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Original article

Influence of alcohol on newly developed metabolic dysfunction-associated fatty liver disease in both sexes: A longitudinal study

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SUMMARY

Background & aims: The influence of changes in alcohol consumption on newly developed metabolic dysfunction-associated fatty liver disease (MAFLD) is unclear. We investigated the influence of alcohol consumption on newly developed MAFLD in both sexes.

Methods: This observational cohort study included 4071 patients who underwent more than two health check-ups between 2015 and 2020 over an interval of more than a year. Generalised estimating equations were used for analyses.

Results: At baseline, the rates of drinking and MAFLD between men and women were 72.5% versus 41.7% and 42.2% versus 22.1%, respectively. At the most recent stage, the rates of an increase in alcohol consumption for men and women were 13.3% and 8.7%, respectively, and 311/1192 (26.1%) men and 155/1566 (9.9%) women had newly developed MAFLD. The odds ratio (OR) for drinking in patients with newly developed MAFLD was 0.863 (men) (95% confidence interval [CI], 0.676–1.102, $p = 0.237$) and 1.041 (women) (95% CI, 0.753–1.439, $p = 0.808$); the OR for women who drank 140–279.9 g/week was 2.135 (95% CI, 1.158–3.939, $p < 0.05$) and that for all drinking categories among women was >1. Several non-invasive fibrosis scores were significantly associated with the quantity of alcohol consumption in patients with newly developed MAFLD ($p < 0.005$).

Conclusions: Alcohol consumption had no significant protective effect against newly developed MAFLD in both sexes, regardless of quantity. Conversely, alcohol consumption ≥140 g/week was a risk factor for newly developed MAFLD in women. The development of liver fibrosis with increased alcohol intake should be considered in patients with MAFLD.

1. Introduction

Although excessive alcohol consumption has been known to cause liver injury [1,2], several studies have shown that light or moderate alcohol consumption has a protective effect against the development of fatty liver, including nonalcoholic fatty liver disease (NAFLD) [3–8]. However, recently, it is recommended that alcohol consumption should best be avoided because of a potential linear dose–response on the pro-fibrogenic and carcinogenic effect of alcohol [9–12].

In 2020, an international expert consensus proposed the term metabolic dysfunction-associated fatty liver disease (MAFLD) [13]. MAFLD underlines the association of fatty liver disease with metabolic dysregulation and does not require the exclusion of excessive alcohol consumption [13,14]. Although the definition of MAFLD has been used and discussed by several international societies and pathophysiological aspects [15–19], MAFLD is not completely accepted globally at present. The components in the MAFLD definition are different from those in NAFLD, and the

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List of abbreviations:

MAFLD	metabolic dysfunction-associated fatty liver disease
NAFLD	nonalcoholic fatty liver disease
BMI	body mass index
WC	waist circumference
AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	gamma-glutamyl transpeptidase
T-CHO	total cholesterol
HDL-C	HDL cholesterol
TG	Triglyceride
LDL-C	LDL cholesterol
FPG	fasting plasma glucose
HbA1c	haemoglobin A1c
HS-CRP	high-sensitivity C-reactive protein
AAR	AST/ALT ratio
APRI	the AST-to-platelet ratio index
FIB-4	the fibrosis-4
IGT	Impaired glucose tolerance
HOMA-IR	Homeostatic model assessment for insulin resistance
GEE	generalised estimating equation
ALDH2	aldehyde dehydrogenase 2

MAFLD criteria may be useful for excluding participants with a lower mortality risk and including participants with a higher risk [20].

Alcohol intake may be an essential factor for advanced liver fibrosis development in patients with MAFLD [13] and the influence of alcohol intake has also been reported to differ between sexes [6,8,21–23], with men being more prone to MAFLD [24,25]. Although there are many reports on the influences of alcohol consumption on NAFLD [3–8,26,27], the influence of changes in alcohol consumption on newly developed MAFLD in both sexes remains unclear, as the diagnostic criteria for MAFLD—which do not include alcohol consumption—are recent. Therefore, we aimed to investigate the association between changes in alcohol consumption including the quantity of alcohol intake and the presence of MAFLD in both sexes.

2. Methods

2.1. Study design and patients

In this longitudinal retrospective cohort study, 19,490 patients who underwent comprehensive regular health check-ups, including abdominal ultrasonography and laboratory examinations, at the Shikoku Central Hospital of the Mutual Aid Association of Public School Teachers (Shikokuchuo, Japan) between April 2015 and March 2020 were enrolled in this study. Patients were excluded if they had incomplete information, had undergone previous liver surgery, visited the hospital for treatment, or were followed up for liver disease (e.g., alcoholic, viral, or drug-induced liver disease). Patients who had undergone regular health check-ups more than twice with an interval of more than a year during the aforementioned period were included. The initial and most recent data from the same patients were used as the baseline and follow-up data, respectively. Finally, a total of 4071 patients were eligible for this study. The study design conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Shikoku Central Hospital of the Mutual Aid Association of Public School Teachers' institutional review board committee approved the study protocol. An opt-out approach was used to obtain informed consent from the patients, and personal information was anonymised during data collection.

2.2. Data collection

The following information was obtained using a self-report questionnaire: drug history and lifestyle habits, such as smoking, alcohol intake, exercise, and diet. Current smokers excluded individuals with a history of smoking habits. The average weekly alcohol intake was classified into five categories: 'none', 'very mild' (0.1–69.9 g/week), 'mild' (70–139.9 g/week), 'moderate' (140–279.9 g/week), and 'severe' (≥280 g/week). Regular exercise was defined as exercising in sessions lasting more than 30 min at least once weekly. The habit of eating before going to bed was defined as eating within 2 h before going to bed at least once weekly. Anthropometric parameters, such as height, weight, body weight, and waist circumference (WC), were recorded for all patients, and body mass index (BMI) was calculated. We used a BMI cut-off of ≥23 kg/m^2 to define overweight and obesity in Asian patients [14]. Blood samples were obtained in the morning after 12 h of overnight fasting. Clinical laboratory tests were conducted to measure the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total cholesterol (T-CHO), HDL cholesterol (HDL-C), triglyceride (TG), LDL cholesterol (LDL-C), uric acid, fasting plasma glucose (FPG), haemoglobin A1c (HbA1c), and high-sensitivity C-reactive protein (HS-CRP). We calculated the AST/ALT ratio (AAR), AST-to-platelet ratio index (APRI), fibrosis-4 (FIB-4) index, and NAFLD fibrosis score to evaluate liver fibrosis and referred to published formulas and cut-offs [28]. 'Hypertension' was defined as blood pressure ≥130/85 mmHg or the use of medications for hypertension. 'Dyslipidaemia' was defined as TG ≥ 150 mg/dL or HDL-C < 40 mg/dL for men or HDL-C < 50 mg/dL for women, or the use of medications for dyslipidaemia. 'Impaired glucose tolerance' (IGT) was defined as FPG ≥ 100 mg/dL or the use of medications for diabetes mellitus.

2.3. Diagnostic criteria for MAFLD

MAFLD was diagnosed based on the evidence of hepatic steatosis on ultrasonography and the presence of one of the following: overweight/obesity, type 2 diabetes mellitus, or evidence of metabolic dysregulation [13,14]. 'Metabolic dysregulation' was defined as the presence of two or more of the following metabolic conditions: WC ≥ 90 cm in men and ≥80 cm in women; blood pressure ≥130/85 mmHg or specific antihypertensive treatment; TG ≥ 150 mg/dL or specific drug treatment; HDL-C < 40 mg/dL in men and <50 mg/dL in women or specific drug treatment; prediabetes (FPG of 100–125 mg/dL or HbA1c of 5.7%–6.4%); and plasma HS-CRP >2 mg/L. Homeostatic model assessment for insulin resistance (HOMA-IR) scores indicated metabolic dysregulation, although this assessment is not generally conducted in Japanese medical check-ups. Therefore, HOMA-IR values were not available in the present study. Newly developed MAFLD was defined as a status change from non-MAFLD to MAFLD. The criteria for hepatic steatosis on ultrasonography were as follows: increased hepatorenal echo contrast, liver brightness, vessel blurring, and/or deep attenuation [29].

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation, while categorical data are expressed as numbers (percentages). The proportion and categorical variables between the two groups and more than two groups were compared using the χ^2 test and m × n χ^2 test, respectively. As the data were not normally distributed, the Mann–Whitney U and Kruskal–Wallis nonparametric tests were used to compare the two groups and more than two groups, respectively. The differences were statistically significant at $p < 0.05$. The generalised estimating equation (GEE) can be used to manage longitudinal data of patients who share common characteristics [30,31]. Therefore, we considered the longitudinal relationship between changes in alcohol consumption and the presence of MAFLD to be best evaluated using a GEE approach. A GEE with a logit link and binomial distribution was used to clarify the association between the quantity of alcohol consumption (i.e., average weekly alcohol consumption) and newly developed MAFLD in the longitudinal analysis. In the primary analysis, we investigated the influence of alcohol consumption on newly developed MAFLD, while adjusting for age, BMI, and WC. In the secondary analysis, we adjusted for lifestyle habits, such as current smoking status, regular exercise, eating before going to bed, and the custom of eating breakfast. In the third analysis, we adjusted for variables associated with metabolic dysregulation, such as hypertension, dyslipidaemia, and IGT. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. All statistical analyses were conducted using SPSS for Windows (version 27.0; IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics according to sex

The prevalence of drinking, fatty liver, and MAFLD, the values of most physical assessment parameters, lifestyle habits, and metabolic dysregulation-related factors were significantly higher in men than in women (Table 1). Among the quantity of alcohol consumption categories, several differences existed in clinical factors such as lifestyle habits, metabolic dysregulation, and non-invasive liver fibrosis scores in men with MAFLD at baseline, while few existed in women (Supplementary Table 1).

3.2. Changes in alcohol consumption and the presence of MAFLD between baseline and the most recent stage

Among men, 57 (10.1%) of the 567 non-drinkers at baseline had started drinking (Table 2). Among 1494 drinkers at the baseline, 122 (8.2%) men had abstained from drinking, whereas 218 (14.6%) had increased and 362 (24.2%) had decreased their weekly alcohol consumption across the drinking categories. At the most recent stage, the rates of an increase and a decrease in alcohol consumption were 13.3% (275/2061) and 17.6% (362/2061), respectively.

Conversely, among women, 77 (6.6%) of 1172 non-drinkers at baseline had started drinking. Among 838 drinkers at baseline, 167 (19.9%) women had abstained from drinking, whereas 97 (11.6%) had increased and 114 (13.6%) women had decreased their weekly alcohol consumption across the drinking categories. At the most recent stage, the rates of an increase and a decrease in alcohol consumption were 8.7% (174/2010) and 14.0% (281/2010), respectively.

Among men, newly developed MAFLD was noted in 311 (26.1%) of the 1192 men without MAFLD at baseline (Supplementary Table 2). Among women, newly developed MAFLD was noted in 155 (9.9%) of the 1566 women without MAFLD at baseline.

3.3. Analysis of the relationship between newly developed MAFLD and the quantity of alcohol consumption

In the analysis of newly developed MAFLD among men, after adjusting for hypertension, dyslipidaemia, and IGT, the OR for drinkers was 0.863 (95% CI, 0.676–1.102, $p = 0.808$) (Table 3). In the analysis, which took into consideration the quantity of alcohol intake, the ORs in the drinking categories for men were varied and not significant. Conversely, among women, after adjusting for hypertension, dyslipidaemia, and IGT, the OR for drinkers was 1.041 (95% CI, 0.753–1.439, $p = 0.808$). When considering the quantity of alcohol intake, the OR for drinking 140–279.9 g/week was 2.135 (95% CI, 1.158–3.939, $p < 0.05$), and ORs for all drinking categories were >1, but not significant.

3.4. Relationship between alcohol consumption and non-invasive liver fibrosis scores in patients with newly developed MAFLD

Among men with newly developed MAFLD, the AAR and FIB-4 index scores were significantly associated with the quantity of alcohol consumption ($p < 0.001$ and $p < 0.005$, respectively) (Table 4). Additionally, there was a non-significant trend for an increase in APRI score as alcohol consumption increased.

Among women with newly developed MAFLD, AAR was significantly associated with the quantity of alcohol consumption ($p < 0.05$).

4. Discussion

In the present study, we investigated the association between alcohol consumption and newly developed MAFLD over time. The principal finding was that alcohol consumption had no significant protective effect against newly developed MAFLD in both sexes, regardless of the quantity of alcohol consumption. Conversely, in women, alcohol consumption ≥140 g/week had an accelerating effect on newly developed MAFLD. In addition, several non-invasive liver fibrosis scores were significantly associated with the quantity of alcohol consumption in patients with newly developed MAFLD.

Alcohol consumption has been reported to cause fatty liver and liver injury [32,33]. In particular, excessive alcohol intake is an established risk factor for chronic liver disease and its development [1,34–40]; however, moderate alcohol intake appears to reduce cardiovascular morbidity and NAFLD incidence, according to several studies [41,42]. Regarding the association between MAFLD and alcohol intake, several studies have indicated that the levels of GGT and liver enzymes, such as AST and ALT, were significantly higher in patients with MAFLD who consumed alcohol than in patients who did not; however, the HbA1c level and HOMA-IR scores showed the opposite trend [28,43]. Moreover, baseline analyses in the present study revealed few differences in clinical factors among the alcohol consumption categories in women with MAFLD (n = 444). However, several factors associated with metabolic dysregulation, liver enzymes, and non-invasive liver fibrosis scores, such as AAR, APRI, and FIB-4 index scores, were significantly elevated with increased alcohol intake in men with MAFLD (n = 869).

Ethanol intake is an essential factor for developing advanced liver fibrosis in patients with MAFLD [13], and its effect differs between sexes [20–22]. Liver disease associated with alcohol intake is more common among men, as they are statistically more likely to consume more alcohol than women, and women are more easily affected by drinking than men [44]. No study with a longitudinal design has investigated the effect of alcohol consumption-related parameters, including liver fibrosis, on newly developed MAFLD in both sexes. The present study showed that alcohol

Table 1
Baseline characteristics of the patients according to sex.

		Total patients	Men	Women	*p*-value
Number	n (%)	4071	2061 (50.6)	2010 (49.4)	
Age	(years)	50.7 ± 9.0	51.6 ± 8.8	49.8 ± 9.1	<0.001
BMI	(kg/m^2)	23.6 ± 3.8	24.5 ± 3.5	22.6 ± 3.8	<0.001
WC	(cm)	83.1 ± 10.1	85.9 ± 9.3	80.2 ± 10.0	<0.001
Current smokers	n (%)	491 (12.1)	463 (22.5)	28 (1.4)	<0.001
Drinkers	n (%)	2332 (57.3)	1494 (72.5)	838 (41.7)	<0.001
Alcohol consumption (g/week)					
None	n (%)	1739 (42.7)	567 (27.5)	1172 (58.3)	<0.001
0.1–69.9		923 (22.7)	405 (19.7)	518 (25.8)	
70–139.9		580 (14.2)	338 (16.4)	192 (9.6)	
140–279.9		827 (20.3)	704 (34.2)	123 (6.1)	
≥280		52 (1.3)	47 (2.3)	5 (0.2)	
Regular exercise	n (%)	1017 (25.0)	704 (34.2)	313 (15.6)	<0.001
Eating before going to bed	n (%)	1563 (38.4)	858 (41.6)	705 (35.1)	<0.001
Custom of having breakfast	n (%)	3665 (90.0)	1806 (87.6)	1859 (92.5)	<0.001
SBP	(mmHg)	122.7 ± 17.4	127.5 ± 16.6	117.9 ± 16.7	<0.001
DBP	(mmHg)	77.9 ± 12.7	82.3 ± 12.5	73.5 ± 11.2	<0.001
Hypertension	n (%)	1723 (42.3)	1158 (56.2)	565 (28.1)	<0.001
T-CHO	(mg/dl)	212.5 ± 36.1	210.7 ± 35.3	214.3 ± 36.7	<0.005
TG	(mg/dl)	110.2 ± 88.0	135.2 ± 109.1	84.6 ± 46.7	<0.001
HDL-C	(mg/dl)	66.9 ± 17.6	60.0 ± 15.6	74.0 ± 16.8	<0.001
LDL-C	(mg/dl)	129.3 ± 32.2	130.9 ± 32.0	127.6 ± 32.3	<0.001
Dyslipidaemia	n (%)	2,048 (50.3)	1,367 (66.3)	681 (33.9)	<0.001
FPG	(mg/dl)	97.5 ± 17.4	101.4 ± 20.8	93.5 ± 11.8	<0.001
HbA1c	(%)	5.6 ± 0.57	5.7 ± 0.68	5.6 ± 0.42	<0.001
IGT	n (%)	1,254 (30.8)	861 (41.8)	393 (19.6)	<0.001
UA	(mg/dl)	5.3 ± 1.4	6.1 ± 1.2	4.5 ± 1.0	<0.001
ALT	(IU/L)	23.6 ± 17.1	28.6 ± 18.2	18.5 ± 14.4	<0.001
AST	(IU/L)	24.0 ± 9.9	26.0 ± 10.1	21.9 ± 9.3	<0.001
GGT	(IU/L)	36.6 ± 40.6	49.1 ± 47.9	23.8 ± 25.7	<0.001
HS-CRP	(mg/L)	1.07 ± 3.66	1.24 ± 4.48	0.90 ± 2.54	<0.001
Positivity of HBsAg	n (%)	38 (0.9)	19 (0.9)	19 (0.9)	0.938
Positivity of HCVAb	n (%)	13 (0.3)	8 (0.4)	5 (0.2)	0.431
Fatty liver	n (%)	1450 (35.6)	953 (46.2)	497 (24.7)	<0.001
MAFLD	n (%)	1313 (32.3)	869 (42.2)	444 (22.1)	<0.001
AAR		1.19 ± 0.40	1.04 ± 0.36	1.33 ± 0.38	<0.001
APRI		0.27 ± 0.15	0.30 ± 0.15	0.24 ± 0.13	<0.001
FIB-4 index		1.18 ± 0.54	1.21 ± 0.56	1.14 ± 0.51	<0.001
NFS		−2.42 ± 0.99	−2.35 ± 1.02	−2.50 ± 0.51	<0.001

Data are presented as mean ± standard deviations for continuous variables and number (%) for categorical variables. *P*-values are based on the χ^2 test or Mann–Whitney U test. Significance is indicated at the 5% level.
AAR, AST/ALT ratio; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, fibrosis-4; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, haemoglobin A1c; HCVAb, HCV antibody; HDL-C, HDL cholesterol; HS-CRP, high-sensitivity C-reactive protein; IGT, impaired glucose tolerance; LDL-C, LDL cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

Table 2
Change in alcohol consumption between baseline and the most recent stage.

Men (n = 2061)							
Baseline			Most recent stage				
		Number	Non-drinkers	Drinkers			
	Alcohol consumption (g/week)		None	0.1–69.9	70–139.9	140–279.9	≥280
Non-drinkers	none	567 (27.5%)	510 (89.9%)	41 (7.2%)	9 (1.6%)	6 (1.1%)	1 (0.2%)
Drinkers	0.1–69.9	405 (19.7%)	93 (23.0%)	193 (47.7%)	95 (23.5%)	24 (5.9%)	0 (0%)
	70–139.9	338 (16.4%)	19 (5.6%)	70 (20.7%)	172 (50.9%)	77 (22.8%)	0 (0%)
	140–279.9	704 (34.2)	10 (1.4%)	22 (3.1%)	117 (16.6%)	533 (75.7%)	22 (3.1%)
	≥280	47 (2.3%)	0 (0%)	0 (0%)	0 (0%)	31 (66.0%)	16 (34.0%)
Women (n = 2010)							
Baseline			Most recent stage				
		Number	Non-drinkers	Drinkers			
	Alcohol consumption (g/week)		none	0.1–69.9	70–139.9	140–279.9	≥280
Non-drinkers	none	1172 (58.3%)	1095 (93.4%)	64 (5.5%)	10 (0.9%)	2 (0.2%)	1 (0.1%)
Drinkers	0.1–69.9	518 (25.8%)	149 (28.8%)	291 (56.2%)	65 (12.5)	13 (2.5)	0 (0)
	70–139.9	192 (9.6%)	11 (5.7%)	80 (41.7%)	85 (44.3)	16 (8.3)	0 (0)
	140–279.9	123 (6.1%)	7 (5.7%)	8 (6.5)	23 (18.7)	82 (66.7)	3 (2.4)
	≥280	5 (0.2%)	0 (0%)	0 (0)	1 (20.0)	2 (40.0)	2 (40.0)

Table 3
Relationship between newly developed MAFLD and the quantity of alcohol consumption.

	Alcohol consumption (g/week)	OR	OR†	OR‡	OR§
Men (n = 1192)					
Non-drinkers	none	1	1	1	1
Drinkers		0.931 (0.731–1.186)	0.966 (0.752–1.241)	0.933 (0.731–1.191)	0.863 (0.676–1.102)
	0.1–69.9	0.752 (0.528–1.069)	0.865 (0.600–1.247)	0.758 (0.531–1.082)	0.765 (0.532–1.009)
	70–139.9	1.128 (0.822–1.549)	1.169 (0.842–1.625)	1.154 (0.840–1.585)	1.116 (0.804–1.548)
	140–279.9	0.877 (0.663–1.162)	0.866 (0.648–1.159)	0.870 (0.654–1.156)	0.761 (0.573–1.011)
	≥280	1.651 (0.887–3.071)	1.877 (0.963–3.657)	1.605 (0.859–2.998)	1.269 (0.676–2.382)
Women (n = 1566)					
Non-drinkers	none	1	1	1	1
Drinkers		1.172 (0.856–1.606)	1.262 (0.906–1.758)	1.176 (0.858–1.612)	1.041 (0.753–1.439)
	0.1–69.9	1.146 (0.796–1.651)	1.137 (0.773–1.672)	1.147 (0.795–1.655)	1.038 (0.715–1.507)
	70–139.9	1.147 (0.687–1.915)	1.195 (0.696–2.053)	1.163 (0.697–1.940)	1.027 (0.594–1.777)
	140–279.9	1.355 (0.753–2.439)	2.135 (1.158–3.939)	1.356 (0.749–2.457)	1.096 (0.577–2.083)
	≥280	(–)	(–)	(–)	(–)

OR†: adjusted OR for age, BMI, and WC. OR‡: adjusted OR for lifestyle habits. OR§: adjusted OR for hypertension, dyslipidaemia, and IGT.
BMI, body mass index; IGT, impaired glucose tolerance; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; WC, waist circumference.
(–): absence of patients.

consumption was significantly higher in men than in women among all patients (72.5% vs. 41.7%) and in patients with MAFLD (71.1% vs. 35.1%) at baseline. The quantity of alcohol consumption was also significantly greater in men than in women among all patients ($p < 0.001$) and patients with MAFLD ($p < 0.001$) at baseline. Although the effect of the quantity of alcohol consumption on newly developed MAFLD varied in men, regardless of the quantity, alcohol consumption ≥140 g/week was a risk factor for newly developed MAFLD in women.

Regarding liver fibrosis in patients with newly developed MAFLD, several non-invasive liver fibrosis scores increased with an increase in alcohol intake in both men and women with newly developed MAFLD in the present study. More-than-moderate alcohol intake is reported to be a risk factor for the development of liver fibrosis in patients with fatty liver or NAFLD [45,46]. Additionally, even mild alcohol consumption is reported to be associated with worsening of hepatic fibrosis measures in patients with MAFLD [43]. These results suggest that alcohol intake should be avoided because it may accelerate the development of liver fibrosis in patients with newly developed MAFLD.

The strengths of the present study include the investigation of the difference in the effect of alcohol consumption between the sexes on newly developed MAFLD, its longitudinal design, and the use of ultrasonography—simple, non-invasive, widely adopted in medical facilities, and accurate in the evaluation of steatosis. A recent meta-analysis reported that ultrasonography has a sensitivity and specificity of 82% and 80%, respectively, for detecting ≥5% of steatotic hepatocytes on histology and a sensitivity and specificity of 85% and 85%, respectively, for detecting ≥30% of steatotic hepatocytes on histology [47], making the results convincing.

Nevertheless, the present study has several limitations that should be acknowledged. First, this was a single-centre study. Therefore, multicentre studies are required to validate our findings. Second, selection bias is possible because participants were sufficiently conscious of their health as they voluntarily underwent medical check-ups. Therefore, whether an analysis of patients hospitalised for various diseases, including MAFLD, would yield similar results remains unclear. Third, the genotype of aldehyde dehydrogenase 2 (*ALDH2*), which may be associated with fatty liver, was not assessed because this investigation is generally not conducted during medical check-ups. Therefore, *ALDH2* may have affected the findings. Fourth, non-invasive liver fibrosis scores have been used widely and have been shown to be better accuracy in excluding rather than in identifying significant/advanced fibrosis [48–50]. Only four non-invasive liver fibrosis scores were used for the influence of alcohol consumption on newly developed MAFLD in the present study. Therefore, clinical investigations for the usefulness of excluding low-risk patients with developed MAFLD and alcohol consumption using various non-invasive liver fibrosis scores are needed. Finally, we did not obtain detailed information

Table 4
Relationship between alcohol consumption and non-invasive liver fibrosis scores in patients with newly developed MAFLD.

	Alcohol consumption<			AAR	APRI	FIB-4 index	NFS
Men (n = 311)	(g/week)	Number	*p*-value	<0.001	0.426	<0.005	0.701
Non-drinkers	None	90		0.883 ± 0.212	0.279 ± 0.106	1.133 ± 0.517	−2.342 ± 1.042
Drinkers	0.1–69.9	45		0.833 ± 0.202	0.284 ± 0.102	1.077 ± 0.413	−2.441 ± 0.874
	70–139.9	65		0.981 ± 0.262	0.291 ± 0.108	1.198 ± 0.470	−2.259 ± 1.008
	140–279.9	101		1.073 ± 0.363	0.308 ± 0.165	1.273 ± 0.566	−2.247 ± 0.799
	≥280	10		1.215 ± 0.316	0.601 ± 0.747	1.871 ± 1.523	−1.953 ± 1.374
Women (n = 155)	(g/week)	Number	*p*-value	<0.05	0.927	0.966	0.580
Non-drinkers	None	83		1.095 ± 0.299	0.230 ± 0.085	1.128 ± 0.427	−2.375 ± 0.926
Drinkers	0.1–69.9	43		1.139 ± 0.408	0.223 ± 0.076	1.115 ± 0.483	−2.272 ± 0.955
	70–139.9	17		1.177 ± 0.205	0.230 ± 0.085	1.120 ± 0.394	−2.616 ± 0.809
	140–279.9	12		1.329 ± 0.560	0.202 ± 0.060	1.034 ± 0.338	−2.651 ± 0.587
	≥280	0		(–)	(–)	(–)	(–)

Data are presented as mean±standard deviations. *P*-values are based on the Kruskal–Wallis nonparametric test. Significance is indicated at the 5% level.
AAR, AST/ALT ratio; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, Fibrosis-4; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.
(–): absence of patients.

regarding the medications for hypertension, dyslipidaemia, and diabetes mellitus or dietary information, such as volume, calories, and content. Further large-scale studies in other cohorts are needed to resolve these limitations.

5. Conclusion

While alcohol consumption renders patients more prone to MAFLD, the influence of alcohol consumption on newly developed MAFLD differed between sexes in this study. The protective effects of alcohol consumption on newly developed MAFLD were not confirmed. Conversely, alcohol consumption ≥140 g/week was a risk factor for newly developed MAFLD in women. Additionally, the development of liver fibrosis with an increase in the intake quantity of alcohol should be considered in patients with developed MAFLD and findings in the present study may open the way to innovative pathogenic treatment strategies.

Author contributions

Conceptualization: M. Sogabe, T. Okahisa, and M. Nakasono; Data Curation: M. Sogabe and Y. Kida; Formal Analysis: M. Sogabe, K. Kagemoto, H. Miyamoto, and T. Tomonari; Investigation: M. Sogabe, M. Kagawa, and H. Ueda; Methodology: M. Sogabe, H. Tanaka, and K. Okamoto; Project Administration: M. Sogabe; Visualization: M. Sogabe and T. Taniguchi; Writing – original draft preparation: M. Sogabe; Writing – Review & Editing: M. Sogabe, Y. Sato, and T. Takayama. All authors have read and approved the final manuscript.

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Data availability statement

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

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.03.020.

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