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Autoantibody Positivity has No Impact on Histological Parameters in Nonalcoholic Fatty Liver Diseases

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Objectives: **Previous reports on association of autoantibodies with histological severity in nonalcoholic fatty liver disease (NAFLD) have revealed inconsistent results. Therefore, this study was undertaken to find the impact of autoantibodies on histological severity of NAFLD.** ***Methods:*** **All cases with histological diagnosis of NAFLD during January 2016 to January 2021 were included in the study. Laboratory parameters were recorded, and histological assessment was done. The positivity of autoimmune markers was defined as presence of either antinuclear antibody (ANA; titer >1:80), anti-smooth muscle antibodies (ASMA), or anti-liver-kidney-microsomal antibodies (LKM-1; titer >1:40). Serum levels of CK18 - M30 and PIIINP were evaluated to assess the subtle changes in necroinflammatory activity and fibrosis in the liver.** ***Results:*** **Autoantibodies were present in 281/683 (41.1%, 95% CI 37.4–44.9) patients. ANA, ASMA, ANA + ASMA was seen in 20.9% (95% CI 17.9–24.2); 14.5% (95% CI 11.9–17.4); and 5.7% (95% CI 4.1–7.7) cases, respectively. No significant difference was noted between the two groups in terms of age and metabolic tests. No significant difference was noted in the histological parameters between groups with autoantibodies positivity and no-positivity. Mean value of CK18-M30 between cases with negative autoantibody; ANA positivity; ASMA positivity; and combined positivity of autoantibody were 178.2 ± 81.8, 161.6 ± 63.7, 153.2 ± 70.3 and 169.8 ± 42.9, respectively ($P = 0.57$). However, CK18-M30 and PIIINP showed a rising trend with NAFL, NASH, NASH + AIH ($P < 0.001$).** ***Conclusions:*** **Autoantibodies noted in 41% NAFLD cases. No significant necroinflammatory activity or fibrosis associated with presence of antibodies in NAFLD cases. However, CK-18-M30 showed a rising trend from NAFL to NASH to NASH + AIH. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Serum autoantibodies remain an important tool for clinicians in the diagnosis and management of patients with autoimmune liver disease.[1,2] Simplified criteria and the Paris criteria have been internationally accepted for classifying patients as having autoimmune hepatitis and overlap syndrome, respectively.[3,4] Both of these systems take into consideration positive serum autoantibodies such as antinuclear antibody (ANA), anti-smooth muscle antibodies (ASMA), liver kidney microsomal antibodies (LKM-1), soluble liver antigens (SLA), and anti-mitochondrial antibodies (AMA) with their titers.

Insulin resistance, obesity, and other metabolic factors have been closely associated with the pathogenesis of nonalcoholic fatty liver disease (NAFLD).[5–7] However, the presence of autoantibodies has been noted variably in about 20–35% of cases of NAFLD.[8,9] Previous reports on the association of autoantibodies with histological severity in other cohorts have revealed inconsistent results. The significance and impact of these autoantibodies on the histological severity of NASH must be investigated, particularly in the Indian population. Therefore, this study was undertaken to find the impact of autoantibodies on the histological severity of NAFLD. Serum biomarkers CK18-M30 and PIIINP (amino terminal peptide of collagen type III) are used as noninvasive markers to detect subtle changes in activity that may be missed on a semi-quantitative assessment of a liver biopsy.

PATIENTS AND METHODOLOGY

Ethics Statement

All procedures performed in the current study were approved by IRB/institutional ethics committee (F.37/(1)/9/ILBS/DOA/2020/20217/291, dated 06/03/2021) in accordance with the 1964 Helsinki declaration and its later amendments. Formal, written, informed consent was not required with a waiver by the IRB/institutional ethics committee.

Study Population

It was a record-based cross-sectional study performed in the department of pathology at the Institute of Liver and Biliary Sciences, Delhi, India. A total of 1,149 cases with

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Abbreviations: AIH: autoimmune hepatitis; AMA: antimitochondrial antibody; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibodies; HAI: Histological activity Index; LKM-1: anti-liver-kidney-microsomal antibodies; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; SAF score: Steatosis, activity, and fibrosis
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a histological diagnosis of NAFLD from January 2016 to January 2021 were initially included in the study. Clinical information and laboratory parameters including liver tests, a lipid profile, fasting glucose, fasting insulin, HbA1c, and autoimmune marker status were recorded from the hospital information system. Cases with inadequate data, concomitant etiologies (viral and alcohol), and cases with other autoimmune diseases were excluded from the study. Finally, a total of 683 cases were included in the study. Clearance from the institutional ethical committee was obtained.

Autoantibodies

Autoantibodies were tested by indirect immunofluorescence. ANA with a titer of >1:80, and ASMA and LKM-1 with a titer of >1:40 were considered positive. The positivity of autoimmune markers was defined as the presence of at least one of the ANA, ASMA, or LKM-1 antibodies. The demographic, biochemical, serologic, and histological characteristics were initially compared between cases showing any antibody positivity and cases having negative autoantibodies. Following which, a comparison between these parameters was done between subgroups showing ANA, ASMA, or combined positivity for autoantibodies.

Histological Assessment

For histological assessment of activity, all the slides were retrieved, and steatosis, ballooning degeneration, fibrosis, and activity were scored. Steatosis and ballooning were scored as per the standard steatosis, activity, and fibrosis (SAF) scoring system. A modified histological activity index (HAI) for activity was calculated in each case, and the cases were categorized as having minimal, mild, moderate, or severe activity. Cases with F3–F4 fibrosis according to the SAF score were classified as having advanced fibrosis. Cases that met the criteria for NASH but also had histological features of coexisting AIH (such as a high number of lymphoplasmacytic infiltrates, interface activity, pseudorosettes, and emperipolesis) were classified as NASH-AIH overlap. In addition, these cases fulfilled the simplified criteria of the IAIG as having a score of 6 or more (suggestive of probable or definite AIH).

ELISA

Serum levels of CK18 - M30 and PIIINP were evaluated by ELISA using indirect immunofluorescence technique using Human CK-18/KRT 18 (Lot No: E7LK5B2X7T) and Human PIIINP (Lot: B8RLF132K3). We used stored plasma samples from the National Liver Disease Biobank, Delhi. A total of 683 cases were included in the study where the antibody testing was done. Of these, plasma from 130 NAFLD cases was available in the biobank, and 22 cases of AIH were used as the disease control.

Statistical Analysis

All data collected were analyzed using IBM Statistical Package for Social Sciences software (SPSS version 22, IBM Corp., NY, USA). The continuous data were represented as Mean ± SD and categorical as percentages or in terms of frequency, as appropriate. Categorical data were analyzed using Chi-square test or Fisher's exact test, as applicable. For continuous data, the ANOVA–Kruskal––Wallis test followed by post-hoc comparison by the Bonferroni method was employed after checking for normality of distribution. A *P* value of 0.05 is considered significant.

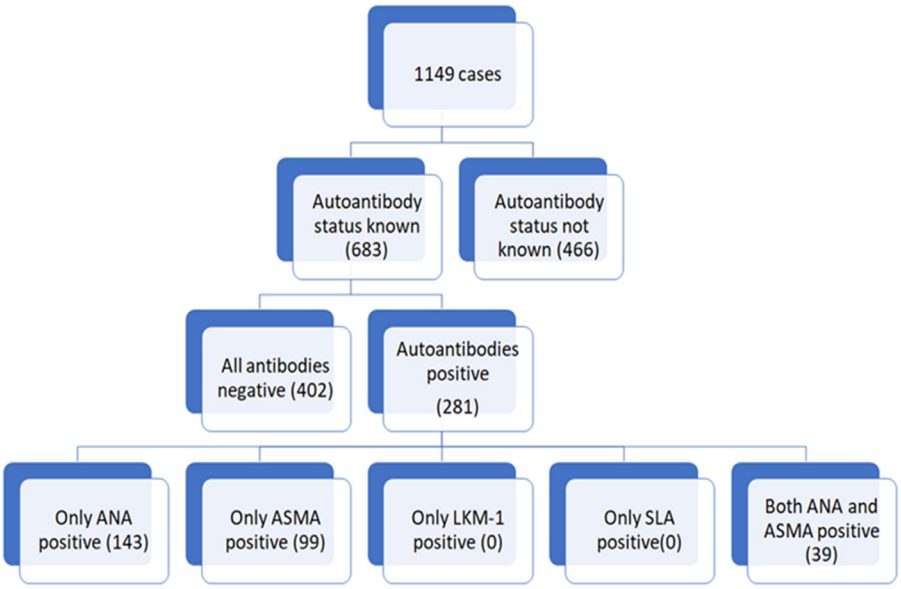

Figure 1 Distribution of cases as per autoantibody positivity.

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RESULTS

In the period between January 2016 and January 2021, 683 cases of NAFLD biopsies, fulfilling the inclusion and exclusion criteria were included in the present study. All antibodies were negative in 402/683 (58.8%) cases, and 281/683 (41.1%) cases had positivity for at least one autoantibody. Within the cases showing autoantibody positivity, 20.9% of the cases showed positivity for ANA only. ASMA positivity and combined positivity of ANA and ASMA were seen in 14.5% and 5.7% of cases, respectively. The distribution of cases with the frequency of autoantibody positivity in NAFLD cases is depicted in Figure 1.

Baseline metabolic and demographic parameters were compared between cases with positive and negative autoantibodies. The mean ages of cases with positive and negative autoantibodies were 45.8 ± 13.1 and 45.85 ± 12.2, respectively. No significant difference was noted between the two groups in terms of age, BMI, platelets, serum IgG, LFT parameters, ferritin, fasting glucose, fasting insulin, HbA1c, and lipid profile. Only the sex ratio showed a significant difference between the two groups (P = 0.001), with a female preponderance in the group showing antibody positivity. Table 1 shows a comparative analysis of baseline demographic and metabolic parameters in cases stratified by individual or combined positivity of autoantibodies and negative autoantibody status. Steatosis, ballooning degeneration, fibrosis, and activity were compared between the groups. No significant difference was noted in the histological parameters between the different groups (Table 2).

Autoantibodies were found to be positive in 119 NAFLD cases and 162 NASH cases after further testing. Whereas, among the autoantibody negatives, 179 were NAFLD and 223 were NASH. There was no significant difference noted between NAFLD and NASH in terms of autoantibody positivity (P = 0.308).

ELISA was performed using CK18-M30 and PIIINP markers on 152 plasma samples from four groups of patients for the detection of activity and fibrosis. The mean values of CK18-M30 between cases with negative autoantibody and cases with ANA positivity, ASMA positivity, and combined positivity of autoantibody were 178.18 ± 81.8, 161.6 ± 63.7, 153.2 ± 70.3, and 169.85 ± 42.9, respectively. No significant difference between the groups was noted between CK18 or PIINP values (P = 0.569 and 0.474, respectively) among the cases with autoantibody positivity versus those without (Table 3). The cutoff of CK18-M30 was 177.5 ng/ml to detect the associated activity in NAFLD cases with an area under the curve (AUC) of 0.82 (95% CI: 0.74–0.89, 0.001), a sensitivity of 76.27%, and a specificity of 75.7%. The cutoff value of PIIINP to detect advanced fibrosis was 1284 ng/ml with an AUC of 0.78 (95% CI:

Table 1 Basic Attributes According to Autoantibodies Status.

Parameters	Autoantibodies negative (n = 402)	Only ANA positive (n = 43)	Only ASMA positive (n = 99)	ANA and ASMA positive (n = 99)	P value
Age[a]	45.85 ± 12.2	46.34 ± 13.7	99 ± 44.0	39 ± 45.7	0.89
BMI (kg/m^2)[a]	27 ± 4	27 ± 4	25.9 ± 3.96	27.1 ± 4.5	0.194
Glucose (Fasting) (mg/dl)[a]	100.9 ± 27	97.1 ± 22.3	110.1 ± 29.7	179.7 ± 54.57	0.06
Insulin (Fasting) (mg/dl)[a]	13.7 ± 7.7	12.9 ± 10.9	12.1 ± 7.8	23.8 ± 9.95	0.05
HbA1c (%)[a]	5.9 ± 1.15	6 ± 0.94	6.2 ± 1.2	6.46 ± 1.5	0.122
Platelet[a]	158.8 ± 75.6	161.6 ± 78.8	153.7 ± 65	164.5 ± 71	0.848
Serum IgG[a]	16.9 ± 5.7	17.3 ± 5.3	17 ± 5.8	17.6 ± 6.9	0.796
Total Bilirubin (mg/dl)[b]	1.1 (0.7–1.7)	1 (0.7–1.5)	0.9 (0.7–1.4)	0.8 (0.6–1.2)	0.188
Aspartate aminotransferases (IU/L)[b]	49 (35–74)	49 (36–73)	50 (38.5–69)	55 (39–84)	0.736
Alanine aminotransferase (IU/L)[b]	46 (30–78.5)	49 (35–71.5)	47 (30–87.5)	52 (30–81.5)	0.927
Alkaline Phosphatase (IU/L)[b]	90 (70–115.5)	95 (77–119.5)	93 (74.5–121.5)	90 (76–123.5)	0.894
Gamma-glutamyl transpeptidase (IU/L)[b]	37 (23–63)	37 (24.2–70)	37 (22–64.5)	63 (33.5–91.5)	0.238
Serum cholesterol (mg/dl)[b]	159 (125–182)	154.5 (126–189)	162 (127–178)	181 (149–217)	0.368
Serum triglyceride (mg/dl)[b]	121 (88–160)	120 (94.5–171.2)	117 (80–190)	128 (95–165)	0.858
Serum low-density lipoproteins (mg/dl)[b]	97.3 (67.7–120)	95.1 (72–120.6)	94.7 (75.1–114.6)	133.4 (85–153.2)	0.238

ANA, antinuclear antibody; ASMA, anti-smooth muscle antibodies.
[a]Mean±SD.
[b]Median (interquartile range).

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Table 2 Histological Parameters Distribution According to Autoantibodies.

	Autoantibodies negative (n = 402)	Only ANA positive (n = 43)	Only ASMA positive (n = 99)	ANA and ASMA positive (n = 99)	*P* value
Steatosis					
Absent	20 (5.2%)	10 (7.1%)	8 (8.2%)	1 (2.6%)	0.374
Mild	192 (49.6%)	71 (50.4%)	41 (41.8%)	16 (42.1%)	
Moderate	133 (34.4%)	50 (35.5%)	36 (36.7%)	13 (34.2%)	
Severe	42 (10.9%)	10 (7.1%)	13 (13.3%)	8 (21.1%)	
Activity					
Minimal	377 (93.8%)	128 (89.5%)	93 (93.9%)	34 (87.2%)	0.099
Mild	22 (5.5%)	14 (9.8%)	5 (5.1%)	3 (7.7%)	
Moderate	3 (0.7%)	1 (0.7%)	1 (1%)	2 (5.1%)	
Ballooning					
Absent	24 (6%)	8 (5.6%)	8 (8.1%)	4 (10.3%)	0.788
Few	283 (70.4%)	102 (71.3%)	64 (64.6%)	24 (61.5%)	
Many	95 (23.6%)	33 (23.1%)	27 (27.3%)	11 (28.2%)	
Fibrosis					
Portal, periportal (F1–F2)	183 (85.1%)	67 (90.5%)	53 (94.6%)	18 (85.7%)	0.215
Advanced fibrosis (F3–F4)	32 (14.9%)	7 (9.5%)	3 (5.4%)	3 (14.3%)	

ANA, antinuclear antibody; ASMA, anti-smooth muscle antibodies.

0.69–0.88, $P < 0.001$), sensitivity of 76.5%, and specificity of 76.2%.

Eleven cases showed features of NASH and AIH (Supplementary Table 1). CK18-M30 and PIIINP mean values increased with NAFL-NASH, NASH + AIH–AIH (P 0.001), and NASH and AIH (P 0.001). Table 4 shows the mean value between the groups.

DISCUSSION

Our study explores the prevalence and significance of autoantibodies in the spectrum of NAFLD cohorts diagnosed on histopathology. We found that 40.9% of cases in the NAFLD cohort were found to have antibody positivity (ANA, ASMA, and LKM-1) in various combinations. Among them, 21.9%, 13.9%, and 0.3% of the cases showed positivity for only ANA, ASMA, and LKM-1; 4.8% of the cases were found to have both ANA and ASMA positivity.

Among the cases showing dual positivity for ANA and ASMA, two cases were found to have overlapping histological features of AIH. Three cases with only ASMA positivity were also reported as NASH-AIH overlap. Three cases of NASH and AIH overlap were found to be ANA positive. However, on seeing the entire cohort, no significant difference was seen in terms of steatosis, inflammation, ballooning, activity (HAI score), or fibrosis. Similar no significant difference in biochemical and demographic parameters were noted.

The prevalence of ANA positivity in NASH was reported to range from 12 to 35%.[10] Paola Loria *et al.* showed the prevalence of non-organ-specific autoantibodies in nonalcoholic fatty liver disease. The prevalence of ANA, SMA, and AMA was 35.7%, 21.4% being positive for ANA and 4.7% for SMA.[8,10] However, the diagnosis of NAFLD in these cases was done on the basis of ultrasonography alone, so histological parameters in different subgroups could not be assessed.

Raj Vuppalanchi *et al.* studied the clinical significance of serum autoantibodies in patients with NAFLD. Autoantibodies were present in 21% of NAFLD patients. Lobular inflammation (46.7% vs. 47.5%), ballooning degeneration (38.5% vs. 42.5%), and advanced fibrosis (33.2% vs. 29.3%) were not different between autoantibody positive and negative NAFLDs. The presence of autoantibodies was

Table 3 Comparison of Serum Biomarkers Levels in Non-alcoholic Fatty Liver Disease with Autoantibodies Status.

	Negative antibodies 72 (55.8%)	ANA positive N = 21 (16.2%)	ASMA positive N = 16 (12.4%)	Both positive N = 20 (15.5%)	*P* value
CK18–M30, ng/ml	178.188 ± 81.8	161.6 ± 63.7	153.2 ± 70.3	169.85 ± 42.9	0.569
PIIINP, ng/ml	1261.6 ± 257.6	1333.9 ± 206.2	1258.2 ± 256.0	1208.2 ± 296.2	0.474

ANA, antinuclear antibody; ASMA, anti-smooth muscle antibodies.

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Table 4 Comparison of Serum Biomarkers Levels in Non-alcoholic Fatty Liver Diseases, NASH + AIH and AIH.

	NAFL 7 (4.6%)	NASH 112 (73.7%)	NASH-AIH 11 (7.2%)	AIH 22 (14.5%)	*P* value
CK18 (Mean ± SD), ng/ml	104 ± 36.6	173.7 ± 74.1	177.5 ± 85	231.9 ± 86.8	0.001
PIIINP(Mean ± SD), ng/ml	781 ± 326.6	1234.8 ± 225	1292.7 ± 191	1338.7 ± 253	0.001

NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis.

independently associated with a lower prevalence of moderate-to-severe steatosis.[11]

Another study concluded that the presence of ANA may be related to the progression of NASH and that a different type of autoimmune mechanism may be involved in the pathogenesis of NASH with ANA compared to the pathogenesis of autoimmune hepatitis. ANA-positive NASH was significantly associated with female gender, a high degree of portal inflammation, interface activity, and hepatocellular ballooning. In addition, an ANA of high titer (320-fold or more) was significantly associated with the histological grade and stage of NASH.[12]

A recent study by Kohut T *et al.* concluded that autoantibody positivity is frequently encountered in pediatric NAFLD (up to 66%). They also identified that the autoantibody positivity was not associated with histological severity. This study further suggested that NAFLD with antibody positivity and ALT >80 IU/L may suggest the risk of NASH.[13]

In NAFLD, autoantibody positivity has no effect on liver pathology. It may be associated with a relatively strong immune response to subtle or persistent inciting stimuli. This hypothesis is potentiated by higher positivity in pediatric patients.

CK-18 M-30 was released due to hepatocyte injury, and PIIINP, a procollagen III cleavage product, is a circulating biomarker of extracellular matrix (ECM) remodeling during liver fibrogenesis.[14–16] We attempted to assess these markers and their relationship with the presence of autoantibodies in this study and found no difference with the presence of autoantibodies.

We observed a rising trend in CK-18 and PIIINP from NAFLD-NASH-NASH + AIH. A study by De Luca-Johnson, J. *et al.* suggested that patients with coincident AIH and NASH were more likely to present advanced liver disease. The elevated noninvasive markers also suggest activity and fibrosis in NASH-AIH cases.[17]

A correlation of necroinflammatory activity with different titers of antibody could not be done due to the unavailability of data. Despite these limitations, the strength of our study was that it was a cross-sectional study with histology and concurrent autoantibody status available in all cases done on a large cohort. In addition, serum biomarkers of activity were used to assess activity in cases with autoantibody positivity to overcome the pitfall of interobserver variability and the comparatively smaller area of the biopsy taken in comparison to the large area of the liver.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Conceptualization: CB; Data curation: KJ; Formal analysis: KJ and AR; Funding acquisition: NA; Investigation: KJ; Methodology: KJ and CB; Project administration: CB; Resources: CB and AR; Software: NA; Supervision: CB; Validation: CB; Visualization: KJ and AR; Roles/Writing – original draft: KJ; Writing – review and editing: CB.

CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.03.005.

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