222 (0.990, 4.985)	0.053	0.216 (0.035, 1.318)	0.097
PT (s)	1.759 (1.386, 2.232)	<0.001	1.514 (1.138, 2.014)	0.004

ALT, alanine aminotransferase; CI, confidence interval; ULN, upper limit of the normal range; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; Tbil, total bilirubin; ALP, alkaline phosphatase; ALB, albumin; GLB, globulin; Hb, hemoglobin; PLT, platelet; RDW, red cell distribution width; IgG, immunoglobulin; PT, prothrombin time; OR, odds ratio.

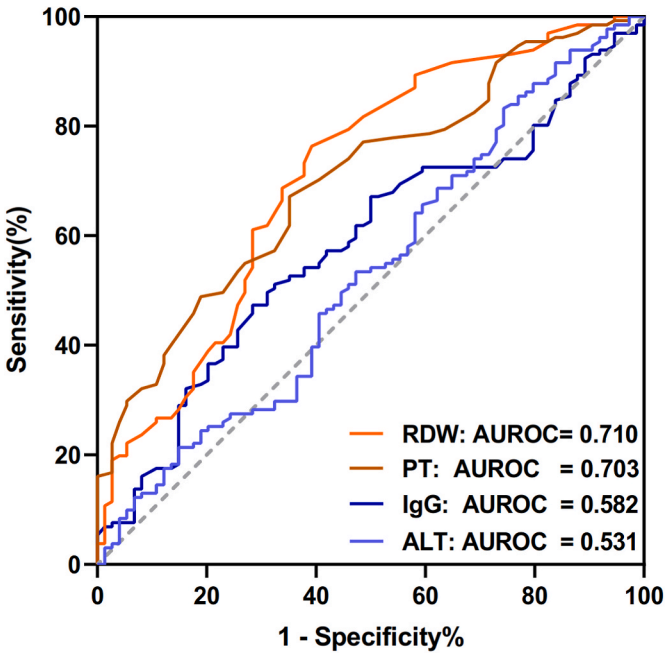

Fig. 4. Receiver operating characteristic curve of different parameters for predicting advanced inflammation in patients with AIH.

Table 3
Risk factors of advanced inflammation in patients with autoimmune hepatitis without advanced fibrosis.

Variable	Univariate		Multivariate	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Age (years)	1.046 (1.009, 1.085)	0.015	1.052 (1.007, 1.100)	0.024
Sex				
Female	Reference			
Male	0.539 (0.184, 1.580)	0.260		
ALT/ULN	1.070 (0.983, 1.165)	0.117		
AST/ULN	1.184 (1.032, 1.359)	0.016	1.159 (0.984, 1.366)	0.077
GGT (U/L)	1.002 (0.999.1.005)	0.171		
Tbil (μmol/L)	1.030 (1.010, 1.050)	0.003	1.007 (0.988, 1.026)	0.486
ALP (U/L)	1.003 (0.997, 1.008)	0.321		
ALB (g/L)	0.812 (0.723, 0.911)	<0.001	0.942 (0.807, 1.099)	0.448
GLB (g/L)	1.022 (0.967, 1.080)	0.450		
Hb (g/L)	0.978 (0.954, 1.004)	0.099	1.001 (0.966, 1.038)	0.960
PLT ($\times 10^9$/L)	0.995 (0.988, 1.001)	0.123		
RDW (%)	1.715 (1.281, 2.297)	<0.001	1.506 (1.012, 2.241)	0.044
IgG/ULN	2.378 (0.648, 8.724)	0.191		
PT (s)	1.719 (1.201, 2.462)	0.003	1.297 (0.853, 1.971)	0.225

ALT, alanine aminotransferase; CI, confidence interval; ULN, upper limit of the normal range; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; Tbil, total bilirubin; ALP, alkaline phosphatase; ALB, albumin; GLB, globulin; Hb, hemoglobin; PLT, platelet; RDW, red cell distribution width; IgG, immunoglobulin; PT, prothrombin time; OR, odds ratio.

0.024) and PT (OR = 1.584, 95 % CI: 1.089–2.304, $P = 0.016$) were independently associated with advanced liver inflammation in AIH patients without cirrhosis. The performance of predicting advanced inflammation were also evaluated (Fig. S8B) and the AUROC of RDW (0.738, 95%CI: 0.656–0.820) was highest.

4. Discussion

AIH is a chronic and progressive inflammation of liver disease, and most identified in middle-aged women [15]. Our study suggested that most patients with AIH were female, and the median age was 54.0 years. One-third of patients had cirrhosis at the time of AIH diagnosed [2] and our study also found that 28.3 % of AIH patients had liver cirrhosis, which is consist with previous reported [16,17]. Moreover, we found that 52.7 % of AIH patients had advanced fibrosis at the time of diagnosis. Thus, early diagnosis of AIH is important for the management of AIH.

Serum transaminase and IgG levels are commonly used to assess hepatitis activity. A previous study showed that ALT, IgG and several other serum variables were significantly positively correlated with liver inflammatory activity in type 1 AIH patients [18]. The present study also found that the proportion of advanced inflammation activity was higher in patients with elevated ALT level compared to patients with normal ALT level. Furthermore, the proportion of advanced inflammation activity was higher in AIH patients with elevated IgG (69.4 %) compared to AIH patients with normal IgG (57.7 %). The addition of normal IgG level only slightly reduced the proportion of advanced inflammation activity, with 51.7 % of patients with normal ALT and IgG levels showing advanced inflammation activity. Our study demonstrated that biochemical markers such as ALT and IgG levels are suboptimal to indicated histologic activity in patients with AIH.

Currently, noninvasive tests have widely used for the assessment of fibrosis in patients with AIH [2,19–21]. It is reported that if the presence of liver fibrosis could be ruled out in CHB patients, the probability of significant inflammation is reduced [10]. They demonstrated that the very low probability (<5 %) of significant inflammation among patients with CHB with ALT below twice ULN in the absence of significant fibrosis [10]. However, in our study, as high as 35 % of patients with normal ALT level without advanced liver fibrosis had advanced inflammation and the proportion was as high as 26.7 % in patients with normal ALT level and IgG in the absence of advanced fibrosis in patients with AIH. Similarly, the proportion of advanced inflammation was surprisingly high in AIH patients with normal ALT and IgG levels with the absence of cirrhosis. In this multicentric study, our findings support the notion that liver biopsy is recommended to evaluate the liver inflammatory in AIH patients with normal ALT and IgG levels even if the presence of advanced fibrosis or cirrhosis can be ruled out.

Identifying the risk factors associated with liver histologic inflammation in AIH patients is important for management of AIH. RDW and PT were identified as factors associated with advanced inflammation in AIH patients in the present study and RDW showed relatively high predictive values of advanced inflammation. In our previous study with limited sample size, we also found that RDW could independently predict significant liver inflammation in patients with AIH [8]. RDW reflects the size variability of erythrocytes in the complete blood and can be used to differentiate the possible cause of anemia together with the mean corpuscular volume more accurately [22]. The increased RDW in AIH patients may be associated with inflammation activity, inflammatory cytokines, portal hypertension [8]. However, more studies are needed to explore the mechanism of elevated RDW in AIH patients. PT is used as a key biochemical marker in liver function, depends on the activity of coagulation factors which derived from liver synthesis, prolonged PT may reflect liver injury in liver disease [23]. Moreover, PT was reported as a risk factor for predicting advanced liver fibrosis in patients with AIH [24].

This study has several limitations. First, our study was a retrospective study and the sample size was relatively small. Further studies with large samples are needed to validate our findings. Second, the cross-sectional study was based on ALT level and IgG level near the time of liver biopsy, and lack of the long-term follow-up data. Thus, whether serum ALT and IgG levels within the normal ranges could be used as surrogate markers for histological disease activity in AIH patients during treatment deserves further investigation. Third, due to the lack of prognostic data of these patients, we could not assess the relationship between the histological activity and prognosis.

In conclusion, the proportion of advanced inflammation was high in patients with AIH with or without advanced fibrosis or cirrhosis, despite normal ALT and IgG levels. Further studies are needed to explore noninvasive markers to evaluate the liver inflammatory activity in patients with AIH.

Credit author statement

All authors contributed to this study at different levels. All authors read and approved the final version.

Study concept and design (Chao Wu, Rui Huang, Yuanwang Qiu); acquisition of data (Jiacheng Liu, Jian Wang, Weihua Wu, Huali Wang, Yilin Liu, Zhiyi Zhang, Shaoqiu Zhang, Yifan Pan, Yiguang Li, Weimao Ding, Li Zhu, Chuanwu Zhu, Jie Li); statistical analysis and interpretation of data (Yun Chen, Jiacheng Liu, Weihua Wu); drafting of the manuscript (Yun Chen, Jiacheng Liu, Jian Wang); critical revision of the manuscript for important intellectual content (Rui Huang, Chao Wu).

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Declaration of competing interest

All authors have no disclosures.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2023.100220.

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