Effect of non-alcoholic fatty liver disease on outcome of primary pci in non-diabetic stemi patients.

Running title: Fatty liver disease and myocardial reperfusion.

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Abstract

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

Methods: 240 non-diabetic patients with STEMI were recruited and underwent PPCI. After revascularization, epicardial reperfusion had been assessed by Thrombolysis in myocardial infarction (TIMI) flow grades (TFG) and TIMI frame count (TFC), and myocardial reperfusion had been assessed by TIMI myocardial perfusion grade (TMP) and ST-segment resolution (STR). NAFLD had been assessed and graded based on abdominal ultrasonography 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 > I was significant in NAFLD group (24 (P< 0.001). Multi-vessel coronary artery disease (CAD) was significant in NAFLD group (63 (56.8%) vs. 23 (17.8%); P< 0.001). Eleven patients of NAFLD group died with no deaths occurred in the other group. Post-procedural myocardial blush grade (MBG) zero and 1 were significant in patients with NAFLD group (P< 0.001). Also, absent STR and TFC 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 non-diabetic patients.

Key words: ST-segment elevation myocardial infarction, non-alcoholic fatty liver disease, primary percutaneous coronary intervention, myocardial perfusion, epicardial perfusion.

Introduction

NAFLD is a common liver disease [(1)]. Diabetes mellitus, insulin resistance, hyperlipidaemia and obesity are predisposing factors for CAD and NAFLD [(2)]. NAFLD increase the risk of acute myocardial infarction (MI) and cardiovascular mortality [(3)]. MBG and STR are two validated measurements of myocardial perfusion and have incremental prognostic value beyond TIMI 3 flow in patients with STEMI [(4)].

This work was designed to study the impact of NAFLD on epicardial and myocardial reperfusion as well as in-hospital and six months out of hospital major adverse cardiac events (MACE) in non-diabetic STEMI patients treated with PPCI.

Patients And Methods

A prospective cross-sectional study included a total number of 251 STEMI patients 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 X-ray system. 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 as hepatitis B or C infection and other condition that may 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 body mass index (BMI) were recorded. The following laboratory data were performed; lipid profile, fasting blood sugar, serum creatinine, alanine transaminase, and creatinine kinase-myocardial band (CK-MB).

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 super-positioning of the non-infarcted myocardium. The angiographic runs have to be long enough to allow filling of the venous coronary system. First; epicardial reperfusion assessed by TFG and TFC as the following: TFG included, Grade zero; no perfusion, Grade one; penetration without perfusion, Grade two; partial perfusion, Grade three; complete perfusion [(7)], then, TFC defined as the number of frames required for the dye to first opacify a standard distal landmark [(8)]. Second; myocardial reperfusion assessed by TMP and STR as the following: TMP Grade zero; Failure of dye to enter the microvasculature, TMP Grade one; Dye slowly enters but fails to exit the microvasculature, TMP Grade two; Delayed entry and exit of dye from the microvasculature, TMP Grade three; Normal entry and exit of dye from the microvasculature [(9)], then, STR: Electrocardiography (ECG) had been done on admission (first ECG) and 90 minutes (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 <70%; improved, residual ST-segment elevation > 70%; unchanged [(10)]. The angiographic data were analysed by 2 independent investigators. Also, syntax score I was calculated for all patients [(11)].

Diagnosis of NAFLD:

The ultrasonographic evaluation had 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 following: zero; normal bright, one; medium bright, a moderate lipid content and two; clearly bright, a severe lipid content and fatty liver) **[(12)]**.

Outcomes and follow up:

The primary outcome had 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 myocardial infarction and/or target lesion revascularization, cardiogenic shock and, stroke) in both groups of patients. For every patient post-procedural left ventricle ejection fraction (LVEF) had been measured by biplane Simpson method. All patients were followed for six months after hospital discharge for re-admission, re-infraction, and cardiovascular mortality.

Statistical analysis:

Data was collected and analysed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York), nominal data were expressed as frequency, while continuous data were

expressed as mean ± SD. We used Chi²-test, student t-test and Multivariate regression analysis. Confidence level was kept at 95%, P was considered significant if < 0.05.

Results

Our study included a total of 251 STEMI patients, we excluded 6 patients for a recently discovered diabetes mellitus, 2 patients who died within 24 hours because of left main thrombosis, one patient for aortic valve prostheses with embolization and 2 patients with acute stent thrombosis. The resulting 240 patients were classified based on abdominal U/S into; NAFLD group and included 111 (46.3%) patients and non-NAFLD group and included 129 (53.7%) patients. Demographic and laboratory data of studied patients is shown in Table 1. Our study revealed that KILLIP class > I, left ventricular failure and Post-procedural LVEF were significant in NAFLD patients (P< 0.001) (Table 2). Post-procedural MBG zero and 1 were significant in NAFLD patients while MBG 2 and 3 were significant in non-NAFLD patients (P< 0.001). Post-procedural TFC and Absent STR were also significant in NAFLD patients (P< 0.001). Multi-vessels disease and Syntax score I were significant in NAFLD patients (P< 0.001) (Table 3). In hospital MACE were insignificant in NAFLD patients. Heart failure hospitalization and Follow up mortality were significant while stent thrombosis was insignificant in NAFLD patients (Table 5). Predictors of MBG and follow up cardiac events included; NAFLD, multi-vessel disease, anterior wall infarct and pain to balloon time (> 4 hours) while NAFLD was the only predictor of absent STR (Table 6). Survival analysis was insignificant between two groups (figure 1).

List of abbreviations:

CAD	Coronary artery disease
ECG	Electrocardiography
FLD	Fatty liver disease
HF	Heart failure
MACE	Major adverse cardiac events
MBG	Myocardial blush grade
MI	Myocardial infarction
NAFLD	Non-alcoholic fatty liver disease
LVEF	Left ventricular ejection fraction
LVF	Left ventricular failure
PPCI	Primary-percutaneous intervention
STEMI	ST-segment elevation myocardial infarction
STR	ST-segment resolution
TFC	TIMI frame count
TFG	TIMI flow grades
TMP	TIMI myocardial perfusion

TABLES:

Table 1: Demographic and laboratory data of studied patients:

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
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 Obese Overweight	 55 (49.5%) 23 (20.7%) 33 (29.7%)	 64 (49.6%) 14 (10.9%) 51 (39.5%)	0.06
Smoking	71 (64%)	80 (62%)	0.43
Family history of CAD	3 (2.7%)	3 (2.3%)	0.54

Table 1: Demographic and laboratory data of studied patients: ***(Cont.)***

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
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 was expressed in form of mean (SD), frequency (percentage). P value was significant if < 0.05. **ALT**, alanine transaminase; **BMI**. Body mass index; **CAD**, coronary artery disease; **CK-MB,** creatine kinase-myocardial band; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **NAFLD**, Non-alcoholic fatty liver disease.

Table 2: Clinical and echocardiographic data in studied patients:

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
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

P value was significant if < 0.05. **LVF**. Left ventricular failure; **NAFLD**, Non- alcoholic fatty liver disease.

Table 3: Outcome in the current study and parameters of reperfusion:

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
pain to balloon time (hours)	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			0.25
0	99 (89.2%)	104 (80.6%)	
1	6 (5.4%)	10 (7.8%)	
2	3 (2.7%)	10 (7.8%)	
3	3 (2.7%)	5 (3.9%)	

Table 3: Outcome in the current study and parameters of reperfusion: *(Cont.)*

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
Infarct related artery			0.50
LAD	65 (58.6%)	74 (57.4%)	
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			< 0.001
0	18 (16.2%)	10 (7.8%)	
1	74 (66.7%)	40 (31%)	
2	19 (17.1%)	76 (58.9%)	
3	0	3 (2.3%)	
Post-procedural TIMI flow			0.25
0	1 (0.9%)	2 (1.6%)	
1	2 (1.6%)	3 (2.3%)	
2	14 (12.6%)	7 (5.4%)	
3	94 (84.7%)	117 (90.7%)	
Post-procedural 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
Multi-vessels CAD	63 (56.8%)	23 (17.8%)	< 0.001
Syntax score	13.5225± 4.02458	9.7674± 3.49668	<0.001

P value was significant if < 0.05. **CAD**, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery, **LVEF**, left ventricular ejection fraction; **NAFLD**, non-alcoholic fatty liver disease; PDA, posterior descending artery; RCA, right coronary artery; **TFC**, TIMI frame count.

Table 4: Degree of agreement between two observers as regarding MBG:

Grade of MBG		Observer B				P value
		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%)	

P value was significant if < 0.05. MBG, myocardial blush grade.

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

	NAFLD group (n= 111)	Non-NAFLD group (n= 129)	P value
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

value was significant if < 0.05. **HF**, heart failure; **NAFLD**, Non- alcoholic fatty liver disease; **VSR**, ventricular septal rupture.

Table 6: Predictors of follow up events, absent MBG and absent STR:

	OR	95%CI	P value
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
Multi-vessel disease	3.33	0.16- 6.56	0.03
pain to balloon (> 4 hour)	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
Multi-vessel CAD	1.23	0.66- 2.30	0.03
pain to balloon (> 4 hour)	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

P value was significant if < 0.05. **OR**, odd's ratio; **CI**, confidence interval; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease.

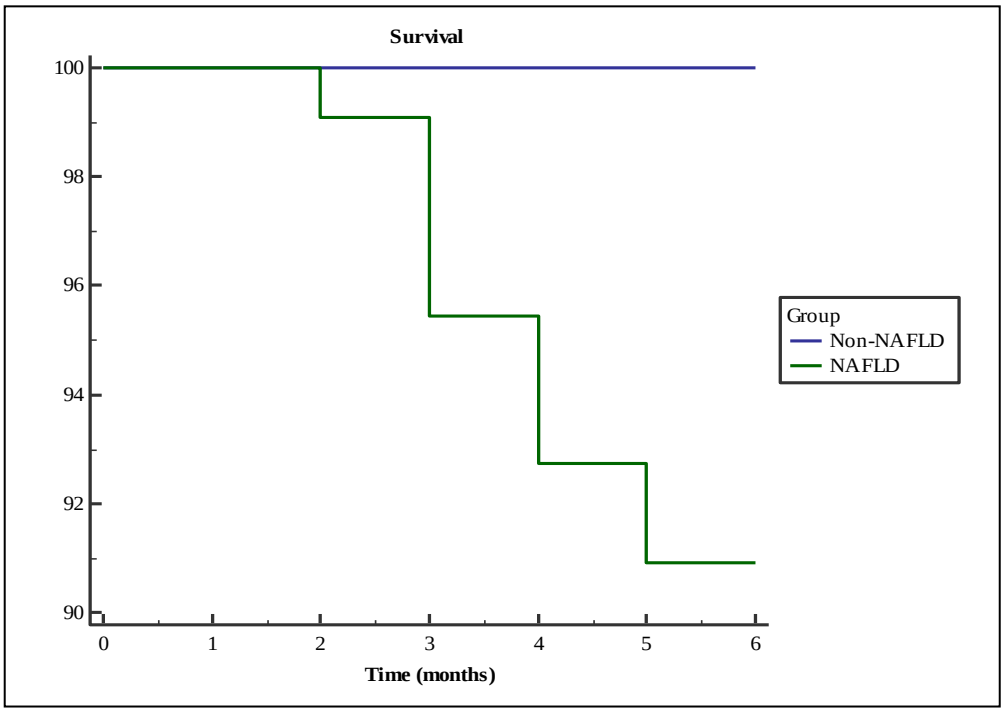

Figure 1: Survival analysis among both studied groups:
There was no significant difference between NAFLD and non-NAFLD group as regard survival analysis (5.95 vs. 6 months; P= 0.28).

Discussion

Several pathophysiologic mechanisms could be postulated by which FLD contributes to impaired microvascular flow. 1; FLD is associated with an increased inflammatory state, as C-reactive protein, which mainly produced by the liver has been shown to be increased in patients with FLD (13). 2; 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). 3; Increased endothelial dysfunction in patients with FLD may also contribute to impaired myocardial perfusion (15). 4; 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 post-procedural MBG zero and 1, absent STR and TFC were significant in patients with NAFLD group while TIMI flow was insignificant between both groups. Also, in our studied patients, NAFLD was correlated with high syntax I score and multi-vessel CAD. Finally, NAFLD was an independent predictor of in-hospital and six months out of hospital cardiac events.

Our study revealed NAFLD prevalence of 46.3% and this agreed with Perera et al who found that the prevalence of NAFLD was 46.7 % among ACS patients (16). Also, it was comparable to 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 NAFLD patients, in other study, Perera et al 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 (16).

Our results agreed with Emre A et al and Keskin M et al as regards MBG (18,19). Absent myocardial perfusion, absent STR and post-procedural TFC were significant in NAFLD patients and this agreed with Emre A et al (18) and Keskin M et al (19) finding. It was noticed that in the majority of our patients, post-procedural TIMI flow was 3, and this is also agreed with Emre A et al (18) and Keskin M et al finding (19). On the other side our finding disagreed with Keskin M et al as regard in-hospital reinfarction and stent thrombosis as Keskin M et al classified FLD to 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 grade 1 and 2 subgroups in which they were insignificant when compared with non-FLD group (19). In our study we couldn't 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 NAFLD patients, on the other side Emre et al found that in-hospital mortality was significantly greater in patients with FLD >3 (18).

AS regard to MBG our results were comparable to Emre A et al finding in which post-procedural MBG zero and 1 were significantly higher in FLD group > 3 and MBG 3 was significantly higher in FLD group < 3. Also, Emre et al reported that FLD> 3 group was an independent predictor of absent MBG and absent STR (18).

As regard to HF hospitalization and post-procedural LVEF our finding was comparable to finding reported with Emre A et al (18). Also, we agreed with Keskin M et al as regard to follow up mortality (19). Our study was concordant with Musso et al finding who confirmed that NAFLD was strongly associated with an increased risk of fatal and non-fatal cardiovascular events (20).

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. Also, one of our limitation was subgrouping of NAFLD patients because of small number of moderate NAFLD. We recommended that Abdominal ultrasound could be done to every patient with STEMI to provide us another predictor of future outcome of STEMI patients treated with PPCI.

Conclusions

NAFLD has a bad outcome on epicardial and myocardial perfusion in the setting of STEMI patients treated with PPCI. Patients with NAFLD had a higher frequency of multi-vessels, coronary affection and associated with in-hospital and follow up cardiac events compared to 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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