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Original Article

Relationship Between Nonalcoholic Fatty Liver Disease and Severity of Coronary Artery Disease in Patients Undergoing Coronary Angiography

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ABSTRACT

Objective: Nonalcoholic fatty liver disease has been connected to coronary artery disease, which is the main cause of mortality. The connection between the degree of nonalcoholic fatty liver disease-induced liver fibrosis and the severity of coronary artery disease is unclear, and it was aimed to be evaluated.

Methods: 200 nonalcoholic fatty liver disease patients over the age of 18 who underwent emergency or elective coronary angiography were included in this study. Both nonalcoholic fatty liver disease fibrosis and fibrosis-4 scores were calculated to determine liver fibrosis stages. Carotid intima-media thickness and SYNergy between Percutaneous Coronary Intervention (PCI) with TAXus and cardiac surgery score were calculated to determine the severity of coronary artery disease.

Results: There was no difference in carotid intima-media thickness between the groups in the fatty liver stages, but when the patients were staged according to nonalcoholic fatty liver disease fibrosis and fibrosis-4 scores, the mean of carotid intima-media thickness increased as the risk of fibrosis increased. When patients were classified into 2 categories based on their median carotid intima-media thickness value, a significant difference was realized in terms of nonalcoholic fatty liver disease fibrosis and fibrosis-4 scores. There was no significant difference in SYNergy between PCI with TAXus and cardiac surgery score when the patients were evaluated according to the fatty liver stages, nonalcoholic fatty liver disease fibrosis and fibrosis-4 scores. Considering severe coronary artery disease (SYNergy between PCI with TAXus and cardiac surgery score > 0 or not) when patients were classified into 2 categories, nonalcoholic fatty liver disease fibrosis was found to be higher in the group with severe coronary artery disease, however, there was no difference in fibrosis-4 scores between the groups.

Conclusion: This study suggests that the frequency and severity of coronary artery disease increase in the progression from simple fatty liver to the fibrotic liver. Our data, supporting the literature, reveal that nonalcoholic fatty liver disease fibrosis is more closely related to the prevalence and severity of coronary artery disease than the fibrosis-4 score.

Keywords: Carotid intima-media thickness, coronary artery disease, nonalcoholic fatty liver disease

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a disorder as the most common chronic liver condition in the Western World characterized by the accumulation of an excessive amount of fat in the hepatocytes that is not caused by alcohol consumption. Fatty liver may progress with clinical conditions such as steatohepatitis, cirrhosis, and hepatocellular carcinoma. Our country is one of the high-prevalence regions, with a global prevalence of 25%.[1,2] The most important finding that determines the natural course of NAFLD is the level of hepatic fibrosis. Although the diagnosis of hepatic fibrosis is definitively made by biopsy, several noninvasive scoring systems with particularly high negative predictive values have been developed.[3] In this respect, 2 of the most frequently used

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scoring systems are the NAFLD fibrosis score (NFS) and the fibrosis-4 (FIB-4) score.

In today's world, the pathology that causes the most mortality is known as coronary artery disease (CAD).[4] Obesity, carbohydrate metabolism disorders [such as insulin resistance and type 2 diabetes mellitus (DM)], metabolic syndrome, and dyslipidemia are frequently associated with NAFLD, all of which are risk factors for coronary artery disease. Considering these risk factors, it is expected that the risk of CAD will increase in those with NAFLD.[5]

Carotid intima-media thickness (CIMT) is an accurate marker that can be measured by noninvasive imaging techniques to show early atherosclerosis, which is used to predict the risk of CAD.[6] SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) score is used to determine the extent and seriousness of CAD and subsequently to evaluate treatment options. SYNTAX score is calculated using coronary angiography images.[7]

The recent increase in the prevalence of NAFLD has made it even more important to investigate its relationship with CAD. Studies evaluating the relationship between fibrosis stages and CAD in NAFLD beyond fatty liver are limited and contradictory. The object of this study was to search the relationship between fibrosis stages and CIMT, and SYNTAX scores.

METHODS

Our study included 200 patients over the age of 18 who had an indication for emergency or elective coronary angiography and were diagnosed with NAFLD. The local ethics committee of Erzincan Binali Yıldırım University, School of Medicine, (Ethics Committee No.: 15/20, dated February 2, 2022) approved the study.

Demographic characteristics and anatomical and physiological measurements of the patients were recorded. After 10 hours of fasting, hemogram (in automated blood counter, XN-1000, Sysmex Corporation, Japan), fasting blood glucose, lipid profile, urea, creatinine, alanine transaminase, aspartate transaminase, albumin (Spectrophotometric Analysis, Beckman Coulter Olympus AU2700 Plus, Chemistry Analyzer, Beckman Coulter, Tokyo, Japan), glycosylated hemoglobin (High-Performance Liquid Chromatography, G8 Tosoh, Japan), thyroid-stimulating hormone (Chemiluminescence Immunoassay System, Centaur XP, Siemens Healthcare, Germany), and C-reactive protein (Nephelometric Method, BN II, Siemens, Munich, Germany) parameters were studied and recorded.

The atherogenic index of plasma (AIP) was calculated by taking the logarithmic transformation of the triglyceride to high-density lipoprotein–cholesterol ratio (TG/HDL-C) in base 10.

The differences between the groups were evaluated by grouping the patients according to NFS risk groups, FIB-4 score risk groups, fatty liver degree, SYNTAX score, and median CIMT value.

Evaluation of Fatty Liver

Fatty liver disease was evaluated by abdominal ultrasonography (radiological evaluation with Toshiba Aplio 500 ultrasonography device) by a radiologist who did not have access to patient data. Patients with fatty liver were divided into 3 stages (stages 1, 2, and 3) as previously described in the literature, taking into account the degree of fatty liver.[8] Patients with a history of alcohol consumption were excluded.

Measurement of Carotid Intima-Media Thickness

Evaluation of the carotid arteries was made by ultrasonography as described in the literature, and 3 measurements were taken from the posterior wall, 1 cm proximal to the bifurcation point of the right and left common carotid arteries and in the nonplaque region, and were calculated by taking their averages.[9]

Calculation of Nonalcoholic Fatty Liver Disease Fibrosis and Fibrosis-4 Scores

Nonalcoholic fatty liver disease fibrosis and FIB-4 scores were calculated using age, body mass index (BMI), presence of diabetes, and biochemical parameters by the formulas specified in the literature.[10]

Calculating SYNergy Between PCI with Taxus and Cardiac Surgery Score

For calculating the SYNTAX score, a stenosis of ≥50% is required in coronary arteries with a diameter of ≥1.5 mm. The SYNTAX score of patients who did not have coronary stenosis to meet these conditions

MAIN POINTS

- Our study shows that the prevalence and severity of coronary artery disease (CAD) increase with the progression from simple fatty liver to the fibrotic liver.
- This study demonstrates that nonalcoholic fatty liver disease fibrosis is more closely related to the prevalence and severity of CAD than the fibrosis-4 score.
- It should be kept in mind that nonalcoholic fatty liver disease and liver fibrosis can be evaluated periodically with noninvasive methods.

was accepted as "0." SYNTAX scoring was performed using angiography images by the cardiologist using the online calculator, as described in the literature, with the link http://syntaxscore.org/calculator/syntaxscore/frameset.htm.[7]

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA) was used for data analysis. The Kolmogorov–Smirnov test was used to examine the distribution of variables. Nonnormally distributed variables were presented as the median and interquartile range (IQR), while normally distributed variables were presented as mean and SD. Student's *t*-test was used for data showing normal distribution when making comparisons between groups. Mann–Whitney *U*-test was used for data with abnormal distribution, and Kruskal–Wallis and Dunn–Bonferroni tests were used for groups with more than 2 groups. The Chi-square test was used in the evaluation of categorical data. The Spearman correlation test was used for nonparametric data in correlation analysis. The statistical significance level was accepted as $P < .05$.

RESULTS

Sociodemographic data and baseline laboratory parameters of the patients who underwent coronary angiography are presented in Table 1. Of the patients, 77 (38.5%) were female and 123 (61.5%) were male. Based on anamnesis and laboratory data, 95 (47.5%) of the patients were diagnosed with type 2 DM. Diabetes mellitus was not present in 105 (52.5%) patients. Of the patients, 68 (34%) were receiving regular treatment for DM (47 only on oral antidiabetics, 4 on insulin only, and 17 on insulin and oral antidiabetics).

Hypertension was found in 123 (61.5%) of the patients according to the anamnesis and physical examination results. Ninety-three (46.5%) of the patients were using regular antihypertensive drugs. Forty-three (21.5%) of the patients were receiving treatment for dyslipidemia (5 patients for hypertriglyceridemia and 38 patients for hypercholesterolemia).

Of the patients, 94 (47%) used regular tobacco products, and the number of active tobacco users was 45 (22.5%). Patients with a history of alcohol use were excluded from the study.

Data of patients according to fatty liver stages are presented in Table 2. When patients were categorized into 3 groups based on NAFLD stage, waist circumference, waist–hip ratio (WHR), AIP, NFS, BMI, systolic blood pressure (BP), triglyceride (TG), and HbA1c were statistically different between the groups.

Table 1. Sociodemographic Data and Basal Laboratory Parameters of Patients Who Underwent Coronary Angiography

Parameters	Mean ± SD
Age (years)	60.9 ± 9.9
Body mass index (kg/m^2)	30.09 ± 5.17
Waist circumference (cm)	102.89 ± 11.15
Waist–hip ratio	0.96 ± 0.07
Systolic blood pressure (mmHg)	125.80 ± 16.64
Diastolic blood pressure (mmHg)	76.89 ± 10.96
TSH (μU/mL)	2.62 ± 3.93
LDL cholesterol (mg/dL)	125.22 ± 34.48
HDL cholesterol (mg/dL)	44.97 ± 9.87
Triglyceride (mg/dL)	162.02 ± 113.44
Total cholesterol (mg/dL)	185.75 ± 49.94
AIP	0.14 ± 0.24
Albumin (g/L)	4.15 ± 0.29
Creatinine (mg/dL)	0.98 ± 0.19
AST (U/L)	23.23 ± 11.14
ALT (U/L)	26.56 ± 20.80
AST/ALT	1.03 ± 0.42
HbA1C (%)	6.85 ± 1.71
Microalbumin/creatinine ratio (mg/g)	47.36 ± 115.57
CIMT mean (mm)	0.80 ± 0.24
NFS	–1.085 ± 1.364
FIB-4 score	1.25 ± 0.70
SYNTAX score	8.37 ± 10.01

AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

Data of patients according to NFS risk groups were presented in Table 3. When patients are categorized into 3 groups according to the NFS risk group there was a statistically significant difference in waist circumference, WHR, systolic BP, albuminuria, mean CIMT, and FIB-4 score parameters.

Data of patients according to FIB-4 score risk groups are presented in Table 4. Due to the insufficient number of patients in the high-risk group, when the middle and high-risk groups are combined and the patients are

Table 2. Data of Patients According to Fatty Liver Stages

Parameters	Group 1 (n = 56, 28%) NAFLD Stage 1	Group 2 (n = 117, 58.5%) NAFLD Stage 2	Group 3 (n = 27, 13.5%) NAFLD Stage 3	*P*
Gender (female/male)*	23/33	45/72	9/18	.794
Age (years)**	62.00 (54.25-67.00)	61.00 (54.50-68.50)	59.00 (54.00-65.00)	.696
Waist circumference (cm)**	99.00 (92.25-106.00)	103.00 (95.00-109.50)	111.00 (106.00-119.00)[a]	**<.001**
Waist–hip ratio**	0.95 (0.89-0.98)	0.96 (0.90-1.01)	1.00 (0.96-1.04)[a]	**.006**
LDL cholesterol (mg/dL)**	125.00 (99.75-146.50)	125.00 (101.00-142.50)	123.00 (101.00-145.00)	.985
AIP**	0.06 (−0.06 to 0.23)[a]	0.14 (−0.03 to 0.33)[ab]	0.22 (0.10-0.35)[b]	**.047**
Albumin (g/L)**	4.22 (3.95-4.35)	4.18 (3.99-4.34)	4.13 (4.04-4.34)	.938
NFS**	−1.529 (−2.333 to −0.476)[a]	−0.949 (−1.999 to −0.134)[ab]	−0.703 (−1.461 to 0.122)[b]	**.015**
Body mass index (kg/m^2)**	27.70 (24.83-30.85)	29.55 (27.11-32.12)	33.29 (29.46-37.26)[a]	**<.001**
Systolic blood pressure (mmHg)**	130 (110-142.5)[a]	120 (110-130)[b]	125 (112.5-140)[ab]	**.048**
Diastolic blood pressure (mmHg)**	80 (70-90)	70 (70-80)	75 (70-90)	.123
TSH (μU/mL)**	1.88 (0.96-3.45)	1.55 (0.96-2.77)	2.11 (1.41-2.90)	.346
HDL cholesterol (mg/dL)**	43 (38.5-54)	44 (38-51)	43.5 (40-48.5)	.683
Triglyceride (mg/dL)**	129 (84.5-161)[a]	134.5 (107-193.5)[ab]	156 (112.75-209.75)[b]	**.026**
Total cholesterol (mg/dL)**	183 (146.5-211.5)	185.5 (152.75-209)	173.5 (147.5-217)	.951
Creatinine (mg/dL)**	0.93 (0.81-1.04)	0.975 (0.87-1.1)	0.94 (0.80-1.03)	.219
AST (U/L)**	18 (15-25)	21 (16-26.25)	20 (16.25-27)	.505
ALT (U/L)**	19 (14.5-26.5)	22 (16-32)	22 (14.5-31.5)	.258
AST/ALT**	1 (0.82-1.27)	0.88 (0.69-1.18)	0.95 (0.72-1.24)	.364
HbA1C (%)**	6.1 (5.6-6.4)[a]	6.25 (5.77-7.7)[ab]	6.6 (6.12-8.85)[b]	**.003**
Microalbumin/creatinine ratio (mg/g)**	8.17 (4.83-20.40)	12.59 (5.17-30.60)	23.98 (4.74-99.82)	.208
CIMT mean (mm)**	0.70 (0.56-0.95)	0.75 (0.60-0.91)	0.87 (0.70-1.09)	.058
FIB-4 score**	1.07 (0.76-1.47)	1.08 (0.80-1.44)	1.14 (0.73-1.46)	.971
SYNTAX score**	3 (0-13.5)	5 (0-13)	9 (0.25-19.75)	.296

*Chi-square test was used.
**Kruskal–Wallis test was used. Descriptors are given as median (25%-75%).
[a,b,c]Groups marked with the same letter are statistically similar, but there is a statistically significant difference at the level of 0.05 between groups with different letters (Dunn–Bonferroni test was used).
AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

categorized into 2 groups according to the FIB-4 risk scoring; the mean WHR, NFS, and CIMT were statistically significant between the groups.

When patients were categorized into 2 groups—1 group in which SYNTAX score cannot be calculated (the group in which individuals have a SYNTAX score = 0) and another group in which can be calculated (with ≥50% stenosis in coronary arteries ≥1.5 mm in diameter), mean values of age, WHR, low-density lipoprotein (LDL) cholesterol, albumin, NFS, HDL cholesterol, cholesterol, creatinine, HbA1c, albuminuria, and CIMT are statistically significantly different between the groups (Table 5).

When patients were categorized into 2 as patients with a calculated SYNTAX score under 23 (n = 123) and SYNTAX score ≥ 23, a statistically significant difference was found only for WHR (Table 6).

When the patients were divided into 2 groups as patients with low and high CIMT values according to the median CIMT (0.75mm); age ($P < 0.001$), waist circumference

Table 3. Data of Patients According to NFS Risk Groups

Parameters	Group 1 (n = 82, 41%) Stage 1: No or Mild Fibrosis	Group 2 (n = 96, 48%) Stage 2: Indefinite Stage	Group 3 (n = 22, 11%) Stage 3: Severe Fibrosis or Cirrhosis	*P*
Gender (female/male)*	28/54	39/57	10/12	.525
Age (years)**	57.00 (50.00-63.00)[a]	62.50 (57.00-68.00)[b]	67.50 (63.50-79.25)[c]	**<.001****
Waist circumference (cm)**	98.50 (92.00-104.50)[a]	106.00 (98.00-111.75)	109.50 (102.50-120.00)	**<.001**
Waist–hip ratio**	0.95 (0.89-1.00)[a]	0.97 (0.91-1.03)[ab]	1.00 (0.95-1.05)[b]	**.030**
LDL cholesterol** (mg/dL)	126.50 (106.50-144.25)	125.00 (99.00-142.75)	110.50 (89.00-144.00)	.528
AIP**	0.15 (–0.04 to 0.31)	0.11 (–0.03 to 0.27)	0.16 (–0.02 to 0.34)	.448
Albumin (g/L)**	4.22 (4.04-4.38)[a]	4.16 (4.01-4.34)[ab]	4.03 (3.74-4.27)[b]	**.046****
NFS**	–2.192 (–2.824 to –1.675)	–0.520 (–0.949 to –0.104)	1.014 (0.773-1.487)	–
Body mass index (kg/m^2)**	27.43 (24.92-30.11)[a]	30.33 (27.58-33.76)	31.94 (28.51-38.76)	**<.001****
Systolic blood pressure (mmHg)**	120 (110-130)[a]	130 (115-140)[b]	130 (110-140)[ab]	**.041**
Diastolic blood pressure (mmHg)**	70 (70-80)	80 (70-88.5)	75 (70-90)	.239
TSH (μU/mL)**	1.73 (1.09-3.21)	1.55 (0.95-2.82)	1.53 (0.96-3.41)	.362
HDL cholesterol (mg/dL)**	44 (38-52.5)	44 (39-51)	44 (39-50.75)	.877
Triglyceride (mg/dL)**	142 (108-193)	130 (95.75-183.25)	135 (94.5-237.75)	.652
Total cholesterol (mg/dL)**	186 (156-210)	180.5 (148.5-211.25)	184.5 (133.25-217.75)	.550
Creatinine (mg/dL)**	0.95 (0.84-1.06)	0.95 (0.85-1.05)	0.89 (0.81-1.15)	.959
AST (U/L)**	20 (16-26)	19 (15.75-24.25)	30 (18.5-39)[a]	**.010****
ALT (U/L)**	24 (17.5-31)[a]	19 (14-27.5)[b]	21 (13-35)[ab]	**.026****
AST/ALT**	0.84 (0.68-1)[a]	1 (0.74-1.25)[b]	1.30 (0.97-1.65)[c]	**<.001****
HbA1C (%)**	5.9 (5.5-6.3)[a]	6.35 (5.8-8.2)	6.8 (6.12-8.57)	**<.001****
Microalbumin/creatinine ratio (mg/g)**	6.88 (4.11-17.86)[a]	12.89 (6.39-30.25)[b]	57.67 (12.23-208.34)[c]	**<.001**
CIMT mean (mm)**	0.65 (0.6-0.8)[a]	0.80 (0.64-1)[b]	0.92 (0.85-1.14)[c]	**<.001**
FIB-4 score**	0.80 (0.63-1.07)[a]	1.17 (0.95-1.46)[b]	2.10 (1.73-2.73)[c]	**<.001**
SYNTAX score**	5 (0-15.5)	6 (0-15)	7.5 (3-12.5)	.396

*Chi-square test was used.
**Kruskal–Wallis test was used. Descriptors are given as median (25%-75%).
***Used in NFS calculation.
[a,b,c]Groups marked with the same letter are statistically similar, but there is a statistically significant difference at the level of 0.05 between groups with different letters (Dunn–Bonferroni test was used).
AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

($P = 0.025$), WHR ($P = 0.003$), NFS ($P < 0.001$), HDL cholesterol, ($P = 0.039$), total cholesterol, ($P = 0.048$), creatinine ($P = 0.003$), ALT ($P = 0.029$), AST/ALT ratio ($P = 0.002$), HbA1c ($P = 0.009$), albuminuria ($P = 0.029$) and FIB-4 score ($P < 0.001$) were statistically significant. However, no significant difference in LDL cholesterol, AIP, BMI, TG, or SYNTAX score was identified between the two groups ($P > 0.05$).

Parameters correlated with the mean CIMT in patients were NFS ($r_s = 0.367$, $P < .001$), FIB-4 score ($r_s = 0.352$, $P < .001$), and fatty liver stages ($r_s = 0.161$, $P = .023$). Similarly, when the patients were divided into 2 groups such as those whose SYNTAX score was calculated and those whose SYNTAX score was not calculated, the SYNTAX score was correlated with NFS ($r_s = 0.210$, $P = .003$).

Table 4. Data of Patients According to FIB-4 Score Risk Groups

Parameters	Group 1 (n = 147, 73.5%) Stage 1: Low Risk	Group 2 (n = 53, 26.5%) Stages 2 and 3: Medium-High Risk	*P*
Gender (female/male)*	58/89	19/34	.644
Age (years)**	58.96 ± 8.89	66.45 ± 10.46	**<.001****
Waist circumference (cm)**	102.41 ± 11.23	104.23 ± 10.93	.312
Waist–hip ratio**	0.95 ± 0.08	0.98 ± 0.06	**.048**
LDL cholesterol (mg/dL)**	126.79 ± 33.75	120.87 ± 36.40	.285
AIP**	0.16 ± 0.25	0.10 ± 0.23	.108
Albumin (g/L)**	4.16 ± 0.29	4.13 ± 0.30	.482
NFS**	–1.49 ± 1.19	0.05 ± 1.17	**<.001**
Body mass index (kg/m^2)***	29.75 (26.91-32.52)	28.44 (25.53-32.39)	.168
Systolic blood pressure (mmHg)***	122.5 (110-131.25)	120 (110-140)	.709
Diastolic blood pressure (mmHg)***	80 (70-80)	80 (70-90)	.122
TSH (μU/mL)***	1.62 (1.02-2.85)	2.21 (0.97-3.33)	.733
HDL cholesterol (mg/dL)***	43.5 (38-51.25)	44 (39-51)	.555
Triglyceride (mg/dL)***	141.5 (107-193)	116 (90.5-158.5)	.063
Total cholesterol (mg/dL)***	186.5 (154-210)	170 (146.5-217)	.395
Creatinine (mg/dL)***	0.95 (0.82-1.05)	0.98 (0.86-1.06)	.248
AST (U/L)***	18 (15-22.25)	29 (21-39)	**<.001********
ALT (U/L)***	21 (15-28.25)	22 (15-36)	.400********
AST/ALT***	0.87 (0.69-1.07)	1.25 (0.97-1.62)	**<.001**
HbA1C (%)***	6.25 (5.7-7.52)	6.2 (5.7-7.75)	.917
Microalbumin/creatinine ratio (mg/g)***	10.07 (4.86-26.37)	11.44 (4.94-63.25)	.161
CIMT mean (mm)***	0.7 (0.6-0.9)	0.9 (0.7-1.02)	**<.001**
FIB-4 score***	0.94 (0.69-1.16)	1.88 (1.55-2.36)	–
SYNTAX score***	4.5 (0-15)	8 (2-14)	.065

*Chi-square test was used.
**_t_-Test was used. Descriptors are given as mean ± SD.
***Mann–Whitney _U_-test was used. Descriptors are given as median (25%-75%).
****Used in FIB-4 score calculation.
AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

DISCUSSION

The pathophysiological mechanisms linking nonalcoholic fatty liver disease and CAD are unclear. It is thought that increased secretion of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin 6 in NAFLD may lead to the development of atherosclerosis by causing endothelial dysfunction.[11] In addition, NAFLD is closely associated with atherogenic dyslipidemia, whose definite contribution to atherosclerosis is known, and insulin resistance, which can cause endothelial dysfunction and plaque formation.[11]

Some studies investigated the relationship between NAFLD and SYNTAX score, and while some of them found similar results to our study,[12-14] there are also studies that found results contrary to our study.[15,16]

In a study conducted by Langroudi et al.[13] in 264 patients without diabetes, no statistically significant difference was realized found between the groups with and without NAFLD in terms of SYNTAX score. They also showed that the stage of NAFLD was not significantly associated with the SYNTAX score. Eissa et al.[12] evaluated the relationship between the NAFLD stage and the SYNTAX

Table 5. Data When Patients Were Divided into 2 Groups as Calculated and Uncalculated SYNTAX Scores

Parameters	Group 1 (n = 73, 36.5%) SYNTAX Score = 0	Group 2 (n = 127, 63.5%) SYNTAX Score > 0	*P*
Gender (female/male)*	41/32	36/91	**<.001**
Age (years)**	57.29 ± 9.15	63.05 ± 9.70	**<.001**
Waist circumference (cm)**	102.71 ± 11.37	103 ± 11.07	.861
Waist–hip ratio**	0.94 ± 0.07	0.97 ± 0.07	**.010**
LDL cholesterol (mg/dL)**	136.65 ± 31.31	118.65 ± 34.61	**<.001**
AIP**	0.12 ± 0.23	0.15 ± 0.25	.401
Albumin (g/L)**	4.23 ± 0.31	4.11 ± 0.27	**.004**
NFS**	−1.493 ± 1.323	−0.851 ± 1.336	**.001**
Body mass index (kg/m^2)***	30.22 (27.12-34.80)	28.73 (26.30-32.04)	.085
Systolic blood pressure (mmHg)***	130 (110-138.75)	120 (110-140)	.962
Diastolic blood pressure (mmHg)***	80 (70-80)	75 (70-85)	.351
TSH (μU/mL)***	1.7 (1.12-3.0575)	1.57 (0.94-3.07)	.324
HDL cholesterol (mg/dL)***	47.5 (41-54.75)	42 (37-50)	**<.001**
Triglyceride (mg/dL)+	148 (108-199.5)	130 (98-183)	.306
Total cholesterol (mg/dL)***	193.5 (174.5-220.75)	171 (146-204)	**<.001**
Creatinine (mg/dL)***	0.90 (0.75-1.02)	1 (0.88-1.08)	**<.001**
AST (U/L)***	21 (16-25)	20 (16-27)	.481
ALT (U/L)***	22 (16-29)	21 (15-32)	.412
AST/ALT***	0.90 (0.72-1.13)	0.95 (0.72-1.26)	.376
HbA1C (%)***	6 (5.52-6.3)	6.4 (5.8-8.2)	**<.001**
Microalbumin/creatinine ratio (mg/g)***	8.17 (4.70-17.58)	14.66 (5.44-40.62)	**.013**
CIMT mean (mm)***	0.65 (0.55-0.89)	0.8 (0.65-1)	**.002**
FIB-4 score***	0.99 (0.74-1.28)	1.11 (0.79-1.51)	.057
SYNTAX score***	0	11 (5-18)	–

*Chi-square test was used.
***t*-Test was used. Descriptors are given as mean ± SD.
***Mann–Whitney *U*-test was used. Descriptors are given as median (25%-75%).
AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

score according to Ultrasonography (USG) and could not detect a significant difference in 85 patients aged ≤45 years. Jana et al.[14] also found no significant difference between the fatty liver stages and the SYNTAX score in 300 patients who have indication for revascularization.

On the contrary, Ağac et al.[15] found the SYNTAX score to be higher in NAFLD patients compared to those without NAFLD and showed that the SYNTAX score increased as the degree of liver fattening in patients with NAFLD increased. Keskin et al. report a significant relationship between NAFLD and SYNTAX score in a study with 360 patients with ST-segment elevation myocardial infarction (STEMI). The SYNTAX score in the group without NAFLD was found to be lower than in the other 3 stages with NAFLD, and the SYNTAX score increased as the degree of the fatty liver increased.[16] Keskin and Ağac excluded patients with a SYNTAX score of "0" in their studies. Since our study included 77 patients without significant coronary artery stenosis (without >50% of stenosis in any coronary artery with a diameter of ≥1.5 mm), our results may differ from the previous studies of Keskin and Ağac.

While there are studies in the literature[17-23] that found a difference in CIMT in patient groups with and without NAFLD, no statistically significant difference was found in a study.[24] In addition, in studies evaluating the relationship between fatty liver stages and CIMT in patients with NAFLD, as in our study, there are studies that found a significant difference in accordance with ours,[17,24] as well as

Table 6. Data from Patients with a SYNTAX Score of 1-22 and a SYNTAX Score of >22

Parameters	Group 1 (n=105, 82.5%) Stage 1: SYNTAX Score 1-22	Group 2 (n=22, 17.5%) Stage 2: SYNTAX Score >22	*P*
Gender (female/male)*	27/78	9/13	.150
Age (years)**	63.00 (55.00-69.00)	64.00 (59.75-73.50)	.122
Waist circumference (cm)**	102.00 (95.50-110.00)	102.50 (91.75-112.25)	.931
Waist–hip ratio**	0.98 (0.94-1.03)	0.93 (0.90-0.98)	**.026**
LDL cholesterol** (mg/dL)	114.00 (89.50-140.00)	126.00 (104.75-155.50)	.096
AIP**	0.14 (–0.03 to 0.30)	0.19 (0.01-0.36)	.516
Albumin (g/L)**	4.10 (3.96-4.32)	4.07 (3.84-4.29)	.356
NFS**	–0.721 (–1.782 to 0.091)	–0.979 (–2.061 to –0.064)	.606
Body mass index (kg/m^2)**	28.88 (26.45-32.04)	28.08 (25.98-32.04)	.686
Systolic blood pressure (mmHg)**	120 (110-140)	125 (110-130)	.615
Diastolic blood pressure (mmHg)**	80 (70-88)	70 (70-80)	.493
TSH (μU/mL)**	1.49 (0.88-2.93)	1.93 (1.1-4.73)	.196
HDL cholesterol (mg/dL)**	42 (38-50)	40.5 (34.5-52)	.321
Triglyceride (mg/dL)**	130 (96-183)	131.5 (103.25-176)	.947
Total cholesterol (mg/dL)**	170 (141-195)	184.5 (155.75-219.5)	.181
Creatinine (mg/dL)**	1 (0.88-1.08)	1.00 (0.85-1.115)	.344
AST (U/L)**	20 (16-27)	17.5 (15-20)	.051
ALT (U/L)**	22 (15-32)	17.5 (12.5-26)	.086
AST/ALT**	0.95 (0.72-1.29)	0.93 (0.69-1.24)	.929
HbA1C (%)**	6.4 (5.9-7.9)	6.25 (5.7-9.45)	.783
Microalbumin/creatinine ratio (mg/g)**	12.44 (4.86 to –44.11)	17.92 (6.16-35.83)	.587
CIMT mean (mm)**	0.8 (0.65-1)	0.72 (0.61-0.99)	.401
FIB-4 score**	1.12 (0.87-1.57)	1.02 (0.71-1.42)	.285
SYNTAX score**	9 (5-15)	26.5 (23-32.5)	–

*Chi-square test was used.
**Mann–Whitney *U*-test was used. Descriptors are given as median (25%-75%).
AIP, atherogenic index of plasma; ALT, alanine transaminase; AST, aspartate transaminase; CIMT, carotid intima-media thickness; FIB-4, fibrosis-4; HbA1C, glycolyzed hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, nonalcoholic fatty liver disease fibrosis score; SYNTAX score, SYNergy between PCI with TAXus and cardiac surgery score; TSH, thyroid-stimulating hormone.

studies that could not detect a difference.[22] Xin et al.[23] followed 3433 patients without NAFLD with a 5-year follow-up prospectively, and NAFLD was detected in 654 patients in a median of 4.3 years. There was a statistically significant difference in terms of CIMT in the group of patients who developed NAFLD. Kim et al.[17] detected and graded NAFLD in 507 patients by USG in 1021 patients aged 30-79 years. While a significant difference was found in terms of CIMT between the group with and without NAFLD, no significant relation was found between the stages of NAFLD and CIMT. Similarly, Petit et al.[24] detected the presence of NAFLD by magnetic resonance imaging, in 61 of 101 patients diagnosed with type 2 DM, and no statistically significant difference was realized between the groups in terms of CIMT. In addition, they could not detect a relationship between the fatty liver stages and CIMT. Targher et al.[22] compared 85 patients with biopsy and USG-proven NAFLD and 160 control groups in terms of CIMT, and CIMT was found to be higher in the NAFLD group. When the patients were divided into 3 stages according to the stages of NAFLD and evaluated in terms of CIMT, they found a statistically significant difference between the groups. In a study conducted by Oni et al.[18] on 4123 participants, they found a higher CIMT value in 729 people who were diagnosed with NAFLD by demonstrating fatty liver with computed tomography. Fracanzani et al.[19] compared 125 patients with NAFLD diagnosed by USG with 250 control groups and found that the CIMT value of NAFLD patients was higher than the control group. Similarly Aygun et al.[20] reported that the CIMT

value was significantly higher in 40 patients with NAFLD compared to the control group. Nahandi et al.[21] found that CIMT values were significantly higher in diabetic patients with NAFLD than in nondiabetic patients. In these studies mentioned, it is difficult to compare the results with our study due to differences in the material method, size of the groups, detection technique of fatty liver, and the prospective/cross-sectional nature of the studies.

There are studies in the literature comparing liver fibrosis in terms of CIMT by evaluating with noninvasive scoring methods, and similar results have been reported with our study.[9,25-27]

Chen et al.[9] evaluated the liver fibrosis grades of 2550 patients with NAFLD and evaluated the relationship between NFS and CIMT. They reported that CIMT increased as the degree of fibrosis increased. Sesti et al.[25] evaluated the liver fibrosis grades of 400 patients with NAFLD using NFS and found a statistically significant difference between NFS groups in terms of CIMT. Shahapure et al.[26] found that the mean CIMT increased significantly as the NFS stage increased in 100 patients diagnosed with type 2 DM and NAFLD. Finally, Arai et al.[27] report that CIMT increased as liver fibrosis level increased with both histopathologically, FIB-4 and NFS scores in 195 biopsy-proven NAFLD patients.

There are very few studies in the literature investigating the relationship between SYNTAX scores and liver fibrosis scores.[28-30] Ali et al.[30] calculated SYNTAX scores by performing coronary angiography in 85 acute coronary syndrome and NAFLD patients aged ≤45 years and found no statistically significant difference between fibrosis grades in terms of SYNTAX score.

In a study conducted by Turan et al.,[29] 109 patients with significant coronary stenosis (≥50% narrowing in ≥1 coronary artery) and 50 patients without significant coronary stenosis were evaluated. A statistically significant difference was realized between these 2 groups in terms of NFS. In our study, 123 patients with significant coronary stenosis and 77 patients without significant coronary stenosis were evaluated with the same method. Similar to Turan's study, NFS was found to be higher in the group with significant coronary artery stenosis.

In a prospective study, Jin et al.[28] followed up 5143 patients with stable coronary angiography-proven CAD (≥50% narrowing of ≥1 coronary artery), for 7 years for cardiovascular events, and 435 patients experienced cardiovascular events. In this study, it was observed that the SYNTAX score increased as the FIB-4 score stage increased, but no statistically significant difference was realized between them. Contrary, as the NFS stage increased, a statistically significant increase was found in the SYNTAX score. In addition, the rate of advanced-stage fibrosis risk detected by both NFS and FIB-4 was found to be higher in the patient group who had a cardiovascular event. In our study, however, there was no statistically significant difference between NFS and FIB-4 score risk groups in terms of SYNTAX score, but NFS was found to be higher in the group whose SYNTAX score could be calculated, and the indirect relationship between SYNTAX score and NFS was revealed. The reason for the different results may be the low number of our patients and the absence of significant coronary stenosis (which the SYNTAX score can be calculated, >0) in all of our patients. In our study, the patients whose SYNTAX scores could be calculated additionally were divided into 2 groups as patients with SYNTAX scores ≥ 23 and patients with SYNTAX scores 1-22. No statistically significant difference was realized in terms of NFS and FIB-4 scores. Such a study has not been found in the literature.

Since NAFLD is the hepatic manifestation of metabolic syndrome, it is associated with parameters such as waist circumference, WHR, and body mass index, and there are studies showing that there is a statistically significant difference between the stages of NAFLD and these parameters.[31,32] Especially waist circumference and waist-hip ratio (WHR) parameters are found to be significantly higher in advanced fibrosis stages when compared with low-stage fibrosis stages.[33] In our study, the relation of metabolic syndrome parameters with NAFLD and liver fibrosis stages was revealed, supporting these findings.

Our study has some limitations. In order to calculate the NAFLD fibrosis score, patients without hepatic steatosis were not included in the study. Therefore, a comparison of the CIMT and SYNTAX scores of the non-NAFLD group could not be made. In addition, the SYNTAX score could not be calculated due to the absence of significant coronary artery stenosis (≥50% stenosis in ≥1 coronary artery) in some of the patients who underwent coronary angiography, so limited results were obtained in comparison with the degrees of adiposity and fibrosis. Since our study is a cross-sectional study, the cause–effect relationship of our findings cannot be revealed.

Despite not being clearly demonstrated from all perspectives, our study suggests that the prevalence and severity of CAD, as assessed by the CIMT and SYNTAX score, increase with the progression from simple fatty liver to fibrotic liver. Our data, supporting the literature, reveal that NFS is more closely related to the prevalence and severity of CAD than the FIB-4 score. It should be kept in mind that NAFLD and liver fibrosis, the frequency of which is increasing, can be evaluated periodically with

noninvasive methods and precautions should be taken in this regard, considering its relationship with the severity of CAD. A methodology and fibrosis score cutoff value should be established for this purpose.

Ethics Committee Approval: The local ethics committee of Erzincan Binali Yıldırım University, School of Medicine, approved the study (Date: February 2, 2022, Number: 15/20).

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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