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ORIGINAL ARTICLE

Patients with non-obstructive coronary artery disease admitted with acute myocardial infarction carry a better outcome compared to those with obstructive coronary artery disease

Yasser Yazied Abdelmonem *, Adel Abdelgawad Bakr, Hossam Ghanem El-Hossary, Mohammed Mahmoud Abdel Ghany

Kasr Alainy, Department of Cardiology, Cairo University Hospitals, Cairo, Egypt

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Abstract *Background:* The characterization of patients who have acute myocardial infarction (AMI) and insignificant coronary stenosis is unclear.
Aim: The present study aimed to investigate the clinical profile, in-hospital and 3-month outcome of AMI patients with insignificant coronary stenosis in comparison with those with significant disease.
Methods: This prospective observational study included 200 consecutive patients admitted with AMI. Group I (100 patients) included patients with insignificant CAD (all lesions $<50\%$ stenosis). Group II (100 patients) included patients with one or more lesions $>70\%$ stenosis. Patients with previous CABG were excluded. Patients with significant CAD had successful total revascularization.
Results: Patients with insignificant CAD were significantly younger (61 vs. 67 years, $p < 0.001$), more likely to be females (41% vs. 23%, $p = 0.006$), less likely to smoke ($p = 0.006$), less likely to have diabetes mellitus ($p < 0.001$), and less likely to have history of CAD ($p = 0.042$) or prior PCI ($p = 0.037$). They were also less likely to have typical anginal pain at presentation (61% vs 91%, $p < 0.001$), less likely to have heart failure at presentation (9% vs 30%, $p < 0.001$), less likely to have ischemic ST-segment changes on presentation (10% vs 46%, $p < 0.001$), lower peak troponin ($p < 0.001$) and CK-MB levels ($p < 0.001$), with lower LDL-C ($p = 0.006$), and higher HDL-C level ($p = 0.020$). They were less likely to be treated with b-blockers ($p = 0.002$), ACEI/ARBS ($p = 0.007$), and higher rates of calcium channel blocker therapy ($p < 0.001$). They had lower prevalence of major adverse clinical events at follow-up (readmission for ACS ($p = 0.009$), need for revascularization ($p = 0.035$), recurrent chest pain ($p = 0.009$), and cardiogenic shock ($p = 0.029$).

* Corresponding author at: 11 saudia Blds, Nozha Street, PO Box: 11371, Cairo, Egypt.
E-mail address: yyazied@kasralainy.edu.eg (Y.Y. Abdelmonem).

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Conclusion: Patients with AMI and insignificant CAD have different clinical profile and outcome compared to those with significant disease.

1. Introduction

Acute coronary syndrome (ACS) is the leading cause of death in the United States, and translates to 17% of the national health expenditure. An important subset of ACS patients is reported to have either normal coronaries (NCs) or non-obstructive coronary artery disease (NOCAD, defined as narrowing <50% lumen diameter) on angiography, with a reported prevalence of (10%).[1]

The etiology and pathogenesis of MI with angiographically normal coronary arteries are still a matter of debate. MI without obstructive CAD (MINOCA) has been reported to be due to plaque disruption, plaque erosion, vasospasm, embolism, spontaneous coronary dissection, and other causes. In addition, transient left ventricular dysfunction syndrome (takotsubo syndrome) is a form of MI without obstructive CAD and may be due to plaque disruption, vasospasm, catecholamine toxicity, autonomic dysfunction, or a combination of these or other causes. Furthermore, myocarditis can present clinically as a syndrome meeting the universal definition of MI, with symptoms potentially attributable to ischemia, ECG changes, and biomarker elevation.[2] Endothelial dysfunction may be an underlying common feature predisposing to the acute event. Additional explanations result in symptoms that may be confused with ACS include, non-ischemic cardiac conditions including pericarditis, aortic dissection and non-cardiac conditions (pulmonary embolism, musculoskeletal causes, reflux esophagitis, esophageal spasm, gastritis or psychosomatic pain).[3]

Clinical history, ECG, cardiac enzymes, echocardiography, and coronary angiography, represent the first-level diagnostic investigations to identify the causes of MINOCA.[4] Imaging modalities such as intravascular ultrasound, optical coherence tomography, CT angiography, and MRI should also be considered to differentiate between plaque rupture, plaque erosion, myocarditis, cardiomyopathy, and takotsubo syndrome.[5] Compared with patients with obstructive CAD, patients with non-obstructive CAD experienced lower rates of major cardiac events but remained at substantial risk and should be treated accordingly.[6]

2. Methods

This prospective observational study included 200 consecutive patients admitted with the diagnosis of AMI to coronary care unit of the Cardiovascular Department in Saudi German Hospital, Riyadh, Saudi Arabia. The study was carried out from June 2013 to May 2015. All cases underwent coronary angiography and were classified into 2 groups: **Group I:** Included 100 patients presented with AMI and angiographically normal or insignificant CAD (lumen diameter <50%)[7] and **Group II (control group)**: Included 100 patients presented with AMI and angiographically significant CAD who underwent successful total revascularization.

2.1. Inclusion criteria

Patients included in our study are those patients presenting with AMI whether ST-segment or non ST-segment elevation myocardial infarction.

2.2. Exclusion criteria

1. Patients with contraindications or who did not undergo cardiac catheterization.
2. Previous CABG.
3. Patients who received thrombolytic therapy.

2.3. Data collection

For the determination of factors associated with insignificant CAD, a standard list of patient characteristics was entered into a multivariable model. The list consisted of age, gender, race, body mass index, diabetes, hypertension, smoking status, family history of CAD, prior myocardial infarction, prior congestive heart failure, prior percutaneous coronary intervention, signs of congestive heart failure at presentation, renal insufficiency, prior stroke, hyperlipidemia, systolic blood pressure, heart rate.

Electrocardiogram was done for all patients for ST segment changes, arrhythmia, and reperfusion after PCI.

Echocardiography to evaluate global and regional left ventricular function.

2.4. Primary outcome

(1) *In-hospital outcome:* Mortality, recurrent angina, development of heart failure, cardiogenic shock, significant arrhythmia requiring treatment.
(2) *Outcome after 3 month follow-up:* Follow-up data were obtained by phone calls, or by periodic outpatient visits up to 3 months for the occurrence of MACE: Cardiac mortality, recurrent ACS, need for revascularization (PCI or CABG), and hospitalization for acute coronary syndromes.

2.5. Secondary outcome

Assess the clinical and laboratory profile of patients with insignificant CAD.

2.6. Statistical analysis

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 14 (MedCalc© Software bvba, Ostend, Belgium). The

D'Agostino-Pearson test was used to examine the normality of numerical data distribution. Owing to marked skewness of their frequency distribution, numerical data were presented as median and interquartile range and inter-group differences were compared non-parametrically using the Mann-Whitney U test. Categorical data were presented as number and percentage and between-group differences were compared using the Pearson chi-squared test or Fisher's exact test, when appropriate. Ordinal data were compared using the chi-squared test for trend.

Multivariable binary logistic regression was used to determine independent predictors of non-significant CAD. Variables found to be significantly associated with the outcome variable by univariable analysis were included in the multivariable regression model. The backward method was used to build up the final model excluding variables that were found not to be independent determinants for the outcome measure. Survival analysis was done using the Kaplan-Meier method. Separate curves were plotted for patients with significant or non-significant CAD, and the log-rank test was used to compare individual Kaplan-Meier curves. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

As regards demographics and clinical characteristics, patients with insignificant CAD were significantly younger (56 (50.0–61.5) vs. 65 (59.0–71.0) years, $p < 0.001$), more likely to be female (41 vs. 23%, $p = 0.006$), more often non-white ($p = 0.032$), less likely to smoke ($p = 0.006$), less likely to have diabetes mellitus ($p < 0.001$), and less likely to have history of CAD ($p = 0.042$) or PCI ($p = 0.037$). However there was no significant difference between both groups regarding other traditional CAD risk factors (hypertension, dyslipidemia, and premature family history of CAD). Also there was no statistically significant difference as regards obesity, history of substance abuse, history of heart failure, anti-ischemic therapy, renal insufficiency, peripheral vascular disease and history of ischemic strokes (Table 1).

Table 1 Demographics and clinical characteristics between non-significant (Group I) and significant (Group II) CAD.

Variable	Group I (n = 100)	Group II (n = 100)	p-value
Age, yr	56 (50.0–61.5)	65 (59.0–71.0)	**<0.001**
Age < 55 yr	44 (44.0%)	21 (21.0%)	**0.001**
Female Gender	41 (41.0%)	23 (23.0%)	**0.006**
Non-white race	51 (51.0%)	36 (36.0%)	**0.032**
BMI > 30 kg/m^2	4 (4.0%)	6 (6.0%)	0.516
Current smoking	29 (29.0%)	48 (48.0%)	**0.006**
History of substance abuse	4 (4.0%)	1 (1.0%)	0.369
History of CAD	9 (9.0%)	19 (19.0%)	**0.042**
History of PCI	4 (4.0%)	11 (11.0%)	**0.037**
History of heart failure	6 (6.0%)	8 (8.0%)	0.579
Anti-ischemic therapy	9 (9.0%)	18 (18.0%)	0.063
Family history of CAD	16 (16.0%)	12 (12.0%)	0.415
Type II DM	36 (36.0%)	61 (61.0%)	**<0.001**
Hypertension	52 (52.0%)	50 (50.0%)	0.777
Dyslipidemia	45 (45.0%)	49 (49.0%)	0.571
Renal insufficiency	4 (4.0%)	5 (5.0%)	1.000
Peripheral vascular disease	0 (0.0%)	2 (2.0%)	0.497
History of stroke	0 (0.0%)	2 (2.0%)	0.497

Data are presented as median (interquartile range) or number (%).

3.2. Clinical presentation

At presentation, group I patients were significantly less likely to present with typical chest pain (61 vs 91%, $p < 0.001$) and Killip Class $\geq$ II (9 vs. 30%, $p < 0.001$). However there was no significant difference between both groups as regards blood pressure and heart rate.

3.3. Electrocardiography (ECG) on admission

Regarding the electrocardiography, patients with insignificant CAD were significantly less likely to have ischemic ST-segment changes on presentation (46% with no ST-T changes) compared with 10% in the significant group ($p < 0.001$), and these patients less likely to have ST-segment elevation (9 vs. 38%, $p < 0.001$), and ST-segment depression on ECG (14 vs. 26%, $p = 0.034$). However there was no significant difference between both groups regarding T-wave inversion.

3.4. Laboratory data

As regards quantitative laboratory data, patients with insignificant CAD had lower elevations in peak troponin I (0.0005 (0–0.74) vs. 53.5 (17.5–80.5), $p < 0.001$), and peak CK-MB levels (4.1 (3.2–5.05) vs. 116.5 (67–218.5), $p < 0.001$) compared with patients with significant CAD. Patients with insignificant CAD significantly presented with lower LDL-C (134.5 (123–186.5) vs. 143.5 (119.5–250), $p = 0.006$), and higher HDL-C levels (42.5 (37–49) vs. 41.5 (31–53), $p = 0.020$). However there was no significant difference between both groups regarding total cholesterol, TG, WBC, hematocrit, blood sugar, HbA1c, and creatinine levels (Table 2).

As regards qualitative laboratory data, patients with insignificant CAD were significantly less likely to have elevation in serum troponin I ($p < 0.001$), CK-MB ($p < 0.001$), leukocytic count ($p < 0.001$), blood sugar ($p < 0.001$), and HbA1c ($p < 0.001$), compared with patients with significant group. However there was no significant difference between both groups regarding total cholesterol, LDL, HDL, TG, hematocrit and creatinine levels.

3.5. Echocardiographic data

As regards echocardiographic data (pre-discharge), patients with insignificant CAD had preserved left ventricular (LV) function by, as compared with significant group ($p < 0.0001$). Regional wall motion showed significantly more abnormalities in the significant CAD patients ($p < 0.001$). Also diastolic dysfunction was significantly more present in the significant CAD patients ($p < 0.001$). However there was

Table 2 Results of quantitative laboratory work-up across groups.

Variable	Group I (n = 100)	Group II (n = 100)	p-value
Peak troponin I, ng/ml	0.0005 (0–0.74)	53.5 (17.5–80.5)	**<0.001**
Peak CKMB, ng/ml	4.1 (3.2–5.05)	116.5 (67–218.5)	**<0.001**
Total cholesterol, mg/dl	177 (144–244)	188.5 (132–298)	0.089
LDL, mg/dl	134.5 (123–186.5)	143.5(119.5–250)	**0.006**
HDL, mg/dl	42.5 (37–49)	41.5 (31–53)	**0.020**
TG, mg/dl	132 (115–192)	135.5 (114–218)	0.053
WBC, 1,000/mm3	7.4 (6.5–8.3)	8.2 (7.1–9.6)	0.086
Hematocrit,%	47.9 (46.7–49.4)	48.3 (46.9–50.0)	0.230
Blood sugar, mg/dl	124 (112.5–255)	126.5 (113–293.5)	0.109
HbA1c, %	6.8 (4.9–8.7)	7.1 (5.2 –9.1)	0.123
Serum creatinine on Admission mg/dl	0.9 (0.8–1.1)	0.98 (0.89–1.1)	0.098

Data are presented as median (interquartile range).

no significant difference between both groups regarding valvular dysfunction.

3.6. Catheterization finding and target vessel stenosis

Among 100 patients with insignificant CAD (Group I), a normal coronary angiogram without any suspected atherosclerosis was present in 44%, whereas the rest (56%) of patients showed signs of atherosclerosis (< 50%). Among patients with coronary stenosis (< 50%), LAD occlusion present in (33.0%), RCA (15.0%), LCX (4.0%), LM (2.0%), LAD & LCX (2.0%).

3.7. In-hospital and discharge medications

Patients with insignificant CAD were significantly less likely to be treated in-hospital with b-blockers (p = 0.002), ACE inhibitor/ARBs (p = 0.007), and higher rates of calcium channel blocker therapy (p < 0.001) (Table 3). This trend continued at discharge (Table 4).

3.8. In-hospital clinical outcome

Patients with insignificant CAD significantly had lower rates of recurrent angina (p = 0.029), and cardiogenic shock (p = 0.029). However there was no significant difference between both groups regarding heart failure, mechanical complications, sustained VT, stroke and in-hospital mortality (Table 5).

Table 3 Medications received during hospital stay across groups.

Medication	Group (n = 100)	Group II (n = 100)	p-value
Nitroglycerin	59 (59.0%)	79 (79.0%)	**0.001**
Beta-blockers	66 (66.0%)	85 (85.0%)	**0.002**
CCB	20 (20.0%)	3 (3.0%)	**<0.001**
ACEI/ARB	43 (43.0%)	62 (62.0%)	**0.007**
Diuretics	9 (9.0%)	10 (10.0%)	0.809
GPIIb/GPIIIa inhibitors	0 (0.0%)	4 (4.0%)	0.121

Data are presented as number (%).

Table 4 Medications prescribed on discharge across groups.

Medication	Group I (n = 100)	Group II (n = 100)	p-value
Beta-blockers	52 (52.0%)	85 (85.0%)	**<0.001**
CCB	20 (20.0%)	3 (3.0%)	**<0.001**
ACEI/ARB	43 (43.0%)	65 (65.0%)	**0.002**
Diuretics	9 (9.0%)	10 (10.0%)	0.809

Data are presented as number (%).

Table 5 In-hospital clinical outcome across groups.

Outcome	Group I (n = 100)	Group II (n = 100)	p-value
Recurrent angina	0 (0.0%)	6 (6.0%)	**0.029**
CHF	7 (7.0%)	7 (7.0%)	1.000
Cardiogenic shock	0 (0.0%)	6 (6.0%)	**0.029**
Mechanical complications	0 (0.0%)	1 (1.0%)	1.000
Sustained VT	1 (1.0%)	4 (4.0%)	0.369
Stroke/TIA	0 (0.0%)	0 (0.0%)	-
In-hospital Mortality	0 (0.0%)	1 (1.0%)	1.000

Data are presented as number (%).

3.9. Outcome after 3 month follow-up

Patients with insignificant CAD significantly had lower prevalence of major adverse clinical events (readmission for ACS (p = 0.009)), and need for revascularization (p = 0.035). However there was no significant difference between both groups regarding cardiac mortality (Table 6).

3.10. Predictors of non-significant CAD

The results of the multivariable model revealed that, the predictors for the presence of insignificant CAD are summarized in Table 7.

3.11. According to Kaplan-Meier analysis

Our results revealed that, 90-day survival rates were similar between both groups (p = 0.156).

4. Discussion

In our study, we attempt to answer the question of whether one can feasibly discriminate, before cardiac catheterization, between these 2 syndromes (AMI with no critical narrowing of a coronary artery vs AMI with coronary stenosis substantial enough to warrant PCI).Our findings are partially in concordance with earlier reports, but also highlight new aspects of this entity.

5. Demographics and baseline characteristics

Compared with AMI registries/reports (Table 8), baseline demographic and clinical characteristics of the current study population showed some differences;

Table 6 Outcome after 3 month follow-up across groups.

Outcome	Group I (n = 100)	Group II (n = 100)	p-value
Readmission for ACS	1 (1.0%)	9 (9.0%)	**0.009**
Need for revascularization	1 (1.0%)	8 (8.0%)	**0.035**
Cardiac mortality	0 (0.0%)	1 (1.0%)	1.000

Data are presented as number (%).

Table 8 Predictors of insignificant CAD.

Variables	p-value
Young age < 55 years	p < 0.001
Female	p = 0.006
Non-white	p = 0.032
No current/recent smoker	p = 0.006
Absence of DM	p < 0.001
No Prior CAD	p = 0.042
No Prior PCI	p = 0.037
A typical chest pain	p < 0.001
Lower elevation in peak troponin I level	p < 0.001
Lower elevation in peak CK-MB level	p < 0.001
Lower LDL-C level	p = 0.006
Higher HDL-C level	p = 0.020
No ST-segment changes on presentation	p < 0.001
Preserved left ventricular (LV) function	p < 0.0001

5.1. Age

In our study, patients with insignificant CAD was significantly younger (p < 0.001), than patients with significant CAD. This was consistent with earlier trials/registries (Table 8). This could be explained by the following: (1) Younger patients have relatively lower prevalence of traditional risk factors such as diabetes mellitus, systemic hypertension, and hyperlipidemia.[8] and (2) patients with normal coronary arteries probably represent a different population of younger patients with a possible tendency for spontaneous thrombosis and other etiologies leading to ACS (e.g., takotsubo cardiomyopathy, variant angina pectoris, microvascular dysfunction).[1]

Table 7 Multivariable binary logistic regression analysis for prediction of insignificant CAD.

Variable retained in the model	B	SE	Sig.	Exp (B)	95% CI for Exp (B) Lower	Upper
Age < 55 yr	0.91	0.53	**0.083**	2.49	0.89	6.98
Female gender	1.85	0.56	**0.001**	6.39	2.15	18.99
Non-white race	1.00	0.48	**0.039**	2.71	1.05	6.98
Non-smoker	1.51	0.52	**0.004**	4.52	1.62	12.64
No hypertension	−1.58	0.58	**0.006**	0.21	0.07	0.64
No dyslipidemia	−1.16	0.57	**0.041**	0.31	0.10	0.96
No family history of CAD	−2.35	0.80	**0.003**	0.10	0.02	0.46
A typical chest pain	2.04	0.68	**0.003**	7.68	2.01	29.39
Lower CK-MB	3.17	0.62	**<0.001**	23.77	7.12	79.36
Constant	−2.58	1.17	**0.027**	0.08		
Model diagnostics						
Hosmer & Lemeshow test	p-value, 0.938					
Accuracy	86%					
Area under the ROC curve (AUC)	0.939 (95% CI, 0.908–0.970; p-value, **<0.0001**)					
Youden index J	0.74					
Associated criterion (probability)	>0.66					
Sensitivity	82%					
Specificity	92%					

5.2. Gender

In our study, patients with insignificant CAD was significantly more likely to be females ($p = 0.006$). This was in concordance with earlier trials/registries (Table 8). Several mechanisms may explain this association: (1) Recent reports from the National Heart, Lung, and Blood Institute sponsored (WISE) study demonstrated that up to 50% of women with chest pain and no obstructive CAD have microvascular dysfunction as identified by coronary velocity response to intracoronary adenosine.[9] (2) Women are believed to more frequently have plaque erosion and thrombus without obstruction and less luminal encroachment of plaques.[10] (3) Positive (outward) remodeling of the coronary arteries, which is known to be more common in women than men, could explain a higher prevalence of non-obstructive disease on angiography in women.[7]

5.3. Race

In our study, patients with insignificant CAD were significantly more often non-white ($p = 0.032$), compared with patients with significant CAD. This was in concordance with Patel et al.,[11] Maddox et al.,[12] and Larsen et al.,[13] but contrast with another study by De Ferrari et al.,[6] who found that no significant difference between both groups as regards race. The high frequency of no obstruction at angiography among black women, has several potential explanations,[7] (1) Endothelial function varies with race, and blacks have been shown to have less vigorous brachial artery vasodilatation in response to endothelium-dependent and endothelium-independent stimulation of blood flow compared with Whites. (2) Young black males have stronger microvascular and macrovascular responses to cold pressor testing. (3) Hypertension causes endothelial dysfunction is more common among blacks. In patients with ischemic symptoms and no significant obstruction on coronary angiography. (4) Left ventricular hypertrophy, a consequence of hypertension is associated with perfusion defects on nuclear imaging as well as depressed coronary vasodilator reserve.

6. Cardiovascular risk factors

6.1. Smoking

In our study, patients with insignificant CAD were significantly less likely to smoke ($p = 0.006$), compared with patients with significant CAD. This was consistent with other earlier reports,[5,11–15] which found that non-obstructive CAD patients were significantly less likely to smoke, whereas others did not find a difference,[1,6,16] (Table 8).

6.2. Diabetes mellitus

In our study, patients with insignificant CAD were significantly less likely to have diabetes mellitus ($p < 0.001$), compared with patients with significant CAD. This was consistent with other earlier reports,[5,6,11,12,14] whereas others did not find a difference,[1,13,16] (Table 8).

The most important findings of our study are that, patients with insignificant CAD had similar prevalence of other traditional CAD risk factors as patients with obstructive CAD (hypertension, dyslipidemia, and obesity). This was in concordance with the recent reports,[1,5,6,15] whereas other studies have demonstrated that patients with insignificant CAD had lower cardiovascular disease risk profiles than patients with obstructive coronary disease.[11,12] Thus, the true understanding of the population characteristics that present with non-obstructive coronary disease is still limited.

6.3. History of CAD and PCI

In our study, patients with insignificant CAD were significantly less likely to have history of CAD ($p = 0.042$), or PCI ($p = 0.037$). This was in concordance with some earlier reports,[5,6,11–13] which found that non-obstructive CAD patients were significantly less likely to have previous CAD or prior PCI, whereas other study did not find a difference.[15]

6.4. Comorbidities

In our study, patients with insignificant CAD had similar prevalence of history of stroke, as patients with significant CAD. This was in contrast to prior studies,[11,12,15] which demonstrated lower rates of prior stroke in patients with non-obstructive coronary artery disease.

In our study, patients with insignificant CAD had similar prevalence of renal insufficiency, as patients with significant CAD. This was in concordance with some earlier reports,[5,6,11,15] but in contrast to other studies.[12,14]

In our study, patients with insignificant CAD had similar prevalence of PVD, as patients with obstructive CAD. This was consistent by the findings of Minha et al.,[15] but in contrast to other studies.[6,12] The small number of our patients was a major factor of the non-significance of many of the study results.

6.5. Clinical presentation

In our study, patients with insignificant CAD were significantly less likely to present with typical chest pain ($p < 0.001$), and this was consistent with Maddox et al.[12] Also less likely to present with Killip Class $\geq$ II ($p < 0.001$), this was in concordance with both the study by Maddox et al.[12], and the study by Minha et al.[15]

In our study, patients with insignificant CAD were significantly less likely to have ischemic ST-segment changes on presentation (46% with no ST-T changes) compared with 10% in the significant group ($p < 0.001$), and these patients less likely to have ST-segment elevation (9 vs. 38%, $p < 0.001$), and ST-segment depression on ECG (14 vs. 26%, $p = 0.034$), with no significant difference between both groups regarding T-wave inversion. This was in concordance with some studies demonstrated that patients with insignificant CAD were significantly less likely to have ischemic ST-segment changes on presentation.[1,5,6,12,15,17]

6.6. Laboratory data

In our study, as regards quantitative laboratory data, patients with insignificant CAD had lower elevations in peak troponin

I ($p < 0.001$), and peak CK-MB levels ($p < 0.001$). This was in concordance with finding by Minha et al.,[1] Patel et al.,[11] and Shi Hyun et al.,[14] whereas other study did not find a difference as regards troponin level.[5]

In our study, as regards qualitative data, patients with insignificant CAD were significantly less likely to have elevation in serum troponin I ($p < 0.001$). This was in concordance with finding by De Ferrari et al.,[6] and Larsen et al.,[13] whereas others did not find a differences between any of these findings.[15,18]

In our study, as regards quantitative laboratory data, patients with insignificant CAD had lower LDL-C level ($p = 0.006$), and this was in concordance with some earlier reports,[14,15] whereas others did not find a difference.[1,5,6]

Patients with insignificant CAD had higher HDL-C level ($p = 0.020$), as compared to significant CAD. This was consistent by the findings of Minha et al.,[15] who found that the NOCAD patients presented with higher HDL-C level ($p = 0.01$), whereas other study by Shi Hyun et al.,[14] did not find a difference.

Other baseline laboratory differences were not significant including (total cholesterol, TG, WBC, hematocrit, blood sugar, and serum creatinine).

6.7. Echocardiographic

Patients with insignificant CAD had preserved left ventricular (LV) function pre-discharge, and even after discharge by 87%, as compared with 55% in the significant group ($p < 0.0001$). This was in concordance with some earlier reports[1,12,13,15] ($p < 0.0001$), whereas other reports,[5,14] demonstrated no differences in left ventricular ejection fraction, between the 2 groups either before or after discharge. Regional wall motion showed significantly more abnormalities in the significant CAD patients ($p < 0.001$). This was consistent by the findings of Hubertus et al.,[18] who reported that analysis of regional wall-motion showed significantly more abnormalities in patients with critical stenosis ($p < 0.05$).

7. Results of coronary angiography

In our study, among patients with insignificant CAD, a normal coronary angiogram without any suspected atherosclerosis was present in 44%, whereas the rest (56%) of patients showed signs of atherosclerosis (>0% and <50%). Among patients with coronary stenosis (>0% and <50%), LAD occlusion present in (33.0%), RCA (15.0%), LCX (4.0%), LM (2.0%), LAD & LCX (2.0%).

7.1. Predictors of insignificant CAD

Our study revealed that the predictors for the presence of insignificant CAD (Table 8).

7.2. In-hospital (<48 h) and discharge medications

The fact is that insignificant CAD patients were less frequently treated with adherence to the recommended guidelines during hospitalization and even at discharge. It is conceivable that after excluding obstructive coronary disease by angiography, many of these patients were stratified as 'low risk patients with chest pain, and were no longer regarded as patients with ACS. Patients with non-obstructive lesions may thus be mistakenly classified as low risk and may not receive adequate secondary prevention measures.[5]

In our study, patients with insignificant CAD were significantly less likely to be treated with thienopyridines ($p < 0.001$), lipid-lowering agents ($p < 0.001$), b-blockers ($p = 0.002$), angiotensin converting enzyme inhibitor/angiotensin receptor blockers ($p = 0.007$), as compared with significant CAD patients. This trend continued at discharge, we found that the presence of insignificant CAD was significantly associated with lower rates of secondary prevention medication (thienopyridines ($p < 0.001$), lipid-lowering agents ($p < 0.001$), b-blockers ($p < 0.001$), angiotensin converting enzyme inhibitor/angiotensin receptor blockers ($p = 0.002$)), as compared with significant CAD patients.

This was in concordance with some earlier reports,[1,6,12,14,15] which demonstrated lower rates of evidence-based medical therapy in patients with insignificant coronary artery disease during hospitalization, and even at discharge.

7.3. Aspirin

In our study, during hospitalization aspirin therapy was similar among the two groups with no significant difference, but at discharge, patients with insignificant CAD were significantly less likely to be treated with aspirin ($p < 0.001$). This was in concordance with some earlier reports by Minha et al.,[1] Patel et al.,[11] and Minha et al.,[15]. Another studies by David et al.,[5] Maddox et al.,[12] Shi Hyun et al.,[14] and Hubertus et al.,[18] demonstrated that patients with insignificant CAD were significantly less likely to be treated with aspirin therapy during hospitalization, and even at discharge.

7.4. Nitroglycerin

In our study, during hospitalization, patients with insignificant CAD were significantly less likely to be treated with nitroglycerin ($p = 0.001$), and this was in concordance with the study by Moreira et al.[3].

7.5. Unfractionated heparin

In our study, during hospitalization, patients with insignificant CAD were significantly less likely to be treated with heparin ($p < 0.001$), and this was in concordance with both the study by Patel et al.,[11] and Minha et al.,[15] whereas Minha et al.,[1] did not find a difference between two groups.

7.6. Calcium channel blockers

In our study, patients with insignificant CAD were significantly treated with higher rates of calcium channel blocker therapy during hospitalization ($p < 0.001$), and even at discharge ($p < 0.001$), and this was in concordance with the studies by Patel et al.,[11] Shi Hyun et al.,[14] and Minha et al.[15] This could be explained by, the use of calcium antagonists to treat

microvascular angina, because of their vasodilator effect on the microcirculation, potentially reducing cardiac work and thereby decreasing myocardial oxygen consumption.[19]

The ideal therapy for patients with insignificant CAD is still under investigation but effective control of risk factors with appropriate vasodilator effect on the microvascular territory will probably contribute to better quality of life.

7.7. Clinical outcome

7.7.1. In-hospital clinical outcome

In our study, patients with insignificant CAD were significantly had lower rates of recurrent angina ($p = 0.029$), and cardiogenic shock ($p = 0.029$). This was in concordance with some earlier reports,[11,12,15] whereas other study did not find a difference.[1]

Pasupathy et al.,[16] found that patients with NOCAD have a significantly reduced all-cause mortality compared with those with OCAD, including a 63% lower in-hospital mortality ($p = 0.001$), and similar findings were repeated in Patel et al.,[11] and Maddox et al.[12] But in the present analysis, there was no significant difference between both groups regarding in-hospital mortality. This could be explained by the small number of patients. Others in hospital outcome were not significant including CHF, pulmonary edema, mechanical complications, sustained VT, and stroke/TIA.

7.8. Clinical follow-up

In our study, at 3 months, patients with insignificant CAD were significantly had lower rates of readmission for ACS ($p = 0.009$), and need for revascularization ($p = 0.035$), with no significant difference between both groups regarding cardiac mortality. Similar mortality between two groups could be explained by small number of patients and the relatively short duration of follow-up (3 months) might have precluded our ability to detect differences between the groups as regards mortality.

Most previous studies have demonstrated that the prognosis of patients with ACS who have insignificant CAD were generally reported as favorable as compared to significant CAD, Minha et al.,[1] De Ferrari et al.,[6] Larsen et al.,[13] Minha et al.,[15] Pasupathy et al.,[16] and Alejandro et al.,[17] which found that patients with insignificant CAD had lower rates of major adverse cardiovascular events.

7.9. Discharge diagnosis

In our study, as regards discharge diagnosis, patients with insignificant CAD were diagnosed by 74.0% 'Unstable Angina' compared with 20.0% in the significant patients ($p < 0.0001$). The frequency of 'NSTEMI' (17.0%) in insignificant vs. (37.0%) in significant patients, ($p < 0.0001$) and 'STEMI' was more frequently diagnosed in the significant group (43.0 vs. 9% in insignificant, ($p < 0.0001$)). Our data showed that the possible causative factors in our insignificant CAD patients were coronary spasm (6%), myocardial bridge (1%), spontaneous thrombolysis (3%), coronary ectasia (3%), probability of myocarditis (1%), pericarditis (3%), aortic stenosis (1%), and GERD or esophageal disorders (2%), whereas the eventual etiology remains uncertain in the majority of patients.

7.10. Limitations

(1) Small number of patients and the relatively short duration of follow-up (3 months) might have precluded our ability to detect differences between the groups. (2) Only patients that underwent coronary angiography were evaluated, so a selection bias of patients referred for coronary angiography may have influenced the results. (3) Angiographic information was limited to the degree of stenosis in coronary arteries, and no information on lesion characteristics, thrombus, intravascular ultrasound, or coronary flow was available. (4) Coronary stenosis was measured by visual estimation by experienced angiographers rather than by quantitative evaluation, consistent with clinical practice worldwide. However, regardless of how precisely measured, the angiogram of a complex lesion poorly represents the real lumen size. (5) Intravascular imaging and coronary artery vasospasm provocation tests were not routinely performed, which could have better differentiated between atherothrombotic and nonatherothrombotic causes.

8. Conclusion

(1) The absence of atherosclerosis in patients with ACS remains an uncommon but problematic finding in patients undergoing coronary angiography. (2) Female sex, young age, non-white, absence of diabetes, less smoking, less ST-segment changes, lower elevations in peak troponin, and peak CK-MB levels were all associated with coronary angiography showing no significant stenosis. (3) Our data suggest that patients with a normal angiogram had a good prognosis in spite of their baseline clinical presentation.

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Disclosures

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