Predictors and Outcomes of Acute Coronary Syndrome in Patients with Insignificant Coronary Artery Disease

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Abstract

Background: We aimed to investigate the predictors, in-hospital and 3-months outcomes of acute coronary syndrome (ACS) patients with insignificant stenosis on a coronary angiogram.

Methods: This prospective study included 200 consecutive patients admitted with a diagnosis of ACS to the coronary care unit. All patients underwent cardiac catheterization and were classified into two groups: group I (insignificant coronary artery disease (CAD): lumen diameter <50%) and group II (significant CAD: one or more vessels >70% diameter stenosis).

Results: Patients with insignificant CAD were significantly younger (p<0.001), more likely to be female (p=0.006), less likely to smoke (p=0.006) or have diabetes mellitus (p<0.001) or a history of CAD (p=0.042) or coronary interventions (p=0.037). These patients were also less likely to have ischemic ST-segment changes on presentation (p<0.001) and lower elevations in peak troponin I (p <0.001) and CK-MB levels (p <0.001). Patients with insignificant CAD had lower rates of in-hospital adverse clinical outcome (recurrent angina: p=0.029) and cardiogenic shock (p=0.029)), with similar rates of in-hospital mortality between both groups. Regarding 3-months outcomes, these patients had lower rates of readmission for ACS (p=0.009), and need for revascularization (p=0.035), with similar rates of 90-day mortality between both groups.

Conclusion: Among patients with ACS, female sex, younger age, the absence of diabetes, less smoking, less ST-segment changes and lower troponin I and CK-MB levels, were all associated showing insignificant stenosis on coronary angiography. The outcomes of these patients were better than those with significant disease in spite of similar baseline clinical presentation.

Keywords: Acute coronary syndrome; Coronary artery disease; Coronary angiography; Outcomes

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**INTRODUCTION**

Acute coronary syndrome (ACS) is a common term, used to describe acute myocardial ischemia. Acute ischemia is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination of superimposed intracoronary thrombosis. It is associated with an increased risk of cardiac death and myonecrosis (1). It encompasses acute myocardial infarction (MI) and unstable angina. The pathophysiology of ACS often involves local and systemic inflammation leading to coronary plaque rupture and thrombus formation (2). A significant number of patients presenting with ACS may have insignificant coronary stenosis on cardiac catheterization (<50%), or have lesions that were considered insignificant in the past (3).

There are various etiologies for insignificant coronary stenosis. Coronary artery plaques may grow into the wall of a vessel without significant luminal narrowing, a phenomenon known as coronary artery remodeling (4). Coronary vasospasm leading to transient narrowing of the coronary artery has been demonstrated in patients without coronary artery disease (CAD) by ergonovine provocation tests at cardiac catheterization (5). Non-ischemic causes primary myocardial disorders, congestive heart failure with diastolic dysfunction, amyloidosis, and hypothyroidism can increase cardiac troponins in patients without ischemia (6). Moreover, rarer conditions have been reported, such as “tako-tsubo” cardiomyopathy, a syndrome characterized by no significant epicardial CAD, mild myocardial necrosis, and apical ballooning (7). Cardiac X syndrome presents with angina-like chest pain. It is caused by coronary endothelial dysfunction and subsequent microvascular ischemia due to the flow limitation in small vessels (8).

While the outcomes for patients with insignificant or normal coronaries are better than for patients with significant coronary disease, the treatment of these patients is not clear, as evidenced by the clinically significant lower utilization rates of aspirin, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors (ACEIs), and higher rates of calcium channel blockers (CCBs) use. Also, patients without epicardial CAD may require specific targeted therapies such as antithrombotic, anti-vasospastic, antihypertensive, anti-inflammatory, or antianginal medications (9). This study was aimed to determine the predictors and outcome of ACS in patients with insignificant CAD.

**METHODS**

2.1. Study Population: This prospective observational study included 200 consecutive patients admitted for ACS to the coronary care unit of the Cardiology department in the Saudi German Hospital, Aseer, Saudi Arabia. The study was carried out over the period from January 2016 to June 2017. All cases underwent coronary angiography and were classified into two groups: Group I included 100 patients with angiographically normal or insignificant CAD (lumen diameter <50%) and Group II (control group) included 100 patients with angiographically significant CAD. The demographic features and clinical-angiographic profile were collected for each patient and were correlated with the extent and severity of coronary artery lesions.

For the analysis by age, we categorized patients based on age in years (< 55), (55–69), and (≥ 70). The age threshold of 55 years was selected based on its use in the ongoing National Heart,
Lung, and Blood Institute (NHLBI). The race was defined by the Office of Management and Budget (OMB) broad race categories developed in 1997 to White, Black or African American, Asian, American Indian/Alaska Native, and Native Hawaiian and other Pacific Islander. Non-obstructive CAD at angiography was defined as the absence of ≥50% stenosis in any major epicardial vessel. Angiograms with segments described as having even minimal luminal irregularities were categorized as non-obstructive (or mild) CAD. We excluded Patients with contraindications to cardiac catheterization, previous CABG, or patients who received thrombolytic therapy.

2.2. Study methods: The files of all patients were revised on regular basis and data were collected in unique report forms. All eligible patients underwent the following: Full medical history with special emphasis on conventional risk factors for CAD: Age, diabetes mellitus (DM), hypertension, dyslipidemia, cigarette smoking, family history of premature CAD: CAD in male first-degree relative <55 years or CAD in female first-degree relative <65 years. The patients further underwent clinical examination with special emphasis on weight, body mass index (BMI), heart rate and rhythm on admission and systolic and diastolic blood pressures at the time of the study. Twelve-lead electrocardiogram (to classify patients into STEMI or NSTEMI), laboratory evaluation with special emphasis on cardiac biomarkers (CK, CK-MB, Troponin I) and lipid profile, transthoracic echocardiogram (Philips IE 33, to assess the chambers size, the presence and degree of valvular heart disease, global and regional left ventricular systolic function and diastolic function) were performed. Data were regularly collected about the medications that the recruited patients had received since the admission. These include the following medications: Antiplatelet agents, Anticoagulants, Beta-blockers, ACE-I, ARBs. Coronary angiography was performed to evaluate the extent of atherosclerosis and Revascularization (PCI or CABG).

2.3. Study Outcomes: Primary outcomes were divided to In-hospital outcomes (mortality, recurrent angina, Development of heart failure, Development of pulmonary edema, Development of cardiogenic shock and severe arrhythmia requiring treatment) and Outcome after 3 months of follow up (Cardiac mortality, Recurrent ACS, Revascularization (PCI or CABG), and Hospitalization for acute coronary syndromes). Secondary outcome included the clinical and laboratory profile of patients with insignificant CAD.

2.4. Statistical analysis: Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and Medal© version 14 (MedCalc© Software bvba, Ostend, Belgium). The D’Agostino-Pearson test was used to examine the normality of numerical data distribution. Owing to the 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 frequency and percentage and between-group differences were analyzed using the Chi-square test or Fisher’s exact test, when appropriate.

Multivariable binary logistic regression was used to determine independent predictors of an insignificant CAD. Variables found to be significantly associated with the outcome variable by univariate 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 a
significant or insignificant 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.

**RESULTS**

3.1. 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), non-white (p=0.032), less likely to smoke (p=0.006) or have DM (p<0.001) or a history of CAD (p=0.042) or PCI (p=0.037). However, no significant differences were recorded between both groups regarding other traditional CAD risk factors (hypertension, dyslipidemia, and family history of CAD); Table 1 and Figure 1.

3.2. Clinical presentation, ECG and Laboratory data on admission: Group I patients were significantly less likely to present with typical chest pain (61 vs. 91%, p<0.001) or have ischemic ST-segment changes on presentation (46% with no ST-T changes compared with 10% in the significant CAD group; p<0.001). They had lower elevations in peak troponin I (0.0005 [0–0.74] vs. 53.5 [17.5–80.5], p<0.001), peak CK-MB levels (4.1 [3.2–5.05] vs. 116.5 [67–218.5], p<0.001), 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), compared with patients with significant CAD. However, there were no significant differences between both groups regarding blood pressure, heart rate, total cholesterol, and triglycerides; Table 2.

3.3. In-hospital echocardiographic data: Patients with insignificant CAD had preserved left ventricular function by 87%, as compared with 55% in the significant stenosis group (p<0.0001). Regional wall motion showed significantly more abnormalities in the significant CAD patients (p<0.001). However, no significant difference was noted between both groups regarding valvular dysfunction.

3.4. In-hospital medications (< 48 h): Patients with insignificant CAD were significantly less likely to be treated with nitroglycerin (p=0.001), heparin (p<0.001), thienopyridines (p<0.001), lipid-lowering agents (p<0.001), b-blockers (p=0.002), ACEIs/ARBs (p=0.007), and higher rates of CCB therapy (p<0.001). However, there were no significant differences between both groups regarding aspirin, diuretics, and glycoprotein IIb/IIIa inhibitor use.

3.5. In-hospital and three months follow-up outcomes: Patients with insignificant CAD had significantly lower rates of recurrent angina (p=0.02) and cardiogenic shock (p=0.02). However, no significant difference was recorded between both groups regarding heart failure, pulmonary edema, mechanical complications, sustained ventricular tachycardia, stroke and in-hospital mortality. As regards the clinical follow-up outcome, patients with insignificant CAD had a lower prevalence of major adverse clinical events (readmission for ACS: p=0.009) and the need for revascularization (p=0.035). There was no significant difference between both groups regarding cardiac mortality.

3.6. Predictors of insignificant CAD and 90-day survival: The results of multivariate model revealed that the predictors for insignificant CAD were younger age (<55 yr), female sex, non-white race, lack of recent/current smoking, no hypertension, no dyslipidemia, no family history of CAD, atypical chest pain, and lower peak CK-MB level. The accuracy of this model was (86%): probability (>0.66), sensitivity (82%), and specificity (92%). With regards to the Kaplan-Meier analysis, our results revealed that the 90-day survival rates were similar between both groups (p= 0.156).
Table (1): Demographics and clinical characteristics between insignificant (Group I) and significant (Group II) coronary artery disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insignificant CAD (Group I) N=100</th>
<th>Significant CAD (Group II) N=100</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr.</td>
<td>56 (50 – 61.5)</td>
<td>65 (59 – 71)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age &lt;55, yr.</td>
<td>44 (44%)</td>
<td>21 (21%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Female Gender</td>
<td>41 (41%)</td>
<td>23 (23%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Non-white race</td>
<td>51 (51%)</td>
<td>36 (36%)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Current smoking</td>
<td>29 (29%)</td>
<td>48 (48%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>History of CAD</td>
<td>9 (9%)</td>
<td>19 (19%)</td>
<td>0.042*</td>
</tr>
<tr>
<td>History of PCI</td>
<td>4 (4%)</td>
<td>11 (11%)</td>
<td>0.037*</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>6 (6%)</td>
<td>8 (8%)</td>
<td>0.579</td>
</tr>
<tr>
<td>Anti-ischemic therapy</td>
<td>9 (9%)</td>
<td>18 (18%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>16 (16%)</td>
<td>12 (12%)</td>
<td>0.415</td>
</tr>
<tr>
<td>Type II DM</td>
<td>36 (36%)</td>
<td>61 (61%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (52%)</td>
<td>50 (50%)</td>
<td>0.777</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>45 (45%)</td>
<td>49 (49%)</td>
<td>0.571</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or frequency (%). CAD: Coronary artery disease, DM: Diabetes Mellitus, * Statistically significant

Table (2): Clinical presentation, electro-cardiography and laboratory values of patients with insignificant (Group I) and significant (Group II) coronary artery disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insignificant CAD (Group I) N=100</th>
<th>Significant CAD (Group II) N=100</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical chest pain</td>
<td>61 (61%)</td>
<td>91 (91%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77.5 (75 – 80)</td>
<td>75 (70 – 80)</td>
<td>0.199</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>130 (120 – 150)</td>
<td>140 (120 – 150)</td>
<td>0.749</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>80 (75 – 90)</td>
<td>80 (75 – 85)</td>
<td>0.822</td>
</tr>
<tr>
<td>No ST-T changes</td>
<td>46 (46%)</td>
<td>10 (10%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Elevated ST segment</td>
<td>9 (9%)</td>
<td>38 (38%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Depressed ST segment</td>
<td>14 (14%)</td>
<td>26 (26%)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Peak troponin I, ng/ml</td>
<td>0.0005 (0 – 0.74)</td>
<td>53.5 (17.5 – 80.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Peak CK-MB, ng/ml</td>
<td>4.1 (3.2 – 5.05)</td>
<td>116.5 (67 – 218.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>177 (144 – 244)</td>
<td>188.5 (132 – 298)</td>
<td>0.089</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>134.5 (123 – 186.5)</td>
<td>143.5 (119.5 – 250)</td>
<td>0.006*</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>42.5 (37 – 49)</td>
<td>41.5 (31 – 53)</td>
<td>0.020*</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>132 (115 – 192)</td>
<td>135.5 (114 – 218)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Data are presented as frequency (%) or median (interquartile range). HDL: High-density lipoprotein, LDL: Low-density lipoprotein cholesterol, TG: Triglycerides, * statistically significant
DISCUSSION

Despite the several advances in interventional cardiology in general (10, 11) and the management of CAD specifically (12), ACS remains the leading cause of death worldwide. An important subset of ACS patients is reported to have either normal coronaries (NCs) or non-obstructive coronary artery disease (NOCAD, defined as narrowing of <50% in lumen diameter on angiography) with a reported prevalence of 10% (13). Our study aimed to determine the predictors and outcomes of ACS patients with insignificant CAD.

We found that young age, female gender, non-white race are predictors of an insignificant CAD. Minha et al. found that NOCAD patients tend to be younger (14); this is partly due to the low prevalence of traditional risk factors in young patients (13). A meta-analysis has reported a higher association of female gender with MI and NOCAD (15). Positive (outward) remodeling of the coronary arteries, which is known to be more common in women than in men, could explain the higher prevalence of NOCAD in women (16). Larsen et al. and Maddox et al. demonstrated that NOCAD patients were more frequently black (17, 18). However, their data were in contrast with another study by De Ferrari et al. who found no significant difference between both groups as regard race (19). Endothelial function varies with race; 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 (13). Moreover, we found that absence of risk factors, such as smoking, DM and history of CAD or PCI could be another predictor of an insignificant CAD, which is consistent with the results of two studies (20, 21).

The most important finding of our study is that NOCAD patients had a similar prevalence of other traditional CAD risk factors as patients.
with obstructive CAD (hypertension, dyslipidemia, and obesity). This is in concordance with some recent reports (14, 19, 21) and in contrast with others (9, 18). Thus, the true understanding of the population characteristics that present with NOCAD is still limited. With regards to the clinical presentation, we found that NOCAD patients are less likely to present with atypical chest pain and were less likely to have ischemic ST-segment changes. This is in concordance with some previous studies (18, 20). We also found preserved left ventricular function pre-discharge on echocardiography in NOCAD patients, which confirms the results of earlier reports (14, 18).

In our study, a comparison of the medical therapy given at 48 h of admission showed significant differences between the two groups. Patients with insignificant CAD were significantly less likely to be treated with thienopyridines, lipid-lowering agents, b-blockers and ACEIs/ARBs. This was in concordance with some earlier reports (14, 18, 19), which demonstrated lower rates of evidence-based medical therapy in patients with insignificant coronary artery disease during hospitalization.

In our study, as regards the in-hospital clinical outcome, patients with insignificant CAD had lower rates of recurrent angina and cardiogenic shock. Pasupathy et al. reported a 63% lower in-hospital mortality in NOCAD patients (15). However, we found no significant difference between both groups regarding in-hospital mortality. This could be explained by the small number of patients in our study. The 3-months outcome of NOCAD was significant for lower rates of readmission for ACS and the need for revascularization. Similar mortality between the two groups at three-month follow-up could be explained by the small number of patients and the relatively short duration of follow-up (3 months).

Most previous studies have demonstrated that prognosis of patients with ACS who have insignificant CAD was generally reported as favorable as compared to significant CAD. Pasupathy et al. showed that patients with NOCAD have a significantly reduced all-cause mortality compared with those with OCAD, including a 41% lower 12-month mortality (15), while Minha et al. found that NOCAD patients exhibited a significantly lower MACE rate at 30 days compared to patients from the OCAD group (14).

Our study has some limitations. The Small number of patients and the relatively short duration of follow-up (3 months) may have precluded our ability to detect differences between the groups. Patients who underwent coronary angiography only were evaluated, 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. Coronary stenosis was measured by visual estimation by experienced angiographers rather than by quantitative evaluation. Intravascular imaging and coronary artery vasospasm provocation tests were not routinely performed, which could have better differentiated between atherothrombotic and non-atherothrombotic causes.

**Conclusion**

Female sex, young age, non-white, the 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. Our data suggest that patients with normal coronaries or insignificant CAD have a better prognosis than those with significant
stenosis in spite of similar baseline clinical presentation.

**Abbreviations**

ACS: Acute coronary syndrome  
CAD: Coronary artery disease  
NOCAD: Non-obstructive coronary artery disease

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**Conflict of interest:** None

**References**


