***British Journal of Medicine & Medical Research***
***5(12): 1502-1513, 2015, Article no.BJMMR.2015.170***
***ISSN: 2231-0614***

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# Study of the Relationship between Metabolic Syndrome Score and Angiographic Severity of Coronary Artery Disease According to the Presence of Diabetes

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author MBB wrote the protocol, first draft of the manuscript and managed the literature search. Authors DR and VV designed and managed the study. Author DSB performed the statistical analysis and author AR managed the literature search. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/BJMMR/2015/13713
Editor(s):
(1) Gaetano Santulli, College of Physicians & Surgeons Columbia University Medical Center New York, NY, USA.
Reviewers:
(1) Robert Chilton, Professor of Medicine, University of Texas Health Science Center, San Antonio, Texas 78261, USA.
(2) Anonymous, Bhagwan Mahavir Medical Research Centre, Hyderabad, Telangana, India.
(3) Anonymous, Hormozgan University of Medical Sciences, Iran.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=719&id=12&aid=6967

***Original Research Article***

***Received 29th August 2014***
***Accepted 4th November 2014***
***Published 15th November 2014***

## ABSTRACT

**Background:** The relationship between metabolic syndrome score and coronary artery disease severity is unclear in the presence of diabetes.
**Hypothesis:** The hypothesis of this study is to assess whether there is a relationship between metabolic syndrome score and coronary artery disease angiographic severity and whether or not the severity of the relationship differs in the presence of diabetes.
**Methods:** We consecutively enrolled 132 metabolic syndrome patients who underwent their first coronary angiography. We used four angiographic scores and compared the relationship between metabolic syndrome score and angiographic coronary artery disease severity or clinical presentation between diabetic and non-diabetic subjects.
**Results:** Individuals with both metabolic syndrome and diabetes (n=64) had significantly higher

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metabolic syndrome scores, acute coronary syndromes, double and triple vessel disease, higher coronary score, extent score, severity score, and atherosclerotic score than metabolic syndrome patients without diabetes (n=68). A significant correlation was apparent between metabolic syndrome and coronary atherosclerotic scores in patients without diabetes. In contrast, we did not observe any significant correlation between metabolic syndrome score and coronary atherosclerotic scores in patients with diabetes. Multivariate regression analysis revealed that metabolic syndrome score is an independent predictor of atherosclerotic score in non-diabetics.

**Conclusion:** While the relationship between metabolic syndrome score and angiographic coronary artery disease severity was disguised by the presence of diabetes, the metabolic syndrome score was related to the extent of coronary atherosclerosis in Indian patients without diabetes. Calculating the metabolic syndrome score might provide additional information for predicting the extent of coronary artery disease in patients with angina without diabetes.

*Keywords: Atherosclerotic score; coronary artery disease; diabetes; metabolic syndrome score.*

## 1. INTRODUCTION

Cardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to 23.3 million by 2030 [1,2]. Increasingly, the populations affected are those in low- and middle-income countries, where 80% of these deaths occur [1]. Afflicted individuals are typically younger than individuals from higher-income countries and have more limited human and financial resources [2,3].

Metabolic syndrome (MS) represents a constellation of interrelated risk factors of metabolic origin—metabolic risk factors—that appear to directly promote the development of atherosclerotic CVD [4]. The metabolic and underlying risk factors that are components of MS include abdominal obesity, atherogenic dyslipidaemia, hypertension, insulin resistance with or without glucose intolerance, low-grade inflammation and a prothrombotic state.

MS is considered a clinical predictor of CVD [5-7] and patients with MS have a higher incidence of coronary artery disease (CAD) than individuals without MS [8,9]. However, it is still contentious whether the CAD risk associated with MS is above and beyond the risk allied with its individual components [10,11]. Previous studies have reported that as the number of markers of MS (MS score) increases, the angiographic severity of CAD also increases [12-15]. In addition, the value of MS in predicting CAD risk in patients with diabetes mellitus (DM) is contentious, since these patients could have an augmented risk of CAD irrespective of the diagnosis of MS. Some studies have indicated that cardiovascular incidents were significantly associated with high density lipoprotein cholesterol (HDL-C) levels, systolic blood pressure (SBP), sex and total cholesterol (TC), but not with the presence of MS as defined by the ATP III criteria for patients with DM [16]. Likewise, MS, as defined by the International Diabetes Federation (IDF) criteria, was not predictive of CAD in Chinese patients with DM [17]. Moreover, it has been suggested that the prediction of CAD by MS is primarily based on high fasting blood glucose levels [14] and that the relationship between MS score and CAD severity was unclear in the presence of DM [18,19].

The association of MS score with CAD severity has not yet been investigated in India. In this context, the primary aim of this study was to evaluate whether MS score is allied with CAD severity in a cohort of Indian patients undergoing coronary angiography. Our secondary aim was to determine whether or not the relationship between MS score and CAD severity differs in the presence of DM.

## 2. METHODS

The study was conducted between April 2012 and December 2013 at Sri Venkateswara Institute of Medical Sciences, a tertiary health-care center located in Tirupati, Andhra Pradesh, India.

### 2.1 Inclusion Criteria

We included 132 consecutive patients with MS at least 18 years old who were admitted for their first elective coronary angiography because of chronic stable angina (CSA) or unstable angina (UA). A diagnosis of CSA or UA was made according to the American College of Cardiology and the American Heart Association (ACC/AHA) joint guidelines [20,21].

## 2.2 Exclusion Criteria

Patients were excluded if they had acute ST-segment elevation myocardial infarction, a history of previous myocardial infarction or any Q waves on the 12-lead electrocardiogram (ECG), heart failure, a history of percutaneous coronary intervention (PCI), a coronary artery bypass graft, type 1 DM, cancer, systemic inflammatory disease, chronic kidney disease, or severe liver disease. Patients who did not provide consent for the study were also excluded.

## 2.3 Data Collection

A detailed clinical history was recorded from all the participants regarding their age, sex, history of hypertension, DM status, smoking, prior myocardial infarction, PCI and coronary artery bypass grafting, and family history of CAD. All patients underwent complete respiratory, cardiovascular and neurological clinical examinations. At the end of a normal expiration, waist circumference (WC) was measured in the fasting state using a non-stretchable flexible tape in a horizontal position (just above the iliac crest), with the subject standing erect and facing forward and the observer seated in front of the subject. Body mass index (BMI) was calculated as body mass (kg) divided by height squared ($m^2$). SBP and diastolic blood pressure (DBP) were measured to the nearest 5 mmHg using a mercury sphygmomanometer with subjects in a sitting position after having relaxed for 5minutes. Hypertension was diagnosed according to the Joint National Committee 7criteria [22].

Blood samples were obtained early in the morning, after overnight fasting, prior to elective coronary angiography. Fasting plasma glucose (FPG) was measured using the glucose oxidation-peroxidation method. DM was defined according to the American Diabetes Association 2011 criteria [23]. Serum TC, triglycerides (TG) and HDL-C concentrations were quantified using commercially available kits on an auto-analyzer (Synchron CX9 from Beckman Coulter Inc., USA). Low density lipoprotein cholesterol (LDL-C) was calculated using Friedwald's formula [24]. A resting 12-lead ECG was performed for each patient.

## 2.4 Metabolic Syndrome Score

In the present study, the criteria advocated by the IDF 2005 consensus, which places an emphasis on ethnic inheritance in the diagnosis of obesity, was used to diagnose patients with MS [25]. Any patient exhibiting abdominal obesity (defined as WC ≥ 90 cm in males and ≥ 80 cm in females) and at least two risk factors – (i) hypertension (blood pressure ≥ 130/≥ 85 mmHg) or treatment for previously diagnosed hypertension;(ii) FPG ≥ 100 mg/dL or previously diagnosed DM; (iii) TG≥ 150 mg/dL or specific treatment for hypertriglyceridemia; (iv) HDL-C<40 mg/dL in males and <50 mg/dL in females or specific treatment for this type of lipid abnormality – was diagnosed with MS. The MS score was defined as the number of MS components present (range: 3–5).

## 2.5 Angiographic Studies

Coronary angiography was performed in all patients with MS under local anesthesia using the Modified Seldinger technique with a radial or femoral artery approach. For evaluating the degree of coronary stenosis, quantitative coronary angiography (QUANTOCOR, Siemens, Erlangen, Germany) was performed. The coronary arteries were divided into 15 segments as per the guidelines of the AHA [26]. Each segment was then graded according to the most severe diameter reduction detected, as follows: grade 0: <25% stenosis, grade 1: <50% stenosis, grade 2: <75% stenosis, grade 3: >75% stenosis, and grade 4, occlusion defined as a >95% diameter stenosis with a severely reduced or no antegrade flow [27]. The vessels with diameter less than 1-mm or segments downstream of grade 4 stenoses were not analyzed. The grade of luminal narrowing was determined following a consensus between two experienced interventional cardiologists. Four scoring categories, described in detail by Ledru et al. [28] were used to describe coronary atherosclerosis. The coronary score was defined by the number of coronary arteries showing stenosis with more than a 75% diameter reduction. The extent score was estimated as the number of segments with lesions exhibiting a stenosis of grade 1 or above, adjusted to the 15 coronary segments. The severity score was calculated as the average grade of the diseased coronary segments. The atherosclerotic score was calculated as the average severity of all analyzable segments. Atherosclerosis involving the left main, proximal left anterior descending and left circumflex arteries, as well as the first three segments of the right coronary artery, was defined as proximal coronary atherosclerosis, whereas atherosclerosis involving the other coronary segments was defined as distal coronary atherosclerosis.

### 2.6 Statistical Analyses

Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are presented as percentages. A comparison of categorical variables between groups was performed using the chi-squared test. An analysis of normality was performed using the Kolmogorov-Smirnov test. A comparison of continuous variables was performed using the independent samples *t*-test or a Mann-Whitney U test for any comparisons of two data sets. The correlation of the MS score with various anthropometric and biochemical variables was evaluated using Spearman's rank correlation coefficient analysis. The relationship between the MS score and the extent of coronary atherosclerosis was evaluated in the whole cohort and diabetic and non-diabetic subjects using one-way analysis of variance. Multivariate regression analysis was performed to identify the independent predictors of the atherosclerotic score, which represents the total atherosclerotic burden that was normalized to the total number of segments visualized in a particular patient. A two-tailed p-value of <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS software, version 16.0, for Windows (SPSS Inc., Chicago, IL, USA).

### 2.7 Ethics Statement

The study was conducted with the approval of the ethics committee of Sri Venkateswara Institute of Medical Sciences [Protocol IEC No: 238/22-05-2012]. There was no economic burden on the participating patients. All investigations were performed as part of routine investigations. In accordance with the ethical guidelines of the 1975 Declaration of Helsinki, informed consent was obtained from each participant.

## 3. RESULTS

### 3.1 Baseline Characteristics

A summary of the clinical, anthropometric and biochemical characteristics of the patients with MS is listed in Table 1. A total of 132 patients, including 82 men and 50 women, with a mean age of 53.1±9.2 years, were included in the present study. Eighty-four patients (63.63%) had hypertension and 64 patients (48.48%) had DM; among the patients with DM, 49 were self-reported as taking medication for DM. DM was detected de novo in 15 patients. Among the 68 patients without DM, 37 (54.42%) had impaired fasting glucose (IFG). The mean WC and BMI of the cohort were 96.57±6.74 cm and 26.65±3.30 $kg/m^2$, respectively. The mean SBP and DBP were 125.43±14.71 mmHg and 77.90±7.91 mmHg, respectively. The mean FPG, TC, LDL-C, HDL-C and TG levels were 120.42±29.30 mg/dL, 192.36±35.49 mg/dL, 120.95±33.71 mg/dL, 35.69±8.26 mg/dL and 159.30±38.43 mg/dL, respectively. The mean MS score of the patients was 3.90±0.76. We found three MS components in 45 patients (34.09%), four components in 54 patients (40.91%) and five components in 33 patients (25.00%). CSA was apparent in 68 patients (51.52%), whereas UA was apparent in 64 patients (48.48%).

The patients with DM were significantly older and had higher WC, SBP, DBP, FPG, TC, LDL-C, TG and HDL-C levels, as well as higher mean MS scores compared with patients without DM. There was no significant difference in gender distribution, prevalence of smoking and hypertension, family history of CAD and BMI between the two groups (with or without DM). UA was a significant finding at presentation in patients with DM (p=0.001), whereas CSA was more prevalent in patients without DM (p=0.001).

Table 2 shows that patients presenting with UA had significantly higher mean MS scores than patients with CSA (p<0.001). As shown in Table 3, compared with patients without DM, patients with DM had significantly fewer normal coronary artery segments (grade 0); moreover, they were more likely to have mildly diseased segments(grade 1), moderately diseased segments (grade 2), severely diseased segments (grade 3) or completely occluded segments (grade 4). Patients with MS and DM had significantly higher coronary score (p<0.001), extent score (p<0.001), severity score (p=0.01) and atherosclerotic score (p<0.001) compared with patients without DM.

Table 3 also shows that patients with MS and DM had significantly more diseased segments in proximal (p<0.001) as well as distal locations (p=0.004) compared with patients with MS but without DM. In both groups, there was a significant number of diseased segments in proximal location compared with the distal location, but the statistical significance was higher in patients with DM (p<0.001 vs. p=0.04).

Table 4 shows the correlation between MS score and various anthropometric and biochemical parameters. Spearman's rank correlation analysis showed that the MS score was positively correlated with age, WC, SBP, DBP, FPG, TG and negatively correlated with HDL-C level. There was no correlation between MS score and BMI, TC and LDL-C level, respectively.

A significant correlation was observed between MS score and all angiographic scores (coronary score: p<0.001; extent score: p<0.001; severity score: p<0.001; atherosclerotic score: p<0.001; Table 5a).

We also investigated whether any relationship was present between MS score and coronary atherosclerotic scores in patients with DM compared with patients without DM (Table 5b). A significant correlation was apparent between MS and coronary atherosclerotic scores in patients without DM (coronary score, p<0.001; extent score, p<0.001; severity score, p=0.001; atherosclerotic score, p<0.001). In contrast, we did not observe any significant correlation between MS score and coronary atherosclerotic scores in patients with DM (coronary score, p=0.563; extent score, p=0.964; severity score, p=0.228; atherosclerotic score, p=0.317).

Table 5c shows the results of forward step-wise analysis of the best predictors of the atherosclerotic score in patients with MS without DM. WC, MS score, FPG, HDL-C and SBP were identified as independent predictors of atherosclerotic score.

## 4. DISCUSSION

We assessed the relationship between MS score and CAD severity determined using coronary angiography, and found that the MS score influenced CAD severity in Indian patients without DM but not in those with DM.

**Table 1. Baseline clinical, anthropometric and biochemical characteristics of patients**

| **Variable** | **Entire cohort [n=132]** | **$MS^+$-$DM^+$ [n=64]** | **$MS^+$-$DM^-$ [n=68]** | ***p-value***** |
|---|---|---|---|---|
| Age [years] * | 53.19±9.21 | 55.15±9.00 | 51.35±9.09 | 0.01 |
| Gender [M:F] | 82:50 | 37:27 | 45:23 | 0.32 |
| Smoking, No. [%] | 52 [39.39%] | 20 [31.25%] | 32 [47.05%] | 0.06 |
| Hypertension, No.[%] | 84 [63.63%] | 41[64.06%] | 45 [66.17%] | 0.80 |
| Family h/o CAD, No. [%] | 11 [8.34%] | 6 [9.3%] | 5 [7.35%] | 0.64 |
| WC [cm]* | 96.57±6.74 | 98.76±8.14 | 94.51±4.22 | <0.001 |
| BMI [kg/$m^2$]* | 26.65±3.30 | 26.43±3.18 | 26.86±3.41 | 0.45 |
| SBP [mmHg] * | 125.43±14.71 | 128.71±16.57 | 122.35±12.04 | 0.01 |
| DBP[mmHg]* | 77.90±7.91 | 79.70±9.01 | 76.20±6.31 | 0.01 |
| FPG [mg/dl]* | 120.42±29.30 | 136.93±31.61 | 104.88±15.31 | <0.001 |
| TC [mg/dl]* | 192.36±35.49 | 201.12±40.02 | 187.88±30.23 | 0.03 |
| LDL-C [mg/dl]* | 120.95±33.71 | 131.82±37.85 | 120.13±29.56 | 0.05 |
| HDL-C [mg/dl]* | 35.69±8.26 | 33.01±7.66 | 36.33±8.79 | 0.02 |
| TG [mg/dl]* | 159.30±38.43 | 167.51±36.18 | 151.57±39.14 | 0.01 |
| **MS score** | | | | |
| 3, No. [%] | 45 [34.09%] | 09 [14.06%] | 36 [52.95%] | |
| 4, No. [%] | 54 [40.91%] | 27 [42.19%] | 27 [39.70%] | <0.001 |
| 5, No. [%] | 33 [25.00%] | 28 [43.75%] | 05 [7.35%] | |
| MS score* | 3.90±0.76 | 4.29±0.70 | 3.54±0.63 | <0.001 |
| **Indication for coronary angiography** | | | | |
| CSA | 68 [51.52%] | 23 [35.94%] | 45[66.18%] | 0.001 |
| UA | 64 [48.48%] | 41 [64.06%] | 23[33.82%] | 0.001 |

*MS: metabolic syndrome; DM: diabetes mellitus; M: F: male: female; CAD: coronary artery disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; CSA: chronic stable angina; UA: unstable angina*

** Expressed as mean ± SD*

*** p value represents a significant result between diabetic and non-diabetic MS patients*

**Table 2. MS scores in patients with CSA and UA**

| | CSA (n=68) | UA (n=64) | *p value* |
|---|---|---|---|
| **MS Score:** | | | |
| 3 (%) | 35 | 10 | |
| 4 (%) | 22 | 32 | <0.001 |
| 5 (%) | 11 | 22 | |
| Mean MS score (±SD) | 3.63±0.75 | 4.20±0.68 | <0.001 |

*MS: metabolic syndrome; CSA: chronic stable angina; UA: unstable angina*

**Table 3. Angiographic profile in patients with DM (MS+-DM+) vs patients without DM (MS+-DM-)**

| | $MS^+$-$DM^+$ | $MS^+$-$DM^-$ | *p- value* |
|---|---|---|---|
| **Mean grades of involvement of coronary arteries*** | | | |
| Grade 0 (normal) | 8.84±2.02 | 10.50±2.09 | <0.001 |
| Grade 1 (mild) | 1.94±0.88 | 1.62±0.76 | 0.02 |
| Grade 2 (moderate) | 1.15±0.59 | 0.83±0.56 | 0.002 |
| Grade 3 (severe) | 1.37±0.76 | 0.85±0.60 | <0.001 |
| Grade 4 (occlusion) | 0.55±0.53 | 0.34±0.46 | 0.007 |
| **Angiographic Score*** | | | |
| Coronary score* | 1.92±0.76 | 1.16±0.61 | <0.001 |
| 0 veseels, % | 4.70 | 10.30 | |
| 1 vessel, % | 18.80 | 64.70 | <0.001 |
| 2 or 3 vessels, % | 76.50 | 25.00 | |
| Extent score* | 4.97±1.06 | 3.70±1.31 | <0.001 |
| Severity score* | 2.02±0.40 | 1.84±0.39 | 0.01 |
| Atherosclerotic score* | 0.81±0.27 | 0.55±0.27 | <0.001 |
| **Location of diseased segments** | | | |
| Proximal* (normalized to 6 segments) | 2.94±0.73 | 2.04±0.84 | <0.001 |
| Distal* (normalized to 9 segments) | 2.12±0.70 | 1.79±0.61 | 0.004 |
| *p-value* | <0.001 | 0.04 | |

*MS: metabolic syndrome; DM: diabetes mellitus*

Several studies have shown that MS predicts cardiovascular events and DM [8,29-31], although it is unclear whether MS predicts cardiovascular risk better than its individual components [32,33]. The value of the MS in predicting CAD risk in patients with DM is controversial, since these patients could have an augmented CAD risk, irrespective of the MS diagnosis. Previous studies indicated that cardiovascular incidents were significantly associated with HDL-C, SBP, sex, and TC but not with the presence of MS, as defined by the ATP III criteria for patients with DM [16]. Similarly, MS, as defined by the IDF criteria, was not predictive of CAD in Chinese patients with DM [17].

Some studies reported that MS score was more useful for predicting CAD severity than the presence or absence of MS [12,14]. Moreover, it has been suggested that CAD prediction by MS is primarily based on high FPG levels [14], and the relationship between MS score and CAD severity was unclear in the presence of DM [18,19].

Consistent with previous studies [12,14,18], we observed that MS score demonstrated a significant positive correlation with atherosclerotic burden in the coronary vasculature, as assessed by scores described by Ledru et al. [28]. The highlight of the scoring system used in our study is that, similar to the Gensini score, it also considers hemodynamically insignificant lesions. Previous studies clearly showed that these nonsevere lesions could become unstable, leading to myocardial infarction and death [34-36]. A positive correlation of MS score with atherosclerotic burden is further supported by a virtual histology-intravascular ultrasound (VH-IVUS) study by Zheng et al. [37], which demonstrated that an increase in plaque-plus-media burden, necrotic core diameter, and number of thin-cap fibroatheromas was significantly correlated with a higher MS score.

**Table 4. Correlation between MS score with anthropometric and biochemical parameters in the entire study population (n=132)**

| Variable | Correlation coefficient (rho) | *p-value* |
|---|---|---|
| AGE | 0.416 | <0.001 |
| WC | 0.412 | <0.001 |
| BMI | 0.117 | 0.18 |
| SBP | 0.437 | <0.001 |
| DBP | 0.308 | <0.001 |
| FPG* | 0.462 | <0.001 |
| TG | 0.335 | <0.001 |
| HDL-C | -0.413 | <0.001 |
| LDL-C | 0.062 | 0.48 |
| TC | 0.049 | 0.58 |

*WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol*

** Correlation with FPG was calculated for non-diabetic patients only.*

To investigate the relationship between MS score and CAD in patients with DM, we divided our cohort into two groups based on the presence of DM. We found a significant association between MS score and the atherosclerotic score in $MS^+$-$DM^-$ (n=68) but not in $MS^+$-$DM^+$ (n=64) patients. In addition to MS score being an independent predictor for CAD severity in patients without DM, multiple regression analysis also revealed that WC, FPG, HDL-C, and SBP predicted CAD severity. This differential relationship is consistent with a number of other studies [18,38,39]. Some experts suggest that increased cardiovascular risk coupled with MS principally arises from the presence of DM, which should be excluded from the definition of MS [40]. Liang et al. [41] concluded that since DM is a very strong CVD predictor, the five MS components and other nontraditional CVD markers did not improve CVD prediction beyond the input of DM. Kim et al. [14] concluded that the predictive ability of MS for CAD is based almost entirely on high FPG and individual traits, with high BP and low HDL-C appearing to act synergistically as CAD risk factors. In our study, diabetic patients exhibited higher MS scores and significantly higher age, WC, SBP, FPG, TG, and TC and lower HDL-C compared with nondiabetic patients. All these factors might contribute to the accelerated progression of atherosclerosis. Therefore, in the presence of DM, MS score does not seem useful for the predicting the extent of CAD.

Patients with MS and DM had significantly higher coronary, extent, severity, and atherosclerotic scores compared with patients without DM. The former also had significantly more diseased coronary artery segments along the length of the coronary vasculature. We also observed that patients with MS had significantly more proximal segment disease, irrespective of their DM status. The higher proportion of coronary lesions in patients with DM might be caused by a more severe cardiovascular risk profile compared with that of patients without DM. Ertek et al. [19] reported that Gensini scores were significantly higher in MS patients with DM. Similarly, Yoon et al. [18] concluded that MS patients with DM had the highest coronary atherosclerosis scores, followed by patients with DM without MS, patients with MS without DM, and patients with neither MS nor DM (4.5±3.3, 3.8±4.3, 3.1±3.4, and 1.6±2.8, respectively). Two studies [28,42] compared angiographic profiles of patients with or without DM (without considering MS) and concluded that patients with DM had significantly higher coronary, extent, and atherosclerotic scores. However, the results were conflicting regarding severity score. Both these studies demonstrated that patients with DM had a significant number of diseased segments in the proximal coronary vasculature, but exhibited inconsistent results concerning the number of segments located in the distal coronary vasculature. However, such differences are likely explained by the use of different lesion quantification techniques and population-based differences.

We found that patients having both MS and DM had significantly fewer normal segments (grade 0); instead, they were more likely to have mild (grade 1), moderate (grade 2), and severe (grade 3) stenoses compared with MS patients without DM, perhaps because DM itself is associated with accelerated atherosclerosis. The increased prevalence of total or subtotal vessel occlusion in patients with DM might be caused by an increased intrinsic susceptibility of moderate stenosis to subacute arterial thrombosis, possibly as a result of a combination of endothelium dysfunction [43], platelet hyperaggregation, and impaired fibrinolytic activity [44,45]. However, none of the patients in our study had a history of infarction or Q waves on an ECG. Ledru et al. [28] compared the pattern and severity of CAD in diabetic versus non-diabetic patients (without MS) and found that diabetic patients had significantly fewer normal segments and more abnormal segments compared to with nondiabetic patients.

**Table 5a. Relationship between the MS score and the coronary atherosclerotic scores in the entire cohort**

| Angiographic scores | MS score | | | *p-value* |
|---|---|---|---|---|
| | 3 (n=45) | 4 (n=54) | 5 (n=33) | |
| Coronary score | 1.02±0.75 | 1.70±0.63 | 2.06±0.75 | <0.001 |
| Extent score | 3.71±1.65 | 5.25±1.22 | 5.97±1.36 | <0.001 |
| Severity score | 1.69±0.43 | 2.00±0.36 | 2.02±0.35 | <0.001 |
| Atherosclerotic score | 0.49±0.27 | 0.78±0.21 | 0.97±0.32 | <0.001 |

*MS: metabolic syndrome*

**Table 5b. Relationship between the MS score and the coronary atherosclerotic scores as a function of the presence of DM**

| | $MS^+DM^+$ | | | | $MS^+DM^-$ | | | |
|---|---|---|---|---|---|---|---|---|
| Angiographic scores* | MS score | | | *p-value* | MS score | | | *p-value* |
| | 3 (n=9) | 4 (n=27) | 5 (n=28) | | 3 (n=36) | 4 (n=27) | 5 (n=5) | |
| Coronary score | 1.67±1.22 | 1.96±0.65 | 1.97±0.70 | 0.563 | 0.86±0.49 | 1.40±0.50 | 2.00±0.71 | <0.001 |
| Extent score | 4.88±1.54 | 4.96±0.94 | 5.01±1.05 | 0.964 | 3.167±1.32 | 4.18±1.01 | 5.01±1.01 | <0.001 |
| Severity score | 1.83±0.58 | 2.00±0.34 | 2.02±0.38 | 0.228 | 1.68±0.40 | 2.01±0.31 | 2.06±0.34 | 0.001 |
| Atherosclerotic score | 0.69±0.36 | 0.85±0.20 | 0.82±0.29 | 0.317 | 0.42±0.20 | 0.64±0.16 | 1.10±0.43 | <0.001 |

*MS: metabolic syndrome; DM: diabetes mellitus; ACS: acute coronary syndrome*
** Expressed as mean ± SD*

**Table 5c. Forward step-wise analysis of independent predictors of coronary atherosclerotic score in MS patients without DM**

| | β | SE | *p-value* |
|---|---|---|---|
| **Atherosclerotic score** | | | |
| WC | .542 | .005 | .000 |
| MS score | .444 | .035 | .000 |
| FPG | .211 | .002 | .002 |
| HDL | -.160 | .001 | .022 |
| SBP | .130 | .001 | .036 |

*WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TGL: triglycerides; HDL-C: high-density lipoprotein cholesterol; TCL: total cholesterol; LDL-C: low-density lipoprotein cholesterol; MS: metabolic syndrome*

In agreement with the results of Yoon et al., patients with UA had higher MS scores than patients with CSA [18]. Atherosclerosis is currently considered a multistep disease involving chronic inflammation at every stage, from commencement to progression and, eventually, plaque rupture [46]. As the number of individual MS components increases, the levels of inflammatory markers including CRP [47], TNF-α [48], and IL-18 [49] increase, along with plasminogen activator inhibitor-1 increases activity [50]. These findings suggest that an accumulation of individual MS components is likely to increase vascular inflammation, leading to heightened CAD activity. Furthermore, Zheng et al. [37] demonstrated that compared with patients without MS or DM, individuals with MS or DM had an increased plaque-plus-media burden, a greater necrotic core diameter, and more frequent thin-cap fibroatheromas in coronary arterial trees, thereby implying a greater plaque vulnerability. Marso et al. [51] showed that patients with either MS or DM had higher 3-year major adverse cardiac event rates compared with a normal cardiometabolic group. In addition, lesion length, plaque burden, necrotic core, and calcium content were significantly greater in nonculprit lesions in patients with acute coronary syndrome (ACS). Although these two IVUS-based studies did not include patients with both MS and DM, plaque vulnerability may further increase if patients have both conditions. In patients with higher MS scores, the increased inflammation and number of vulnerable lesions with increasing MS score would explain the increase in ACS presentations.

The importance and increased frequency of glucose metabolism abnormalities among patients recommended for elective coronary angiography with suspected CAD were highlighted by the detection of 15 cases of de novo DM in patients unaware of their condition and by the large number of patients without DM that appeared to have IFG. Such phenomena have been reported in other studies investigating patients with coronary lesions [52,53].

## 5. LIMITATIONS

Our study had several limitations. First, we used a cross-sectional design; however, CAD develops over time, and the duration of MS components can also affect the study endpoint. Second, the study group included only Indian patients undergoing their first coronary angiography, and therefore, the findings cannot be generalized to all CAD patients. Third, using coronary angiography to study CAD has certain disadvantages, including underestimation of early development of atheroma; in particular, compensatory enlargement of the vessel wall may obscure early atheromatous plaques that would not cause significant lumen deformation. Infiltrating and diffuse atheromas may also be underestimated because of the absence of coronary segments that could act as a normal reference. Differences in the atherosclerosis indices in MS patients with or without DM might be even greater than those we found because DM by itself can cause diffuse atheromatous disease. Although the use of IVUS may help overcome this limitation, coronary angiography is the most frequently used method worldwide for assessing CAD. Moreover, the angiographic CAD burden scoring systems are reportedly strongly correlated with one another and the IVUS plaque burden, and moderately correlated with IVUS plaque area [54].

## 6. CONCLUSION

Although the relationship between MS score and angiographic CAD severity may be disguised by the presence of DM, the MS score was related to coronary atherosclerosis severity in Indian patients without DM. Calculating the MS score might provide additional information for predicting the extent of CAD in patients with angina without DM. WC, MS score, FPG, HDL-C, and SBP were identified as independent predictors of the atherosclerotic score in patients with MS but without DM. We found significantly higher MS scores; increased incidence of UA; and higher coronary, extent, severity, and atherosclerotic scores in MS patients with DM compared with MS patients without DM. Patients with UA exhibited significantly higher MS scores than patients with CSA. Patients with MS had a higher incidence of proximal disease than distal disease, irrespective of their DM status.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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