ORIGINAL ARTICLE

Relationship between the prevalence and severity of non-alcoholic fatty liver disease and coronary artery disease: Findings from a cross-sectional study of a referral center in northeast Iran

Arash Gholoobi,* Mehrnoosh Gifani,[†] Aida Gholoobi,^{‡,¶} Saeed Akhlaghi,[§] Masoud Pezeshki Rad[†] and Vafa Baradaran Rahimi* [®]

*Department of Cardiovascular Diseases, Faculty of Medicine, [†]Department of Radiology, Faculty of Medicine, [‡]Metabolic Syndrome Research Center, [§]Department of Biostatistics, School of Health, Mashhad University of Medical Sciences and [§]Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, Mashhad, Iran

Key words

coronary angiography, coronary artery disease, dyslipidemia, non-alcoholic fatty liver disease, ultrasonography.

Accepted for publication 13 April 2022.

Correspondence

Vafa Baradaran Rahimi, Department of Cardiovascular Diseases, Faculty of Medicine, Mashhad University of Medical Sciences, Azadi Square, Vakil Abad Highway, Mashhad 9177948564, Iran.

Email: baradaranrv@mums.ac.ir, vafa_br@yahoo.com Masoud Pezeshki Rad, Department of Radiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran. Email: pezeshkiradm@mums.ac.ir

Declaration of conflict of interest: The authors declare no conflict of interest.

Author contribution: Arash Gholoobi contributed to the conceptualization, methodology, and supervision. Mehrnoosh Gifani contributed to the investigation and data curation. Aida Gholoobi contributed to the writing—original draft. Saeed Akhlaghi contributed to the formal analysis, methodology, and software. Masoud Pezeshki Rad contributed to the conceptualization, methodology, supervision, and funding acquisition. Vafa Baradaran Rahimi contributed to the formal analysis, writing original draft, and writing—review and editing.

Funding support: Mashhad University of Medical Sciences900181

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered the most common and emerging cause of chronic liver disease

Abstract

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent worldwide, and cardiovascular diseases are the most common cause of death in NAFLD patients. The present study aimed to evaluate the possible relationship between the presence and severity of NAFLD and coronary artery disease (CAD).

Methods: A cross-sectional study was conducted on 296 patients (122 men and 174 women, with mean age 54.10 \pm 9.33 years) referred to the catheterization laboratory of Imam Reza Hospital affiliated to the Mashhad University of Medical Sciences, Mashhad, Iran, for elective coronary angiography to investigate the presence and severity of CAD. Additionally, all patients underwent abdominal ultrasonography (USG) to detect NAFLD and its severity.

Results: Among the 296 patients, 187 (63.2%) had CAD and 160 (50.1%) had NAFLD. NAFLD patients had significantly higher prevalence of obesity (odds ratio [OR] = 1.047, 95% confidence interval [CI] = 1.002-1.094), hypertension (OR = 1.909, 95% CI = 1.027-3.55), hyperlipidemia (OR = 3.474, 95% CI = 1.862-6.482), and CAD (OR = 2.009, 95% CI = 1.100-3.669). The percentage of patients with normal vessels was higher in the non-NAFLD group, followed by the group with mild and severe NAFLD (P < 0.001). However, single- and multi-vessel disease incidences among the non-NAFLD, mild, and severe NAFLD groups were 36.1, 43.1, and 63.7%, respectively. Interestingly, the percentage of patients with two-vessel stenosis was significantly higher in severe NAFLD patients than mild and non-NAFLD patients (P < 0.001).

Conclusion: The prevalence and severity of NAFLD were independently associated with CAD. Mild NAFLD was primarily observed among patients with normal and non-obstructive coronary artery patients, while severe NAFLD was more frequent in extensive CAD patients with multi-vessel disease.

worldwide.¹ Currently, it has been estimated that the prevalence rate of NAFLD is approximately 25% globally and 27.4% in Asia.² The prevalence of NAFLD is still increasing as a result of

JGH Open: An open access journal of gastroenterology and hepatology **6** (2022) 330–337

© 2022 The Authors. JGH Open published by Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium,

provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

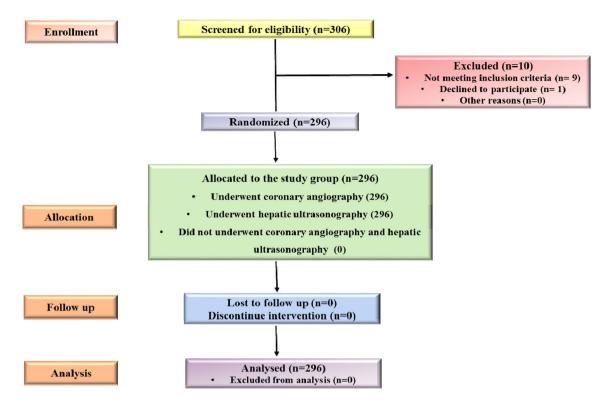


Figure 1 Flowchart of the study.

the ongoing global epidemic of obesity, insulin resistance, and type-2 diabetes mellitus (DM). It has been reported that NAFLD affects over 80 million patients in the United States and may reach over 100 million in 2030. This will have a crucial impact on the public healthcare costs and the need for liver transplantation.^{3,4}

NAFLD patients have a higher risk of cardiovascular diseases (CVD), diabetes, and carcinoma and a higher mortality rate than non-NAFLD patients.⁵ Additionally, CVD are the most common cause of death among NAFLD patients. It has been emphasized that NAFLD patients are twice more likely to die of CVD than liver diseases.⁴ A meta-analysis of 34 000 individuals highlighted that the risk of developing both fatal and nonfatal cardiovascular events increases to 65% in NAFLD patients.⁶ Therefore, recognizing and managing CVD in patients with NAFLD is of great importance.⁷ The pathogenesis responsible for developing CVD among NAFLD patients may be related to vascular endothelial dysfunction, pro-atherogenic dyslipidemia, myocardial remodeling, and heart failure.⁸

Therefore, in the present study, we aimed to investigate the association between the prevalence and severity of NAFLD and the prevalence and extent of coronary artery disease (CAD).

Methods

Ethical statement. This study was confirmed by the ethics committee of Mashhad University of Medical Sciences (IR. MUMS.900181), and all participants gave signed, written informed consent.

Study population. This study was conducted on all 306 patients referred to the catheterization laboratory of Imam Reza Hospital affiliated to Mashhad University of Medical Sciences, Mashhad, Khorasan Razavi province, Iran, for elective coronary angiography from February 2012 to January 2013. After applying the exclusion criteria, 296 patients were found eligible and enrolled on the study (Fig. 1).

Inclusion and exclusion criteria. Patients referred to the catheterization laboratory of Imam Reza Hospital for elective coronary angiography were included in the study. The indication of coronary angiography was based on the discretion of the referring cardiologist. All cases had suspected symptoms of CVDs such as chest pain with high pre-test probability for CAD, recent acute coronary syndrome (ACS), positive exercise stress testing, or myocardial perfusion imaging.⁹

The exclusion criteria were patients with chronic kidney disease, known history of viral hepatitis, chronic liver disease, positive serum hepatitis B antigen or anti-hepatitis C viral antibody, history of sudden weight loss or weight loss surgery in the past year, and the use of drugs that may induce steatosis, such as corticosteroids, androgens, methotrexate, amiodarone, tamoxifen, and sodium valproate within the previous 3 months or for more than 6 months in the last 2 years.

Evaluation of outcome. Demographic information of patients, including age, sex, body mass index (BMI), history of hypertension (HTN), DM, dyslipidemia, use of medications, and personal history of other diseases, was documented after

enrolment using a questionnaire. In addition, fasting blood glucose and blood pressure were measured after being admitted to the hospital. All patients underwent coronary angiography by an interventional cardiologist followed by hepatic ultrasonography (USG) by a radiologist.

HTN was diagnosed as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or treatment with any anti-hypertensive drugs. DM was defined as fasting blood glucose ≥126 mg/dL, or random blood glucose greater than 200 mg/dL, or the current use of antidiabetic drugs. Dyslipidemia was defined as plasma triglycerides (TGs) level ≥150 mg/dL, or plasma low-density lipoprotein cholesterol (LDL-c) level ≥130 mg/dL, or plasma high-density lipoprotein cholesterol (HDL-c) level ≤50 mg/dL for women and ≤40 mg/dL for men, or the use of lipid-lowering medications. Furthermore, BMI was considered normal for BMI ≤25 kg/m², overweight for 25 ≤ BMI ≤ 30 kg/m², and obese for BMI ≥30 kg/m².

Coronary angiography. All the coronary angiograms were evaluated and reported by an interventional cardiologist who was blind to the hepatic sonography results. Coronary angiography was performed via the femoral route, using the Judkins technique and an Artis zee angiography unit (Siemens, Germany). Multiple views were obtained in all the patients, visualizing the left anterior descending and the circumflex coronary arteries, with at least four views of the left coronary system and two views of the right coronary artery. Coronary angiograms were recorded on compact disks in DICOM format. CAD was then defined as the presence of stenosis ≥50% in diameter compared to an adjacent normal segment of the main branches of the coronary artery. The extent of CAD was assessed by the number of vessels involved (vessel score) as follows: single-vessel disease (SVD), two-vessel disease (2VD), and three-vessel disease (3VD). The group of patients with the stenosis severity less than 50% on angiograms was defined as the non-obstructive coronary disease (NOB) group.10

In this study, patients were divided into two main groups: those without significant CAD, including normal coronary arteries (NCA), and NOB patients and with CAD including SVD, 2VD, and 3VD.

Hepatic ultrasonography. Abdominal USG (Siemens G40 with a 5-MHz transducer) was performed a day after or before coronary angiography and after the eighth fasting period by a radiologist who was blind to the medical history, laboratory findings, and coronary angiography results of the patients. USG was performed in the supine position. Various ultrasonographic features of focal liver lesions were observed by subcostal and intercostal approaches. Three ultrasonographic criteria for diagnosing NAFLD were studied: hepato-renal echo contrast and hyperechoic appearance of liver, posterior beam attenuation, and the blurring of vessels.

In this study, patients were divided into two main groups: non-NAFLD and NAFLD, including its mild and severe forms. Mild NAFLD is described as a minimal diffuse increase in hepatic echogenicity and normal visualization of the diaphragm and intrahepatic vessel contours. Severe NAFLD contained a marked increase in the hepatic parenchymal echotexture with poor or non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver.^{11,12}

Statistical analysis. Data were analyzed using the SPSS version 22 statistical software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.01 software (GraphPad Software Inc., San Diego, CA, USA) and were expressed according to parametric or nonparametric as means \pm SD or number with percentage, respectively. The normality of the data was checked with the Kolmogorov–Smirnov test. The comparison between categorical variables was made using the Chi-square test. When appropriate, the comparison between continuous variables was performed using one-way ANOVA for parametric data or Mann–Whitney *U* tests for nonparametric data. Logistic regressions were applied to introduce predictors of NAFLD and CAD. *P*-values ≤0.05, 0.01, and 0.001 were considered statistically significant.

Results

Demographic characteristics. Among the total number of 296 patients enrolled to the study, 174 (58.8%) were female and 122 (41.2%) were male, with a mean age of 54.1 ± 9.33 years (Table 1). Moreover, 100 (33.8%) patients had normal BMI, 47 (15.9%) patients were overweight, and 149 (50.3%) were obese (Table 1).

Assessment of the coronary artery angiogram of the patients revealed that 109 (36.8%) had NCA or NOB and 187 (63.2%) had CAD (Table 1). In addition, USG results showed that 136 (49.9%) patients had no NAFLD, 102 (34.5%) had mild NAFLD, and 58 (19.6%) had severe NAFLD (Table 1).

Demographic characteristics of NAFLD and CAD patients. The mean age of patients with and without NAFLD were 54.54 ± 8.42 and 53.59 ± 10.31 years, respectively

 Table 1
 Demographic characteristics of the patients enrolled the study

Demographic characteristic	Value	Total	
Gender (n, %)			
Male	122 (41.2%)	296 (100%)	
Female	174 (58.8%)		
Age (years)			
$Mean\pmSD$	54.1 ± 9.33		
Range	35–78		
BMI (n, %)			
Normal	100 (33.8%)	296 (100%)	
Overweight	47 (15.9%)		
Obese	149 (50.3%)		
CAD (n, %)			
Yes	187 (63.2%)	296 (100%)	
No	109 (36.8%)		
NAFLD (<i>n</i> , %)			
No	136 (49.9%)	296 (100%)	
Mild	102 (34.5%)		
Severe	58 (19.6%)		

BMI, body mass index; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease.

Table 2 Demographic characteristics of non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) patients

Characteristic	Non-NAFLD	Mild NAFLD	Severe NAFLD	P-value
Age (years, mean \pm SD)	53.59 ± 10.31	54.54 ± 8.42	55.14 ± 9.31	0.381*
BMI (kg/m ² , <i>n</i> , %)				
Normal	75 (55.1%)	94 (39.5%)	6 (10.3%)	<0.001*
Overweight	12 (8.8%)	39 (16.4%)	8 (13.8%)	
Obese	49 (36%)	105 (44.1%)	44 (75.9%)	
Total	136 (100%)	102 (100%)	58 (100%)	
Gender (n, %)				
Male	55 (45.1%)	49 (40.2%)	18 (14.8%)	0.101 [‡]
Female	81 (46.6)	53 (30.5%)	40 (23%)	
Total	136 (100%)	102 (100%)	58 (100%)	
Characteristic	CAD		Non-CAD	<i>P</i> -value
Age (years, mean \pm SD)	51.04 ± 9.26		55.84 ± 8.94	<0.001 [§]
BMI (kg/m ²)				
Normal	38 (20.1%)		62 (57.9%)	<0.001 [¶]
Overweight	39 (20.6%)		8 (7.5%)	
Obese	112 (59.3%)		37 (34.6%)	
Gender (n, %)				
Male	70 (57.4%)		52 (42.6%)	<0.001 [¶]
Female	70 (40.2%)		104 (59.8%)	

[†]Comparison between the non-NAFLD and NAFLD groups using Student's *t*-test.

*Comparison between the non-NAFLD, mild NAFLD, and severe NAFLD groups using Chi-square test.

[§]Comparison between CAD and non-CAD groups using Student's *t*-test.

[¶]Comparison between the CAD and non-CAD groups using Chi-square test.

BMI, body mass index; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease.

(P = 0.381, Table 2). The mean BMI of the individuals was $32.16 \pm 6.14 \text{ kg/m}^2$ in the NAFLD group and $27.61 \pm 6.71 \text{ kg/m}^2$ in the non-NAFLD group (P < 0.001). Among the non-NAFLD patients, 75 (55.1%) had normal weight, 12 (8.8%) were overweight, and 49 (36%) were obese. In addition, NAFLD patients had a significantly higher BMI than non-NAFLD patients (P < 0.001, Table 2).

Furthermore, our results also showed that NAFLD was observed in 54.9% male and 53.4% female patients (P = 0.814, Table 2). Interestingly, mild NAFLD was more frequent in men, while severe NAFLD was more frequent in women. However, there was no significant relationship between NAFLD severity and gender (P = 0.101, Table 2).

As can be seen from Table 2, the mean age of CAD patients (51.04 ± 9.26) was significantly lower than that of non-CAD patients (55.84 ± 8.94 , P < 0.001, Table 2). In addition, the percentage of patients with normal BMI was significantly more in the non-CAD (57.9%) group than in the CAD group (20.1%, P < 0.001, Table 2). Moreover, CAD patients had higher BMI levels than non-CAD patients (P < 0.001, Table 2).

Our results also showed that CAD was present in 57.4% of men and 40.2% of women patients (P = 0.004, Table 2). In contrast, CAD was less frequent in women (59.8%) than in men (42.6%) (P = 0.004, Table 2).

Frequency and severity of NAFLD according to the history of different disorders. The frequency and severity of NAFLD and non-NAFLD patients according to the history of HTN, DM, and dyslipidemia are shown in Table 3. Results of this study show that the frequency and severity of NAFLD is highly related to the incidence of HTN, DM, and dyslipidemia (P < 0.001, P = 0.025, and P < 0.001, respectively, Table 3).

In addition, our results reveal that the incidence of HTN, dyslipidemia, NAFLD is significantly higher in the CAD group than in the non-CAD group (P < 0.001 for all cases, Table 3). Surprisingly, the mild NAFLD group had the highest incidence among the CAD groups (P < 0.001, Table 3).

Frequency and severity of NAFLD and CAD. The percentage of non-CAD patients was 52.2% in non-NAFLD, 29.4% in mild NAFLD, and 13.8% in severe NAFLD patients (P < 0.001, Fig. 2a). The incidence of SVD, 2VD, and 3VD among the mild NAFLD patients was 14.7, 20.6, and 7.8%, respectively (Fig. 2a). Furthermore, 10.3, 50.0, and 3.4% of the severe NAFLD patients had SVD, 2VD, and 3VD, respectively (Fig. 2a). Interestingly, the percentage of patients with 2VD was significantly higher in the severe NAFLD group than in the mild NAFLD and non-NAFLD groups (P < 0.001, Fig. 2a).

Our results also reveal that the percentage of non-NAFLD patients is higher in the non-CAD group (65%) than in the CAD groups (P < 0.001, Fig. 2b). Moreover, patients with mild NAFLD was 27.5% in NCA, 49.1% in NOB, 40.5% in SVD, 29.2% in 2VD, and 37.1% in 3VD (Fig. 2b). Additionally, severe NAFLD was mostly observed in the 2VD group (40.3%) among all groups (P < 0.001, Fig. 2b).

Table 3 Frequency and severity of non-alcoholic fatty liver disease (NAFLD) according to the history of different disorders

Disease (n, %)	Non-NAFLD	Mild NAFLD	Mild NAFLD Severe NAFLD		
Hypertension					
No	101 (74.3%)	44 (43.1%)	17 (29.3%)	<0.001	
Yes	35 (25.7%)	58 (56.9%)	41 (70.7%)		
Total	136 (100%)	102 (100%)	58 (100%)		
Diabetes mellitus					
No	119 (87.5%) 79 (77.5%)		42 (72.4%)	(2.4%) 0.025	
Yes	17 (12.5%)	23 (22.5%)	16 (27.6%)		
Total	136 (100%)	102 (100%)	58 (100%)		
Dyslipidemia					
No	114 (83.8%)	50 (49%) 23 (39.7%)		<0.001	
Yes	22 (16.2%)	52 (51%)	35 (60.3%)		
Total	136 (100%)	102 (100%)	58 (100%)		
Disease (n, %)	Non-CAD		CAD	<i>P</i> -value [‡]	
Hypertension					
No	114 (73.1%)		48 (34.3%)	<0.001	
Yes	42 (29.6%)		92 (65.7%)		
Diabetes mellitus					
No	132 (84.6%)		108 (77.1%)	0.1	
Yes	24 (15.4%)		32 (22.9%)		
Dyslipidemia					
No	116 (74.4%)		71 (50.7%)	<0.001	
Yes	40 (25.6%)		69 (49.3%)		
NAFLD					
No	87 (55.8%)		49 (35%)	<0.001	
Mild	139 (89.1%)		99 (70.7%)		
Severe	17 (10.9%)		41 (29.3%)		

[†]Comparison between the NAFLD and non-NAFLD groups using Chi-square test.

*Comparison between the CAD and non- CAD groups using Chi-square test.

CAD, coronary artery disease.

Multivariate logistic regression predicting the frequency of NAFLD. The results of logistic regression analysis of BMI, HTN, dyslipidemia, and CAD for the frequency of NAFLD are showed in Table 4. We found that BMI (odds ratio [OR] = 1.047, 95% confidence interval [CI] = 1.002– 1.094), HTN (OR = 1.909, 95% CI = 1.027–3.55), hyperlipidemia (OR = 3.474, 95% CI = 1.862–6.482), and CAD (OR = 2.009, 95% CI = 1.100–3.669) are the independent risk factors of NAFLD (Table 4). Interestingly, hyperlipidemia had the highest relationship with the frequency of NALFD among the other factors (Table 4).

Discussion

NAFLD is strongly associated with metabolic syndrome and its prevalence is increasing worldwide.¹³ The present cross-sectional study included 296 patients (41.2% men and 58.8% women, with a mean age of 54.1 \pm 9.33 years) who underwent coronary angiography followed by USG. Our results show that the prevalence and severity of NAFLD are independently associated with the CAD. Interestingly, mild NAFLD is observed among normal and NOB patients, while severe NAFLD is more frequent in severe CAD in patients with multi-vessel disease.

We found that the percentage of patients with NAFLD was 50.1% among the patients who underwent elective coronary angiography. In accordance with our results, Perera *et al.* reported that NAFLD was observed in 46.67% of patients with nonfatal ACS in Sri Lanka.¹⁴ Similarly, NAFLD was seen in 55.2% of Brazilian patients,¹⁵ 53.06% of Turkish patients,¹⁶ and 53.78% of Finnish patients¹⁷ who underwent diagnostic coronary angiography for ACS.

Our results also found that the mean BMI was higher in NAFLD patients $(32.16 \pm 6.14 \text{ kg/m}^2)$ than in non-NAFLD patients $(27.61 \pm 6.71 \text{ kg/m}^2)$. Interestingly, 76% of obese patients had NAFLD. In line with our results, Dunn *et al.* noticed that the mean BMI was $30.8 \pm 7.5 \text{ kg/m}^2$ in non-NAFLD patients and $36.7 \pm 8.5 \text{ kg/m}^2$ in NAFLD patients with type 2 diabetes.¹⁸ Additionally, the mean BMI was higher in NAFLD patients $(32 \pm 2.3 \text{ kg/m}^2)$ than in non-NAFLD patients $(27 \pm 1.4 \text{ kg/m}^2)$ with metabolic syndrome.¹⁹ Olubamwo *et al.* also found that the mean BMI was $24.3 \pm 1.9 \text{ kg/m}^2$ in non-NAFLD, $27.3 \pm 1.9 \text{ kg/m}^2$ in mild NAFLD, and $30.9 \pm 3.3 \text{ kg/m}^2$ in severe NAFLD patients with the ACS.¹⁷

The prevalence of NAFLD in male (55%) patients was slightly higher than in female (53.5%) patients in our study; however, mild NAFLD was more frequent in males, whereas severe NAFLD was more frequent in females. Contrary to our results,

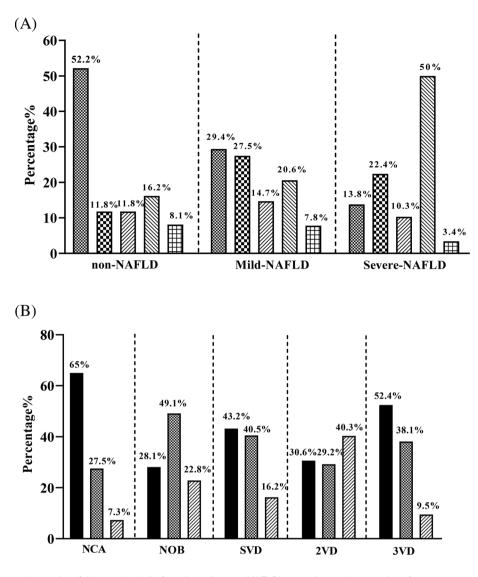


Figure 2 Frequency and severity of (a) non-alcoholic fatty liver disease (NAFLD) according to the severity of coronary stenosis and (b) coronary artery disease according to the severity of NAFLD; data are expressed as a percentage of patients. (a): (m), normal coronary arteries (NCA); (m), non-obstructive vessel (NOB); (m), single-vessel disease (SVD); (m), two-vessel disease (2VD); (m), three-vessel disease (3VD). (b): (m), Non-NAFLD; (m), mild-NAFLD; (m), severe NAFLD.

Table 4 Multivariate logistic regression predicting the frequency of non-alcoholic fatty liver disease (NAFLD) among the study participants

Covariates	Logistic regression model coefficient	OR	95% CI	<i>P</i> -value
BMI	0.046	1.047	1.002-1.094	0.042
Hypertension	0.647	1.909	1.27-3.550	0.041
Hyperlipidemia	1.245	3.474	1.862-6.482	<0.001
CAD	0.698	2.009	1.100-3.669	0.023

CAD, coronary artery disease; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Agarwal *et al.* reported that the prevalence of NAFLD was 58.1% in men and 56% in women with type 2 diabetes.²⁰ Perera *et al.* also found that the prevalence of NAFLD was higher in male (53.6%) patients with ACS than in female (46.4%) patients.¹⁴ In a Korean population with a history of CVD, the

percentage of male patients with NAFLD was found to increase with increase in the NAFLD stages.²¹ Additionally, the prevalence of CAD was higher in male patients than in female patients in our study. In accordance, several previous studies have emphasized the higher rate of CAD in male patients.^{22,23}

The present study results show that the prevalence and severity of NAFLD are highly related to the incidence of HTN, DM, and dyslipidemia, with the latter showing the most robust relationship. These results are in line with those of multiple previous studies regarding the risk factors of NAFLD in CAD patients.^{14,24–26} Additionally, Kim et al. found that the proportion of patients with HTN (hazard ratio [HR] = 1.43, 95% CI = 1.37-1.48), DM (HR = 1.37, 95% CI = 1.34-1.41), and dyslipidemia (HR 1.34, 95% CI = 1.31-1.38) increased with the increase in NAFLD stages in the Korean population with a history of cardiovascular diseases.²¹ Similarly, a study in Nagasaki, Japan, suggested that NAFLD was significantly associated with hypercholesterolemia and hypertriglyceridemia in elderly men and with HTN, hypercholesterolemia, low HDL cholesterol, hypertriglyceridemia, and DM in elderly women.²⁷ Agarwal et al. also reported that the prevalence of HTN, DM, and dyslipidemia was 71.4, 69, 55.8%, respectively, in NAFLD patients with type-2 diabetes.²⁰

Our results also reveal that the prevalence of HTN and dyslipidemia is higher in CAD patients than non-CAD patients. Contrary to our results, Açikel *et al.* noticed that the prevalence of risk factors such as DM, dyslipidemia, and HTN was significantly higher in CAD patients than in non-CAD patients.²⁴ Similarly, CAD patients showed a higher incidence of hypertension, dyslipidemia, DM, and metabolic syndrome than non-CAD patients with type-2 diabetes.^{28,29}

Interestingly, we found that the presence and severity of NAFLD were strongly associated with the presence and extent of CAD (OR = 2.009, 95% CI = 1.1-3.669). Non-NAFLD patients were more likely to have normal angiography, while 2VD was observed in patients with most severe NAFLD. Additionally, NOB, which is related to the early stages of atherosclerosis, was mostly seen in NAFLD patients. In agreement with our results, Wong et al. found that CAD is more prevalent in NAFLD patients (84.6%) than in non-NAFLD patients (64.1%). They reported that NAFLD was associated with CAD (OR = 2.31, 95% CI = 1.46-3.64).³⁰ Recently, Montemezzo *et al.* examined the results of 136 patients with the ACS in Brazil. They found that CAD has present in 93.42% of NAFLD and in 56.45% of non-NAFLD patients; the severity of NAFLD was also correlated with the presence of CAD.¹⁵ Choi et al. studied 134 patients who underwent elective coronary angiography in Kangwon, South Korea. They found that 80.4% of patients with CAD had NAFLD and that coronary artery stenosis was strongly associated with NAFLD in a grade-dependent manner. They also pointed out that NAFLD was a significant and independent predictor of CAD (OR = 1.685, 95% CI = 1.051-2.702).³¹ Another similar study also supported the association between NAFLD and significant CAD in type 2 diabetic patients (OR = 2.128, 95%) CI = 1.035 - 4.337).³²

The results of this study may provide a beneficial background for future studies to modify the guidelines for the management of CAD patients. In addition, NAFLD patients would benefit from advice on lifestyle and risk factor modifications.

In summary, NAFLD patients had a significantly higher prevalence of obesity, HTN, and hyperlipidemia. In addition, the prevalence and severity of NAFLD were independently associated with the prevalence and extent of CAD. Mild NAFLD was mostly observed among normal vessel and NOB patients, while severe NAFLD was more frequent in extensive CAD patients with multi-vessel disease.

Acknowledgment

This study was financially supported by the research council of Mashhad University of Medical Sciences (Grant Number: 900181).

Data availability statement. Data is available from the corresponding author upon reasonable request.

References

- Wang XJ, Malhi H. Nonalcoholic fatty liver disease. Ann. Intern. Med. 2018; 169: Itc65–itc80.
- 2 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver diseasemeta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016; 64: 73–84.
- 3 Carr RM, Oranu A, Khungar V. Nonalcoholic fatty liver disease: pathophysiology and management. *Gastroenterol. Clin. North Am.* 2016; 45: 639–52.
- 4 Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. *Gastroenterology*. 2020; **158**: 1851–64.
- 5 Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J. Gastroenterol. 2017; 23: 8263–76.
- 6 Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Nonalcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J. Hepatol. 2016; 65: 589–600.
- 7 Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, Alla VM. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2017; **11**(Suppl. 1): S209–s16.
- 8 VanWagner LB, Wilcox JE, Colangelo LA *et al.* Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: a population-based study. *Hepatology*. 2015; 62: 773–83.
- 9 Saadat S, Yousefifard M, Asady H, Jafari AM, Fayaz M, Hosseini M. The most important causes of death in Iranian population; a retrospective cohort study. *Emergency*. 2014; **3**: 16–21.
- 10 Chen SH, He F, Zhou HL, Wu HR, Xia C, Li YM. Relationship between nonalcoholic fatty liver disease and metabolic syndrome. J Dig Dis. 2011; 12: 125–30.
- 11 Saadeh S, Younossi ZM, Remer EM *et al.* The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology*. 2002; 123: 745–50.
- 12 El-Koofy N, El-Karaksy H, El-Akel W *et al.* Ultrasonography as a non-invasive tool for detection of nonalcoholic fatty liver disease in overweight/obese Egyptian children. *Eur. J. Radiol.* 2012; 81: 3120–3.
- 13 Engin A. Non-alcoholic fatty liver disease. Adv. Exp. Med. Biol. 2017; 960: 443–67.
- 14 Perera N, Indrakumar J, Abeysinghe WV, Fernando V, Samaraweera WMCK, Lawrence JS. Non alcoholic fatty liver disease increases the mortality from acute coronary syndrome: an observational study from Sri Lanka. *BMC Cardiovasc. Disord.* 2016; 16: 37.
- 15 Montemezzo M, AlTurki A, Stahlschmidt F, Olandoski M, Rodrigo Tafarel J, Precoma DB. Nonalcoholic fatty liver disease and coronary artery disease: big brothers in patients with acute coronary syndrome. *ScientificWorldJournal*. 2020; **2020**: 8489238.

- 16 Keskin M, Hayıroğlu M, Uzun AO, Güvenç TS, Şahin S, Kozan Ö. Effect of nonalcoholic fatty liver disease on in-hospital and long-term outcomes in patients with ST-segment elevation myocardial infarction. *Am. J. Cardiol.* 2017; **120**: 1720–6.
- 17 Olubamwo OO, Virtanen JK, Voutilainen A, Kauhanen J, Pihlajamäki J, Tuomainen TP. Association of fatty liver index with the risk of incident cardiovascular disease and acute myocardial infarction. *Eur. J. Gastroenterol. Hepatol.* 2018; **30**: 1047–54.
- 18 Dunn MA, Behari J, Rogal SS *et al.* Hepatic steatosis in diabetic patients does not predict adverse liver-related or cardiovascular outcomes. *Liver Int.* 2013; 33: 1575–82.
- 19 Alper AT, Hasdemir H, Sahin S *et al*. The relationship between nonalcoholic fatty liver disease and the severity of coronary artery disease in patients with metabolic syndrome. *Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir.* 2008; **36**: 376–81.
- 20 Agarwal AK, Jain V, Singla S *et al.* Prevalence of non-alcoholic fatty liver disease and its correlation with coronary risk factors in patients with type 2 diabetes. *J. Assoc. Physicians India.* 2011; **59**: 351–4.
- 21 Kim JH, Moon JS, Byun SJ *et al.* Fatty liver index and development of cardiovascular disease in Koreans without pre-existing myocardial infarction and ischemic stroke: a large population-based study. *Cardiovasc. Diabetol.* 2020; **19**: 51.
- 22 Agaç MT, Korkmaz L, Cavusoglu G et al. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. Angiology. 2013; 64: 604–8.
- 23 Boddi M, Tarquini R, Chiostri M *et al.* Nonalcoholic fatty liver in nondiabetic patients with acute coronary syndromes. *Eur. J. Clin. Invest.* 2013; 43: 429–38.
- 24 Açikel M, Sunay S, Koplay M, Gündoğdu F, Karakelleoğlu S. Evaluation of ultrasonographic fatty liver and severity of coronary atherosclerosis, and obesity in patients undergoing coronary angiography. *Anadolu Kardiyol. Derg.* 2009; **9**: 273–9.

- 25 Arslan U, Kocaoğlu I, Balcı M, Duyuler S, Korkmaz A. The association between impaired collateral circulation and non-alcoholic fatty liver in patients with severe coronary artery disease. *J. Cardiol.* 2012; 60: 210–4.
- 26 Sung KC, Ryan MC, Wilson AM. The severity of nonalcoholic fatty liver disease is associated with increased cardiovascular risk in a large cohort of non-obese Asian subjects. *Atherosclerosis*. 2009; 203: 581–6.
- 27 Akahoshi M, Amasaki Y, Soda M *et al.* Correlation between fatty liver and coronary risk factors: a population study of elderly men and women in Nagasaki, Japan. *Hypertens. Res.* 2001; **24**: 337–43.
- 28 Targher G, Bertolini L, Rodella S *et al.* Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care.* 2007; 30: 2119–21.
- 29 Gholoobi A, Askari VR, Naghedinia H, Ahmadi M, Vakili V, Baradaran RV. Colchicine effectively attenuates inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) in patients with non-ST-segment elevation myocardial infarction: a randomised, doubleblind, placebo-controlled clinical trial. *Inflammopharmacology*. 2021; 29: 1379–87.
- 30 Wong VW, Wong GL, Yip GW *et al.* Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. *Gut.* 2011; **60**: 1721–7.
- 31 Choi DH, Lee SJ, Kang CD *et al.* Nonalcoholic fatty liver disease is associated with coronary artery disease in Koreans. *World J. Gastroenterol.* 2013; 19: 6453–7.
- 32 Idilman IS, Akata D, Hazirolan T, Doganay Erdogan B, Aytemir K, Karcaaltincaba M. Nonalcoholic fatty liver disease is associated with significant coronary artery disease in type 2 diabetic patients: a computed tomography angiography study 2. J. Diabetes. 2015; 7: 279–86.