

# American Journal of Health, Medicine and Nursing Practice (AJHMN)



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### Abstract

**Purpose:** The SYNTAX Score is a crucial tool to grade angiographic complexity and risk stratification of patients for revascularization. Excessive coronary calcification can lead to adverse outcomes after percutaneous coronary intervention (PCI), and it represents an essential part of SYNTAX score calculation. The sensitivity in detecting any CAC by CT is much higher than in ICA. Our purpose is to evaluate the impact of CT-enhanced calcium detection on SYNTAX score in the evaluation of complex coronary anatomy.

**Methodology:** This study was conducted at Beni-suef University Hospital and National Heart Institute from December 2019 to January 2021. Fifty consecutive male patients were enrolled, Their Coronary CT Angiography showed significant MVD; then, conventional coronary angiography was done. The additive value, rather than the comparative value, of adding Calcification from CT to CA syntax score (CT enhanced SYNTAX (CTeSx)), was assessed regarding its impact on the classification of complexity.

**Findings:** Using a CTeSX Vs CA Sx results in Lower Possibilities of Low Syntax group (39% vs 24%) (P-value <0.001) and a higher Possibilities of High Syntax score (23% vs 52% P-value 0.004).

**Recommendation:** CTeSX results in a significant change in the percentage of all complexity categories with a higher possibility to categorize complex anatomy.

**Keywords:** SYNTAX Score, Complex coronary anatomy, Calcification, Coronary CT.

## Background

Since its introduction, invasive coronary angiography has been the gold standard diagnostic method to guide revascularization procedures. Proper assessment and accurate grading of complexity in multivessel disease are essential to successful management. The SYNTAX Score is a crucial tool to grade angiographic complexity and risk stratify patients being considered for revascularization<sup>1</sup>; it is an independent predictor of major adverse cardiac events. The SYNTAX score has been integrated into both the European<sup>2</sup> and American<sup>3</sup> revascularization guidelines for the risk stratification of patients with complex coronary artery disease, facilitating the choice of the most appropriate revascularization modality. A higher SYNTAX score is associated with a worse outcome in patients undergoing PCI<sup>4</sup>. Excessive coronary calcification can lead to adverse outcomes after percutaneous coronary intervention (PCI)<sup>5</sup>, and it represents an essential part of SYNTAX score calculation. Coronary calcification can be assessed qualitatively by invasive CCA using ANCS classification. In contrast, intravascular ultrasound is more sensitive. It allows quantitative assessment of arterial calcification<sup>6</sup>, and MDCT is a well-established, non-invasive tool that permits accurate measurement of CCS using the Agatston method<sup>7</sup>. The sensitivity in detecting any CAC using ICA was 43%, with a specificity of 92% and an accuracy of 55%. The sensitivity of important CAC identification by ICA was 19%, the specificity 99%, and the accuracy 61%<sup>8</sup>. CCTA shows a high accuracy (91.6%) for all calcified plaques, the sensitivity (97.8%) and NPV (99.4%) are excellent, the specificity (90.1%) is relatively high, while the PPV (71.2%) is moderate<sup>9</sup>.

## Rationale

Data showed that CT syntax is comparative to CA-based SYNTAX (CASx). This study assessed the additive value rather than the comparative value of adding Calcification from CT to CA syntax score (CT enhanced SYNTAX). CT enhanced SYNTAX (CTeSx) score may result in recategorizing patients into different categories, which will optimize plans and techniques.

## Patients and Methods

This study was conducted at Beni-suef University Hospital and National Heart Institute from December 2019 to January 2021. We enrolled fifty consecutive male patients whose Coronary CT Angiography showed significant MVD; then, conventional coronary angiography was done for them and their ages above 50 years. This study's duration between CCTA and conventional CA is 2-4 weeks. CT enhanced SYNTAX is achieved by calculating the SYNTAX score from coronary angiography and substituting the entry for heavy calcification value based on the degree of calcification of the estimated segment from CT for each lesion.

All patients were subjected to:

1. Written informed consent for both CCTA and conventional CA.
2. Complete history taking regarding cardiac symptoms (chest pain, dyspnea, palpitation, edema, syncopal attack, hemoptysis), presence or absence of cardiovascular risk factors (DM, HTN, Smoking, IHD, previous cardiac surgery, stroke, TIA, history of bronchial asthma, allergy especially to contrast and regular medications).
3. 12-lead surface electrocardiogram (ECG): It confirms AF, multiple PVCs, sinus tachycardia, and CAD.

4. Laboratory profile including serum creatinine was performed three times; 1st one before CT to exclude patients with renal impairment from the study and to determine the baseline serum creatinine, while the 2nd one was done just before CA and the last one was done after both tests to follow up any post-procedure rising in serum creatinine.

### **Statistical analysis**

As indicated, quantitative data were presented as numbers (%) or mean + SD. Quantitative data were tested by normality by the Shapiro-Wilk test. Normally distributed data (Syntax score and lesion segment score) were presented as mean (SD), and data following other distributions were presented as median (interquartile range). Data recorded by coronary angiography were considered as being the reference measurement. The significance of the difference between paired data measured by MSCT and coronary angiography was tested by McNemar or McNemar-Bowker test, as indicated. The importance of the difference between paired data of normally distributed quantitative data was tested in the paired Student t-test. The significance of the difference between paired data of variables following other distributions was tried by the non-parametric Wilcoxon sign rank test. The non-parametric Spearman's correlation test measured the correlation of paired data.

### **Results**

The current study was conducted at Beni-suef University Hospital and National Heart Institute and included 46 male patients with MVD or LMT disease. Both invasive coronary angiography and CT coronary angiography were done for all patients for coronaries assessment. They considered invasive coronary angiography as a gold standard for SYNTAX score assessment. Four patients were excluded from the study (2 patients could not hold breathing during scanning, and two had frequent extrasystoles).

### **Patient characteristics and demographic data**

The studied population included 46 (100%) males with MVD or LMT disease. The mean age was  $56 \pm 6.04$  years SD. The average body weight was  $80 \pm 15.3$  kg SD. The average BMI was  $26 \pm 4.1$  SD. The prevalence of various cardiovascular risk factors among the study population is Diabetes at 41%, Hypertension at 58%, smoking at 21%, and dyslipidemia at 15%.

### **Scan data**

Average heart rate during scanning was between  $67.5 \pm 17.7$  beats/min (range 55 to 80). Thirty patients (65%) were under oral B-blocker medication at the time of the CT scan. Eight patients (17%) with increased heart rate (mean  $77.5 \pm 10.6$  beats/min, range 70 to 85) received B-blockers before the scan, also 22 (47%) patients were given sublingual nitrates who did not have aortic stenosis or any other contraindications of nitrates. The average scan time of CCTA was significantly shorter,  $12 \text{ sec} \pm 3 \text{ sec}$ , compared with  $839 \text{ sec} \pm 285 \text{ sec}$  as the total fluoroscopic time during diagnostic CA.

### **Evaluation of total syntax score by CCTA and Coronary Angiography**

Calculating the difference between the two measurements for each patient (Syntax MSCT Syntax CA). The mean of that difference (4.087) and its standard deviation (4.27). This was statistically significant.



**Table 1: Difference between CCTA and CA in assessment SYNTAX score**

| CCTA vs. CA       | Mean of the difference | Std. Deviation of the difference | P-value |
|-------------------|------------------------|----------------------------------|---------|
| Difference SYNTAX | 4.087                  | 4.27                             | <0.001  |

The total syntax scores calculated by either modality were categorized accordingly

**Table 2: Difference between CCTA and CA in the decision of revascularization**

|      | Low (0-22) | Intermediate (23-32) | High (>32) |
|------|------------|----------------------|------------|
| CCTA | 10(21%)    | 11 (23.9%)           | 25 (54%)   |
| CA   | 17 (36%)   | 16 (34.7%)           | 13 (28%)   |

In this study, 8 cases (17%) were candidates for PCI based on the SYNTAX score assessed by CA, but their decision was changed to heart team decision when CCTA calculated SYNTAX. And 12 cases (26%) were candidates for the heart team based on the SYNTAX score assessed by CA. Still, their decision was changed to CABG when CCTA calculated SYNTAX & the difference was mainly because of heavy calcifications detected by CCTA. But all CABG cases based on CA were also CABG based on CCTA. Among this group, 83% of patients had higher scores owing to dense calcifications, 50% of patients had higher scores due to characteristics of total occlusion lesions, about 41% of patients had LMT lesions, and 33% of patients had diffusely diseased segments.

Finally, the agreement between decisions taken by either modality was tested by Cohen Kappa statistics. Kappa values of 0.2-0.4, >0.5, >0.7 and >0.8 were considered as fair, moderate, good and excellent agreement; respectively. The calculated Kappa value was equal to 0.367, indicating an only fair agreement between decisions CCTA agreed with CA 52.9%, 29.4%, and 100% of PCI, heart team referral, and CABG cases, as shown below

**Table 3: Difference between CCTA and CA in total SYNTAX score**

|                         | Total SYNTAX score CA |            |      | Kappa |
|-------------------------|-----------------------|------------|------|-------|
|                         | Within decision       |            |      |       |
| Total SYNTAX score CCTA | PCI                   | Heart team | CABG | 0.36  |
| Within decision         | 52.9%                 | 29.4%      | 100% |       |

### Heavy calcifications

According to the Agatston scoring system, the total coronary calcium score ranged from zero to 888, a mean of  $50 \pm 146$  units. Despite the presence of only 3 cases (6%) by CA with the average score of  $0.13 \pm$  of SD 0.4 (during calculating syntax score); 42 patients (91%) showed calcified lesions by CCTA with an average score of  $5.4 \pm$  SD 3.6 (during calculating syntax score). Both modalities showed a significant difference in comparing CCTA with CA in assessing calcifications.

**Table 4: Detection of calcification by CT**

|                | <b>CCTA</b> | <b>CA</b> | <b>P-value</b> |
|----------------|-------------|-----------|----------------|
| Calcifications | 5.4±3       | 0.13±0.4  | <0.001         |

**CT enhanced SYNTAX (CTeSX) vs Coronary angiography SYNTAX (CASx)**

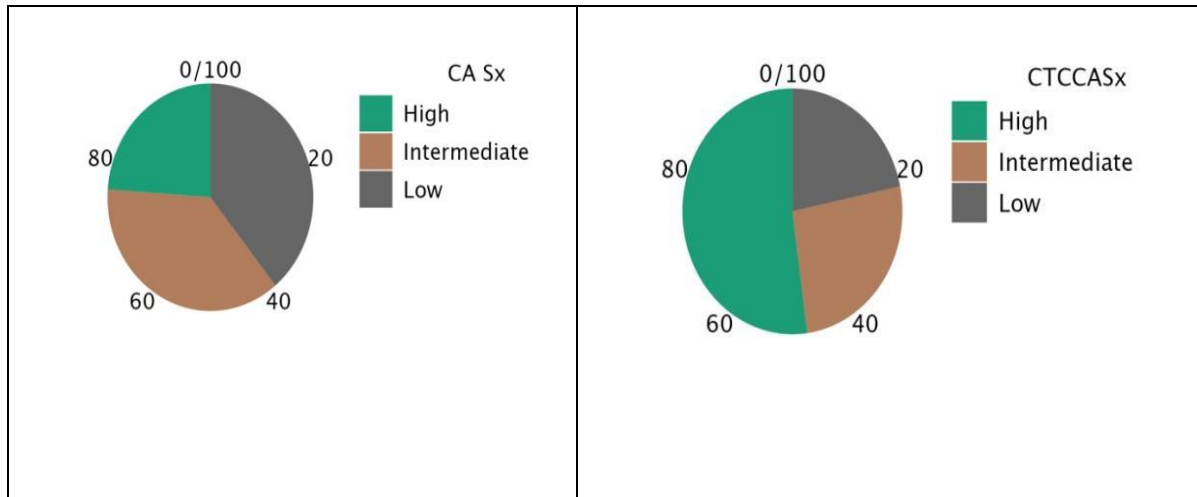
1. Possibilities of Low Syntax group is significantly decreased: with CASx 18 patients (39%) vs 10 patients with CTeSX (24%) (P-value <0.001)
2. Possibilities of High Syntax was significantly increased: 11 patients (23%) by CASx vs 24 patients (52%) by CTeSX P-value 0.004
3. Intermediate group significance was numerically lower, but statistically non significantly decrease: 17 patients by CASx (36%) vs. 12 patients by CTeSX (26%) P-value 0.28
4. SYNTAX >22 groups are significantly increased: 28 patients by CASx Vs. 36 patients by CTeSX, which is translated into more referrals for heart team discussion before planning a decision
5. Eight cases changes from <22 by CASx to >22 by CTeSX; represent 17% of the study cohort

**Table 5: Frequencies for CASx**

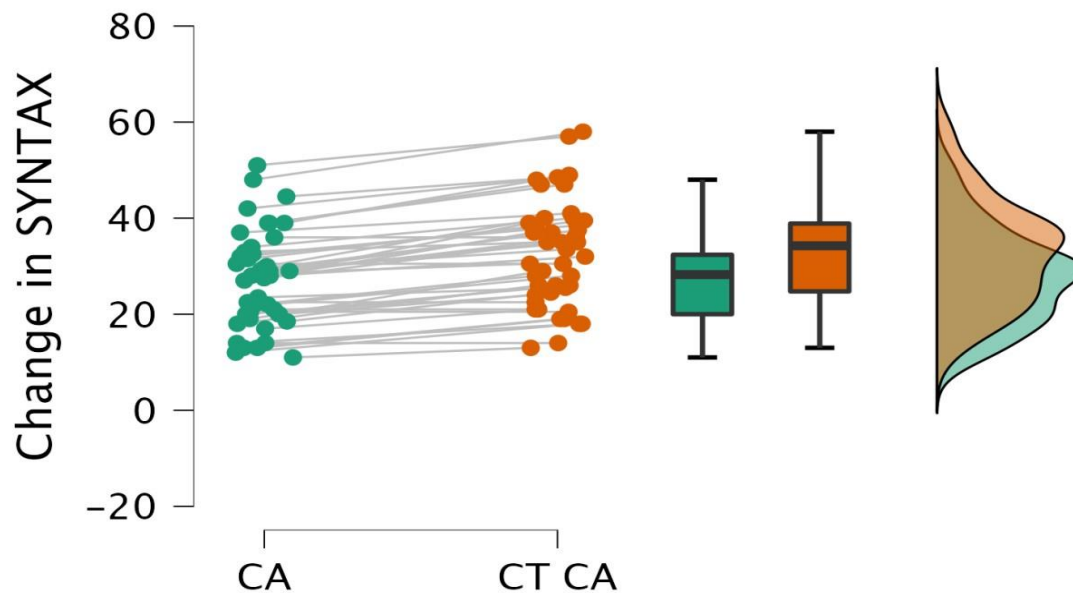
| <b>CASx</b>  | <b>Frequency</b> | <b>Percent</b> | <b>Valid Percent</b> | <b>Cumulative Percent</b> |
|--------------|------------------|----------------|----------------------|---------------------------|
| High         | 11               | 23.913         | 23.913               | 23.913                    |
| Intermediate | 17               | 36.957         | 36.957               | 60.870                    |
| Low          | 18               | 39.130         | 39.130               | 100.00                    |
| Missing      | 0                | 0.000          |                      |                           |

**Table 6: Frequencies for CTeSX**

| <b>CASx</b>  | <b>Frequency</b> | <b>Percent</b> | <b>Valid Percent</b> | <b>Cumulative Percent</b> |
|--------------|------------------|----------------|----------------------|---------------------------|
| High         | 24               | 52.174         | 52.174               | 52.174                    |
| Intermediate | 12               | 26.087         | 26.087               | 78.261                    |
| Low          | 10               | 21.739         | 21.739               | 100.000                   |
| Missing      | 0                | 0.000          |                      |                           |
| <b>Total</b> | <b>46</b>        | <b>100.000</b> |                      |                           |



**Figure 1: Syntax score by ICA and CTcASx**



**Figure 2: Change of SYNTAX score from ICA**

**Discussion**

The SYNTAX score (<http://www.syntaxscore.com>) was prospectively developed for the SYNTAX trial to grade the anatomical complexity of coronary lesions in patients with LM or three-vessel disease<sup>1</sup> In the cohort of the SYNTAX trial, and subsequently, in external validation cohorts, the SYNTAX score was found to be an independent predictor of long-term major adverse cardiac and cerebrovascular events (MACCE) and death in patients treated with PCI but not CABG<sup>2</sup>. The SYNTAX score remains the most widely used and validated risk score to guide the

choice of revascularization in patients with multivessel disease. Significant limitations of this score include the cumbersome scoring system required for each lesion and the interobserver variability in its calculation<sup>3</sup>.

The SYNTAX II score and the revised SYNTAX Score II 2020 were retrospectively developed from the SYNTAX trial cohort to incorporate clinical variables in addition to the anatomic variables. These scores demonstrate modest discrimination in predicting adverse clinical events after revascularization<sup>4</sup>. However, there are discrepancies in the current major society guidelines about the usefulness of SYNTAX score guidance for revascularization. The ACC/AHA revascularization guidelines 2021<sup>5</sup> gave a weak recommendation (class 2b) to assess CAD complexity using the SYNTAX score to guide revascularization<sup>6</sup>. In contrast, the ESC revascularization guidelines (2018)<sup>7</sup> gave a Class I recommendation for calculating the Syntax Score, if left main or multivessel revascularization is considered. This innate discrepancy defect in the SYNTAX score urges further improvement to bypass the interobserver variation. Our study proposes an enhancement of the score by adding information about significant calcification of each coronary segment based on CCTA assessment rather than CA assessment.

While calcification assessment for each segment is an essential part of SYNTAX score calculation, coronary angiography is not a sensitive diagnostic tool for calcification assessment. Calcification was detected only in 6% of patients by coronary angiogram, while CCTA detected calcification in 91% of cases. Moreover, calcification was significantly higher when assessed by CCTA vs. CA alone. By calculating the SYNTAX score from coronary angiogram and entering the points for coronary calcification assessment based on CCTA to calculate a CT enhanced SYNTAX score (CTeSX). CTeSX results in a significant change in the percentage of all complexity categories. A significantly lower percentage of Low Syntax score group (24% Vs 39%) (P-value <0.001) and higher percentage of High Syntax score group (52% Vs 23%) (P-value 0.004). The need for Heart team decision was also significantly increased when CTeSX is used due to higher percentages of the non-low score; (58% vs. 75%, P-value 0.005).

## Conclusion

Enhancing SYNTAX calculation by integrating detection of calcification from CCTA significantly impacts categories of complexity. Assessment of the impact of the enhanced score on heart team decision, plan of revascularization, and long-term outcome needs further research.

## Recommendation

The addition of a substantial calcification score from CT to the SYNTAX score results in a considerable shift in the percentage of all complexity categories with a higher probability of categorizing complex anatomy.

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