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ORIGINAL ARTICLE

Retrospective Cohort Study

Evaluation of autoimmune phenomena in patients with nonalcoholic fatty liver disease on the basis of liver pathology

Yu-Jin Zhu, Yan Zhang, Yao Rao, Yong Jiang, Yong-Gang Liu, Jian-Zhou Li, Jia-Qi Yuan, Ying Zhao, Wen-Wen Zheng, Lin Ma, Chun-Yan Wang, Jia Li

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Abstract

BACKGROUND

Autoimmune phenomena can be used in some patients with nonalcoholic fatty liver disease (NAFLD) in the clinic, but these patients are not autoimmune hepatitis patients.

AIM

To determine whether autoimmunity is present in patients with NAFLD, this study was performed.

METHODS

A total of 104 patients with NAFLD diagnosed by liver biopsy at Tianjin Second

People's Hospital between 2019 and 2023 were enrolled. The patients were divided into three groups according to their biopsy results: The NAFL (n = 36), nonalcoholic steatohepatitis (n = 51), and liver cirrhosis groups (n = 17).

RESULTS

The differences in IgA, an immune marker, among the three groups of patients were statistically significant (P = 0.025). In all NAFLD patients, antinuclear antibody and anti-smooth muscle antibody were the most common autoantibodies. The antinuclear antibody detection rate was the highest at 48.1%. The cirrhosis group had the highest autoantibody positivity rate (64.7%). Portal enlargement is also common in NAFLD patients. The rates of positivity for portal lymphoplasmacytic infiltration, small bile duct hyperplasia and interfacial hepatitis were highest in the cirrhosis group; the differences between the cirrhosis group and the other two groups were significant (P < 0.05). Hepatocellular rosettes were identified only in the cirrhosis group (11.8%).

CONCLUSION

Autoimmune phenomena occur in NAFLD patients, especially in patients with NAFLD-related cirrhosis, in whom this phenomenon may be more pronounced.

Key Words: Nonalcoholic fatty liver disease; Liver pathology; Autoantibody; Autoimmunity; Clinical indicator

Core Tip: Based on biopsy results, we divided 104 patients into three groups for a retrospective cohort study to assess the immune phenomena in patients with nonalcoholic fatty liver disease (NAFLD). Final discovery: NAFLD patients were positive for several autoantibodies. ANA is the most common antibody in NAFLD patients. Portal enlargement was the most common alteration. The incidences of limiting plate disruption and small bile duct hyperplasia are high in patients with NAFLD-related cirrhosis. Some patients had hepatocellular rosettes and were positive for antibodies. These findings indicate that autoimmune phenomena may be more pronounced in patients with NAFLD-related cirrhosis.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of fatty deposits in the liver that can be detected by imaging or histologic examination when drug factors, heavy alcohol consumption, and hereditary diseases have been excluded as causes. The incidence of NAFLD is increasing annually. In recent years, the incidence rate of NAFLD in adults has reached approximately 6.3%-45% globally, and the incidence rate is approximately 29.62% in Asia[1,2]. This increase in incidence is related to lifestyle, regional factors, dietary differences, genetic background, *etc*. The disease spectrum of NAFLD can be categorized into simple fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). NAFLD has an insidious and slow progression, and approximately 15% patients have NASH. However, the incidence of cirrhosis is several times greater in patients with NASH than in patients with NAFLD.

Autoantibodies can be produced through the stimulation of proinflammatory factors, and IFN-α produced by the exogenous stimulation of dendritic cells further increases the production of cytokines. Subsequently, immune cells differentiate into autoimmune plasma cells and produce autoantibodies. This consequence is a nonspecific immune response, and a small number of autoantibody-positive cells can be found in the healthy population[3-5]. Autoimmune hepatitis (AIH) is often suspected when autoantibodies are detected. As reported in 2022 in the article "Autoimmune serology testing in clinical practice: An updated roadmap for the diagnosis of autoimmune hepatitis[6]", antinuclear antibody (ANA) is the most sensitive marker of AIH, and ANA and smooth muscle antibodies (SMA) are the autoantibodies with the highest positivity rates in AIH patients. On this basis, we found that NAFLD patients also exhibit autoimmune phenomena. Previous studies have indicated that the rate of ANA and/or SMA positivity in NASH patients is approximately 30%[4], suggesting that autoimmunity may be present in NASH patients. However, studies on the presence of autoimmunity in the overall NAFLD population are lacking. Our main aim was to further explore the autoimmune phenomenon in NAFLD patients on the basis of previous studies. We included three histological stages of NAFLD and conducted a systematic review of clinical features, biochemical parameters, autoantibody detection rates, and changes in hepatic pathological changes in three stages; such analyses have been uncommon in previous studies.

Table 1 Comprehensive diagnosis score system for autoimmune hepatitis (1999)

Parameters/clinical characteristics	Scoring	Parameters/clinical characteristics	Scoring
Women	+2	Drug history	
Ratio of ALP (normal upper limit multiple) to AST (or ALT) (normal upper limit multiple)		Positive	-4
< 1.5	+2	Negative	+1
1.5-3.0	0	Average alcohol intake (g/d)	
> 3.0	-1	< 25	+2
Serum γ-Ratio of globulin or IgG to normal value		> 60	-2
> 2.0	+3	Histological examination of the liver	
1.5-2.0	+2	Interfacial hepatitis	+3
1.0-1.5	+1	Mainly lymphocyte-plasma cells	+1
< 1.0	0	Hepatocytes showed rosette-like changes	+1
ANA, ASMA or LKM-1 titer		No such manifestations	-5
> 1:80	+3	Bile duct alterations	-3
1:80	+2	Other changes	-3
1:40	+1	Other immune diseases	+2
< 1:40	0	Other available parameters	
AMA positive	-4	Other specific autoantibodies (SLA/LP, LC-1, ASGPR, pANCA) are positive	+2
Hepatitis virus markers		HLA-DR3 or DR4	+1
Positive	-3	Response to treatment	
Negative	+3	Completely; recurrence	+2; +3
Interpretation of total points			
Before treatment		Before treatment	
Clear AIH	≥ 16	Clear AIH	≥ 18
Possible AIH	10-15	Possible AIH	12-17

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ANA: Antinuclear antibody; AMA: Anti-mitochondrial antibody; ASMA: Anti-smooth muscle antibody; LKM-1: Anti-liver-kidney microsome type 1; AIH: Autoimmune hepatitis.

MATERIALS AND METHODS

Data collection

A total of 104 patients who attended Tianjin Second People's Hospital and underwent liver puncture pathology to confirm the diagnosis of NAFLD between 2019 and 2023 were retrospectively included.

All the included patients met the requirements stipulated in the Guidelines for Prevention and Control of Nonalcoholic Fatty Liver Disease (2018 Update): Imaging or histologic evidence of diffuse hepatic steatosis and the absence of ethanol abuse and other causes that can lead to hepatic steatosis. The patients were diagnosed *via* liver biopsy with clear pathological findings. Pathologically, they are categorized into the following three groups: (1) Simple fatty liver (NAFL); (2) NASH; and (3) Fatty cirrhosis[7].

The exclusion criteria were as follows: (1) Alcoholic liver disease and drug-induced liver disease; (2) AIH[8] (Table 1 and Table 2); (3) Viral hepatitis; (4) Incomplete information; (5) No histologic examination of liver puncture; and (6) HCC.

Liver-controlled attenuation parameters (CAPs) were determined as follows: CAP values were measured *via* transient elastography (FibroScan 502, Echosens, France). The subjects who underwent the procedure had an empty stomach for 2 hours before examination. The physician was located on the right side of the subject, and the probe was placed in the 7th, 8th and 9th intercostal spaces of the subject; the probe was placed as close to perpendicular to the plane as possible. CAP was measured *via* an M-type probe (3.5 MHz). The CAP values (in dB/m) of 3 cm^3 of subcutaneous liver tissue, ranging from 2.5 cm to 6.5 cm, were measured and recorded. Biochemical indices were assessed with a HITACH1 automatic biochemical instrument-7180 (purchased from Japan Co., Ltd.). Routine blood detection was performed with a Syex XN-2000 (purchased from Syex, Japan). The ANA, anti-mitochondrial antibody (AMA), and ASMA levels in human laryngeal epithelioma cancer (Hep-2) cells, frozen rodent liver tissue, and kidney tissue substrates were measured by indirect

Table 2 Simplified diagnosis of autoimmune hepatitis by the international autoimmune hepatitis group

Variables	Criteria	Score	Remarks
ANA or SMA	≥ 1:40	1	It is equivalent to the lowest titer of ANA 1:100 commonly used in China
ANA or SMA	≥ 1:80	2	Maximum 2 points when multiple items appear at the same time
LKM-1	≥ 1:40	2	
SLA	Positive	2	
IgG	> upper limit of normal value. > 1.1 times the upper limit of normal value	1; 2	
Liver histology	AIH compliant. Typical AIH manifestations	1; 2	Interfacial hepatitis, lymphocyte-plasma cells infiltration in the confluent zone and lobules, rosettes of hepatocytes, and penetration are considered to be characteristic hepatic histologic changes, with three of the four being typical
Excluding viral hepatitis	Yes	2	
= 6 points: Suspected AIH ≥ 7 points: Confirmed AIH			

ANA: Antinuclear antibody; SMA: Smooth muscle antibodies; LKM-1: Anti-liver-kidney microsome type 1; SLA: Anti-soluble liver antigen; AIH: Autoimmune hepatitis.

immunofluorescence. The reagents used were purchased from Omeng, Germany. The AMA-M2, sp100, and gp210 levels were measured *via* linear immunofluorescence (LIA) using IMTEC-Liver-LIA 5, which was purchased from Human, Germany[9]. The initial dilution was 1:100, but owing to the differences in detection reagents, 1:40, which is the most commonly used starting dilution titer internationally, was utilized. To ensure the rigor of the study, we did not include titers and used "positive" and "negative" to express the results. The length of the ultrasound-guided liver puncture samples was > 1.0 cm in all patients. The samples were embedded in paraffin after 10% neutral fixation, dehydration and immersion and then stained with HE. Special staining included Masson staining (to observe fibrosis), reticular fiber staining (to observe fibrosis), Prussian blue iron staining (to observe iron deposition and waxy deposition), and immunohistochemical staining of cytokeratin (CK19) (to observe bile duct hyperplasia). Pathological tests were performed by two experienced pathologists and ultimately confirmed by a chief pathologist.

Statistical analyses were performed with SPSS 25.0 software. Normal data were analyzed by one-way analysis of variance and are expressed as mean ± SD. Nonnormal data were analyzed by the rank-sum test and are expressed as median (25^{th}-75^{th} percentiles). Count data are expressed as rates (%), and the χ^2 test was used. The Bonferroni method was applied for comparisons between groups. Differences were considered statistically significant at $P < 0.05$.

This research study was conducted in strict accordance with the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Second People's Hospital of Tianjin.

RESULTS

In general, the male-female ratio of all patients was 47:57, and the sex distributions of the groups did not significantly differ. The mean age was 46.0 ± 14.8 years, with means of 46.8 ± 2.2 years in the NAFL group, 42.4 ± 2.1 years in the NASH group, and 55.0 ± 3.4 years in the cirrhosis group. The difference in age between the cirrhosis group and the NASH group was statistically significant ($P < 0.05$).

Comparison of the body mass index and CAP among the three groups

The mean CAPs in the NAFL, NASH, and cirrhosis groups were 245.65 ± 35.672 dB/m, 308.47 ± 38.663 dB/m, and 270.20 ± 55.695 dB/m, respectively. The mean CAP of all three groups was greater than the normal level (> 240 dB/m), and it was significantly greater in the NASH group. The differences among the three groups were statistically significant ($P < 0.001$), and the differences between the NASH group and the other two groups were statistically significant ($P < 0.001$ and $P = 0.01$). The mean body mass index (BMI) were 24.75 ± 2.520 kg/m^2 in the NAFL group, 28.35 ± 4.269 kg/m^2 in the NASH group and 29.38 ± 4.499 kg/m^2 in the cirrhosis group. The BMIs of all three groups were in the overweight range and tended to increase with disease progression. The differences among the three groups were significant ($P = 0.001$), and the differences between the NAFL group and the other two groups were significant ($P = 0.003$ and 0.003). Data were missing for some patients.

Comparison of the prevalence of diabetes and hypertension in NAFLD patients

Diabetes mellitus (23.1%) was found in 24 patients with NAFLD: 6 (16.7%) in the NAFL group, 12 (23.5) in the NASH group, and 6 (35.3%) in the cirrhosis group. Furthermore, 29 NAFLD patients were diagnosed with hypertension (27.9%): 5 (13.9%) in the NAFL group, 17 (33.3%) in the NASH group, and 7 (41.2%) in the cirrhosis group. The overall prevalence

rates of diabetes and hypertension were similar. The prevalence rates of the three groups of patients tended to increase with the progression of the disease. The differences in the incidence of diabetes and hypertension among the three groups were not statistically significant.

Comparison of biochemical indices among the three groups

The differences among the three TG groups were significant ($P < 0.001$), and the differences between the NASH group and the other two groups were statistically significant ($P < 0.001$ and $P = 0.001$). The differences in cholesterol, high density lipoprotein, low density lipoprotein, and fasting blood glucose levels among the three groups were not statistically significant. However, the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels significantly differed among the three groups ($P < 0.001$ and $P < 0.001$). The ALT levels in the NASH group were greater than those in the other two groups ($P < 0.001$ and $P = 0.004$), and the AST levels in the NAFL group were lower than those in the other two groups ($P < 0.001$ and $P = 0.037$). The alkaline phosphatase or glutamyl transferase levels did not significantly differ among the three groups. The total bilirubin and direct bilirubin levels tended to increase with disease progression, but no significant differences were identified among the three groups. In terms of immunological indices, the differences in IgA among the three groups were significant ($P < 0.05$), and the difference between the NAFL group and the cirrhosis group was statistically significant ($P = 0.02$) (Table 3).

Comparison of autoantibody detection rates among the three groups of NAFLD patients

A total of 51% patients with NAFLD had autoantibodies. The autoantibody positivity rate in NAFLD patients was highest for ANA (48.1%), followed by anti-SMA (ASMA) (6.7%), anti-SSA-RO60 (5.8%), anti-sp100 (3.9%), and anti-SSA-RO52 (3.9%). The rate of positivity for the fluorescent subtypes of ANA was highest in nuclear speckles, followed by those in cytoplasmic speckles, the nuclear homogeneous area, and nucleoli. The rates were lowest for discrete nuclear dots and cytoplasmic fibrils. Some NAFLD patients are positive for AMA (M2), anti-sp100, and anti-gp210. The positivity rates of anti-gp210 and anti-sp100 antibodies tended to decrease with disease progression, and the autoantibody positivity rate did not significantly differ among the three groups.

Among the patients in the cirrhosis group, 64.7% were positive for autoantibodies, and this rate was greater than those in the other two groups (55.6% and 43.1%, respectively). There was no statistically significant difference among the three groups. The percentages of ANA-, anti-SSA-RO52/60- and anti-SSB-positive patients were greater in the cirrhosis group than in the other two groups, but these rates did not significantly differ among the three groups. The rates of nuclear granular ANA, ASMA, anti-gp210, and anti-sp100 positivity were the highest in the NAFL group (Table 4).

Comparison of pathological microscopic features among the three groups of NAFLD patients revealed the following

In addition to extrahepatic steatosis, ballooning, and lobular inflammation, the pathological microscopic changes in NAFLD patients included portal enlargement, perisinusoidal fibrosis, small bile duct changes, interface hepatitis, and hepatocellular rosettes. The positivity rate was highest for portal enlargement (83.7%), followed by interface hepatitis (18.3%), small bile duct hyperplasia (16.3%), portal lymphoplasmacytic infiltration (9.6%), bile duct paucity (2.9%) and hepatocellular rosettes (1.9%). The rates of positivity for portal area enlargement were highest in the NASH group; the differences in the rates of positivity for portal area enlargement were not statistically significant among the three groups. The rates of positivity for portal lymphoplasmacytic infiltration were highest in the cirrhosis group, and the differences between the cirrhosis group and the other two groups were statistically significant ($P < 0.05$). The positivity rate of small bile duct hyperplasia increased with disease progression and was significantly greater in the cirrhosis group. The incidence of small bile duct hyperplasia significantly differed among the three groups of patients ($P < 0.001$), including between the cirrhosis group and the other two groups ($P < 0.05$). Bile duct paucity occurred in only 3 patients, and the percentage of positive patients was high in the cirrhosis group (11.8%). However, the difference was not statistically significant. The percentage of patients with interface hepatitis increased significantly with disease progression in the cirrhosis group ($P < 0.001$), and the differences between the cirrhosis group and the other two groups were statistically significant ($P < 0.001$ and $P = 0.001$). Hepatocellular rosettes were present only in patients in the cirrhosis group ($P = 0.025$) (Table 5).

DISCUSSION

NAFLD has become the foremost cause of liver function abnormalities. It is related to the development of type 2 diabetes mellitus, coronary artery heart disease, and other diseases and seriously jeopardizes people's health. Previous studies have shown that the rate of autoantibody positivity in NASH patients is greater than that in the healthy population, suggesting that the autoimmune phenomenon may exist in NASH patients. To further explore the autoimmune phenomenon in the overall NAFLD population, we included 104 patients diagnosed with NAFLD by liver puncture biopsy at our hospital within 4 years and compared the biochemical indices, autoantibody positivity rates, and hepatic pathological manifestations of these patients to assist in the diagnosis and treatment of NAFLD at different stages. This study has several main findings. NAFLD is a highly heterogeneous disease that is closely associated with metabolic dysfunction diseases, such as obesity, type 2 diabetes and metabolic syndrome. We found that triglyceride (TG) content was not proportional to the severity of the disease, and the accumulation of TG was previously shown to be the first step in the pathological development of NAFLD progressing to NASH[10,11]. In a study by Li *et al*[12], the TG content was significantly reduced only in patients with cirrhosis[12], which is consistent with our findings. ALT and AST are usually used to reflect liver damage, and Ma *et al*[13] reported that 25% of NAFLD patients and 19% of NASH patients had

Table 3 Comparison of biochemical indexes among the three groups

	NAFL (*n* = 36)	NASH (*n* = 51)	Cirrhosis (*n* = 17)	F/H	*P* value
FBG	5.65 (5.20, 6.17)	6.07 (5.49, 6.64)	5.04 (4.86, 6.87)	4.413	0.110
CHO	5.50 (4.72, 6.36)	5.71 (5.06, 6.88)	5.14 (4.24, 6.11)	3.614	0.164
TG	1.44 (0.97, 1.69)[b]	1.93 (1.46, 2.46)	1.25 (0.97, 1.46)[c]	21.567	0.000
HDL	1.47 (1.26, 1.79)	1.37 (1.24, 1.53)	1.42 (1.15, 1.56)	3.219	0.200
LDL	3.59 (2.08, 4.42)	3.82 (3.03, 4.57)	3.23 (2.54, 3.92)	4.738	0.094
ALT	31.55 (21.80, 63.45)[d]	83.50 (50.00, 156.60)	33.30 (16.95, 73.95)[e]	20.514	0.000
AST	24.00 (18.33, 35.10)	46.00 (34.10, 76.00)[f]	42.70 (24.35, 53.50)[g]	26.408	0.000
ALP	79.50 (68.00, 100.23)	77.80 (66.30, 87.30)	82.60 (70.20, 107.35)	0.866	0.648
GGT	89.95 (39.53, 129.03)	69.00 (45.50, 100.90)	58.80 (30.95, 93.45)	1.718	0.424
TBIL	15.10 (12.23, 25.15)	13.90 (12.20, 16.60)	17.81 (12.10, 22.75)	5.088	0.079
DBIL	1.70 (1.40, 3.85)	1.90 (1.40, 2.40)	2.20 (1.20, 2.95)	0.446	0.800
IgG	12.16 (10.64, 13.52)	10.95 (10.04, 13.09)	11.77 (9.83, 15.33)	2.586	0.275
IgM	0.89 (0.72, 1.21)	0.85 (0.60, 1.09)	1.07 (0.85, 1.36)	3.501	0.174
IgA	2.46 ± 0.89[a]	2.72 ± 0.88	3.21 ± 1.13	3.839	0.025

[a]*P* = 0.02 *vs* cirrhosis group.
[b]*P* < 0.001 *vs* cirrhosis group.
[c]*P* = 0.001 *vs* NASH group.
[d]*P* < 0.001 *vs* NASH group.
[e]*P* = 0.004 *vs* NASH group.
[f]*P* < 0.001 *vs* NAFL group.
[g]*P* = 0.037 *vs* NAFL group.
FBG: Fasting blood glucose; CHO: Cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Glutamyl transferase TBIL: Total bilirubin; DBIL: Direct bilirubin.

normal ALT levels[13]. In this study, the ALT and AST levels were greater than normal in 74.5% and 62.8% of the patients in the NASH group, respectively. Furthermore, these levels were significantly greater than those in the NAFL and cirrhosis groups, suggesting that liver inflammation was more pronounced in the NASH group.

Immunoglobulins affect cellular immunity and can also activate the humoral immune response, which has a bidirectional regulatory effect on the immune response[14]. With the progression of NAFLD, the level of immunoglobulin in the serum gradually increases. These findings suggest that immunoglobulin deposition occurs in the hepatocytes of patients with NAFLD and is involved in the pathological process of liver injury, which is proportional to the severity of fatty liver disease and closely correlated with indicators of liver fibrosis[15]. Elevated serum IgA levels are common in patients with NAFLD and are an independent predictor of advanced liver fibrosis[16]. In this study, we confirmed that the difference in the immunomarker IgA among the three groups was statistically significant and that the cirrhosis group had significantly higher levels of IgA than did the NAFL group. This finding is consistent with the above findings, but the IgG and IgM levels did not significantly differ among the three groups.

This study revealed that 51% patients were positive for at least one autoantibody. The rates of positivity were highest for ANA (48.1%) and ASMA (6.7%), and the highest rates of positivity for ANA subtypes were those for nuclear granulomas (24%) and cytoplasmic granulomas (9.6%). These positivity rates are greater than those previously reported for NAFLD patients of approximately 21%-35% for autoantibodies and approximately 23% for ANA. This discrepancy may be due to the limited inclusion of autoantibodies in previous studies and related to geographic region, ethnicity, and population[3,17]. The rates of speckled and nuclear homogeneous ANA subtypes were high in previous studies, but articles have described ANA subtypes. Thus, additional multicenter studies are needed. ASMA is most commonly observed in type I AIH patients, with a positivity rate of approximately 3%-5% in patients with NAFLD[6,18]. This rate is similar to that of the present study. AMA (M2), anti-sp100, and anti-gp210 positivity was detected in some NAFLD patients, and these antibodies were specific for primary biliary cholangitis (PBC). Although PBC was excluded in the enrolled patients after confirmation of the diagnosis by liver puncture, the possibility that the patients were in the early stage of PBC or that the amount of punctured tissue was limited was not excluded. This study also revealed that the cirrhosis group had the highest positivity rate for anti-SSA and anti-SSB. Previous studies have reported that anti-SSA-RO and anti-SSB-La are associated with autoimmune diseases, such as SLE and SS. However, the significance of their presence in patients with NAFLD remains unclear, and further studies are needed. We also found that the autoantibody positivity rate was not significantly different among the three groups. However, in the cirrhosis group, the autoantibody positivity rate was 64.7%, which was greater than that in the other two groups. Current research suggests that autoantibodies may be associated with an immune predisposition that is related to the *HLA* genotype[19]. Loria *et al*[20]

Table 4 Comparison of autoantibody detection rates in three groups, *n* (%)

	NAFLD (*n* = 104)	NAFL (*n* = 36)	NASH (*n* = 51)	Cirrhosis (*n* = 17)	H	*P* value
Antibody[1]	53 (51.0)	20 (55.6)	22 (43.1)	11 (64.7)	0.702	0.242
ANA	50 (48.1)	18 (50)	21 (41.2)	11 (64.7)	2.909	0.233
Cytoplasmic speckled	10 (9.6)	3 (8.3)	4 (7.8)	3 (17.6)	1.514	0.521
Nuclear speckled	25 (24.0)	11 (30.6)	10 (19.6)	4 (23.5)	1.388	0.500
Nuclear homogeneous	9 (8.6)	3 (8.3)	5 (9.8)	1 (5.9)	0.255	0.880
Nuclear discrete nuclear nots	2 (1.9)	1 (2.8)	0	1 (5.9)	2.552	0.279
Nuclear nucleolar	8 (7.7)	2 (5.6)	3 (5.0)	3 (17.6)	2.839	0.242
Cytoplasmic fibrillar	1 (1.0)	0	1 (2.0)	0	1.049	0.592
AMA (M2)	3 (2.9)	1 (2.8)	2 (3.9)	0	1.435	1
ASMA	7 (6.7)	4 (11.1)	2 (3.9)	1 (5.9)	1.780	0.450
Anti-sp100	4 (3.9)	3 (8.3)	1 (2.0)	0	2.286	0.374
Anti-gp210	2 (1.9)	1 (2.8)	1 (2.0)	0	0.703	1
Anti-SSA-RO52	4 (3.9)	2 (5.6)	1 (2.0)	1 (5.9)	1.476	0.493
Anti-SSA-RO60	6 (5.8)	2 (5.6)	2 (3.9)	2 (11.8)	1.707	0.448
SSB-La	3 (2.9)	2 (5.6)	0	1 (5.9)	3.437	0.167
Others[2]	10 (9.6)	3 (8.3)	4 (7.8)	3 (17.6)	1.643	0.494

[1]Autoantibody was positive for any autoantibody.
[2]Anti-Jo-1, ACA, Anti-ribosomal p protein antibody, (anti nucleosome antibody, ANuA), Anti-U1-snRNP antibody, Anti-SM-D antibody.
NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; ANA: Antinuclear antibody; AMA: Anti-mitochondrial antibody; ASMA: Anti-smooth muscle antibody.

Table 5 Comparison of pathologic microscopic features in three groups, *n* (%)

	NAFLD (*n* = 104)	NAFL (*n* = 36)	NASH (*n* = 51)	Cirrhosis (*n* = 17)	*P* value
Portal enlargement	87 (83.7)	27 (75.0)	46 (90.2)	14 (82.4)	0.188
Portal lymphoplasmacytic infiltration	10 (9.6)	1 (2.8)[a]	3 (5.9)[a]	6 (35.3)	0.0022
Small bile duct changes					
Hyperplasia	17 (16.3)	3 (8.3)[b]	5 (9.8)[1,b]	9 (52.9)[2]	< 0.001
Paucity	3 (2.9)	0	1 (2.0)	2 (11.8)	0.069
Interface hepatitis	19 (18.3)	1 (2.8)[b]	8 (15.7)[a]	10 (58.8)	< 0.001
Hepatocellular rosettes	2 (1.9)	0	0	2 (11.8)	0.025

[1]1 patient with both bile duct paucity and hyperplasia.
[2]2 patients had both bile duct paucity and hyperplasia.
[a]$P < 0.05$ *vs* cirrhosis group.
[b]$P < 0.001$ *vs* cirrhosis group.
NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.

suggested that TG is responsible for the production of inflammatory factors by adipose tissue/monocytes and thus leads to liver injury and ANA production. Another study revealed that the production of autoantibodies in NAFLD may be a result of the accumulation of hepatic NKT cells, which have been reported to promote fibrosis in various liver diseases [21-23]. However, a consensus as to whether autoantibody positivity is associated with hepatocellular inflammation, fibrosis, and a worse prognosis in patients with NAFLD is lacking. Although evidence suggests that autoantibodies and immunoglobulins are associated with histologically higher grades of inflammation or fibrosis[24-27], some studies have questioned this conclusion[17,19,20]. More studies are needed to clarify the relationship between autoantibodies and NAFLD-related cirrhosis.

In addition to the characteristic NAFLD pathological manifestations of steatosis, ballooning, and lobular inflammation [28], other pathological changes were observed in this study. Portal enlargement (83.7%) and interface hepatitis (18.3%) were the most common pathological features. As reported by Elizabeth, portal inflammation scores are associated with a definite steatohepatitis diagnosis[27]. Pathologically, patients with cirrhosis not only exhibit collagen deposition, neovascularization, and perisinusoidal fibrosis but also exhibit small bile duct hyperplasia, interface hepatitis, and hepatocellular rosettes, which tend to increase with disease progression and increase significantly with progression to the cirrhosis stage. Typically, only a few bile ducts are present in the liver, and the biliary system is proliferative in patients with cirrhosis of different causes[29]. Multiple signaling pathways and hormones are involved in regulating bile duct proliferation. When NAFLD-related cirrhosis occurs, the number of bile ducts subsequently increases, which is consistent with our findings[30]. A recent study from the United States reported the histologic features of different histologic stages [31] and revealed that the histologic features of cirrhosis included portal inflammatory infiltration, interface hepatitis, bile duct damage, and ductular reactions. Interface hepatitis was present in 60% of NAFLD patients, and positivity was significantly increased in the cirrhosis stage, which is consistent with our findings. Hepatocellular rosettes, which are multiple hydropic degenerated hepatocytes arranged in an adenoidal pattern after an inflammatory factor attack, reflect the response of hepatocytes to injury. Hepatocellular rosettes were present in two patients in this study, and both of these rosettes appeared in the cirrhotic stage, suggesting that patients with cirrhosis may have a strong immune response.

In our study, AIH was excluded in all the patients enrolled in the group according to the AIH rating scale in the Chinese guidelines[8]. The common clinical pathological manifestations of AIH are interface hepatitis, portal lymphoplasmacytic infiltration and hepatocellular rosettes. In our study, in addition to the common pathological manifestations of extrahepatic steatosis, ballooning, lobular inflammation and perisinusoidal fibrosis, NAFLD patients also presented with the three abovementioned pathological changes. The most common pathological change was interface hepatitis (15.4%), which was mostly mild, followed by portal lymphoplasmacytic infiltration (9.6%) and hepatocellular rosettes (1.9%). We could not diagnose AIH on the basis of only pathological examination results. However, NAFLD patients with one or two typical pathological manifestations of AIH may be important for determining whether they eventually progress to AIH.

Autoimmune phenomena occur in NAFLD patients, especially in patients with NAFLD-related cirrhosis, in whom this phenomenon may be more pronounced; this finding may explain the rapid progression of the disease in some cirrhosis patients. However, evidence concerning whether hormone therapy should be applied to this group of patients is lacking because hormone therapy may improve immune-related inflammation but exacerbate steatosis in patients with NASH, which in turn further exacerbates the patient's condition.

The main limitation of this study is the uneven distribution of the number of people in each group. Further large-sample multicenter studies should be carried out, and long-term follow-up should be conducted to observe whether the immune phenomenon is related to the poor outcome of patients with NAFLD so that timely interventions can be made to slow the progression of this disease.

CONCLUSION

Autoantibodies are present in patients with NAFLD. ANA and ASMA were the most common antibodies. Some patients with NAFLD were positive for AMA (M2), anti-sp100 and anti-gp210. In terms of histology, portal enlargement was common, in addition to other characteristic changes. Patients with NAFLD-related cirrhosis had high incidences of interface hepatitis, small bile duct hyperplasia, and portal lymphoplasmacytic infiltration as well as a high autoantibody positivity rate. Furthermore, some patients had hepatocellular rosettes, suggesting that the autoimmune phenomenon may be more pronounced in patients with cirrhosis.

FOOTNOTES

Author contributions: Zhu YJ and Zhang Y wrote the manuscript; Rao Y, Zhao Y, Zheng WW, and Ma L contributed to data collation; Zhu YJ, Zhang Y and Li J contributed to statistical analysis; Liu YG contributed to liver pathology reading; Li JZ, Yuan JQ, Jiang Y, Wang CY and Li J contributed to manuscript revision; Wang CY and Li J contributed to research supervision; Wang CY contributed to project design.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Tianjin Second People's Hospital Institutional Review Board.

Informed consent statement: This study does not involve a substantial invasion of the subject's privacy and does not involve more than minimal risk to the subject. The waiver of informed consent will not adversely affect the rights and health of the subjects. This study does not involve personal privacy or commercial interests. Therefore, a waiver of informed consent has been applied to the Medical Ethics Committee of Tianjin Second People's Hospital.

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