PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Coronary Atherosclerotic Burden Assessed by SYNTAX Scores and Outcomes in Surgical, Percutaneous, or Medical Strategies: a retrospective cohort study
AUTHORS	Scudeler, Thiago; Farkouh, Michael; Hueb, Whady; Rezende, Paulo; Campolina, Alessandro; Martins, Eduardo; Godoy, Lucas; Soares, Paulo; Ramires, Jose; Kalil Filho, Roberto

VERSION 1 – REVIEW

REVIEWER	Kurtul, Alparslan Ankara Numune Education and Research Hospital Nephrology Clinic, Cardiology
REVIEW RETURNED	27-Mar-2022

GENERAL COMMENTS	In this study researchers aimed to investigate the value of SYNTAX scores for predicting cardiovascular events in patients with multivessel CAD. They found that, diabetes was independent predictor of mortality at 5 years in multivariate analysis of the PCI cohort. They concluded that in patients with multivessel CAD, coronary atherosclerotic burden alone was not associated with significantly increased risk of death and MACCE. Overall, the study is well conducted and delivers potentially interesting observation in patients with CAD. But, the manuscript has some limitations. My detailed suggestions are below; 1. There is no description of approval of this study by the Ethics Committee in your facility. 2. Please give a chart for study inclusion and exclusion more clearly. 3. In Table 1, blood pressure and pulse rate should be added. Although all numeric variables were indicated as mean +/- SD in Tables, variables which were not normally distributed should be indicated using median and interquartile range. Statistical method for comparison of them between groups should be appropriately selected. 4. In order to emphasize the clinical importance of SYNTAX score in patients with diabetes and CAD, please also cite and discuss the following work.(Kurtul BE, Kurtul A, Yalçın F. Predictive value of the SYNTAX score for diabetic retinopathy in stable coronary artery disease patients with a concomitant type 2 diabetes mellitus. Diabetes Res Clin Pract. 2021 Jul;177:108875. doi: 10.1016/j.diabres.2021.108875.) 5. There are some grammar and vocabulary mistakes, which warrant revision.

REVIEWER	Williams, Michelle University of Edinburgh

REVIEW RETURNED	11-Apr-2022

GENERAL COMMENTS	This study looks at the association between three invasive coronary angiography derived scores and events in a retrospective analysis of patients undergoing invasive coronary angiography Title Needs to state that invasive this is based on invasive coronary angiography Abstract Results need improved , needs to contain numbers for the findings that are being stated Introduction Needs to include that the syntax score is with invasive coronary angiography Methods Needs to talk about ethics and informed consent Weighted kappa is needed for agreement if there are several groups As this paper is abut three scores these need better defined in the methods, and their similarities and differences highlighted. A table or figure would be good for this Not sure what you mean by using CABG as the reference How were endpoints discovered , phone, records, other? Results 136 patients didn't have their data analysed - why not? Did no one have single vessel disease? What was the indication for imaging? Observer agreement needs to be presented for the other scores as well What variables were chosen to include and not include in the multivariable models? AUC need 95% confidence intervals and p values are needed if you are saying there is a difference Discussion The main finding is that the original syntax score does not discriminate in terms of subsequent mortality, the new score is better but still not particularly good. This should be clearly stated in the first paragraph. All the scores include atherosclerotic burden in terms of presence of stenoses, but do not truly assess atherosclerotic burden like IVUS or CT do, so that comparison between scores is not a fair one. When discussing reference 12 you need to say that this was on computed tomography. Limitations section needed - one centre, small number, retrospective, significant selection bias as it is only patients undergoing invasive coronary angiography, only invasive coronary angiography assessment. Figures are very small to analyse. P values are needed on the first km curves as well. What are the p values on the ROC curves? P values for comparisons are needed.

VERSION 1 – AUTHOR RESPONSE

Dr. Alparslan Kurtul, Ankara Numune Education and Research Hospital Nephrology Clinic

Comments to the Author:

In this study researchers aimed to investigate the value of SYNTAX scores for predicting cardiovascular events in patients with multivessel CAD. They found that, diabetes was independent predictor of mortality at 5 years in multivariate analysis of the PCI cohort. They concluded that in patients with multivessel CAD, coronary atherosclerotic burden alone was not associated with significantly increased risk of death and MACCE. Overall, the study is well conducted and delivers potentially interesting observation in patients with CAD. But, the manuscript has some limitations. My detailed suggestions are below;

1. There is no description of approval of this study by the Ethics Committee in your facility.

Thank you for your comments. The journal editor made the same observation. This has been added to the text and highlighted in red.

2. Please give a chart for study inclusion and exclusion more clearly.

Thank you for this suggestion. This information was withdrawn, at the request of the editor, due to the limitation of figures and tables. For clarity, these data were described in a supplementary table and highlighted in red.

Table S1. Inclusion and exclusion criteria.

Inclusion criteria
•□Multivessel CAD (defined as stenosis ≥ 70% in at least 2 of the 3 main coronary arteries)

•□Preserved LVEF
•□Stable CAD
Exclusion criteria
•□Refractory angina or acute MI requiring emergency revascularization
•□Ventricular aneurysm requiring surgical repair
•□Left ventricular ejection fraction of <40%
•□Previous PCI or CABG
•□Single-vessel CAD
•□History of congenital heart disease, valvular heart disease, or cardiomyopathy
•□Patients unable to understand or cooperate with the protocol requirements
•□Left main coronary artery stenosis of ≥50%
•□Suspected or known pregnancy
•□Another coexisting condition that was a contraindication to CABG or PCI.

3. In Table 1, blood pressure and pulse rate should be added. Although all numeric variables were indicated as mean +/- SD in Tables, variables which were not normally distributed should be indicated using median and interquartile range. Statistical method for comparison of them between groups should be appropriately selected.

Thank you for the observation. I agree that demographic, laboratory and clinical data must be fully explained. We have added vital signals to the table 1. We have revised Table 1 to include median and interquartile range when appropriate.

	PCI (n = 573)	**CABG (n = 572)**	**MT (n = 574)**	**p Value**
Age at randomization, yr	59.78 ± 8.8	61.75 ± 8.97	60.69 ± 8.59	0.222
Male	378 (66.0)	397 (69.4)	383 (66.7)	0.428
Current smoker	124 (21.6)	163 (28.5)	126 (22.0)	<0.001

Hypertension	488 (85.2)	469 (82.0)	453 (78.9)	0.023
Diabetes	292 (51.0)	294 (51.4)	334 (58.2)	0.023
Previous MI	269 (46.9)	242 (42.3)	222 (38.7)	0.018
COPD	4 (0.7)	26 (4.5)	15 (2.6)	<0.001
PAD	15 (2.6)	64 (11.2)	19 (3.3)	<0.001
BMI, kg/m^2	27.74 ± 4.55	27.70 ± 4.09	27.92 ± 4.41	0.547
Systolic blood pressure, mm Hg	126.4 ± 16.1	127.8 ± 16.0	128.0 ± 15.4	0.487
Diastolic blood pressure, mm Hg	72.7 ± 10.7	73.1 ± 10.6	74.2 ± 11.0	0.097
Heart rate, bpm	69.5 ± 11.3	68.7 ± 10.7	69.0 ± 10.8	0.234
Total cholesterol, mg/dL	197.85 ± 55.16	197.50 ± 50.92	194.60 ± 49.28	0.466
LDL cholesterol, mg/dL	122.30 ± 43.30	122.48 ± 42.35	120.69 ± 42.64	0.684
HDL cholesterol, mg/dL	38.57 ± 10.25	39.46 ± 10.66	40.06 ± 11.40	0.068
Triglycerides, mg/dL	183.71 ± 151.51	176.55 ± 109.93	172.67 ± 123.99	0.175
Glucose, mg/dL	131.07 ± 52.70	131.08 ± 55.66	138.10 ± 61.32	0.147
Glycated hemoglobin, %	6.81 ± 1.70	6.70 ± 1.64	7.01 ± 1.81	0.004
Creatinine, mg/dL	1.04 ± 0.26	1.07 ± 0.26	1.07 ± 0.40	0.107
LVEF, %	61.3 ± 9.3	61.1 ± 8.7	60.9 ± 9.8	0.725
Positive treadmill test	391 (68.2)	378 (66.1)	347 (60.5)	<0.001
Angina CCS class				

I	69 (12.0)	60 (10.5)	124 (21.6)	<0.001
II	293 (51.2)	367 (64.2)	314 (54.7)	
III	193 (33.7)	121 (21.2)	127 (22.1)	
IV	18 (3.1)	24 (4.2)	9 (1.6)	
Coronary anatomy				
2-vessel disease	229 (40.0)	135 (23.6)	155 (27.0)	<0.001
3-vessel disease	344 (60.0)	437 (76.4)	419 (73.0)	
LAD disease	535 (93.4)	547 (95.6)	557 (97.0)	0.012
LMCAD	20 (3.5)	158 (27.6)	13 (2.3)	<0.001
SYNTAX score	17.22 ± 6.55	24.18 ± 8.20	19.46 ± 7.56	<0.001
SYNTAX score II	28.13 ± 7.97	25.03 ± 10.52	21.69 ± 8.53	<0.001
Residual SYNTAX score	8.43 ± 6.39	4.31 ± 4.92	19.46 ± 7.56	<0.001
Surgery off-pump	NA	249 (43.7)	NA	-
Left internal thoracic artery	NA	559 (97.7)	NA	-
BMS use	369 (64.4)	NA	NA	-
DES use	204 (35.6)	NA	NA	-
No. of graft vessels	NA	2.9 ± 0.7	NA	-
Total number of stents	2.1 ± 1.0	NA	NA	-

Values are presented as mean ± SD, median (interquartile range), or number (%).

Legend: BMI = body mass index; BMS = bare metal sent; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; DES = drug eluting stent; HDL = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LDL = low-density lipoprotein

cholesterol; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection function; MI = myocardial infarction; PAD = peripheral artery disease; NA = not available.

4. In order to emphasize the clinical importance of SYNTAX score in patients with diabetes and CAD, please also cite and discuss the following work (Kurtul BE, Kurtul A, Yalçın F. Predictive value of the SYNTAX score for diabetic retinopathy in stable coronary artery disease patients with a concomitant type 2 diabetes mellitus. Diabetes Res Clin Pract 2021;177:108875. doi: 10.1016/j.diabres.2021.108875.)

In fact, it is well established that the atherosclerotic burden is more pronounced in diabetes and this, in turn, is an additional factor in coronary heart disease. Kurtul's study clearly showed this relationship. In this study, authors found that the SYNTAX Score is independently associated with the occurrence of Diabetes Retinopathy in patients with type 2 diabetes. This data were added to the text and highlighted in red.

Additionally, a recent study conducted by Kurtul et al identified a strong correlation between diabetic retinopathy and atherosclerotic burden measured by the SYNTAX Score [18].

5. There are some grammar and vocabulary mistakes, which warrant revision.

Thank you for the observation. The manuscript has been edited by a native English speaker.

Dr. Michelle Williams, University of Edinburgh

Comments to the Author:

This study looks at the association between three invasive coronary angiography derived scores and events in a retrospective analysis of patients undergoing invasive coronary angiography.

Thank you for the constructive comments that will substantially improve the manuscript.

Title
Needs to state that invasive this is based on invasive coronary angiography.

Important note. Due to limited character count, we chose not to specify that the SYNTAX Score was obtained by invasive angiogram because this is the standard approach to calculate the score. This point will be clarified in the Introduction section.

Abstract:

Results need improved, needs to contain numbers for the findings that are being stated.

Very well observed. We have added this information to the abstract.

Results A total of 1,719 patients, whose mean age was 60.74±8.78 years, underwent PCI (n = 573), CABG (n = 572), or MT (n = 574) alone. The SS was not considered an independent predictor of 5-year death and MACCE in the PCI (low, intermediate and high SS for death 6.5%, 6.8% and 4.3%, p=0.745; for MACCE 27.1%, 34.8%, 42.9%, p=0.122), CABG (low, intermediate and high SS for death 5.7%, 8.0% and 12.1%, p=0.194; for MACCE 15.9%, 19.1% and 20.3%, p=0.620) and MT (low, intermediate and high SS for death 6.8%, 6.9% and 6.5%, p=0.993; for MACCE 24.3%, 28.5% and 25.8%, p=0.580) cohorts. The SSII (low, intermediate and high SSII, 3.6% vs. 7.9% vs. 10.5%, respectively, p <0.001) was associated with a higher risk of death in the overall population. Within each treatment strategy, SSII was associated with a significant incidence in death at 5 years, especially in CABG patients with intermediate and high SSII (low, intermediate and high SSII, 1.8%, 9.7% and 10.0%, respectively, p = 0.004) and in MT patients with high SSII (low, intermediate and high SSII,

5.0%, 4.7% and 10.8%, p = 0.031). SSII demonstrated a better predictive accuracy for death compared with SS and rSS.

Introduction

Needs to include that the syntax score is with invasive coronary angiography.

Thank you. We chose not to specify that the SYNTAX Score was obtained by invasive angiogram because it is established that angiography is invasive and the score is based on this angiography.

Methods:

Needs to talk about ethics and informed consent.

Thank you for the observation. This requirement was requested by the editor and added to the text and highlighted in red.

Weighted kappa is needed for agreement if there are several groups.

Thank you for pointing this out. The Weighted kappa was calculated and added to the text. We have added the sentences below to the manuscript.

Coefficients ranging from 0.21 to 0.40 are considered fair, from 0.41 to 0.60 moderate, from 0.61 to 0.80 substantial, and over 0.81 excellent. For ordinal variables, the weighted kappa coefficient was used to express the degree of agreement inter-observer and intra-observer.

The intra-observer and inter-observer weighted kappa scores according to SS tertile (≤22, 23 to 32, ≥33) were 0.68 and 0.61, respectively, indicating a substantial agreement.

As this paper is about three scores these need better defined in the methods, and their similarities and differences highlighted. A table or figure would be good for this.

Great observation. This data was attached to the supplement, due to the limitation of tables / figures. See table S2 in the supplement.

Table S2. **SYNTAX scores subgroups definition.**

SYNTAX scores	**Low**	**Intermediate**	**High**
SS	≤22	23 to 32	≥33
SSII	<18.7	18.7 to 25.7	>25.7
rSS	0 to 4	>4 to 8	>8

Legend: SS = SYNTAX score; SSII = SYNTAX score II; rSS = residual SYNTAX score.

Not sure what you mean by using CABG as the reference.

For methodological reasons, CABG is used as a reference to percutaneous treatment. In this sense, we also use CABG as a reference to medical treatment.

How were endpoints discovered, phone, records, other?

Relevant question. The MASS-Trial is a study group founded over 40 years ago, dedicated to comparing different therapeutic strategies. It has a functional structure for long-term patient follow-up for different research protocols. In this way, our visits are conducted face-to-face with all data stored in our own database.

Results:

136 patients didn’t have their data analyzed - why not?

Good question. These patients interrupted their follow-up with the MASS group a long time ago. We were unable to contact these patients. We have added this information to the manuscript.

A total of 136 patients were lost to follow-up.

Did no one have single vessel disease?

Excellent question. Assuming that patients with single vessel disease have a different prognosis from multivessel disease, we chose not to include them in the study. In addition, the SYNTAX Score would show a discrepant score for patients with single vessel disease. Thus, to homogenize the sample, we only included multivessel disease.

What was the indication for imaging?

Thank you for your question. The indication for cardiac catheterization was the presence of angina or the detection of ischemia in routine non-invasive studies.

Observer agreement needs to be presented for the other scores as well.

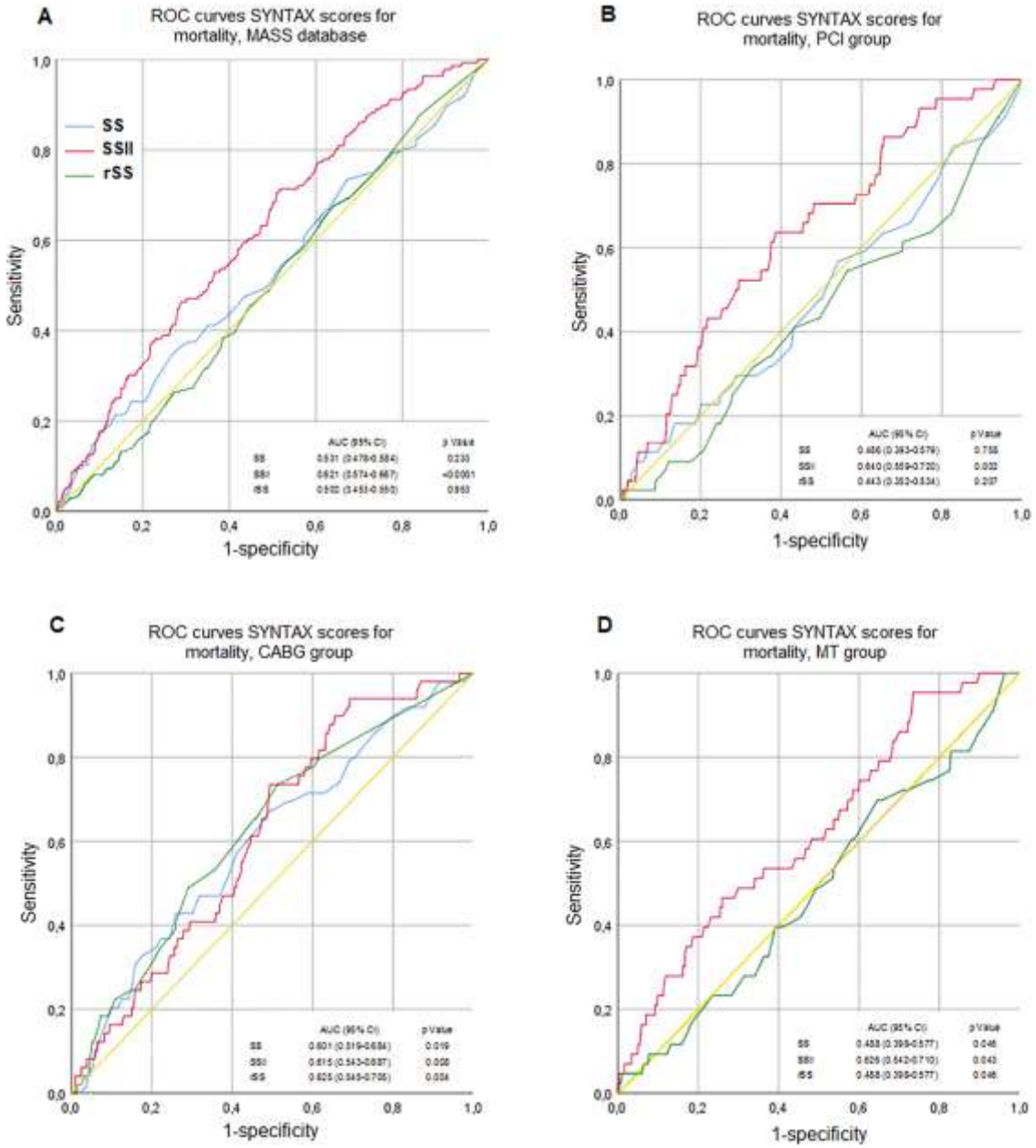
Good question. The agreement was made only for the SS, as the other scores derive from it.

What variables were chosen to include and not include in the multivariable models?

Thank you for your question. For univariate analysis, we selected the following variables: gender (female vs. male); Diabetes (yes vs. not); previous myocardial infarction (yes vs. not); treadmill test (positive vs. negative); coronary disease (2-vessel vs. three vessel); chronic obstructive pulmonary disease (yes vs. not); peripheral artery disease (yes vs. not); angina (yes vs. not); left main coronary artery disease (yes vs. not); hypertension (yes vs. not); SS (low, intermediate and high); SSII (low, intermediate and high); and rSS (low, intermediate and high). The variables with a probability value of <0.20 in the univariate analysis were included in the backward stepwise multivariable model (Diabetes, treadmill test, SSII, and SSII).

AUC need 95% confidence intervals and p values are needed if you are saying there is a difference.

Thank you. We have added this information to the manuscript.



Discussion

The main finding is that the original syntax score does not discriminate in terms of subsequent mortality, the new score is better but still not particularly good. This should be clearly stated in the first paragraph.

You are absolutely correct. The SYNTAX Score is a tool that analyzes anatomical aspects of coronary artery disease. It simply tries to indicate paths for surgical or percutaneous

procedures. The results obtained by the interventions (Death, MI or additional intervention) must be attributed to the disease and, in part, to the interventions. SYNTAX only scores atherosclerotic burden.

All the scores include atherosclerotic burden in terms of presence of stenoses, but do not truly assess atherosclerotic burden like IVUS or CT do, so that comparison between scores is not a fair one. When discussing reference 12 you need to say that this was on computed tomography.

Again, you are absolutely right. The atherosclerotic load might not be directly related to the occurrence of events. These only occur with the destabilization of the atherosclerosis plaque. Atherosclerotic burden with stable plaques remains chronically stable. IVUS and Optical Coherence Tomography are much more sensitive in detecting this condition. We have added this information to the manuscript.

"...assessed by coronary computed tomography angiography..."

Limitations section needed - one centre, small number, retrospective, significant selection bias as it is only patients undergoing invasive coronary angiography, only invasive coronary angiography assessment.

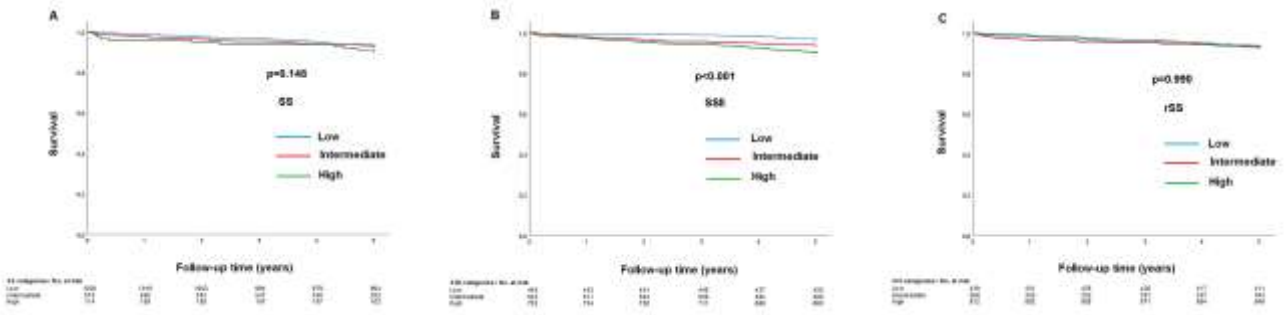
Thank you for your observation. We have added this information to the manuscript.

This study has a few limitations that need to be acknowledged. First, this was a retrospective study, with the intrinsic biases associated with this type of study. However, predictors and outcome variables were collected prospectively. Second, revascularization strategies and standards of practice changed over time. These changes occurred in all study patients, irrespective of the therapeutic group they were placed in at the initiation of the study. Third, the sample size of our study is limited, which may compromise statistical power. Last, the data were collected in a single center, which may limit the generalizability of our results. Nevertheless, the homogeneity of treatment reduces the limitations of the present study.

Figures are very small to analyze. P values are needed on the first km curves as well. What are the p values on the ROC curves? P values for comparisons are needed.

Thank you very much for pointing this out. We have added p values in the first KM curves and the ROC curves.

Figure 1 Kaplan-Meier Survival Curves for All-cause Mortality According to SYNTAX Scores.



ROC curves with p values previously presented.