Comparison of Primary Percutaneous Coronary Intervention outcomes in patients with fatty liver Versus patients without fatty liver in ST- Segment Elevation Myocardial Infarction

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Abstract

Background: Limited data exist on the effect of nonalcoholic fatty liver disease (FLD) in the setting of acute coronary syndromes.

Aim: The aim of this study was to evaluate the impact of FLD on myocardial perfusion and six months of follow-up for major adverse cardiac events (MACE) in the setting of ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Subjects and Methods: We studied 122 patients (mean age 57 + 11 years and 88% were men) who underwent primary PCI for STEMI by abdominal ultrasound within 72 hours of admission. FLD was graded according to a semi-quantitative severity score as mild (score <3) or moderate to severe (score ≥3). Myocardial perfusion was determined by measuring myocardial blush grade (MBG) and ST-segment resolution (STR) analysis. Patients were divided into 2 groups according to FLD score (<3 or ≥3).

Results: Patients with FLD score ≥3 were more likely to have multivessel disease (39% vs22% p = 0.032), absent myocardial perfusion (MBG 0/1, 58% vs 19%, p <0.0001), lower prevalence of post-procedural Thrombolysis In Myocardial Infarction (TIMI) 3 flow grade in the group with FLD ≥3 (62% vs 80%, p = 0.033), but no difference in the in-hospital MACE rate (17% vs 12%, p = 0.39).

Conclusions: we concluded that the presence of FLD score ≥3 in STEMI patients treated with primary PCI correlated significantly with poor perfusion outcomes as assessed by both reduced MBG and TIMI flow score and lower EF both in-hospital and at six-months follow-up. However, we found no statistically significant increase in MACE rates both in-hospital and at follow up after six months.

Keywords: Fatty liver, Myocardial infarction, Coronary intervention

Introduction

Non-alcoholic fatty liver disease has emerged as a growing public health problem worldwide, because many patients with more severe forms of nonalcoholic fatty liver disease will have major cardiovascular events and will ultimately die from cardiovascular disease before advanced liver disease develops.[1]

In the new ERA, primary PCI became the preferred treatment for opening of the infarct related artery in patients presenting with acute STEMI, however microvascular obstruction with diminished myocardial perfusion occurs in a large proportion of patients with patent epicardial vessel, which is associated with an increased infarct size, reduced recovery of ventricular function and increased mortality. [2]

Limited data exist on the role of non-alcoholic fatty liver disease (FLD) as a potential independent risk factor in the setting of acute coronary syndromes. We found that despite similar high rates of Thrombolysis

In Myocardial Infarction 3 after primary PCI, these patients with Fatty Liver Disease FLD score ≥3 are more likely to have impaired myocardial perfusion which may contribute to adverse in-hospital outcome. [3] The global incidence rate of acute myocardial infarction AMI was 8.6 million.[4] According to Euro Heart Survey, the in-hospital mortality rate of patients with STEMI ranges from 6% to 14%.[5]The objective of primary PCI is to restore normal blood flow in the infarct-related artery. Previous studies have shown that preservation of the microcirculation is critical for a positive clinical outcome. Several diagnostic techniques have been employed to evaluate tissue-level microvascular perfusion in the last decade. Thrombolysis in Myocardial Infarction (TIMI) grades correlate with the final infarct size in patients with AMI treated with thrombolysis. However, the TIMI flow cannot be used as reliable markers of myocardial tissue perfusion after reperfusion therapy.[6] Despite normal coronary patency, tissue perfusion may be impaired or absent. Myocardial blush grade (MBG) has been well validated as an angiographic technique to assess myocardial perfusion in patients with STEMI. It is strongly related to prognosis in patients undergoing primary PCI for STEMI.[7]

MATERIALS AND METHODS

This study was a prospective observational study. It was conducted at Al-Fayoum University and Dar Al Fouad hospitals from 01/06/2017 to 01/06/2019. It included 122 patients presenting to the ER with acute STEMI for primary PCI. The patients were divided into 2 groups; Group A that included 53 patients with fatty liver and Group B that included 69 patients without fatty liver.

Inclusion criteria:

- Patients from both genders at any age presenting to ER with STEMI within 12 hours from the beginning of chest pain.

Exclusion criteria:

- Patients presenting to ER after 12 hours from the beginning of chest pain.
- Patients with end stage liver disease.

Every patient was subjected to the following:

- **History taking with special stress on** risk factors for coronary artery disease including:

a- Smoking:[8]

b- Hypertension:[9]

c- Diabetes Mellitus: [10]

d- Family history:[11]

e- Dyslipidemia [12]

- **General and Local examination**
- **Laboratory investigations including:**

Three sets of Creatine kinase MB (ck-MB) and high sensitivity Troponin quantitative assessment by obtaining serum specimen anticoagulated with EDTA and centrifuged on admission, after 8 hours and after 16 hours then daily untill normalisation**.**

- Twelve lead ECG in the ER and every 8 hours for the first 24 hours. ECG criteria to diagnose STEMI were used according to European society of cardiology. [13]
- Assessment of left ventricular function by transthoracic echocardiography was done once during admission and another time after six months using a GE S6 machine by an S4-2 probe with frequency ranging from 1 to 4 MHz. The left ventricular ejection fraction (LVEF) was calculated according to the American Society of Echocardiography by using modified Simpson's method.[14] In addition, the wall motion score index (WMSI) was used where contractility of the individual segments was scored as follows: 1- normal or hypercontractile; 2- hypokinesia; 3- akinesia; 4- dyskinesia. The WMSI was calculated by dividing the sum of the score of each segment by the number of visualized segments. [15]
- All patients were given 300mg of Aspirin and 180mg of Ticagerlor as loading dose on admission.

- All primary PCI procedures were performed using femoral or radial approaches with a 6-French left guiding catheter, At the start of the procedure, intravenous unfractionated heparin 10000 IU was given. The number of vessels affected were noted as well as the severity and sites of all lesions.
  - The blood flow in the infarct-related artery (IRA) was graded according to the Thrombolysis in Myocardial Infarction (TIMI) grading system in several orthogonal views to obtain TIMI flow grades, which are graded from 0-3 according to levels of coronary blood flow assessed during PCI.[16]
  - We also assessed myocardial perfusion using myocardial blush grade which was performed visually with a cine-film at a 25 frame/s rate in the left lateral position, MBG was defined as: 0: (No myocardial blush or contrast) to 3: Normal myocardial blush or contrast density, comparable to that of a non-infarct related artery. [17]
- Abdominal ultrasound within 72 hrs of admission to assess the presence and severity of FLD using 3.5-MHz scanner attached to a high-resolution ultrasound machine (Philips). The presence of FLD was diagnosed when the liver-kidney difference was >0. The severity of FLD was graded semi-quantitatively according to a scale from 0 to 8 points, on the basis of liver-kidney differences (0 to 3 points), deep attenuation (0 to 1 point), blurring of diaphragm (0 to 1 point) and/or of the hepatic vein (0 to 1 point) and/or of the gallbladder wall (0 to 1 point), and the presence of focal sparing (0 to 1 point).[18]
- Follow up was done for six months after discharge using clinical follow up, major adverse cardiac events (MACE), as re-infraction, stroke, and acute heart failure. In- hospital mortality had been recorded.
- Follow up of statin intolerance was also done, looking for myopathy (muscle pains with elevated serum CK > 4 ULN), or elevated liver enzymes (ALT > 3 ULN).[12]
- Assessment and follow up of mitral regurgitation by transthoracic echocardiography was done during admission and after six months. This was done using the vena contracta, and measuring regurgitant jet area indexed to left atrial area [19]

RESULTS

1. Demographic data

There was no statistically significant difference between mean age values and gender distribution in the two groups (*P*-value = 0.346 &0.094, Effect size = 0.173&1.578 respectively). Females are 1.578 folds more prone to fatty liver than males.

2. Risk Factors

There was no statistically significant difference between prevalence of hypertension, DM , Dyslipidemia , family history of premature coronary artery disease and Smoking in the two groups

In the two groups (*P*-value = 0.064, 0.061, 0.144 , 0.745 and 0.893 respectively)

3. TIMI flow

Patients with fatty liver showed significantly lower mean TIMI flow scores than those without fatty liver (*P*-value = 0.020).

There was a statistically significant higher prevalence of post-procedural TIMI 3 flow in non-fatty liver group 79.7% vs 62.2% in fatty liver group, (P-value: 0.033).

4. MBG scores

Patients with fatty liver showed significantly lower mean MBG scores than those without fatty liver (*P*-value <0.001).

The prevalence of absent myocardial perfusion (MBG 0/1) showed a statistically significant higher prevalence in fatty liver group 58.5% vs 18.8% in fatty liver group, (P-value: 0.0001).

5. Wall Motion Score Index (WMSI)

At baseline as well as after 6 months; patients with fatty liver showed statistically significantly higher mean WMSI scores than those without fatty liver (*P*-value = 0.041 and 0.016, respectively).

As regards the changes in WMSI after 6 months; there was no statistically significant change in WMSI scores after 6 months in each group (*P*-value = 0.506 and 0.317), respectively.

6. Ejection Fraction (EF)

At base line as well as after 6 months; patients with fatty liver showed statistically significantly lower mean EF than those without fatty liver (*P*-value = 0.020) and (*P*- value = 0.015), respectively.

As regards the changes in EF after 6 months; there was no statistically significant change in EF after 6 months in each group (*P*-value = 0.932 and 0.362), respectively.

7. Follow up Echo

There was no statistically significant difference between follow up Echo findings in the two groups (*P*-value = 1).

8. LMCA

There was no statistically significant difference between LMCA in the two groups (*P*- value = 0.926).

9. Cardiac Enzymes

There was no statistically significant difference between mean peak CKMB and peak Troponin in the two groups (*P*-value = 0.435 and 0.485), respectively.

10. Multivessel disease

There was a statistically significant difference between prevalence of Multivessel coronary disease in the two groups (*P*-value = 0.0318)

11. Individual MACE

There was no statistically significant difference between prevalence of death, heart failure and myocardial infarction in the two groups (*P*-value = 1, 0.394 and 0.132), respectively.

12. Statin intolerance

Patients with fatty liver showed statistically significantly higher mean initial ALT than those without fatty liver (*P*-value = 0.005). As regards prevalence of statin intolerance, there was no statistically significant difference between the two groups (*P*-value <0.092).

Table 1: Demographic data of the two groups

Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (d)*
Mean	SD	Mean	SD		
57.9	10.3	56	11.4	0.346	0.173

**: Significant at P ≤ 0.05*

Table 2: Descriptive statistics and results of Chi-square test for comparison between gender distribution in the two groups

Gender	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Male	44	83	64	92.8	0.094	1.578
Female	9	17	5	7.2		

**: Significant at P ≤ 0.05*

Table 3: Descriptive statistics and results of Chi-square test for comparison between prevalence of hypertension in the two groups

Hypertension	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Yes	32	60.4	30	43.5	0.064	1.981
No	21	39.6	39	56.5		

**: Significant at P ≤ 0.05*

Table 4: Descriptive statistics and results of Chi-square test for comparison between prevalence of Diabetes mellitus in the two groups

Diabetes mellitus	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Yes	29	54.7	26	37.7	0.061	1.998
No	24	45.3	43	62.3		

**: Significant at P ≤ 0.05*

Table 5: Descriptive statistics and results of Chi-square test for comparison between prevalence of Dyslipidemia in the two groups

Dyslipidemia	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Yes	16	30.2	13	18.8	0.144	1.863
No	37	69.8	56	81.2		

**: Significant at P ≤ 0.05*

Table 6: Descriptive statistics and results of Fisher's Exact test for comparison between prevalence of family history in the two groups

Family history	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Yes	5	9.4	5	7.2	0.745	1.333
No	48	90.6	64	92.8		

**: Significant at P ≤ 0.05*

Table 7: Descriptive statistics and results of Chi-square test for comparison between prevalence of smoking in the two groups

Smoking	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value	*Effect size (OR)*
	n	%	n	%		
Yes	26	49.1	33	47.8	0.893	1.051
No	27	50.9	36	52.2		

**: Significant at P ≤ 0.05*

Table 8: Descriptive statistics and results of Mann-Whitney U test for comparison between TIMI flow scores in the two groups

Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
3 (0 – 3)	2.47 (0.82)	3 (0 – 3)	2.73 (0.71)	0.02

**: Significant at P ≤ 0.05*

Table 9: Descriptive statistics and results of Chi-square test for comparison between prevalence of TIMI 3 flow in the two groups

Fatty liver (n = 53)			No fatty liver (n = 69)		*P*-value
	n	%	n	%	
TIMI 3	33	62.2	55	79.7	0.033
TIMI < 3	20	37.8	14	20.2	

**: Significant at P ≤ 0.05*

Table 10: Descriptive statistics and results of Mann-Whitney U test for comparison between MBG scores in the two groups

Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
1 (0 – 3)	1.45 (0.93)	2 (0 – 3)	2.15 (0.83)	<0.001*

**: Significant at P ≤ 0.05*

Table 11: Descriptive statistics and results of Chi-square test for comparison between prevalence of no-reflow phenomenon (MBG 0/1) in the two groups

	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	N	%	n	%	
MBG 0/1	31	58.5	13	18.8	0.0001
MBG 2/3	12	41.5	56	81.2	

**: Significant at P ≤ 0.05*

Table 12: Descriptive statistics and results of Mann-Whitney U test for comparison between WMSI scores in the two groups and Wilcoxon signed-rank test for the changes within each group

Time	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
Base line	1.5 (1 – 2.12)	1.5 (0.3)	1.37 (1 – 2.18)	1.38 (0.31)	0.041*
6 months	1.5 (1 – 2.18)	1.5 (0.31)	1.37 (1 – 2.18)	1.37 (0.28)	0.016*
P-value	0.506		0.317		

**: Significant at P ≤ 0.05*

Table 13: Descriptive statistics and results of repeated measures ANOVA test for comparison between EF in the two groups as well as the changes in each group

**: Significant at P ≤ 0.05*

Time	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	Mean	SD	Mean	SD	
Base line	49.7	11.4	54.4	12.4	0.020*
6 months	54.1	11	59.2	11.3	0.015*
P-value	0.932		0.362		

Table 14: Descriptive statistics and results of Fisher's Exact test for comparison between follow up Echo findings in the two groups

Echo	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	n	%	n	%	
Dropped EF	0	0	1	1.4	
LV THR	0	0	1	1.4	1
Tampona de	1	1.9	1	1.4	
Normal	52	98.1	66	95.7	

**: Significant at P ≤ 0.05*

Table 15: Descriptive statistics and results of Chi-square test for comparison between LMCA in the two groups

LMCA	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	n	%	n	%	
Lesion	8	15.1	10	14.5	0.926
No lesion	45	84.9	59	85.5	

**: Significant at P ≤ 0.05*

Table 16: Descriptive statistics and results of Mann-Whitney U test for comparison between **peak** CE in the two groups

CE	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
Peak CKMB	146 (100 – 1623)	236.6 (245.2)	131 (34 – 1489)	214.6 (199.5)	0.435
Peak Troponin	2804 (230 – 10000)	4040 (3153.1)	2214 (110 – 10000)	3843.7 (3033.1)	0.485

**: Significant at P ≤ 0.05*

Table 17: Descriptive statistics and results of Chi-square test for comparison between prevalence of Multivessel disease in the two groups

Multivessel disease	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	n	%	n	%	
Yes	21	39.6	15	21.7	0.0318
No	32	60.4	54	78.3	

**: Significant at P ≤ 0.05*

Table 18: Descriptive statistics and results of Chi-square test and Fisher's Exact test for comparison between individual MACE in the two groups

MACE	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	n	%	n	%	
Death	0	0	1	1.4	1
Heart failure	9	17	8	11.6	0.394
Myocardial infarction	0	0	4	5.8	0.132

**: Significant at P ≤ 0.05*

Table 19: Descriptive statistics and results of Mann-Whitney U test for comparison between statins in the two groups

Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
46 (11 – 148)	57.8 (39.9)	26 (8 – 145)	35.9 (27.3)	0.005*

**: Significant at P ≤ 0.05*

Table 20: Descriptive statistics and results of Chi-square test for comparison between statin intolerance in the two groups

	Fatty liver (n = 53)		No fatty liver (n = 69)		*P*-value
	N	%	n	%	
Statin intolerance	17	32.1	13	18.8	<0.092

**: Significant at P ≤ 0.05*

DISCUSSION

The major findings of the present study were

(1) Patients with FLD score ≥3 were more likely to have abnormal myocardial perfusion as assessed by both reduced MBG and TIMI flow score.
(2) Patients with FLD score ≥3 had higher WMSI scores both in- hospital and at six-month follow-up.
(3) Patients with FLD score ≥3 had lower EF both in-hospital and at six-month follow-up.
(4) Patients with FLD score ≥3 had higher baseline ALT levels but didn't have statistically significant statin intolerance in the six-month follow-up.
(5) Patients with FLD score ≥3 were more likely to have multivessel disease (39.5% vs 22.1%).
(6) Patients with FLD score ≥3 had no statistically significant increased MACE rates both in-hospital and at follow up after six months.

Limited data exist on the impact of FLD in the setting of acute coronary syndromes. ***Boddi et al***[20] studied ninety-five non-diabetic STEMI patients and graded the NAFLD using a similar score to our study. They reported that NAFLD was associated with a three-fold risk of multivessel disease. There were also higher ALT levels in NAFLD group but did not reach statistical significance. However, unlike our study The TIMI 3 flow was similar in both groups. This difference could be attributed to the different study population and exclusion of diabetic patients.

In concordance with our findings, ***Emre et al***[3] studied 186 nondiabetic patients undergoing primary PCI for STEMI and graded the NAFLD using a similar score to our study. They found that Patients with NAFLD were more likely to have absent myocardial perfusion and was not independently associated with CVD death. However, they suggested that NAFLD was independently associated with increased in-hospital CVD events. And found no difference in post-procedural TIMI 3 flow grade between the 2 groups. The differences in results could be attributed to different patient population and different intervention technique as they used bare metal stents while in our study all stents were Everolimus and Sirolimus drug eluting stents.

Wong et al[21] conducted a prospective cohort on 612 patients undergoing coronary angiograms without known liver disease using ultrasonography. They found that NAFLD was associated with significant CAD needing percutaneous coronary interventions at baseline, similar to our study they found that NAFLD was not significantly associated with fatal and non-fatal CVD events. They had a contradictory finding that NAFLD was associated with lower CVD mortality which might be due to more interventions in the NAFLD group.

Keskin et al[22] studied NAFLD as a risk factor for coronary artery disease. The study group consisted of 360 patients with STEMI. The patients were classified according to a similar score to our study. Patients with NAFLD had higher rates of in-hospital mortality, stent thrombosis, and long-term mortality. Again, differences could be due to different study population and longer follow- up period of 3 years.

Sinn et al[23] conducted a retrospective cohort study, involving 111,492 adults over 40 years old, without history of CVD, liver disease, or cancer at baseline who participated in a regular health screening exam between 2003 and 2013. Fatty liver was diagnosed by ultrasonography. NAFLD was associated with an increased incidence of myocardial infarction independently of established risk factors. In addition, this association was similar in participants with and without evidence of more advanced NAFLD as indicated by the NFS. NAFLD patients may need to be carefully monitored and managed early to prevent myocardial infarction.

Similarly, ***Zeb et al***[24] conducted a prospective cohort study on 4119 participants free of CVD and known liver disease at baseline (The Multi-Ethnic Study of Atherosclerosis) using non-enhanced computed

tomography (N=728 with NAFLD) and found that NAFLD was independently associated with an increased all-cause death and nonfatal CVD events. Differences could be due to different patient population and longer follow up as patients were followed for a mean of 7.6 years.

Fracanzani et al[25] conducted a prospective cohort study including 125 patients with NAFLD and 250 age- and sex-matched control individuals without known liver diseases using ultrasonography. They found that NAFLD was independently associated with non-fatal CVD events. Differences could be due to different patient population and longer follow up as patients were followed for a mean of 10 years.

Not in contrary to our findings ***Kim et al***[26] had a population-based cohort, n=11154 adults (NHANES 1988-94) followed for 14.5 years, NAFLD diagnosed by using ultrasonography was not associated with increased all-cause and CVD mortality in the whole cohort. However, NAFLD with advanced hepatic fibrosis was independently associated with increased all-cause and CVD mortality.

El Azeem et al[27] had a Prospective observational cohort, n=1150 Egyptian subjects with normal liver function and without history of CVD (747 subjects completed the follow-up); using ultrasonography found that NAFLD was significantly associated with an increased risk of non-fatal CVD events. The patient population was different as the study excluded patients with CVD history and were followed-up for 3 years.

In line with our findings regarding the relation of NAFLD to Statin intolerance, ***Tikkanen et al***[28] concluded that high-dose atorvastatin was safe in patients with abnormal liver tests, probably because of NAFLD, reduced transaminase levels, and also reduced MACE twice more in these patients compared with those with normal liver biochemistry.

Kothari et al[29] stated that Statins reduce the risk of cardiovascular morbidity and mortality in patients with NASH and dyslipidemia and stated that comprehensive review of the safety and efficacy of statins in patients with chronic liver disease, including patients with NAFLD, concluded that statins were safe for the management of dyslipidemia in patients with NASH.

In the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study 1600 patients with coronary heart disease, followed-up for a mean of 3 years, a post hoc analysis showed that statin therapy reduced the risk for MACE by 68% in patients with abnormal liver tests[30]. Furthermore, this statin-related relative risk reduction was greater in patients with abnormal liver tests than in those with normal liver tests. Therefore, they concluded that Statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild-to-moderately abnormal liver tests that are potentially attributable to non-alcoholic fatty liver disease.

Targher et al[31] conducted another study that found the prevalence of FLD in nondiabetic patients with STEMI was relatively high and similar to the prevalence found in diabetic and obese patients in general population in Western countries. He found that patients with moderate-to-severe FLD were younger, had a greater occurrence of multivessel disease, and showed atherogenic dyslipidemia

Conclusions: we concluded that the presence of FLD score $\geq$3 in STEMI patients treated with primary PCI correlated significantly with poor perfusion outcomes as assessed by both reduced MBG and TIMI flow score and lower EF both in-hospital and at six-months follow-up. However, we found no statistically significant increase in MACE rates both in-hospital and at follow up after six months

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