ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 May 6; 10(13): 3969-4326

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 10 Number 13 May 6, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Clinical and Translational Research

Retrospective Cohort Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 13 May 6, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 13 May 6, 2022

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 13 May 6, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Kai Zhang, PhD, Professor, Department of Psychiatry, Chaohu Hospital of Anhui Medical University, Hefei 238000, Anhui Province, China. zhangkai@ahmu.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
May 6, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2022 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 May 6; 10(13): 4097-4109

DOI: 10.12998/wjcc.v10.i13.4097

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Metabolic dysfunction is associated with steatosis but no other histologic features in nonalcoholic fatty liver disease

Yi-Ning Dai, Cheng-Fu Xu, Hong-Ying Pan, Hai-Jun Huang, Mei-Juan Chen, You-Ming Li, Chao-Hui Yu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C, C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Di Sessa A, Italy; Protopapas AA, Greece; Ulaşoglu C, Turkey; Yang M, United States

Received: July 26, 2021
Peer-review started: July 26, 2021
First decision: August 19, 2021
Revised: September 1, 2021
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: May 6, 2022

Yi-Ning Dai, Cheng-Fu Xu, You-Ming Li, Chao-Hui Yu, Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Yi-Ning Dai, Hong-Ying Pan, Hai-Jun Huang, Mei-Juan Chen, Center for General Practice Medicine, Department of Infectious Diseases, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, Zhejiang Province, China

Corresponding author: Chao-Hui Yu, MD, PhD, Chief Doctor, Professor, Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. zyyyych@zju.edu.cn

Abstract

BACKGROUND

Recently, nonalcoholic fatty liver disease (NAFLD) has been renamed metabolic-associated fatty liver disease (MAFLD). Based on the definition for MAFLD, a group of non-obese and metabolically healthy individuals with fatty liver are excluded from the newly proposed nomenclature.

AIM

To analyze the histologic features in the MAFLD and non-MAFLD subgroups of NAFLD.

METHODS

Eighty-three patients with biopsy-proven NAFLD were separated into MAFLD and non-MAFLD groups. The diagnosis of MAFLD was established as hepatic steatosis along with obesity/diabetes or evidence of metabolic dysfunction. The histologic features were compared according to different metabolic disorders and liver enzyme levels.

RESULTS

MAFLD individuals had a higher NAFLD activity score (P = 0.002) and higher severity of hepatic steatosis (42.6% Grade 1, 42.6% Grade 2, and 14.8% Grade 3 in MAFLD; 81.8% Grade 1, 13.6% Grade 2, and 4.5% Grade 3 in non-MAFLD; P = 0.007) than the non-MAFLD group. Lobular and portal inflammation, hepatic ballooning, fibrosis grade, and the presence of nonalcoholic steatohepatitis (NASH) and significant fibrosis were comparable between the two groups. The higher the liver enzyme levels, the more severe the grades of hepatic steatosis

(75.0% Grade 1 and 25.0% Grade 2 in normal liver function; 56.6% Grade 1, 39.6% Grade 2, and 3.8% Grade 3 in increased liver enzyme levels; 27.8% Grade 1, 27.8% Grade 2, and 44.4% Grade 3 in liver injury; $P < 0.001$). Patients with liver injury (alanine aminotransferase > 3 × upper limit of normal) presented a higher severity of hepatocellular ballooning ($P = 0.021$). Moreover, the grade of steatosis correlated significantly with hepatocellular ballooning degree ($r = 0.338$, $P = 0.002$) and the presence of NASH ($r = 0.466$, $P < 0.001$).

CONCLUSION

Metabolic dysfunction is associated with hepatic steatosis but no other histologic features in NAFLD. Further research is needed to assess the dynamic histologic characteristics in NAFLD based on the presence or absence of metabolic disorders.

Key Words: Nonalcoholic fatty liver disease; Metabolic associated fatty liver disease; Liver histology; Hepatic steatosis; Fibrosis

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Non-obese and metabolically healthy patients with fatty liver are excluded from the definition of metabolic-associated fatty liver disease (MAFLD), but their clinical course has seldom been demonstrated. We analysed a group of nonalcoholic fatty liver disease (NAFLD) subjects, and found that the MAFLD subgroup had a higher NAFLD activity score and higher severity of hepatic steatosis than the non-MAFLD subgroup. There was no difference in other histologic features, including lobular and portal inflammation, balloon degeneration, and fibrosis, between the MAFLD and non-MAFLD patients. The grade of steatosis correlated positively with the hepatocellular ballooning degree, and the presence of nonalcoholic steatohepatitis. We believe that our study can provide insight into the histologic features of various subsets of fatty liver disease.

Citation: Dai YN, Xu CF, Pan HY, Huang HJ, Chen MJ, Li YM, Yu CH. Metabolic dysfunction is associated with steatosis but no other histologic features in nonalcoholic fatty liver disease. *World J Clin Cases* 2022; 10(13): 4097-4109

URL: https://www.wjgnet.com/2307-8960/full/v10/i13/4097.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i13.4097

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), characterized by the presence of steatosis in > 5% of hepatocytes without other causes of liver injury, including excess alcohol consumption, has become a growing social health problem[1]. NAFLD covers a broad spectrum of disease severity[2-5], ranging from simple fatty liver to nonalcoholic steatohepatitis (NASH), and can even lead to cirrhosis and hepatocellular carcinoma. Currently, it is widely accepted that many cases of cryptogenic cirrhosis actually result from NAFLD, in which steatosis vanishes in the late cirrhotic stage.

Metabolic dysfunction is generally defined as obesity, type 2 diabetes mellitus (T2DM), and conditions including excess weight around the waist, hypertension, hyperlipidaemia, prediabetes, and insulin resistance. Currently, it is well recognized that NAFLD originates from an underlying condition of systemic metabolic dysfunction and represents the hepatic manifestation of metabolic syndrome (MS). Actually, it should not be defined as a state of "exclusion", such as the exclusion of excess alcohol consumption or viral hepatitis. A group of experts have recently suggested that the outdated nomenclature of NAFLD should be renamed metabolic-associated fatty liver disease (MAFLD)[6,7]. Briefly, evidence of hepatic steatosis along with metabolic disorders establishes a diagnosis of MAFLD.

While MAFLD represents the majority of those previously diagnosed with NAFLD in clinical practice, a group of non-obese and metabolically healthy individuals with fatty liver are excluded from MAFLD based on the international expert consensus statement[8]. With regard to this subset of fatty liver, the clinical course and outcomes have seldom been demonstrated. In this study, we aimed to analyze the hepatic histologic characteristics in the MAFLD and non-MAFLD subgroups of NAFLD. In addition, we conducted subgroup analyses according to the presence of obesity, glycemia, and liver enzyme levels to explore histologic features in various subsets of fatty liver disease.

MATERIALS AND METHODS

Study design and patients

Patients diagnosed with NAFLD, based on the presence of steatosis in more than 5% of hepatocytes with the exclusion of other chronic liver diseases and alcohol consumption, were recruited at Zhejiang Provincial People's Hospital. They were further divided into MAFLD and non-MAFLD groups. MAFLD was defined as hepatic steatosis along with one of the following three standards, *i.e.*, obesity [body mass index (BMI) ≥ 23 kg/m^2], T2DM, or evidence of metabolic dysfunction. The latter was based on the presence of at least two of the following metabolic abnormalities: Waist circumference (WC) ≥ 90 cm in men and ≥ 80 cm in women; blood pressure ≥ 130/85 mmHg or diagnosis of high blood pressure under specific drug treatment; serum triglycerides (TG) ≥ 1.70 mmol/L or specific drug therapy; serum high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L for men and < 1.3 mmol/L for women, or under specific drug therapy; fasting glucose between 5.6 to 6.9 mmol/L, or 2-h post-load glucose between 7.8 to 11.0 mmol/L, or HbA1c level between 5.7% to 6.4%, which indicate a condition with prediabetes; homeostasis model assessment for insulin resistance (HOMA-IR) score ≥ 2.5; and high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L[8]. Non-MAFLD referred to NAFLD participants without obesity, T2DM, or the above metabolic disorders. In particular, "alternative causes" of steatosis, such as medications, celiac disease, severe surgical weight loss, starvation, or total parenteral nutrition, were not allowed for inclusion. However, we did not assess disorders of lipid metabolism, genetic abnormalities, or other rare metabolic disorders as possible causes for non-MAFLD.

The exclusion criteria were as follows: (1) Children or adolescents less than 18 years old; (2) excessive alcohol drinkers (weekly ethanol consumption more than 140 g in men and 70 g in women); (3) documented hepatitis B or C; (4) other chronic liver disease (*e.g.*, autoimmune liver disease, drug-induced liver injury, or hereditary disorders); (5) dysfunction of coagulation; and (6) cirrhosis, malignancy, severe organ dysfunctions such as cardiopulmonary dysfunction, renal inadequacy, or pregnancy.

Asian subjects with a BMI < 23 kg/m^2 were defined as having lean NAFLD. The diagnosis of T2DM was in reference to the widely accepted international criteria[9]. In addition, the participants were classified into three groups according to their liver enzyme levels: Normal liver function, increased liver enzyme level, and liver injury[10]. Increased liver enzyme levels were defined as any liver enzyme level above the upper limit of normal (ULN), with an alanine aminotransferase (ALT) level < 3-fold of the ULN. Liver injury conformed to ALT concentrations > 3-fold of the ULN.

All eligible subjects received liver biopsy, and written informed consent was obtained from each participant. The study was in agreement with the Declaration of Helsinki and was approved by the Ethics Committee, People's Hospital of Hangzhou Medical College.

Clinical and laboratory evaluations

Anthropometric data were obtained for each subject by a well-trained nurse. We calculated BMI as the weight divided by the square of the height (g/m^2). WC refers to the minimum circumference between the umbilicus and the xiphoid process[11]. Systolic and diastolic blood pressures (SBP and DBP) were measured using a sphygmomanometer with the subject in a sitting position.

Blood biochemistry tests evaluating ALT, aspartate transferase (AST), alkaline phosphatase (AKP), gamma-glutamyltransferase (GGT), albumin (ALB), globulin (GLB), cholinesterase (CHE), uric acid (UA), TG, total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), glucose, complete blood counts, and hs-CRP were performed in our clinical laboratory using automatic analysers.

Liver histology

Experienced doctors performed ultrasound-guided percutaneous liver biopsy using the MAX-CORE Disposable Core Biopsy Instrument (Bard Peripheral Vascular, Inc., Mexico), with specimens fixed, paraffin-embedded, and stained with haematoxylin and eosin (H&E) and Masson's trichrome.

A skilled liver pathologist who was unaware of the participants' clinical data reviewed the slides of liver biopsies. All eligible liver biopsy slides in this study were qualified for grading and staging of the histologic features.

A threshold of 5% macrovesicular steatosis established a diagnosis of NAFLD[12]. Steatosis was graded as the percentage of liver parenchyma replaced by fat: (1) 5%-33%; (2) 34%-66%; or (3) more than 66%[13]. Lobular inflammation was scored on a scale of 0-3: (0) none; (1) mild; (2) moderate; and (3) many. In addition, portal inflammation and hepatocellular ballooning were scored as follows: (0) none; (1) mild inflammation or few balloon cells; and (2) more than mild or prominent ballooning. The degree of fibrosis was divided as "(0) none; (1a) slight perisinusoidal fibrosis, (1b) moderate perisinusoidal fibrosis, (1c) periportal/portal fibrosis; (2) perisinusoidal and periportal/portal fibrosis; (3) bridging fibrosis; and (4) cirrhosis". Fibrotic stage ≥ 2 was considered significant fibrosis. The NAFLD activity score (NAS) was documented as the summation of the scores for steatosis, lobular inflammation, and ballooning. A NAS of ≥ 5 confirmed the diagnosis of NASH, while a NAS of < 3 was considered non-NASH. If the NAS was between 3 and 4, we diagnosed NASH when pathohistological features, including steatosis, lobular inflammation, and ballooning, existed simultaneously.

Statistical analysis

All statistical analyses were conducted with SPSS software (version 23) for Windows. Continuous variables are presented as the mean ± SD, and categorical variables are presented as numbers (percentages). The independent *t*-test or the chi-squared test was used to evaluate differences between groups. One-way analysis of variance (ANOVA) was performed for multiple comparisons. Bivariate correlations between steatosis grade and other histologic parameters were examined using Spearman's correlation test. A two-sided P value < 0.05 was considered statistically significant.

RESULTS

Clinical and histologic characteristics of the patients

A total of 83 patients with biopsy-proven NAFLD were included in the study, with 54 males and 29 females. Among them, 61 subjects suffered from MAFLD, while the other 22 had NAFLD without overweight or metabolic dysfunction (defined as the non-MAFLD group). Demographic and laboratory information for the enrolled population is summarized in Table 1.

MAFLD patients had significantly higher body weight (73.65 ± 13.10 *vs* 60.31 ± 7.48 kg, $P < 0.001$), BMI (26.43 ± 3.38 *vs* 21.93 ± 1.09 kg/m^2, $P < 0.001$), and WC (89.87 ± 8.53 *vs* 80.91 ± 3.93 cm, $P < 0.001$) than the non-MAFLD group. Moreover, the blood pressures in the MAFLD group were higher than those in the non-MAFLD group ($P = 0.009$ for SBP and $P = 0.016$ for DBP). In addition, subjects with MAFLD had lower HDL-C ($P = 0.018$) and elevated TG ($P < 0.001$) and glucose ($P = 0.003$) than the non-MAFLD participants. The liver functions in the two groups were not significantly different.

Grade 1 steatosis was found in 44 (53.0%), and grades 2-3 steatosis was found in 39 individuals (47.0%). Lobular inflammation was found in 79 (95.2%) and absent in 4 (4.8%) patients. Portal inflammation was found in 73 (95.2%) and absent in 10 (4.8%) patients. Sixteen patients (19.3%) had hepatocellular ballooning, while 67 (80.7%) did not. Fibrosis of any degree was present in 59 (71.1%) and absent in 24 patients (28.9%). Among the 83 biopsy-proven NAFLD patients, 19 (22.9%) had NASH, and 15 (18.1%) had significant fibrosis. Figure 1 demonstrates the representative histological images to provide an overview of the pathological changes.

Histologic characteristics according to MAFLD

The comparison of histologic characteristics between the MAFLD and non-MAFLD subgroups is shown in Figure 2. There was a significant difference in steatosis degree. Compared with non-MAFLD subjects, MAFLD subjects had a higher severity of hepatic steatosis (42.6% Grade 1, 42.6% Grade 2, and 14.8% Grade 3 in MAFLD; 81.8% Grade 1, 13.6% Grade 2, and 4.5% Grade 3 in non-MAFLD; $P = 0.007$, Figure 2A). The MAFLD group also had a higher NAS than the non-MAFLD group (3.11 ± 1.29 *vs* 2.41 ± 0.67, $P = 0.002$, Figure 2H). However, lobular and portal inflammation, hepatic ballooning, fibrosis grade, and the presence of NASH and significant fibrosis were comparable between the two groups (P = 0.461, 0.091, 0.251, 0.151, 0.228, and 0.749, respectively; Figure 2B-G).

Histologic characteristics according to obesity and glycemia

There were 56 obese NAFLD patients and 27 lean NAFLD patients based on a BMI threshold of 23 kg/m^2. Among the lean NAFLD patients, five were defined as having MAFLD, one of whom had T2DM, three of whom had hypertriglyceridemia and low HDL-C, and the other had low HDL-C and elevated postprandial glucose levels.

Similarly, obese NAFLD patients had a higher severity of hepatic steatosis (41.1% Grade 1, 44.6% Grade 2, and 14.3% Grade 3 in obese NAFLD; 77.8% Grade 1, 14.8% Grade 2, and 7.4% Grade 3 in lean NAFLD; $P = 0.007$, Figure 2A) and higher NAS (3.16 ± 1.32 *vs* 2.44 ± 0.70, $P = 0.002$, Figure 2H) than lean NAFLD patients. However, obese NAFLD patients had milder portal inflammation than their lean counterparts (16.1% Grade 0, 82.1% Grade 1, and 1.8% Grade 2 in obese NAFLD; 3.7% Grade 0, 74.1% Grade 1, and 22.2% Grade 2 in lean NAFLD; $P = 0.003$, Figure 2C). As presented in Figure 2, lobular inflammation, ballooning, fibrosis grade, and the presence of NASH and significant fibrosis were comparable between the two groups (P = 0.247, 0.116, 0.250, 0.098, and 1.000, respectively).

Ten patients suffered from T2DM; 27 had prediabetes, while the other 46 had normal blood sugar. There were no significant differences among individuals based on glycemia in terms of any histologic characteristic (steatosis: $P = 0.260$; lobular inflammation: $P = 0.400$; portal inflammation: $P = 0.676$; balloon degeneration: $P = 0.717$; fibrosis: $P = 0.563$; NAS: $P = 0.141$; NASH: $P = 0.849$; significant fibrosis: $P = 0.357$) (Figure 2).

Histologic characteristics according to liver function

Based on the markers of liver injury, 12 patients presented with normal liver function, 53 had elevated liver enzyme levels, and 18 had liver injury (ALT > 3 × ULN). As shown in Figure 2A, the higher the liver enzyme levels, the more severe the grades of hepatic steatosis (75.0% Grade 1 and 25.0% Grade 2 in normal liver function; 56.6% Grade 1, 39.6% Grade 2, and 3.8% Grade 3 in increased liver enzyme levels;

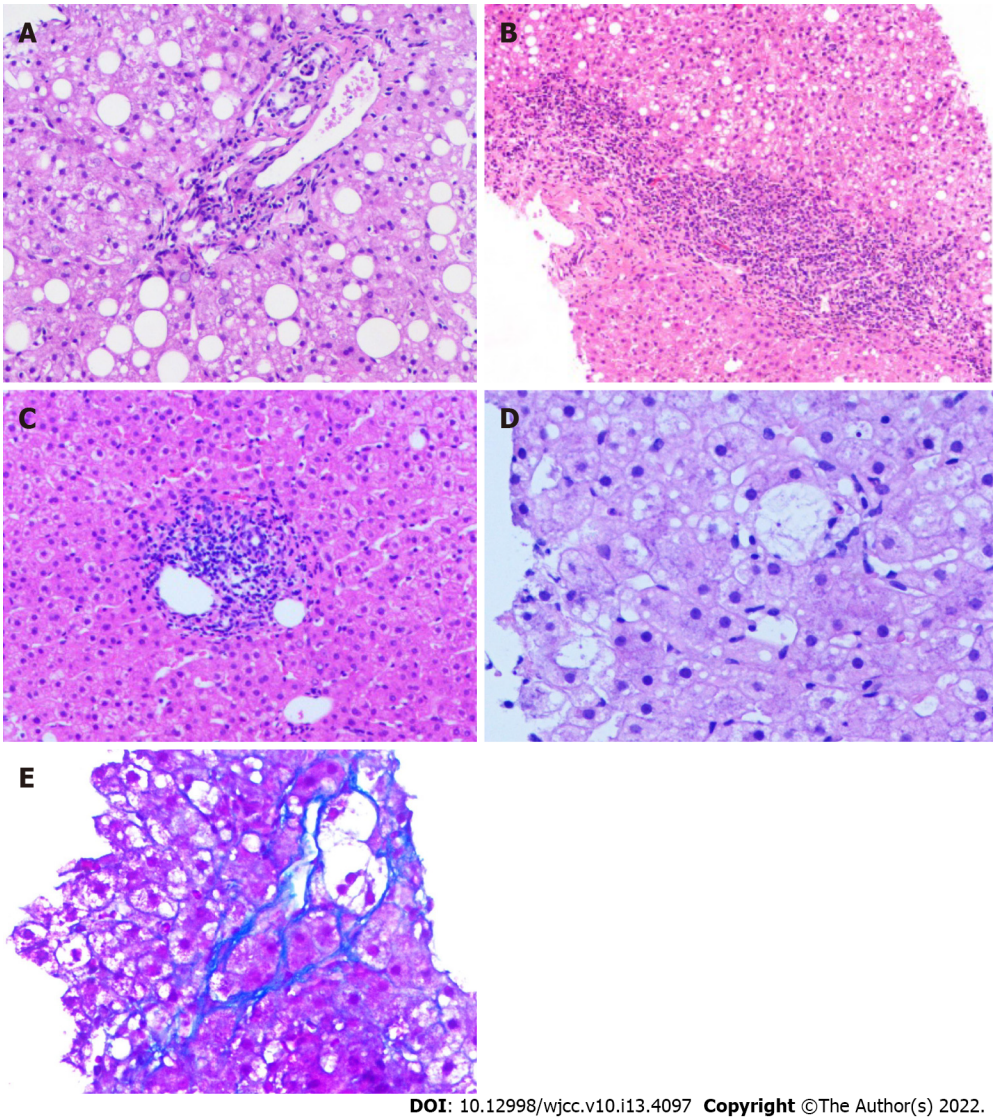
Table 1 Clinical characteristics of study participants

	MAFLD (*n* = 61, male 39[a])		Non-MAFLD (*n* = 22, male 15[a])		*P* value
	mean	SD	mean	SD	
Age	42.23	12.62	41.23	12.08	0.743
Height (m)	1.66	0.08	1.65	0.08	0.640
Weight (kg)	73.65	13.10	60.31	7.48	< 0.001
BMI	26.43	3.38	21.93	1.09	< 0.001
WC (cm)	89.87	8. 53	80.91	3.93	< 0.001
SBP (mmHg)	126.11	14.50	118.36	10.12	0.009
DBP (mmHg)	77.30	8.68	71.82	8.72	0.016
HR (per min)	77.51	9.10	76.05	8.25	0.492
WBC (× 10^9/L)	6.22	1.29	5.76	1.25	0.153
Neu%	58.75	8.33	57.42	9.77	0.573
HGB (g/L)	146.20	16.66	149.23	15.57	0.447
PLT (× 10^9/L)	213.95	70.66	201.18	59.33	0.416
hs-CRP (mg/L)	2.39	2.78	1.92	1.08	0.284
ALB (g/L)	45.14	4.42	43.41	4.32	0.117
GLB (g/L)	28.62	4.37	29.06	3.76	0.656
UA (μmol/L)	372.82	103.65	341.05	73.45	0.128
TG (mmol/L)	2.54	1.63	1.32	0.53	<0.001
TC (mmol/L)	4.89	1.26	4.68	0.91	0.441
LDLC (mmol/L)	2.84	0.93	2.67	0.57	0.334
HDLC (mmol/L)	1.03	0.23	1.15	0.17	0.018
ALT (U/L)	85.43	60.31	65.36	38.65	0.081
AST (U/L)	53.28	31.67	46.32	26.15	0.318
GGT (U/L)	84.36	52.04	60.45	50.48	0.067
ALP (U/L)	100.34	29.11	94.95	25.03	0.412
ChE (U/L)	9756.44	1990.84	8791.95	1987.90	0.059
GLU (mmol/L)	5.56	1.01	4.99	0.63	0.003

[a]*P* value for gender = 0.720.

MAFLD: Metabolic associated fatty liver disease; SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; WBC: White blood cell count; Neu: Neutrophil cell; HGB: Hemoglobin; PLT: Platelet; hs-CRP: High-sensitivity C-reactive protein; ALB: Albumin; GLB: Globulin; UA: Uric acid; TG: Triglycerides; TC: Total cholesterol; LDLC: Low-density lipoprotein cholesterol; HDLC: High-density lipoprotein cholesterol; ALT: Alanine aminotransferase; AST: Aspartate transferase; GGT: Gamma-glutamyltransferase; ALP: Alkaline phosphatase; ChE: Cholinesterase; GLU: Fasting glucose.

27.8% Grade 1, 27.8% Grade 2, and 44.4% Grade 3 in liver injury; $P < 0.001$). Moreover, the liver injury group presented with much graver hepatocellular ballooning (91.7% Grade 0 and 8.3% Grade 2 in normal liver function; 86.8% Grade 0, 7.5% Grade 1, and 5.7% Grade 2 in increased liver enzyme levels; 55.6% Grade 0, 33.3% Grade 1, and 11.1% Grade 2 in liver injury; $P = 0.021$; Figure 2D). There was one case of NASH in the normal liver function group (8.33%), eight patients with NASH in the group with increased liver enzyme levels (15.09%), and ten patients with NASH in the liver injury group (55.56%, $P = 0.001$; Figure 2F). The NASs in the three groups were 2.50 ± 1.00, 2.70 ± 1.01 ($P = 0.545$ *vs* the normal liver function group), and 3.89 ± 1.37 ($P = 0.003$ *vs* the normal liver function group, $P = 0.002$ *vs* the group with increased liver enzymes), respectively (Figure 2H). No significant differences in fibrosis grades ($P = 0.223$) or the presence of significant fibrosis ($P = 0.097$) were seen among the three groups (Figure 2E and G). In addition, there was no significant difference in terms of lobular ($P = 0.496$) or portal inflammation ($P = 0.190$) in the comparison of the three groups according to liver function (Figure 2B and C).



DOI: 10.12998/wjcc.v10.i13.4097 **Copyright** ©The Author(s) 2022.

Figure 1 Representative histological images of liver biopsy specimens (haematoxylin and eosin staining). A: Steatosis (× 200); B: Lobular inflammation (× 100); C: Portal inflammation (× 100); D: Balloon degeneration (× 400); E: Fibrosis (× 400).

Correlations between degree of steatosis and severity of other hepatic histologic features

Interestingly, steatosis grade correlated significantly with hepatocellular ballooning degree (r = 0.338, P = 0.002) and the presence of NASH (r = 0.466, P < 0.001). In contrast, Spearman's analysis did not find any correlation between steatosis grade and other hepatic histologic features, including inflammation or fibrosis (Table 2).

DISCUSSION

Generally, NAFLD accompanies obesity and its comorbidities[14]. Nevertheless, it can also occur in individuals within a BMI cut-off of 25 kg/m^2 in Caucasians and 23 kg/m^2 in Asians, the so-called "lean" NAFLD[15]. There is growing evidence that lean patients with metabolic disorders display superior ectopic fat accumulation, with higher risks of fatty liver and cardiovascular disease[16-18]. A recent study identified that non-obese NAFLD patients with MS presented a comparable degree of liver histologic severity to their obese counterparts without MS[19]. While weight gain and insulin resistance are well-known predictors of long-term outcomes of NAFLD[20,21], other metabolic disorders also play a crucial role in NAFLD pathogenesis. Herein, a nomenclature of MAFLD was proposed based on the presence of fatty liver and metabolic dysfunction. According to the definition of MAFLD, a group of lean and metabolically healthy individuals are not included. In this study, we focused on the comparison of histologic characteristics between the non-MAFLD and MAFLD subgroups of NAFLD, with the purpose of demonstrating the histologic performance of lean NAFLD without metabolic disorders.

Table 2 Correlations between degree of steatosis and severity of other hepatic histologic features

Histologic feature	Correlation (*r*)	*P* value
Lobular inflammation	0.122	0.272
Portal inflammation	0.005	0.968
Balloon degeneration	0.338	0.002
Liver fibrosis	0.060	0.588
Significant liver fibrosis	0.151	0.172
NASH	0.466	< 0.001

NASH: Nonalcoholic steatohepatitis.

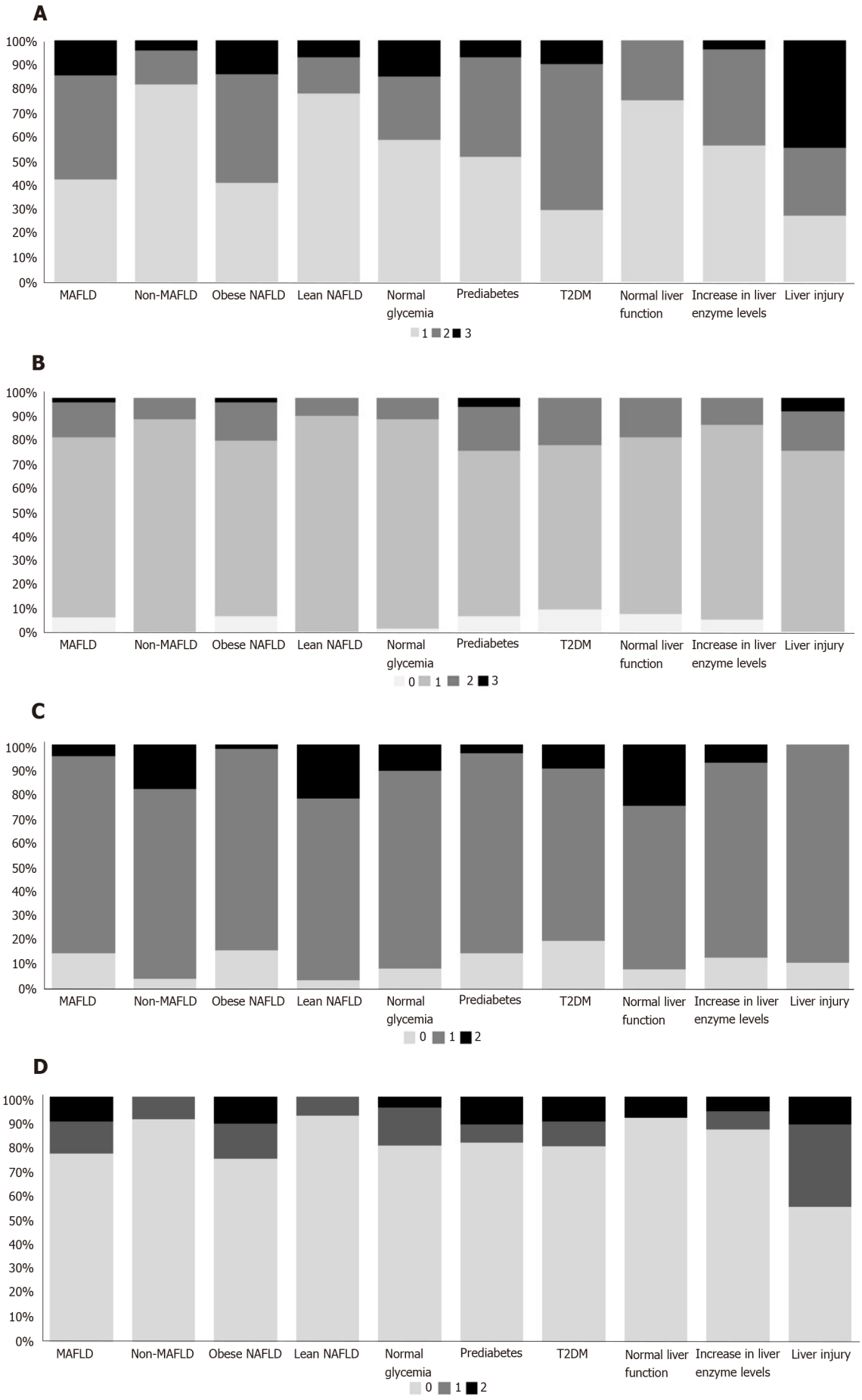
The results of this study indicated that MAFLD individuals had a higher NAS than non-MAFLD individuals. Specifically, the difference in NAS originated from the severity of steatosis other than inflammation or balloon degeneration. While the grades of inflammation and balloon degeneration were similar between the two groups, there was also no difference in the presence of NASH or significant fibrosis. Given the substantial heterogeneity of MAFLD, sub-classifications might present with different histologic features and lead to different clinical outcomes[22]. Therefore, subgroup analyses were conducted according to the presence of elements of metabolic syndrome. Similar results were observed in obese and lean NAFLD individuals, except for the difference in degrees of portal inflammation. However, diabetes was not associated with any hepatic histologic features.

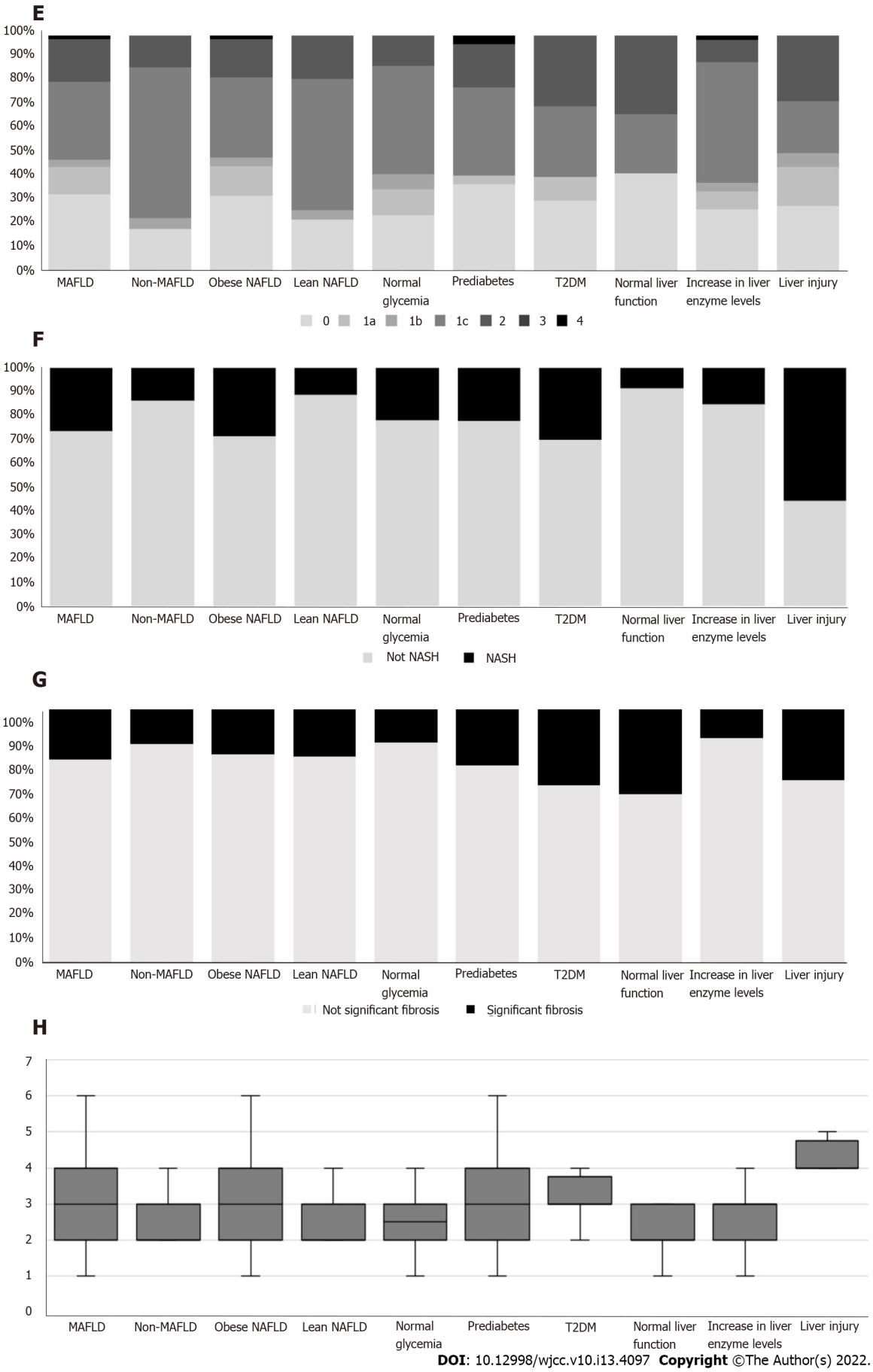
It has been proven that NASH rather than simple fatty liver is related to a worse prognosis. Hepatic steatosis with minimal or no inflammation appears to follow a comparatively benign clinical course[23-25]. Nevertheless, a longitudinal study showed that only fibrosis stage instead of other histologic features of NASH was related to end-stage liver diseases and all-cause mortality, and long-term prognosis did not depend upon a diagnosis of NASH but hepatic fibrosis[12]. Moreover, fibrosis develops not only in those with steatohepatitis but also in those with steatosis alone[26]. As shown in this study, steatosis grade had a positive correlation with ballooning degree and the presence of NASH. While steatosis and other histologic alterations represent a continuous process, the current histologic assessment cannot reflect the dynamic changes of liver histology or represent future disease progression. That is, the more severe steatosis grade in the MAFLD group might possibly result in advanced fibrosis in the future, consequently leading to a poorer outcome. However, this hypothesis needs to be verified in a longitudinal, large-cohort study.

Recently, NAFLD has been reconsidered as the correct name for fatty liver owing to metabolic factors, and experts have appealed to revise its nomenclature based on the following reasons. First, NAFLD is a condition of "exclusion", while metabolic liver disease coexists with other causes of liver injury, such as chronic viral hepatitis, alcohol consumption, and autoimmune liver diseases. Currently, fatty liver disease has a dichotomous division into simple fatty liver and NASH, which remains a great matter of debate due to its limit of capturing the complete spectrum of disease course[2]. As mentioned above, fibrosis has been considered the major determinant of adverse outcomes[12,25]. Consequently, perhaps NAFLD should be regarded similarly to other chronic liver diseases, paying particular attention to the degrees of activity and fibrosis. With a wide spectrum of disease severities of NAFLD, ranging from simple fatty liver, NASH, cirrhosis, and even hepatocarcinoma, more precise subphenotypes of the disease and appropriate patient stratification should be proposed according to the heterogeneous pathogenesis. Given the currently recognized pathogenesis of fatty liver, MAFLD, which focuses on the presence of obesity and metabolic disorders along with hepatic steatosis, is recommended to be a more suitable definition. In the meantime, although the "overwhelming majority" of the previously called NAFLD patients will meet the criteria for MAFLD, we should also make great efforts to map the landscapes of those individuals with NAFLD not presenting obesity, T2DM, or evidence of metabolic dysfunction. A study revealed that NAFLD patients who cannot be diagnosed with MAFLD may have severe hepatic steatosis, significant liver injury, and fibrosis[27]. Another study indicated that the MAFLD criteria seem to be less accurate in identifying a higher cardiometabolic risk in obese children [28]. Therefore, emphasis on MAFLD alone might lead to underestimation of the progression of fatty liver disease and cardiometabolic risk.

According to the results of this study, metabolic dysfunction is associated with only steatosis but no other histologic features in NAFLD. Thus, whether the renaming of NAFLD to MAFLD is rational still requires further studies on the dynamic histologic changes and long-term clinical outcomes between the MAFLD and non-MAFLD subgroups.

However, liver enzymes, particularly ALT, as markers of liver injury have repeatedly failed to identify a large number of patients with hepatic injury. Previous studies have indicated that advanced inflammation or fibrosis is present in many hepatitis B patients with persistently normal ALT levels[29,


A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
MAFLD
Non-MAFLD
Obese NAFLD
Lean NAFLD
Normal glycemia
Prediabetes
T2DM
Normal liver function
Increase in liver enzyme levels
Liver injury
1 2 3
B
0 1 2 3
C
0 1 2
D
0 1 2



DOI: 10.12998/wjcc.v10.i13.4097 **Copyright** ©The Author(s) 2022.

Figure 2 Comparison of histologic features and the presence of nonalcoholic steatohepatitis and significant fibrosis in the metabolic-

associated fatty liver disease and non-metabolic-associated fatty liver disease subgroups of nonalcoholic fatty liver disease, obese nonalcoholic fatty liver disease and lean nonalcoholic fatty liver disease, nonalcoholic fatty liver disease according to glycemia, and nonalcoholic fatty liver disease according to liver function. A: Steatosis grade (P = 0.007 in the comparison between metabolic-associated fatty liver disease (MAFLD) and non-MAFLD; P = 0.007 in the comparison between obese and lean nonalcoholic fatty liver disease (NAFLD); P = 0.260 in the comparison among normal glycemia, prediabetes and type 2 diabetes mellitus (T2DM); P < 0.001 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); B: Lobular inflammation (P = 0.461 in the comparison between MAFLD and non-MAFLD; P = 0.247 in the comparison between obese and lean NAFLD; P = 0.400 in the comparison among normal glycemia, prediabetes and T2DM; P = 0.496 in the comparison among normal liver function, increased liver enzyme levels and liver injury); C: Portal inflammation (P = 0.091 in the comparison between MAFLD and non-MAFLD; P = 0.003 in the comparison between obese and lean NAFLD; P = 0.676 in the comparison among normal glycemia, prediabetes, and T2DM; P = 0.190 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); D: Balloon degeneration (P = 0.251 in the comparison between MAFLD and non-MAFLD; P = 0.116 in the comparison between obese and lean NAFLD; P = 0.717 in the comparison among normal glycemia, prediabetes, and T2DM; P = 0.021 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); E: Fibrosis grade (P = 0.151 in the comparison between MAFLD and non-MAFLD; P = 0.250 in the comparison between obese and lean NAFLD; P = 0.563 in the comparison among normal glycemia, prediabetes, and T2DM; P = 0.223 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); F: Presence of nonalcoholic steatohepatitis (P = 0.228 in the comparison between MAFLD and non-MAFLD; P = 0.098 in the comparison between obese and lean NAFLD; P = 0.849 in the comparison among normal glycemia, prediabetes, and T2DM; P = 0.001 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); G: Presence of significant fibrosis (P = 0.749 in the comparison between MAFLD and non-MAFLD; P = 1.000 in the comparison between obese and lean NAFLD; P = 0.357 in the comparison among normal glycemia, prediabetes, and T2DM; P = 0.097 in the comparison among normal liver function, increased liver enzyme levels, and liver injury); H: NAFLD activity score (3.11 ± 1.29 in MAFLD *vs* 2.41 ± 0.67 in non-MAFLD, P = 0.002; 3.16 ± 1.32 in obese NAFLD *vs* 2.44 ± 0.70 in lean NAFLD, P = 0.002; 2.83 ± 1.08, 3.00 ± 1.39, and 3.20 ± 1.23 in normal glycemia, prediabetes, and T2DM, respectively, overall P = 0.141; 2.50 ± 1.00, 2.70 ± 1.01, and 3.89 ± 1.37 in normal liver function, increased liver enzyme levels, and liver injury, respectively, overall P < 0.001). T2DM: Type 2 diabetes mellitus; NAFLD: Nonalcoholic fatty liver disease; MAFLD: Metabolic-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis.

30]. Although this study found that higher liver enzymes were associated with more severe histologic performance (higher grades of steatosis, balloon degeneration, higher NAS, and larger proportions of NASH), there were still a number of cases with NASH and significant fibrosis with normal or mildly elevated liver function. Therefore, NAFLD with normal liver function can still have significant disease activity and might progress to hepatic decompensation.

This study had several limitations. The major reason was the small size of the study population, especially for the non-MAFLD group, because fatty liver without metabolic dysregulations is relatively rare. Second, due to the cross-sectional nature of this research, we were unable to follow up on the course of the disease. The current histologic features cannot reflect the possible different risks for future disease progression between MAFLD and NAFLD without metabolic dysfunctions. Third, we did not analyze any biomolecules involved in the pathogenesis and progression of MAFLD and NAFLD. Finally, the definition of MAFLD actually includes those patients that also have concomitant conditions, such as alcohol consumption and chronic viral hepatitis. Therefore, further investigation and characterization of this group of MAFLD patients are urgently needed.

CONCLUSION

In conclusion, MAFLD presents with more severe hepatic steatosis and a higher NAS than the non-MAFLD subgroup of NAFLD. However, there are no differences in other hepatic histologic characteristics, including inflammation and fibrosis, between the two groups. Further longitudinal large-cohort studies are needed to discover the dynamic histologic features and prognosis in NAFLD based on the presence or absence of metabolic disorders.

ARTICLE HIGHLIGHTS

Research background

Non-obese and metabolically healthy patients with nonalcoholic fatty liver disease (NAFLD) are excluded from the definition of metabolic-associated fatty liver disease (MAFLD), but their clinical course has been seldom demonstrated.

Research motivation

To study the hepatic histologic characteristics in various subsets of NAFLD based on different metabolic disorders and liver enzyme levels.

Research objectives

To compare the histologic features in various subsets of NAFLD.

Research methods

A total of 83 patients with biopsy-proven NAFLD were divided into MAFLD and non-MAFLD groups. MAFLD was defined as hepatic steatosis along with obesity/diabetes or evidence of metabolic dysfunction. The histologic features were compared in different subgroups.

Research results

The MAFLD subgroup had a higher NAFLD activity score and higher severity of hepatic steatosis than the non-MAFLD subgroup of NAFLD. There were no differences for other histologic features including lobular and portal inflammation, balloon degeneration, and fibrosis between MAFLD and non-MAFLD. The higher the liver enzyme levels, the more severe the grades of hepatic steatosis. Patients with liver injury had a higher severity of hepatocellular ballooning. The grade of steatosis correlated positively with hepatocellular ballooning degree, and presence of nonalcoholic steatohepatitis.

Research conclusions

Metabolic dysfunction is related to hepatic steatosis in NAFLD, but other histologic features including inflammation and fibrosis are similar in the MAFLD and non-MAFLD subgroups.

Research perspectives

Dynamic histologic characteristics should be assessed in more NAFLD patients based on the presence or absence of metabolic disorders.

ACKNOWLEDGEMENTS

We thank Dr. Yu LL for the assistance in histopathological assessment.

FOOTNOTES

Author contributions: Yu CH and Li YM contributed to the study design; Dai YN, Xu CF, and Chen MJ contributed to data collection; Huang HJ and Chen MJ analyzed the data; Dai YN drafted the manuscript; Xu CF and Yu CH contributed to critical comments on the manuscript; Pan HY contributed to the manuscript revision.

Supported by the National Natural Science Foundation of China, No. 81800507; the Public Welfare Project of the Science and Technology Agency, Zhejiang Province, No. LGF18H030010; and Medical and Health Research Project of Zhejiang Province, No. 2018KY256 and No. 2019KY294.

Institutional review board statement: This study was approved by the People's Hospital of Hangzhou Medical College Institutional Review Board (No. 2021QT257).

Informed consent statement: All study participants provided informed written consent prior to liver biopsy.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Yi-Ning Dai 0000-0002-7735-1381; Cheng-Fu Xu 0000-0002-6172-1253; Hong-Ying Pan 0000-0002-8433-3851; Hai-Jun Huang 0000-0002-4871-7479; Mei-Juan Chen 0000-0002-7114-0225; You-Ming Li 0000-0001-9279-2903; Chao-Hui Yu 0000-0003-4842-3646.

S-Editor: Yan JP
L-Editor: Wang TQ
P-Editor: Yan JP

REFERENCES

1 **Sarin SK**, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, Jia J, Tian Q, Aggarwal R, Muljono DH, Omata M, Ooka Y, Han KH, Lee HW, Jafri W, Butt AS, Chong CH, Lim SG, Pwu RF, Chen DS. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2020; **5**: 167-228 [PMID: 31852635 DOI: 10.1016/S2468-1253(19)30342-5]

2 **Brunt EM**, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA; NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology* 2011; **53**: 810-820 [PMID: 21319198 DOI: 10.1002/hep.24127]

3 **Wong VW**, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, Fan J, Goh KL, Hamaguchi M, Hashimoto E, Kim SU, Lesmana LA, Lin YC, Liu CJ, Ni YH, Sollano J, Wong SK, Wong GL, Chan HL, Farrell G. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; **33**: 70-85 [PMID: 28670712 DOI: 10.1111/jgh.13857]

4 **Leoni S**, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. *World J Gastroenterol***24**: 3361-3373 [PMID: 30122876 DOI: 10.3748/wjg.v24.i30.3361]

5 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Diabetologia* 2016; **59**: 1121-1140 [PMID: 27053230 DOI: 10.1007/s00125-016-3902-y]

6 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]

7 **Fouad Y**, Waked I, Bollipo S, Gomaa A, Ajlouni Y, Attia D. What's in a name? *Liver Int* 2020; **40**: 1254-1261 [PMID: 32301554 DOI: 10.1111/liv.14478]

8 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]

9 **Jia W**, Weng J, Zhu D, Ji L, Lu J, Zhou Z, Zou D, Guo L, Ji Q, Chen L, Dou J, Guo X, Kuang H, Li L, Li Q, Li X, Liu J, Ran X, Shi L, Song G, Xiao X, Yang L, Zhao Z; Chinese Diabetes Society. Standards of medical care for type 2 diabetes in China 2019. *Diabetes Metab Res Rev* 2019; **35**: e3158 [PMID: 30908791 DOI: 10.1002/dmrr.3158]

10 **Lei F**, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, Cai J, Lin L, Ouyang S, Wang X, Yang C, Cheng X, Liu W, Li H, Xie J, Wu B, Luo H, Xiao F, Chen J, Tao L, Cheng G, She ZG, Zhou J, Wang H, Lin J, Luo P, Fu S, Ye P, Xiao B, Mao W, Liu L, Yan Y, Chen G, Huang X, Zhang BH, Yuan Y. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020; **72**: 389-398 [PMID: 32359177 DOI: 10.1002/hep.31301]

11 **Woo J**, Ho SC, Yu AL, Sham A. Is waist circumference a useful measure in predicting health outcomes in the elderly? *Int J Obes Relat Metab Disord* 2002; **26**: 1349-1355 [PMID: 12355330 DOI: 10.1038/sj.ijo.0802080]

12 **Angulo P**, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015; **149**: 389-97.e10 [PMID: 25935633 DOI: 10.1053/j.gastro.2015.04.043]

13 **Tiniakos DG**. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis: histological diagnostic criteria and scoring systems. *Eur J Gastroenterol Hepatol* 2010; **22**: 643-650 [PMID: 19478676 DOI: 10.1097/MEG.0b013e32832ca0cb]

14 **ZELMAN S**. The liver in obesity. *AMA Arch Intern Med* 1952; **90**: 141-156 [PMID: 14943295 DOI: 10.1001/archinte.1952.00240080007002]

15 **Younes R**, Bugianesi E. NASH in Lean Individuals. *Semin Liver Dis* 2019; **39**: 86-95 [PMID: 30654392 DOI: 10.1055/s-0038-1677517]

16 **Stefan N**, Schick F, Häring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. *Cell Metab* 2017; **26**: 292-300 [PMID: 28768170 DOI: 10.1016/j.cmet.2017.07.008]

17 **Eshraghian A**, Nikeghbalian S, Geramizadeh B, Kazemi K, Shamsaeefar A, Malek-Hosseini SA. Characterization of biopsy proven non-alcoholic fatty liver disease in healthy non-obese and lean population of living liver donors: The impact of uric acid. *Clin Res Hepatol Gastroenterol* 2020; **44**: 572-578 [PMID: 31611031 DOI: 10.1016/j.clinre.2019.09.002]

18 **Kawaguchi T**, Torimura T. Is metabolic syndrome responsible for the progression from NAFLD to NASH in non-obese patients? *J Gastroenterol* 2020; **55**: 363-364 [PMID: 31781941 DOI: 10.1007/s00535-019-01650-1]

19 **Kim D**, Kim W, Joo SK, Han J, Kim JH, Harrison SA, Younossi ZM, Ahmed A. Association between body size-metabolic phenotype and nonalcoholic steatohepatitis and significant fibrosis. *J Gastroenterol* 2020; **55**: 330-341 [PMID: 31535207 DOI: 10.1007/s00535-019-01628-z]

20 **Fan JG**, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol* 2017; **67**: 862-873 [PMID: 28642059 DOI: 10.1016/j.jhep.2017.06.003]

21 **Li H**, Guo M, An Z, Meng J, Jiang J, Song J, Wu W. Prevalence and Risk Factors of Metabolic Associated Fatty Liver Disease in Xinxiang, China. *Int J Environ Res Public Health* 2020; **17** [PMID: 32168920 DOI: 10.3390/ijerph17061818]

22 **Idalsoaga F**, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease: Two Intertwined Entities. *Front Med (Lausanne)* 2020; **7**: 448 [PMID: 32974366 DOI: 10.3389/fmed.2020.00448]

23 **Dam-Larsen S**, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol* 2009; **44**: 1236-1243 [PMID: 19670076 DOI: 10.1080/00365520903171284]

24 **Kleiner DE**, Brunt EM, Wilson LA, Behling C, Guy C, Contos M, Cummings O, Yeh M, Gill R, Chalasani N, Neuschwander-Tetri BA, Diehl AM, Dasarathy S, Terrault N, Kowdley K, Loomba R, Belt P, Tonascia J, Lavine JE, Sanyal AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Association of Histologic Disease Activity With Progression of Nonalcoholic Fatty Liver Disease. *JAMA Netw Open* 2019; **2**: e1912565 [PMID: 31584681 DOI: 10.1001/jamanetworkopen.2019.12565]

25 **Vilar-Gomez E**, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, Eslam M, Gonzalez-Fabian L, Alvarez-Quiñones Sanz M, Conde-Martin AF, De Boer B, McLeod D, Hung Chan AW, Chalasani N, George J, Adams LA, Romero-Gomez M. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. *Gastroenterology* 2018; **155**: 443-457.e17 [PMID: 29733831 DOI: 10.1053/j.gastro.2018.04.034]

26 **Siddiqui MS**, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, Dimick-Santos L, Friedman SL, Greene K, Kleiner DE, Megnien S, Neuschwander-Tetri BA, Ratziu V, Schabel E, Miller V, Sanyal AJ; Liver Forum Case Definitions Working Group. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. *Hepatology* 2018; **67**: 2001-2012 [PMID: 29059456 DOI: 10.1002/hep.29607]

27 **Huang J**, Kumar R, Wang M, Zhu Y, Lin S. MAFLD criteria overlooks a number of patients with severe steatosis: Is it clinically relevant? *J Hepatol* 2020; **73**: 1265-1267 [PMID: 32819754 DOI: 10.1016/j.jhep.2020.06.016]

28 **Di Sessa A**, Guarino S, Umano GR, Arenella M, Alfiero S, Quaranta G, Miraglia Del Giudice E, Marzuillo P. MAFLD in Obese Children: A Challenging Definition. *Children (Basel)* 2021; **8** [PMID: 33806784 DOI: 10.3390/children8030247]

29 **Huang H**, Sun Z, Pan H, Chen M, Tong Y, Zhang J, Chen D, Su X, Li L. Serum metabolomic signatures discriminate early liver inflammation and fibrosis stages in patients with chronic hepatitis B. *Sci Rep* 2016; **6**: 30853 [PMID: 27498553 DOI: 10.1038/srep30853]

30 **Wang H**, Xue L, Yan R, Zhou Y, Wang MS, Cheng MJ, Hai-Jun Huang. Comparison of histologic characteristics of Chinese chronic hepatitis B patients with persistently normal or mildly elevated ALT. *PLoS One* 2013; **8**: e80585 [PMID: 24260428 DOI: 10.1371/journal.pone.0080585]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2022 Baishideng Publishing Group Inc. All rights reserved.