Effect of nonalcoholic fatty liver disease on outcome of primary percutaneous coronary intervention in nondiabetic patients with ST-segment elevation myocardial infarction

Abdel N.M.A. Hegazy[a], Mahmoud Abdelsabour[a], Hatem Abdelrahman[a], Mohamed A.A. Abozaid[b], Yehia T. Kishk[a]

Departments of [a]Cardiology, [b]Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Abdel N.M.A. Hegazy, Department of Cardiology, Faculty of Medicine, Assiut University, Assiut, Egypt.
Tel: +20 102 082 8122;
e-mail: hegazyaborenad@yahoo.com

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Introduction
The effect of nonalcoholic fatty liver disease (NAFLD) on outcome of patients with ST-segment elevation myocardial infarction is controversial. The purpose of the study aimed to assess the effect of NAFLD on myocardial and epicardial reperfusion after primary percutaneous coronary intervention (PPCI) among nondiabetic patients.

Patients and methods
A total of 240 nondiabetic patients with ST-segment elevation myocardial infarction were recruited and underwent PPCI. After revascularization, epicardial reperfusion had been assessed by thrombolysis in myocardial infarction (TIMI) flow grades and TIMI frame count, and myocardial reperfusion had been assessed by TIMI myocardial perfusion grade and ST-segment resolution. NAFLD had been assessed and graded based on abdominal ultrasonography and then the patients were subdivided into NAFLD group (111 patients) and non-NAFLD group (129 patients).

Results
The overall prevalence of NAFLD in the current study was 46.5%. Clinically, KILLIP class more than I was significant in NAFLD group [24 ($P < 0.001$)]. Multivessel coronary artery disease was significant in NAFLD group [63 (56.8%) vs. 23 (17.8%); $P < 0.001$]. Eleven patients of NAFLD group died, whereas no deaths occurred in the other group. Postprocedural myocardial blush grades 0 and 1 were significant in patients with NAFLD group ($P < 0.001$). Moreover, absent ST-segment resolution and TIMI frame count were significant ($P < 0.001$) in NAFLD group. Finally, NAFLD was an independent predictor for in-hospital and follow-up cardiac events.

Conclusions
NAFLD is considered an independent risk factor for the occurrence of in-hospital and follow-up adverse cardiac events after PPCI in nondiabetic patients.

Keywords:
epicardial perfusion, nonalcoholic fatty liver disease, primary percutaneous coronary intervention, myocardial perfusion, ST-segment elevation myocardial infarction

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease [1]. Diabetes mellitus, insulin resistance, hyperlipidemia, and obesity are predisposing factors for coronary artery disease (CAD) and NAFLD [2]. NAFLD increases the risk of acute myocardial infarction (MI) and cardiovascular mortality [3]. Myocardial blush grade (MBG) and ST-segment resolution (STR) are two validated measurements of myocardial perfusion and have incremental prognostic value beyond TIMI 3 flow in patients with ST-segment elevation myocardial infarction (STEMI) [4].

This work was designed to study the effect of NAFLD on epicardial and myocardial reperfusion as well as in-hospital and 6-month out-of-hospital major adverse cardiac events (MACE) in nondiabetic STEMI patients treated with primary percutaneous coronary intervention (PPCI).

Patients and methods

A prospective cross-sectional study included 251 patients with STEMI based on criteria of the Fourth Universal Definition of Myocardial Infarction [5], for whom PPCIs were performed using Philips-Allura Xper FD 10/10-DS Interventional radiograph system (Philips). Recruitment of patients was done between the first of July 2016 and the first

of July 2017 after obtaining approval from the Local Ethical Committee (17200522) and written consent from all participants. All procedures performed in the study were in accordance with the ethical standards of institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

We excluded any patient with alcohol intake, diabetes mellitus, liver cirrhosis, risk factors for liver damage such as hepatitis B or C infection, and other conditions that may be associated with NAFLD [6].

Baseline evaluation

All enrolled patients were subjected to full history taking and thorough clinical evaluation. Anthropometric measures including weight, height, and BMI were recorded. The following laboratory data were performed: lipid profile, fasting blood sugar, serum creatinine, alanine transaminase, and creatinine kinase-myocardial band.

Assessment of epicardial and myocardial perfusion

Immediately after PPCI, epicardial and myocardial reperfusion had been assessed and graded on the angiograms. For every patient, the best projection had been chosen to assess the myocardial region of infarct-related coronary artery, preferably without superpositioning of the noninfarcted myocardium. The angiographic runs have to be long enough to allow filling of the venous coronary system. First, epicardial reperfusion was assessed by TIMI flow grades (TFG) and TIMI frame count (TFC) as follows: TFG included grade 0, no perfusion; grade 1, penetration without perfusion; grade 2, partial perfusion; and grade 3, complete perfusion [7]. Then, TFC was defined as the number of frames required for the dye to first opacify a standard distal landmark [8]. Second, myocardial reperfusion was assessed by TIMI myocardial perfusion (TMP) and STR as follows: TMP grade 0, failure of dye to enter the microvasculature; TMP grade 1, dye slowly enters but fails to exit the microvasculature; TMP grade 2, delayed entry and exit of dye from the microvasculature; and TMP grade 3, normal entry and exit of dye from the microvasculature [9], then, STR was assessed by ECG, which was done on admission (first ECG) and 90 min (second ECG) after PPCI. The second ECGs had been classified concerning STR into the following grades: no residual ST-segment elevation, normalized; residual ST-segment elevation less than 70%, improved; and residual ST-segment elevation more than 70%, unchanged [10]. The angiographic data were analyzed by two independent investigators. Moreover, syntax score I was calculated for all patients [11].

Diagnosis of nonalcoholic fatty liver disease

The ultrasonographic evaluation was performed within three days of admission. This scan aimed to detect NAFLD, using a high-resolution ultrasound machine (Aplio; Toshiba Medical Systems Corporation, Tochigi, Japan). All scans had been performed by one physician who was unaware of the patient's previous data. Ultrasound assessment of hepatic steatosis depends on the brightness of the liver, and accordingly, we classified patients into three groups as follows: 0, normal bright; 1, medium bright, a moderate lipid content; and 2, clearly bright, a severe lipid content, and fatty liver [12].

Outcomes and follow-up

The primary outcome included the assessment of TFG, TFC, MBG, and STR in both groups of patients. Secondary outcomes included the incidence of in-hospital MACE (all-cause death, nonfatal acute MI and/or target lesion revascularization, cardiogenic shock, and stroke) in both groups of patients. For every patient, postprocedural left ventricle ejection fraction (LVEF) had been measured by biplane Simpson method. All patients were followed for 6 months after hospital discharge for readmission, reinfraction, and cardiovascular mortality.

Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science, version 20; IBM, Armonk, New York, USA). Nominal data were expressed as frequency, whereas continuous data were expressed as mean ± SD. We used χ^2 test, Student t test, and multivariate regression analysis. Confidence level was kept at 95%. P value was considered significant if less than 0.05.

Results

Our study included 251 patients with STEMI. We excluded six patients for a recently discovered diabetes mellitus, two patients who died within 24 h because of left main thrombosis, one patient for aortic valve prostheses with embolization, and two patients with acute stent thrombosis. The resulting 240 patients were classified based on abdominal ultrasound into NAFLD group, which included 111 (46.3%) patients, and non-NAFLD group, which included 129 (53.7%) patients. Demographic and laboratory data of studied patients are shown in Table 1. Our study revealed that

KILLIP class more than I, left ventricular failure, and postprocedural LVEF were significant in patients with NAFLD ($P < 0.001$) (Table 2). Postprocedural MBG 0 and 1 were significant in patients with NAFLD, whereas MBG 2 and 3 were significant in non-NAFLD patients ($P < 0.001$). Postprocedural TFC and absent STR were also significant in patients with NAFLD ($P < 0.001$). Multivessel disease and Syntax score I were significant in patients with NAFLD ($P < 0.001$) (Tables 3 and 4). In-hospital MACEs were insignificant in patients with NAFLD. Heart failure hospitalization and follow-up mortality were significant, whereas stent thrombosis was insignificant in patients with NAFLD (Table 5). Predictors of MBG and follow-up cardiac events included NAFLD, multivessel disease, anterior wall infarct, and pain to balloon time (>4 h), whereas NAFLD was the only predictor of absent STR (Table 6). Survival analysis was insignificant between the two groups (Fig. 1).

Table 1 Demographic and laboratory data of studied patients

	NAFLD group (*n*=111)	Non-NAFLD group (*n*=129)	*P*
Age (years)	54.06±10.73	51.27±12.30	0.06
Male sex	88 (79.3)	108 (83.7)	0.23
Class of BMI			
Normal	55 (49.5)	64 (49.6)	0.06
Obese	23 (20.7)	14 (10.9)	
Overweight	33 (29.7)	51 (39.5)	
Smoking	71 (64)	80 (62)	0.43
Family history of CAD	3 (2.7)	3 (2.3)	0.54
Hypertension	28 (25.2)	27 (20.9)	0.26
Dyslipidemia	0	2 (1.6)	0.28
Previous CAD	16 (14.4)	14 (9.9)	0.19
Cholesterol (mg/dl)	169.27±30.57	169.18±32.34	0.98
LDL (mg/dl)	106.54±25.08	105.36±26.66	0.73
HDL (mg/dl)	49.09±9.23	48.08±7.46	0.39
Triglyceride (mg/dl)	127.38±42.28	132.41±41.23	0.35
Glucose (mg/dl)	99.35±6.63	99.95±6.42	0.47
ALT (U/L)	53.81±37.73	50.37±37.02	0.47
Creatinine (mg/dl)	0.92±0.32	0.81±0.28	0.45
CK-MB (mg/dl)	254.27±184.90	234.56±175.53	0.39

Data were expressed in form of mean±SD, *n* (%). ALT, alanine transaminase; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease. *P* value was significant if less than 0.05.

Table 2 Clinical and echocardiographic data in studied patients

	NAFLD group (*n*=111)	Non-NAFLD group (*n*=129)	*P*
Hospital stay (days)	2.62±0.46	2.42±0.86	0.20
Anterior wall infarction	63 (56.8)	73 (56.6)	0.54
KILLIP class >I	24 (21.6)	6 (4.7)	<0.001
Clinical LVF	24 (21.6)	5 (3.9)	<0.001
Pulmonary edema	3 (2.7)	0	0.09
Cardiogenic shock	4 (3.6)	0	0.87
Arrhythmia	20 (18)	18 (14)	0.42
Post-procedural LVEF (%)	48.45±8.35	52.22±8.17	<0.001

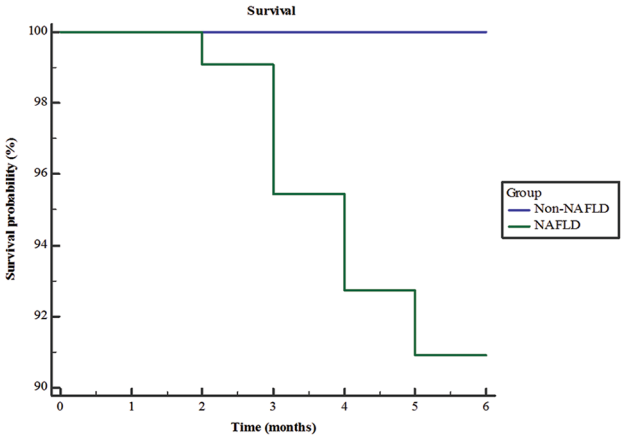
Data were expressed in form of mean±SD, *n* (%). LVEF, left ventricle ejection fraction; LVF, left ventricular failure; NAFLD, nonalcoholic fatty liver disease. *P* value was significant if less than 0.05.

Discussion

Several pathophysiologic mechanisms could be postulated by which FLD contributes to impaired microvascular flow. First, FLD is associated with an increased inflammatory state, as C-reactive protein, which is mainly produced by the liver, has been shown to be increased in patients with FLD [13]. Second, FLD is related to an increased prothrombotic state. Fibrinogen and plasminogen activator 1 levels have also been found to be elevated in patients with FLD [14]. Third, increased endothelial dysfunction in patients with FLD may also contribute to impaired myocardial perfusion [15]. Fourth, increased oxidative stress associated with FLD may cause microvascular spasm [14]. The main finding of the present study revealed that NAFLD was correlated with myocardial reperfusion abnormalities. Our results showed that postprocedural MBG 0 and 1, absent STR, and TFC were significant in patients with NAFLD group, whereas TIMI flow was insignificant between both groups. Moreover, in our studied patients, NAFLD was correlated with high syntax I score and multivessel CAD. Finally, NAFLD was an independent predictor of in-hospital and 6-month out-of-hospital cardiac events.

Our study revealed NAFLD prevalence of 46.3%, and this agreed with Perera *et al.*[16] who found that the prevalence of NAFLD was 46.7% among patients with

Figure 1



Survival analysis among both studied groups: There was no significant difference between NAFLD and non-NAFLD groups regarding survival analysis (5.95 vs. 6 months; *P*=0.28). NAFLD, nonalcoholic fatty liver disease.

Table 3 Outcome in the current study and parameters of reperfusion

	NAFLD group (*n*=111)	Non-NAFLD group (*n*=129)	*P*
Pain to balloon time (h)	5.17±1.98	4.75±1.66	0.40
GPIIb/IIIa inhibitor	52 (46.8)	42 (32.6)	0.05
Thrombus aspiration	25 (22.5)	37 (28.7)	0.17
Baseline TIMI flow			
0	99 (89.2)	104 (80.6)	0.25
1	6 (5.4)	10 (7.8)	
2	3 (2.7)	10 (7.8)	
3	3 (2.7)	5 (3.9)	
Infarct related artery			
LAD	65 (58.6)	74 (57.4)	0.50
RCA	28 (25.2)	38 (39.5)	
LCX	11 (9.9)	10 (7.7)	
Diagonal artery	1 (0.9)	4 (3.1)	
Obtuse marginal artery	6 (5.4)	1 (0.8)	
PDA	0	2 (1.6)	
MBG			
0	18 (16.2)	10 (7.8)	<0.001
1	74 (66.7)	40 (31)	
2	19 (17.1)	76 (58.9)	
3	0	3 (2.3)	
Postprocedural TIMI flow			
0	1 (0.9)	2 (1.6)	0.25
1	2 (1.6)	3 (2.3)	
2	14 (12.6)	7 (5.4)	
3	94 (84.7)	117 (90.7)	
Postprocedural TFC (%)	31.07±10.76	25.30±10.93	<0.001
Non-STR	50 (45)	14 (10.9)	<0.001
Use of stent	103 (92.8)	118 (91.5)	0.44
Multivessels CAD	63 (56.8)	23 (17.8)	<0.001
Syntax score	13.5225±4.02458	9.7674±3.49668	<0.001

Data were expressed in form of mean±SD, *n* (%). CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; NAFLD, nonalcoholic fatty liver disease; MBG, myocardial blush grade; PDA, posterior descending artery; RCA, right coronary artery; STR, ST-segment resolution; TFC, TIMI frame count. *P* value was significant if less than 0.05.

Table 4 Degree of agreement between two observers regarding myocardial blush grade

Grade of MBG	Observer B				*P*
	0	1	2	3	
Observer A					
0	22 (84.6)	6 (5.2)	0	0	*P*<0.001
1	4 (15.4)	103 (88.8)	7 (7.3)	0	
2	0	7 (6)	88 (91.7)	0	
3	0	0	1 (1)	2 (100)	

Data were expressed in form of *n* (%). MBG, myocardial blush grade. *P* value was significant if less than 0.05.

ACS. Moreover, it was comparable to the data from China in which NAFLD prevalence was 45.8% in patients with CAD [17].

In our study, 20.7 and 29.7% were obese and overweight, respectively, of patients with NAFLD. In other study, Perera *et al.*[16] reported that more than 80% of his population had a higher-than-normal waist circumference (12.5% were obese), reflecting the higher prevalence of central obesity.

Our results agreed with Emre *et al.*[18] and Keskin *et al.*[19] regarding MBG. Absent myocardial perfusion, absent STR, and postprocedural TFC were significant in patients with NAFLD, and this agreed with the findings of Emre *et al.*[18] and Keskin *et al.* [19]. It was noticed that in the majority of our patients, postprocedural TIMI flow was 3, and this also agreed with the findings of Emre *et al.*[18] and Keskin *et al.* [19]. On the contrary, our finding disagreed with Keskin *et al.*[19] regarding in-hospital reinfarction and stent thrombosis, as Keskin *et al.*[19] classified FLD into three subgroups (minimal, moderate, and severe FLD) and reported that grade 3 subgroup had greater incidence of in-hospital recurrent MI and stent thrombosis in contrast to grades 1 and 2 subgroups, in which they were insignificant when compared with non-FLD group. In our study, we could not classify our patients to subgroups of NAFLD because of small number of moderate NAFLD (21 patients with moderate lipid content and 90 patients with severe lipid content). In-hospital mortality was insignificant in our patients with NAFLD. On the contrary, Emre *et al.*[18] found that in-hospital mortality was significantly greater in patients with FLD more than 3.

Table 5 In-hospital and follow-up cardiac events in studied groups

	NAFLD group (*n*=111)	Non-NAFLD group (*n*=129)	*P*
In-hospital events			
Re-infarction	2 (1.8)	2 (1.6)	0.62
Stent thrombosis	3 (2.7)	3 (2.3)	0.85
VSR	1 (0.9)	0	0.46
Mortality	1 (0.9)	0	0.46
Follow up events			
HF-hospitalization	7 (6.3)	0	<0.001
Stent thrombosis	2 (1.8)	1 (0.8)	0.13
Mortality	10 (9)	0	<0.001

Data were expressed in form of *n* (%). HF, heart failure; NAFLD, nonalcoholic fatty liver disease; VSR, ventricular septal rupture. *P* value was significant if less than 0.05.

Table 6 Predictors of follow-up events, absent myocardial blush grade, and absent ST-segment resolution

	OR	95% CI	*P*
For follow-up cardiac events			
KILLIP class >1	3.91	1.04-14.60	0.04
NAFLD	12.97	1.56-22.03	<0.001
Multivessel disease	3.33	0.16-6.56	0.03
Pain to balloon (>4 h)	2.03	0.76-4.45	0.04
Anterior wall infarction	2.32	1.11-4.56	0.02
For absent myocardial blush			
NAFLD	2.61	0.95-2.73	0.02
Multivessel CAD	1.23	0.66-2.30	0.03
Pain to balloon (>4 h)	1.30	0.73-2.30	0.01
Anterior wall infarction	2.22	1.23-4.03	<0.001
For absent ST-segment resolution			
NAFLD	6.94	3.84-14.14	<0.001

CAD, coronary artery disease; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OR, odd's ratio. *P* value was significant if less than 0.05.

Regarding MBG, our results were comparable to the findings of Emre *et al.*[18] in which postprocedural MBG 0 and 1 were significantly higher in FLD group more than 3, and MBG 3 was significantly higher in FLD group less than 3. Moreover, Emre *et al.*[18] reported that FLD more than 3 group was an independent predictor of absent MBG and absent STR.

Regarding HF hospitalization and post-procedural LVEF, our finding was comparable to the findings reported by Emre *et al.*[18] Moreover, we agreed with Keskin *et al.*[19] regarding follow-up mortality. Our study was concordant with the findings of Musso *et al.* [20], who confirmed that NAFLD was strongly associated with an increased risk of fatal and nonfatal cardiovascular events.

Our study has some limitations like the use of abdominal ultrasonography for assessing and classifying NAFLD and non-NAFLD patients, as liver histology and fibro scan were unavailable. Moreover, one of our limitation was subgrouping of patients with NAFLD because of the small number of moderate NAFLD cases. We recommended that abdominal ultrasound could be done for every patient with STEMI to provide us another predictor of future outcome of patients with STEMI treated with PPCI.

Conclusions

NAFLD has a bad outcome on epicardial and myocardial perfusion in the setting of patients with STEMI treated with PPCI. Patients with NAFLD had a higher frequency of multivessel disease and coronary affection and are associated with in-hospital and follow-up cardiac events compared with patients without NAFLD. NAFLD is considered an independent risk factor for the occurrence of in-hospital and follow-up adverse cardiac events.

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Authors Contributions: M.A. contributed to the conception, design of the work, selection, and clinical examination of patients. A.N.M.A.H. contributed to the conception, design of the work, selection and clinical examination of patients, acquisition and analysis, and creation of new software used in the work. H.A. contributed toward supervision, acquisition and analysis, reviewing, and interpretation of data. M.A.A.A. contributed to design of the work and selection and clinical examination of patient. Y.T.K. contributed to supervision, conception, acquisition and analysis, reviewing, and interpretation of data.

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Conflicts of interest

There are no conflicts of interest.

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