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Original article

Metabolic syndrome is associated with significant hepatic fibrosis and steatosis in patients with nonalcoholic steatohepatitis

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ABSTRACT

Background and aims: Nonalcoholic steatohepatitis (NASH), an inflammatory form of non-alcoholic fatty liver disease, can progress to advanced liver fibrosis, cirrhosis, and liver cancer. Metabolic syndrome (MetS) parallels the prevalence of non-alcoholic fatty liver disease/NASH and increases patients' risk of advanced liver disease. This study aimed to determine whether MetS was associated with the histological progression of NASH.

Methods: Patients with liver biopsy-proven NASH were retrospectively screened and categorized into two groups for each histological feature: with (<2 points) or without (≥2 points) significant hepatic steatosis/inflammation/fibrosis. Multivariable logistic regression was used to explore the association between MetS and histological features.

Results: In total, 386 patients with a median age of 33.0 years were enrolled; among them, 35.2% were female, and 41.2% had MetS. The proportion of significant hepatic fibrosis and steatosis in those with MetS was significantly higher than in those without MetS ($p < 0.05$). Multivariable logistic regression analyses showed that MetS remained significantly associated with significant hepatic fibrosis (adjusted odds ratio: 1.852, 95% confidence interval: 1.042–3.292, $p = 0.036$), and severe hepatic steatosis (adjusted odds ratio: 2.008, 95% confidence interval: 1.030–3.914, $p = 0.041$).

Conclusion: MetS was associated with significant hepatic fibrosis and steatosis in patients with NASH. Our results suggest that NASH patients with MetS should be closely monitored and given targeted intervention and treatment, which may help to prevent disease progression and mitigate the growing burden of NASH.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) affects about 25% of the general population and poses an increasing health and economic burden globally. Nonalcoholic steatohepatitis (NASH), the inflammatory form of NAFLD, may progress to liver fibrosis, cirrhosis, and cancer, which account for the rapidly increasing rates of liver transplantation and liver-related mortality worldwide [1,2]. The pathogenesis of NAFLD/NASH is complex and cannot be explained by a single mechanism; discussion about changing the name from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) is ongoing [3,4]. However, regardless of whether it is incorporated into the name, metabolism-related issues are central in NAFLD pathogenesis. Metabolic syndrome (MetS) is also a worldwide health problem characterized by central obesity, dyslipidemia, impaired glucose tolerance, and high blood pressure. The prevalence of both MetS and NAFLD is increasing, and at increasingly younger ages. Various studies show that NAFLD/NASH and MetS have a bidirectional relationship and influence each other [5,6]. MetS may occur before NAFLD/NASH,

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; MetS, metabolic syndrome; GLU, blood glucose; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; S, hepatic fibrosis stage; F, hepatic steatosis grade; G, hepatic inflammatory grade; LSM, liver stiffness measurement; OR, odds ratio.

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and NAFLD/NASH can also be regarded as a manifestation of MetS to some extent.

NAFLD complications such as cirrhosis and malignant tumors need early intervention to prevent liver failure or mortality. Current studies on the relationship between NAFLD and MetS have focused on insulin resistance, lipid content in the liver, and the cardiovascular system [7,8]. However, few studies have focused on the effects of MetS on histological lesion development in NAFLD/NASH and whether MetS promotes the progression of NAFLD/NASH.

The present study aimed to characterize the clinical features of NASH and investigate the impact of MetS on the histological progression of NASH, thus identifying risk factors that may enable targeted, early intervention in NASH and thereby mitigate disease progression.

2. Patients and methods

2.1. Study design and patients

The inclusion criteria were as follows: (1) admitted to our hospital between January 2003 and July 2020, (2) age ≥18 years old, (3) diagnosed with NASH by liver biopsy (presence of ≥5% hepatic steatosis with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis) [9], and (4) no history of excessive drinking (alcohol consumption <20 g/d for female and <30 g/d for male individuals). The exclusion criteria were as follows: (1) the presence of other liver disease etiologies according to the relevant guidelines (e.g., viral, drug-induced, and autoimmune) [10–12], (2) the presence of other serious systemic diseases and malignant tumors, and (3) incomplete critical clinical data.

2.2. Data collection

The clinical information was collected within 1 week of the liver biopsy and was based on electronic medical records. Data collected included sex, age, body mass index (BMI), MetS status, liver stiffness measurement (LSM), controlled attenuation parameter (CAP), Brunt steatosis grade (F), inflammatory grade (G), fibrosis stage (S), platelets, alanine aminotransferase, aspartate aminotransferase, glucose (GLU), and low- and high-density lipoprotein cholesterol.

2.3. Definition

NASH was defined as steatosis (≥5%), with both lobular inflammation and ballooning degeneration of hepatocytes occurring in a zone 3-predominant distribution [13,14]. MetS was defined as any three of the following features associated with insulin resistance: (1) waist circumference ≥85/≥80 cm for males/females, (2) impaired fasting glycemia or type 2 diabetes mellitus, (3) hypertension, and (4) high-density lipoprotein cholesterol <1.0/1.3 mmol/L for male or female individuals [9]. Normal, overweight and obesity were defined by BMI cutoff values of <24 kg/m^2, 24–27.9 kg/m^2 and ≥28 kg/m^2, respectively, according to the Chinese consensus on obesity prevention and treatment [15].

2.4. Histological evaluation

Liver tissue of ≥15 mm length was extracted from all patients by ultrasound-guided liver biopsy, fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. To avoid bias, each tissue specimen was evaluated independently by two pathologists who together reevaluated the specimen when inconsistencies occurred. Additionally, the degree of steatosis was evaluated by the Brunt grading system (F1, mild (5%–33% steatosis); F2, significant (34%–66% steatosis); F3, severe (>66% steatosis)) [16]. Hepatic inflammatory grade (G) and fibrosis stage (S) were determined based on the Scheuer scoring system [17]. The enrolled patients were then categorized into two groups for each histological parameter (with (score ≥2) or without (score <2) significant hepatic inflammation\fibrosis\steatosis).

2.5. Liver stiffness measurement

LSM was assessed by transient elastography performed by experienced examinators. The measurement was considered reliable if median values of 10 valid shots had an interquartile range (IQR) ≤30% and a success rate ≥60% [18].

2.6. Statistical analyses

Normally distributed continuous variables are expressed as mean ± standard deviation and were compared using an unpaired *t*-test. Non-normally distributed continuous variables are expressed as the median and IQR and were compared using the Mann-Whitney U test. Median age (33.0 years) was used to divide the enrolled patients into two groups. Categorical variables are presented as numbers and percentages and were compared by the Chi-square or Fisher's exact test. Univariable and multivariable logistic stepwise regression was performed to determine the independent factors associated with the severity of NASH features, including hepatic fibrosis, steatosis, and inflammation. Meanwhile, odd ratios (OR) and 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.2.1, http://www.r-project.org/).

3. Results

3.1. Clinical characteristics

A total of 1228 patients with fatty liver were screened, and 386 with confirmed NASH were enrolled (Fig. 1). The median age (IQR) was 33.0 (25.0–48.0) years, 136 (35.2%) patients were female, and 159 (41.2%) patients had MetS. The proportion of patients with a BMI <24 kg/m^2, 24–27.9 kg/m^2, and ≥28 kg/m^2 was 19.9%, 48.2%, and 31.9%, respectively; the proportion of patients with S0 to S4 was 15.3%, 56.0%, 18.9%, 6.7%, and 3.1%, respectively; the proportion of patients with F1 to F3 was 19.2%, 42.2%, and 38.6%, respectively; and the proportion of patients with G1 to G3 was 76.3%, 23.2% and 0.5%, respectively. The enrolled patients were divided into two groups (<2 or ≥2 points) for comparison regarding the degree of hepatic steatosis, inflammation, and fibrosis. The comparisons between the two groups are shown in Table 1; representative histological images for each group are shown in Fig. 2. In addition, we analyzed the subgroup of NASH patients with MetS; these comparisons are shown in Table 2.

3.2. Distribution of histopathological features

In patients with MetS, the proportion of S0–S4 was 14.4%, 47.2%, 23.4%, 10.6%, and 4.4%, respectively, which was significantly different from the 15.8%, 62.2%, 15.8%, 3.9%, and 2.3% in those without MetS ($p = 0.006$). The proportion of MetS patients with mild, significant, and severe steatosis was 13.8%, 50.4%, and 35.8%, which was significantly different from the 22.9%, 36.5%, and 40.64% in those without MetS ($p = 0.013$). However, the two groups had no statistically significant differences in hepatic inflammation ($p = 0.226$, Fig. 3).

3.3. Multivariate logistic regression analyses

Significantly different variables without collinearity identified in univariable analyses were used in multivariable logistic regression analyses to explore independent factors associated with NASH histological severity. The results showed that MetS was significantly associated with a higher stage of hepatic fibrosis (adjusted OR: 1.852, 95% CI: 1.042–3.292, $p = 0.036$, Fig. 4A); and a higher degree of hepatic steatosis

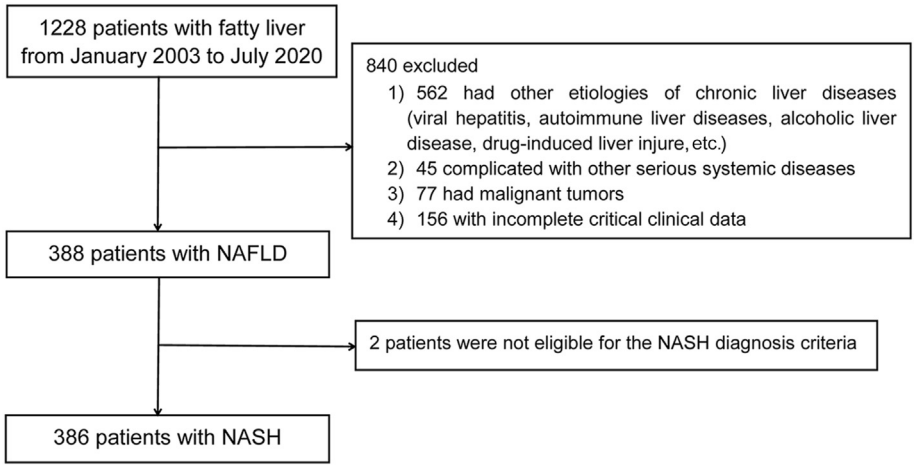

Fig. 1. Flow diagram of study participants.

Table 1
Clinical characteristics of patients with NASH.

	Overall (n = 386)	Fibrosis			Steatosis			Inflammation		
		S < 2 (n = 275)	S ≥ 2 (n = 111)	p value	F1 (n = 74)	F ≥ 2 (n = 312)	p value	G < 2 (n = 294)	G ≥ 2 (n = 92)	p value
Female[#]	136 (35.2)	86 (31.3)	50 (45.0)	0.014	29 (39.2)	107 (34.3)	0.511	87 (29.6)	49 (53.3)	<0.001
Age (yr)*	33.0 (25.0–48.0)	32.0 (25.0–46.0)	38.0 (28.0–52.0)	0.003	40.0 (31.2–52.8)	31.5 (24.0–47.0)	<0.001	33.0 (25.0–46.0)	37.0 (26.0–52.2)	0.047
Age <33 (yr)[#]	194 (50.3)	148 (53.8)	46 (41.4)	0.037	24 (32.4)	170 (54.5)	0.001	151 (51.4)	43 (46.7)	0.513
BMI (kg/m^2)[#]				0.126			0.010			0.257
1	77 (19.9)	61 (21.8)	17 (15.4)		18 (24.3)	59 (18.9)		64 (21.8)	13 (14.2)	
2	186 (48.2)	135 (49.1)	51 (45.9)		43 (58.1)	143 (45.8)		137 (46.6)	49 (53.4)	
3	123 (31.9)	80 (29.1)	43 (38.7)		13 (17.6)	110 (35.3)		93 (31.6)	30 (32.6)	
MetS[#]	159 (41.2)	98 (35.6)	61 (55.0)	0.001	22 (29.7)	137 (43.9)	0.036	114 (38.8)	45 (48.9)	0.109
LSM (kPa)*	6.7 (5.6–8.6)	6.5 (5.4–6.9)	8.7 (7.8–11.5)	<0.001	6.0 (4.8–6.8)	6.8 (6.1–8.8)	<0.001	6.5 (5.5–7.9)	8.0 (6.6–9.9)	<0.001
CAP (db/m) *	311.5 (289–330)	309.0 (287–330)	318 (297–330)	0.158	294 (273–301)	319 (290–334)	<0.001	308 (287–330)	320 (296–335)	0.029
Fibrosis[#]				<0.001			<0.001			<0.001
S0	59 (15.3)	59 (21.5)	0 (0.0)		25 (33.8)	34 (10.9)		55 (18.7)	4 (4.3)	
S1	216 (56.0)	216 (78.5)	0 (0.0)		43 (58.1)	173 (55.4)		180 (61.2)	36 (39.1)	
S2	73 (18.9)	0 (0.0)	73 (65.8)		5 (6.8)	68 (21.8)		42 (14.3)	31 (33.7)	
S3	26 (6.7)	0 (0.0)	26 (23.4)		1 (1.4)	25 (8.0)		12 (4.1)	14 (15.2)	
S4	12 (3.1)	0 (0.0)	12 (10.8)		0 (0.0)	12 (3.8)		5 (1.7)	7 (7.6)	
Steatosis[#]				<0.001			<0.001			<0.001
F1	74 (19.2)	68 (24.7)	6 (5.4)		74 (100.0)	0 (0.0)		69 (23.5)	5 (5.4)	
F2	163 (42.2)	108 (39.3)	55 (49.5)		0 (0.0)	163 (52.2)		123 (41.8)	40 (43.5)	
F3	149 (38.6)	99 (36.0)	50 (45.0)		0 (0.0)	150 (47.8)		102 (34.7)	47 (51.1)	
Inflammation[#]				<0.001			0.001			<0.001
G1	294 (76.3)	235 (85.5)	59 (53.2)		69 (93.2)	225 (72.1)		294 (100)	0 (0.0)	
G2	90 (23.2)	38 (13.8)	52 (46.8)		5 (6.8)	85 (27.2)		0 (0.0)	90 (97.8)	
G3	2 (0.5)	2 (0.7)	0 (0.0)		0 (0.0)	2 (0.6)		0 (0.0)	2 (2.2)	
PLT ≥100 (× 10^9/L)[#]	379 (98.2)	272 (98.9)	107 (96.4)	0.210	72 (97.3)	307 (98.4)	0.878	289 (98.3)	90 (97.8)	>0.999
ALT ≥40 (U/L)[#]	304 (78.7)	215 (78.2)	89 (80.2)	0.766	43 (58.1)	261 (83.7)	<0.001	224 (76.2)	80 (87.0)	0.040
AST ≥40 (U/L)[#]	225 (58.3)	146 (53.1)	79 (71.2)	0.002	20 (27.0)	205 (65.7)	<0.001	158 (53.7)	67 (72.8)	0.002
GLU ≥6.1 (mmol/L)[#]	49 (12.7)	27 (9.8)	22 (19.8)	0.012	5 (6.8)	44 (14.1)	0.130	22 (7.5)	27 (29.3)	<0.001
LDL ≥3.37 (mmol/L)[#]	160 (41.5)	114 (41.5)	46 (41.4)	>0.999	27 (36.5)	133 (42.6)	0.405	116 (39.5)	44 (47.8)	0.193

Note: [#], n (%); *, M (IQR). BMI categories: 1. Normal (BMI <24 kg/m^2), 2. Overweight (BMI: 24–27.9 kg/m^2); 3. Obese (BMI ≥28 kg/m^2).
Abbreviations: NASH, non-alcoholic fatty liver disease; BMI, body mass index; MetS, metabolic syndrome; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; S, fibrosis stage; F, Brunt steatosis grade; G, inflammatory grade; PLT, platelet; ALT, alanine aminotransferase; AST, alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol.

(adjusted OR: 2.008, 95% CI: 1.030–3.914, p = 0.041, Fig. 4B). In addition, age (<33 years, OR: 1.189, 95% CI: 0.996–3.609, p = 0.051) tended to be associated with steatosis (Fig. 4B). The presence of MetS had no impact on hepatic inflammation (OR: 0.729, 95% CI: 0.398–1.337, p = 0.650); whereas female sex (OR: 2.704, 95% CI: 1.401–5.222, p = 0.003), LSM (OR: 1.156, 95% CI: 1.078–1.239, p < 0.001), CAP (OR: 1.009, 95% CI: 1.000–10.278, p < 0.001), and elevated GLU (≥6.1 mmol/L, OR: 4.706, 95% CI: 2.155–10.278, p < 0.001) were high-risk factors significantly associated with hepatic inflammation (Fig. 4C).

We also explored the subgroup of patients with MetS, and found that LSM was significantly associated with a higher stage of hepatic fibrosis (OR: 1.605, 95% CI: 1.308–1.970, p < 0.001, Fig. 4D); age <33 years (OR: 5.878, 95% CI: 1.176–29.371, p = 0.031) and LSM (OR: 1.581, 95% CI: 1.080–2.315, p = 0.018) were high-risk factors significantly

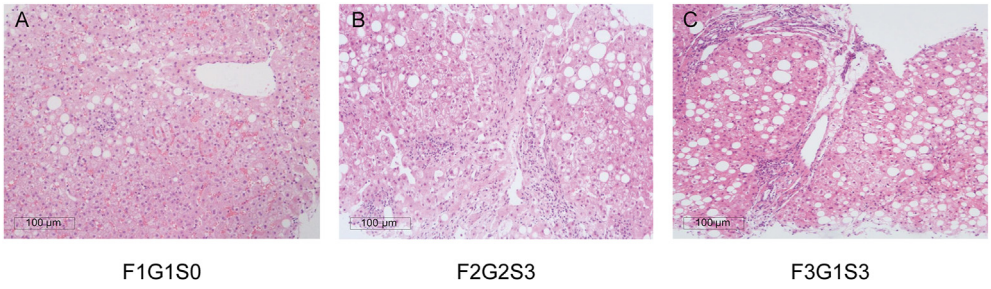

Fig. 2. Representative histological pictures of patients (A, B, and C). F, steatosis; G, inflammation; S, fibrosis.

Table 2
Clinical characteristics of patients in MetS subgroup.

	Overall (n = 159)	Fibrosis			Steatosis			Inflammation		
		S < 2 (n = 98)	S ≥ 2 (n = 61)	p value	F1 (n = 22)	F ≥ 2 (n = 137)	p value	G < 2 (n = 114)	G ≥ 2 (n = 45)	p value
Female[#]	73 (45.9)	41 (41.8)	32 (52.5)	0.253	12 (54.5)	61 (44.5)	0.519	42 (36.8)	31 (68.9)	0.001
Age (yr) *	33.0 (25.0–48.0)	32.0 (25.0–46.0)	38.0 (28.0–52.0)	0.003	40.0 (31.2–52.8)	31.5 (24.0–47.0)	0.004	34.5 (26.0–47.0)	49.0 (29.0–55.0)	0.002
Age<33 (yr)[#]	67 (42.1)	44 (44.9)	23 (37.7)	0.467	2 (9.1)	65 (47.4)	0.001	51 (44.7)	16 (35.6)	0.380
BMI (kg/m^2)[#]				0.475			0.056			0.456
1	17 (10.7)	11 (11.2)	6 (9.8)		3 (13.6)	14 (10.2)		10 (8.8)	7 (15.6)	
2	76 (47.8)	50 (51.0)	26 (42.6)		15 (68.2)	61 (44.5)		56 (49.1)	20 (44.4)	
3	66 (41.5)	37 (37.8)	29 (47.5)		4 (18.2)	62 (45.3)		48 (42.1)	18 (40.0)	
LSM (kPa)*	6.8 (6.0–8.7)	6.5 (5.5–7.5)	8.6 (7.8–11.9)	<0.001	5.8 (4.8–7.1)	7.3 (6.4–8.9)	<0.001	6.6 (5.8–8.1)	8.6 (6.8–10.1)	<0.001
CAP (db/m) *	309.0 (289–330)	306.5 (289–330)	318 (297–330)	0.154	293.5 (289–305)	315 (289–330)	0.007	309 (289–330)	310 (289–328)	0.898
Fibrosis[#]				<0.001			0.001			<0.001
S0	23 (14.5)	23 (23.5)	0 (0.0)		9 (40.9)	14 (10.2)		23 (20.2)	0 (0.0)	
S1	75 (47.2)	75 (76.5)	0 (0.0)		11 (50.1)	64 (46.7)		59 (51.8)	16 (35.6)	
S2	37 (23.3)	0 (0.0)	37 (60.7)		1 (4.5)	36 (26.3)		22 (19.3)	15 (33.3)	
S3	17 (10.7)	0 (0.0)	17 (27.9)		1 (4.5)	16 (11.7)		8 (7.0)	9 (20.0)	
S4	7 (4.4)	0 (0.0)	7 (11.5)		0 (0.0)	7 (5.1)		2 (1.8)	5 (11.1)	
Steatosis[#]				0.006			<0.001			0.253
F1	22 (13.8)	20 (20.4)	2 (3.3)		22 (100.0)	0 (0.0)		19 (16.7)	3 (6.7)	
F2	80 (50.4)	43 (43.9)	37 (60.7)		0 (0.0)	80 (58.4)		56 (49.1)	24 (53.3)	
F3	57 (35.8)	35 (35.7)	22 (36.1)		0 (0.0)	57 (41.6)		39 (34.2)	18 (40.0)	
Inflammation[#]				<0.001			0.254			<0.001
G1	114 (71.7)	82 (83.7)	32 (52.5)		19 (86.4)	95 (69.3)		114 (100.0)	0 (0.0)	
G2	44 (27.7)	15 (15.3)	29 (47.5)		3 (13.6)	41 (29.9)		0 (0.0)	44 (97.8)	
G3	1 (0.6)	1 (1.0)	0 (0.0)		0 (0.0)	1 (0.7)		0 (0.0)	1 (2.2)	
PLT ≥100 (× 10^9/L)[#]	158 (99.4)	97 (99.0)	61 (100.0)	>0.999	22 (100.0)	136 (99.3)	>0.999	113 (99.1)	45 (100)	>0.999
ALT ≥40 (U/L)[#]	122 (76.7)	74 (75.5)	48 (78.7)	0.789	9 (40.9)	113 (82.5)	<0.001	82 (71.09)	40 (88.9)	0.038
AST ≥40 (U/L)[#]	100 (62.9)	54 (55.1)	46 (75.4)	0.016	5 (22.7)	95 (69.3)	<0.001	65 (57.0)	35 (77.8)	0.024
GLU ≥6.1 (mmol/L)[#]	42 (26.4)	23 (23.5)	19 (31.1)	0.377	2 (9.1)	40 (29.2)	0.085	17 (14.9)	25 (55.6)	<0.001
LDL ≥3.37 (mmol/L)[#]	68 (42.8)	41 (41.8)	27 (44.3)	0.892	9 (40.9)	59 (43.1)	>0.999	40 (35.1)	28 (62.2)	0.003

Note: [#], n (%); *, M (IQR). BMI categories: 1. Normal (BMI <24 kg/m^2), 2. Overweight (BMI: 24–27.9 kg/m^2); 3. Obese (BMI ≥28 kg/m^2).
Abbreviations: BMI, body mass index; MetS, metabolic syndrome; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; S, fibrosis stage; F, Brunt steatosis grade; G, inflammatory grade; PLT, platelet; ALT, alanine aminotransferase; AST, alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol.

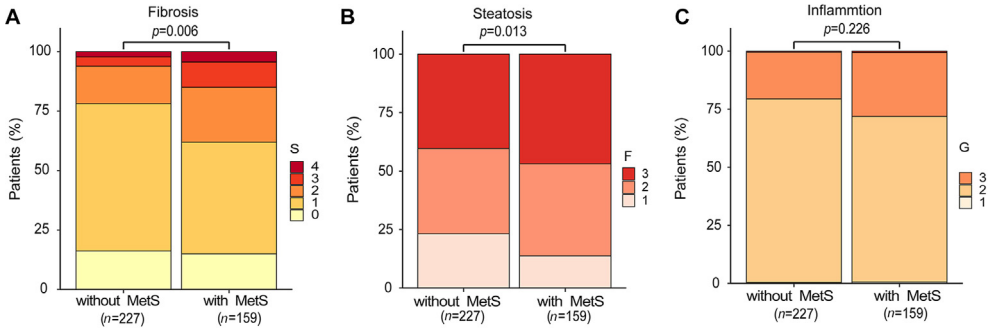

Fig. 3. Distribution of histopathological features in NASH patients. A. Fibrosis (S); B. Steatosis (F); C. Inflammation (G).

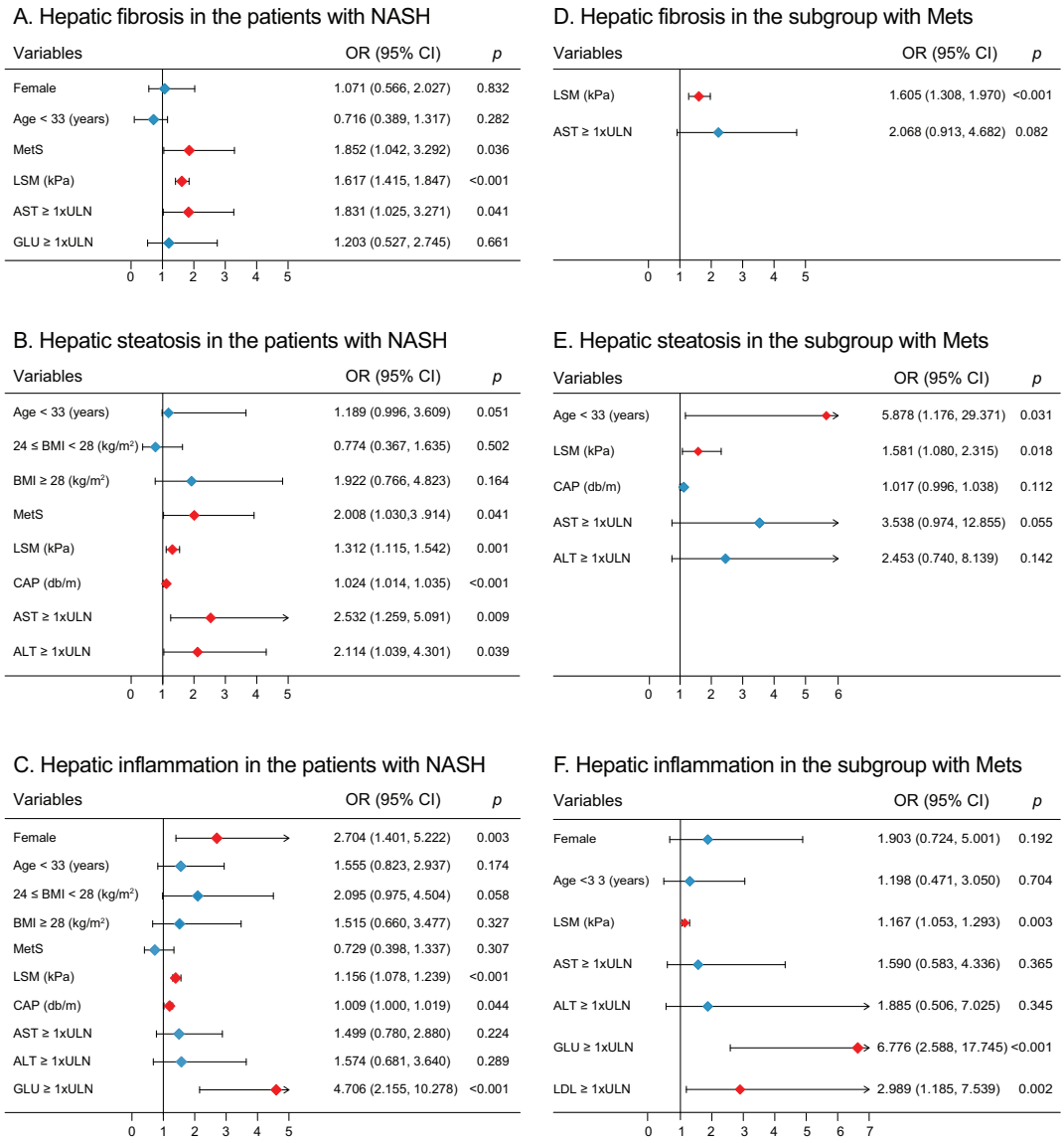

Fig. 4. Factors significantly associated with liver histology based on multivariate logistic regression analysis. Hepatic fibrosis (A); Hepatic steatosis (B); Hepatic inflammation in NASH patients (C); Hepatic fibrosis (D); Hepatic steatosis (E); Hepatic inflammation in MetS subgroup (F). The solid diamonds (red for significant factors, blue for insignificant factors) represent the ORs, and the black lines represent 95% CIs. ALT ULN = 40 U/L, AST ULN = 40 U/L, GLU ULN = 6.1 mmol/L, LDL ULN = 3.37 mmol/L. NASH, nonalcoholic steatohepatitis; OR, odds ratio; CI, confidence interval; BMI, body mass index; CAP, controlled attenuation parameter; GLU, blood glucose; LSM, liver stiffness measurement; MetS, metabolic syndrome; S, fibrosis stage; F, Brunt steatosis grade; G, inflammatory grade; ULN, upper limit of normal.

associated with hepatic steatosis (Fig. 4E). LSM (OR: 1.167, 95% CI: 1.053–1.293, $p = 0.003$), GLU (≥6.1 mmol/L, OR: 6.776, 95% CI: 2.588–17.745, $p < 0.001$) and low-density lipoprotein cholesterol (≥3.37 mmol/L, OR: 2.989, 95% CI: 1.185–7.539, $p = 0.002$) were high-risk factors significantly associated with hepatic inflammation (Fig. 4F).

4. Discussion

The occurrence and progression of hepatic fibrosis in NAFLD/NASH can be predicted by various factors; therefore, early identification and intervention in patients with these factors can significantly improve quality of life and survival rate [19]. Through this cross-sectional, liver biopsy-based study, we found that hepatic steatosis and fibrosis were more severe in NASH patients with MetS than those without MetS. Therefore, early intervention should be adopted in patients with NASH and MetS to block or even reverse the progression of hepatic fibrosis.

NAFLD/NASH, named in 1986, is a chronic liver disease determined by metabolic (i.e., insulin resistance) and genetic factors. MetS is a pathological condition in which the metabolism of protein, fat, carbohydrates, and other substances in the human body is disturbed by poor lifestyle and overnutrition [20,21]. NAFLD/NASH has traditionally been considered the hepatic manifestation of the MetS due to the close association between NAFLD/NASH and MetS features, with insulin resistance being the central pathophysiological process common to both conditions. A previous study showed that NAFLD/NASH was significantly correlated with MetS in etiology, pathogenesis, and risk factors, and that hepatic inflammation and fibrosis could lead to the occurrence and progression of MetS [22]. Although the "chicken and egg" debate still exists with no consensus about which occurs first, whether there is a synergistic effect of NAFLD/NASH and MetS that promotes disease progression is a more clinically significant issue. Previously, a large multicenter study showed that biopsy-confirmed NAFLD/NASH patients with diabetes had a higher cumulative incidence of hepatic fibrosis progression than those without

diabetes, and that diabetes was an independent predictor for fibrosis progression. Moreover, this study also found that NAFLD/NASH patients with diabetes were more likely to have MetS; extrapolation of these results suggests that NAFLD/NASH patients with MetS may therefore have severe hepatic fibrosis. In addition, glycemic control predicts the severity of hepatocyte ballooning and hepatic fibrosis in NAFLD/NASH [23–26], suggesting an association between blood glucose and advanced NASH features. Taken together, these results are consistent with our findings.

We also found that LSM was related to the degree of hepatic fibrosis, steatosis, and inflammation, and that CAP was related to the degree of hepatocyte steatosis and hepatic inflammation. In another study, LSM and CAP measurement were used to diagnose hepatic steatosis and fibrosis in liver transplant recipients [27]. Combined with our findings, this suggests that noninvasive transient elastography could be used to dynamically monitor liver histology, avoiding the damage and inconvenience of a liver biopsy.

Interestingly, we found that younger patients with NASH and MetS presented with more severe hepatic steatosis than older patients, which may be explained by the changing habits of young people, such as irregular schedules, unhealthy diets, high life pressure, and lack of exercise. A survey analysis, including 1319 adolescents and young adults, demonstrated that 40% have evidence of NAFLD/NASH, with 31% at risk of disease progression [28], which also indicated that disease is more likely to progress in younger NAFLD patients. Therefore, young people with NAFLD/NASH should be encouraged to adopt healthy lifestyle habits, be actively followed up, and receive prompt intervention. Furthermore, we found that female individuals had a higher risk of developing severe hepatic inflammation, as reported by previous studies [29]. This might relate to female-specific hormones. Therefore, sex-specific strategies to prevent, diagnose, and treat NAFLD/NASH are critical to improve the related morbidity and mortality. We observed that BMI had no impact on liver histology in NAFLD/NASH, implying that lean/non-obese NAFLD/NASH patients have a similar risk of disease progression to those with high BMI. The pathogenesis of NAFLD/NASH in non-obese patients might be associated with genetic predispositions that result in triglyceride accumulation in the liver and resistance to insulin [30]. Nonetheless, dietary and physical activity factors play important roles in the pathology of non-obese NAFLD/NASH; therefore, healthy lifestyle recommendations should be emphasized when consulting such patients.

The main treatment measures for NAFLD/NASH are improving diet and increasing physical exercise. The Mediterranean diet consists of monounsaturated and polyunsaturated fatty acids (fat makes up 40% of total calories), which is an excellent dietary pattern for NAFLD/NASH patients to reduce hepatic steatosis [31]. In addition, the metabolic indexes of NAFLD/NASH patients are improved to varying degrees by various dietary strategies, including high-protein diets, Paleo diets, intermittent fasting, low-carbohydrate diets, and ketogenic diets [32]. Furthermore, reasonable exercise and weight loss are also required to manage NAFLD/NASH effectively. However, adhering to these lifestyle interventions for prolonged periods is challenging for NAFLD/NASH patients. Therefore, pharmaceuticals targeting MetS (e.g., orlistat, liraglutide, metformin, pioglitazone, and statins) and improving liver injury (e.g., vitamin E, silymarin, and S-adenosylmethionine) are the mainstream therapeutic strategies, although their safety and efficacy still need to be confirmed by high-level standardized clinical studies [33].

The strength of the present study was that the diagnosis of NASH was verified by liver biopsy rather than other noninvasive alternatives, guaranteeing the accuracy of historical assessment and regression analyses. However, this study also had several limitations. First, a single center lacking the inclusion of other races might limit the generalizability of our conclusions to broader populations. Second, the cross-sectional nature of the current study meant that it was not possible to interpret any cause–effect relationships. Third, the retrospective design may introduce biases (e.g., young and middle-aged patients were prone to liver biopsy (n = 363, 94.0% in the study), while old patients were unwilling to accept or were ineligible for liver biopsy (>60 years, $n = 23$, 6.0% in the study). To minimize this bias, we used the median age to categorize patients; however, prospective cohort studies are needed to verify the results.

In conclusion, we demonstrated that MetS is associated with significant hepatic fibrosis and steatosis in a cohort of patients with biopsy-proven NASH, which has important implications for clinical practice and medication development. Our results suggest that NASH patients with MetS should be closely monitored and given targeted intervention and treatment. Greater awareness and development of cost-effective risk stratification strategies are warranted to address the growing burden of NASH.

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Author contributions

Conception, design, supervision, and critical review: D.J. and Z.F.B.; Resources: Z.F.B., X.X.N., and J.J.W.; Data collection and processing: Q.Q.L., D.W., K.X.W., C.G., Y.M.F., C.Y.W., and Z.F.B.; Analysis and interpretation: Q.Q.L. and D.J.; Literature search: Y.T.X.; Writing manuscript: Q.Q.L., Y.T.X., and D.J.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

Since the study was a retrospective study without intervention and there were no patient privacy concerns, the study was approved by the Ethics Committees of PLA General Hospital (No. S2022-192-01).

Informed consent

Written informed consent for liver biopsy was obtained from all enrolled patients, while patient consent for data collection was waived due to the retrospective study design. All of the data collected were used for research purposes only.

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