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Prognostic value of residual SYNTAX score on in-hospital and follow-up clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing pharmacoinvasive strategy

Valor prognóstico do escore SYNTAX residual nos desfechos clínicos intra-hospitalares e de acompanhamento em pacientes com infarto do miocárdio com supradesnivelamento do segmento ST submetidos à estratégia farmacoinvasiva

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ABSTRACT – **Background:** Multivessel coronary artery disease is a challenge in clinical practice. An individualized approach should consider not only the patient characteristics, but also a multidisciplinary approach, together with the Heart Team. Multiple angiographic scores have been proposed with the aim of quantifying the risk associated with multivessel coronary artery disease. Residual SYNTAX score has been proposed as a method to systematically characterize and quantify residual coronary disease after percutaneous coronary intervention. There are few data in the literature correlating the residual SYNTAX score in patients with ST-segment elevation myocardial infarction undergoing pharmacoinvasive strategy. The objective of this study was to evaluate the SYNTAX score and residual SYNTAX score as predictors of in-hospital and medium-term outcomes (180 to 380 days) in patients with multivessel coronary artery disease in the setting of ST-segment elevation myocardial infarction, after successful fibrinolytic therapy. **Methods:** In a cross-sectional, analytical, and prospective study, we evaluated residual SYNTAX score as predictor of in-hospital and medium-term outcomes (6 months to 1 year), in patients with multivessel coronary artery disease, in the setting of ST-segment elevation myocardial infarction after pharmacoinvasive strategy. **Results:** Between August 2019 and December 2020, 108 patients with ST-segment elevation myocardial infarction after fibrinolysis, with reperfusion criteria, were analyzed. The mean SYNTAX score was 13.98 (±4.87) and the mean residual SYNTAX score was 7.56 (±4.47). High residual SYNTAX score was associated with contrast-induced nephropathy and major adverse cardiac event. It was also an independent predictor of major adverse cardiac event with a 9.69-fold increased risk (p=0.0274). **Conclusion:** High residual SYNTAX score confers worse prognosis in patients with ST-segment elevation myocardial infarction after pharmacoinvasive strategy.

Keywords: Myocardial infarction; ST elevation myocardial infarction; Fibrinolysis; Acute coronary syndrome

RESUMO – **Introdução:** A doença arterial coronariana multiarterial é um desafio na prática clínica. Uma abordagem individualizada deve considerar não apenas as características do paciente, mas também um enfoque multidisciplinar, com o *Heart Team*. Diversos escores angiográficos foram propostos com o objetivo de quantificar o risco associado à doença arterial coronariana multiarterial. O escore SYNTAX residual foi proposto como um método para caracterizar e quantificar a doença coronariana residual, de forma sistemática, após intervenção coronária percutânea. Existem poucos dados na literatura que correlacionam o escore SYNTAX residual em pacientes com infarto do

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miocárdio com supradesnivelamento do segmento ST submetidos a uma estratégia farmacoinvasiva. O objetivo deste estudo foi avaliar o escore SYNTAX e o escore SYNTAX residual como preditores de desfechos intra-hospitalares e de médio prazo (180 a 380 dias), em pacientes com doença coronária multiarterial no contexto de infarto do miocárdio com supradesnivelamento do segmento ST, após terapia fibrinolítica bem-sucedida. **Métodos:** Em um estudo transversal, analítico e prospectivo, avaliamos o escore SYNTAX residual como preditor de desfechos intra-hospitalares e de médio prazo (6 meses a 1 ano), em pacientes com doença arterial coronariana multiarterial, no contexto de infarto do miocárdio com supradesnivelamento do segmento ST após estratégia farmacoinvasiva. **Resultados:** Entre agosto de 2019 e dezembro de 2020, foram analisados 108 pacientes com infarto do miocárdio com supradesnivelamento do segmento ST após fibrinólise, com critérios de reperfusão. O escore SYNTAX médio foi 13,98 (±4,87) e o escore SYNTAX residual médio foi 7,56 (±4,47). O escore SYNTAX residual elevado foi associado à nefropatia induzida por contraste e evento cardíaco adverso maior. Também foi um preditor independente de evento cardíaco adverso maior, com risco aumentado 9,69 vezes (p=0,0274). **Conclusão:** O escore SYNTAX residual elevado confere pior prognóstico em pacientes com infarto do miocárdio com elevação do segmento ST após estratégia farmacoinvasiva.

INTRODUCTION

The therapeutic approach to multivessel coronary artery disease (CAD) is a challenge in clinical practice. An individualized approach should not only consider the characteristics of patients, but also a multidisciplinary approach with the Heart Team, composed of clinical, surgical, and interventional cardiologists.

Several angiographic scores were proposed with the objective of quantifying the risk associated with multivessel CAD. Most of these scores were established based on the concept of myocardium at risk and on severity of coronary artery disease.[1] It is known that incomplete revascularization is one of the main factors associated with increased risk of adverse ischemic events. The residual SYNTAX score (rSS) was proposed as a method to systematically characterize and quantify residual coronary disease after percutaneous coronary intervention (PCI).[2] It consists of the subtraction between the initial SYNTAX score and the final SYNTAX score after successful PCI. It has been validated by several studies and has been shown to have good prognostic accuracy for adverse ischemic outcomes after primary PCI.[3] There are few data in the literature correlating SYNTAX score and rSS in patients with ST-segment elevation myocardial infarction (STEMI) undergoing pharmacoinvasive strategy.

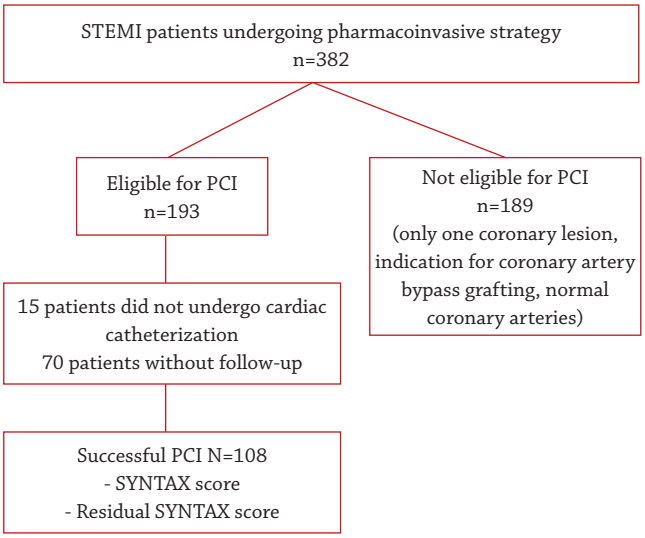
The objective of this study was to evaluate the SYNTAX score and rSS as predictors of in-hospital and medium-term outcomes (180 to 380 days) in patients with multivessel CAD in the setting of STEMI, after successful fibrinolytic therapy.

METHODS

This research was designed and performed as a cross-sectional, analytical, and prospective study of patients hospitalized in a cardiology reference center in the city of Brasília, with diagnosis of STEMI, after undergoing pharmacoinvasive strategy between August 2019 and December 2020. A group of 108 patients was included in the final analysis (Figure 1).

Inclusion criteria were all patients diagnosed with STEMI after fibrinolytic use with clinical and electrocardiographic reperfusion criteria, between August 2019 and December 2020. Exclusion criteria were acute myocardial infarction without ST-segment elevation. The decision to treat culprit-only or staged PCI was based on the coronary anatomy, disease severity, age, comorbidities, and operator's decision. The rSS was calculated after complete revascularization, whenever possible.

Chronic renal failure was defined as an estimated glomerular filtration rate less than 60mL/minute per 1.73m^2. Contrast-induced nephropathy (CIN) was the impairment of renal function gauged as either a rise by 25% in serum creatinine from baseline, or an increase by 0.5mg/dL in absolute serum creatinine value, within 48 to 72 hours after contrast administration. Deaths were classified as cardiovascular or non-cardiovascular. The cause of death was determined by the principal condition that resulted in the death, not the immediate mode of death. Managing physicians employed all pieces of information available, along with clinical expertise, in their adjudication of the cause of death.



STEMI: ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.
Figure 1. Study flowchart.

Death from cardiovascular causes included myocardial infarction and its complications (*e.g.*, arrhythmia, sudden arrest, heart failure), sudden cardiac death, heart failure, stroke, complications of cardiovascular procedures, cardiovascular hemorrhage (*e.g.*, intracranial hemorrhage), non-procedural or non-traumatic vascular rupture (*e.g.*, aortic aneurysm), or hemorrhage causing cardiac tamponade), other cardiovascular causes not included in the above categories, but with a specific, known cardiovascular cause (*e.g.*, pulmonary thromboembolism or peripheral arterial disease). Stroke was a focal neurological deficit of central origin, lasting more than 24 hours (except for death within 24 hours), with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage; a focal neurological deficit of central origin lasting less than 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage.

Continuous data was presented as means with standard deviations and comparative analysis was performed using Student´s *t* or Mann-Whitney rank tests, depending on sample distribution characteristics. Categorical variables were expressed in frequency and percentage and compared with chi-squared or Fisher exact tests. Multivariate analysis to determine independent predictors for major adverse cardiovascular events (MACE) was performed by means of Poisson regression with robust variance, using as an effect measure, the prevalence ratio and its respective confidence intervals. Possible predictors comprised sex, age (<60; ≥60 years), ejection fraction (≤40; >40), hypertension (HTN), diabetes mellitus (DM), dyslipidemia (DLP), chronic renal failure (CRF), previous CAD, smoking and rSS. Poisson regression with robust variance was used because it provides a better estimate of the prevalence ratio, which, in turn, represents more significant effect measures for cross-sectional studies. Receiver Operating Characteristic (ROC) curves were calculated to determine the rSS value that provided the best predictive accuracy for MACE. The Youden index was used to determine the optimal cutoff point in the ROC curve. Next, similar multivariate analysis, which included epidemiological and clinical characteristics at baseline was performed to determine independent predictive factors for rSS. A p-value <0.05 was considered significant. The analyses were conducted using SAS 9.4 application.

The study was approved by the Human Research Ethics Committee and the Research Ethics Committee of University of Brasilia, and registered in the *Plataforma Brasil* (CAAE: 30178719.3.0000.5558), and was in accordance with the ethical principles for research involving human beings established by the Declaration of Helsinki, based on the good clinical research practices. Informed consent was obtained from all participants.

RESULTS

A total of 108 STEMI patients undergoing successful pharmacoinvasive strategy were included. The mean age was 59±10 years, 72.2% were male, 82.4% had hypertension, 33.3% had diabetes and 7.5% had previous coronary artery disease. Clinical and demographic characteristics are described in table 1.

Mortality was 3.7%, three in-hospital deaths and one death in follow-up. The causes of in-hospital death were secondary to coronavirus infection with progression to mixed shock (septic and cardiogenic), and in the follow-up was secondary to lung cancer. The higher bleeding rate by the ACUITY criterion was 2.7%. There were two cases of intracranial hemorrhage, and one case of hemoglobin reduction by >3 g/dL, with evident origin (inguinal hematoma). Angiographic results are described in table 2.

Initially, the optimal cutoff points of the rSS for adverse cardiac events for in-hospital and follow-up between 180 and 380 days were determined.

- In-hospital: area under the ROC curve (AUC) of 0.65 with a 95%CI ranging from 0.44 to 0.86, and the hypothesis test that AUC of 0.50 provided a p-value =0.1505. The optimal cutoff point was equal to 9, which provides a sensitivity of 0.67 with 95%CI 0.22-0.96, and specificity of 0.71 with 95%CI 0.61-0.79, indicated in figure 2.

Table 1. Clinical and demographic characteristics

Age (years)	59±10.88
Male sex	78 (72.2)
Hypertension	89 (82.4)
DM2	36 (33.3)
DLP	77 (71.3)
CRF	24 (22.2)
Smoking	39 (36.1)
History of CAD	8 (7.4)

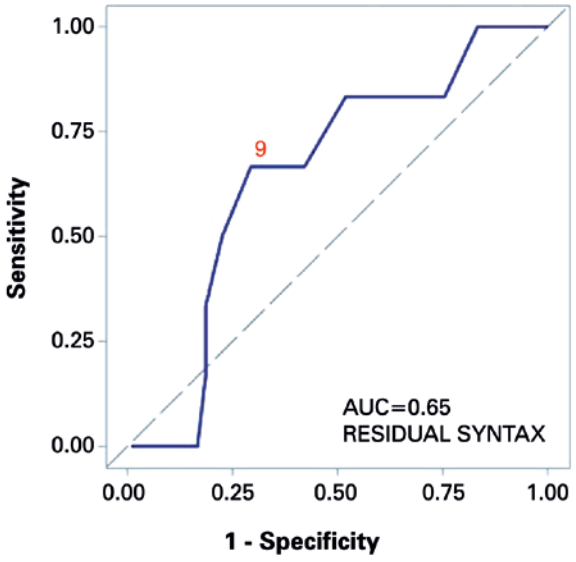
Results expressed as average ± standard deviation or n (%).
DM2: type 2 diabetes mellitus; DLP: dyslipidemia; CRF: chronic renal failure; CAD: coronary artery disease.

Table 2. Angiographic characteristics

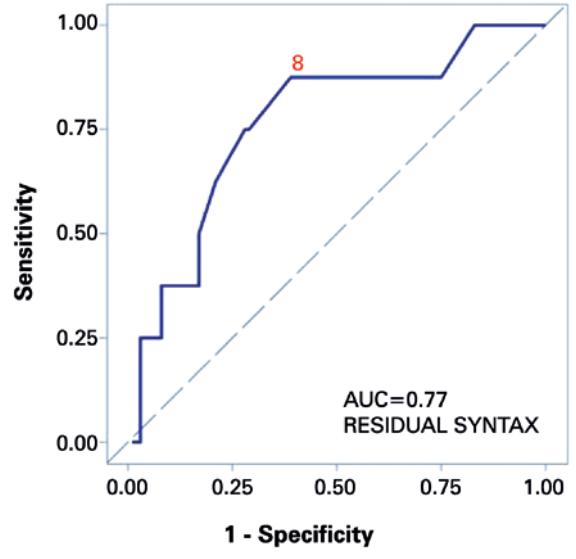
Infarction-related artery	
LAD	53 (49.1)
CX	15 (13.9)
RCA	35 (32.4)
Other	5 (4.6)
Mean SYNTAX score	13.98±4.87
Mean residual SYNTAX score	7.56±4.47

Results expressed as n (%) or avarage ± standard deviation.
LAD: left anterior descending artery; CX: circumflex artery; RCA: right coronary artery.

- 180-380-day follow-up: AUC of 0.77, with a 95%CI ranging from 0.59 to 0.94, and the hypothesis test that AUC of 0.50 provided a p-value=0.0037. The optimal cutoff point was equal to 8, which provides a sensitivity of 0.87 with 95%CI 0.47-1.00, and specificity of 0.61, with 95%CI 0.51-0.71, as indicated in figure 3.



AUC: area under the curve.
Figure 2. Receiver Operating Characteristic curve determining the optimal cutoff point of residual SYNTAX score for in-hospital major adverse cardiovascular events.



AUC: area under the curve.
Figure 3. Receiver Operating Characteristic curve determining the optimal cutoff point of residual SYNTAX score for major adverse cardiovascular events at follow-up (180 to 380 days).

In-hospital results

Patients were dichotomized into categories of high RSS (≥9) and low (<9) in the in-hospital phase. Neither demographic nor clinical characteristics showed significant difference between mean values, or significant association with the cutoff value of the in-hospital rSS, as shown in table 3.

Table 3. Demographic and clinical characteristics according to in-hospital residual SYNTAX score

Variables	rSS <9 (n=74)	rSS ≥9 (n=34)	p-value
Age (years)	58.95±10.86	60.17±11.05	0.587
Ejection fraction (ECHO)	49.38±9.58	51.76±11.68	0.265
Sex			0.504
Female	22 (73.3)	8 (26. 7)	
Male	52 (66.7)	26 (33.3)	
Hypertension			0.272
No	11 (57.9)	8 (42.1)	
Yes	63 (70.8)	26 (29.2)	
Diabetes mellitus			0.769
No	50 (69.4)	22 (33.3)	
Yes	24 (66.7)	12 (33.3)	
Dyslipidemia			0.420
No	23 (74.2)	8 (25.8)	
Yes	51 (66.2)	26 (33.8)	
Chronic renal failure			0.223
No	60 (71.4)	24 (28.6)	
Yes	14 (58.3)	10 (41.7)	
History of CAD			0.705
No	69 (69.0)	31 (31.0)	
Yes	5 (62.5)	3 (37.5)	

Results expressed as average ± standard deviation or n (%).
ECHO: echocardiography; CAD: coronary artery disease.

There was a significant association between rSS and CIN (p=0.036). Patients with CIN were more associated with rSS ≥9 than those without CIN. For the other variables, there was no significant association between rSS and the occurrence or not of cardiac outcomes, as shown in table 4.

Follow-up results

Between 180 and 380 days, patients were divided into two categories: high rSS (≥8) and low rSS (<8). There was a significant association between rSS and CRF (p=0.02). For the other epidemiological or clinical characteristics, there was no significant difference between the mean values or association with rSS, according to table 5.

Table 4. Cardiac outcomes according to in-hospital residual SYNTAX score

Variables	rSS <9 (n=74)	rSS ≥9 (n=34)	p-value
Cardiac death			0.238
No	73 (69.5)	32 (30.5)	
Yes	1 (33.3)	2 (66.7)	
Non-fatal MI			0.532
No	73 (68.9)	33 (31.1)	
Yes	1 (50.0)	1 (50.0)	
TVR			0.315
No	74 (69.2)	33 (30.8)	
Yes	0	1 (100.0)	
TLR			0.315
No	74 (69.2)	33 (30.8)	
Yes	0	1 (100.0)	
CABG			-
No	74 (68.5)	34 (31.5)	
Yes	0	0	
Major bleeding			1.000
No	72 (68.6)	33 (31.4)	
Yes	2 (66.7)	1 (33.3)	
CIN			0.036
No	63 (73.3)	23 (26.7)	
Yes	11 (50.0)	11 (50.0)	
MACE			0.077
No	72 (70.6)	30 (29.4)	
Yes	2 (33.3)	(66.7)	

Results expressed as n (%).
rSS: residual SYNTAX score; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; CABG: coronary artery bypass graft; CIN: contrast-induced nephropathy; MACE: major adverse cardiac event.

Table 5. Epidemiological and clinical characteristics according to residual SYNTAX score at follow-up

Variables	rSS <8 (n=62)	rSS ≥8 (n=46)	p-value
Age, years	58.03±10.16	61.09±11.67	0.150
Ejection fraction (ECHO)	49.50±9.76	50.98±11.03	0.463
Sex			0.923
Female	17 (56.7)	13 (43.3)	
Male	45 (57.7)	33 (42.3)	
Hypertension			0.329
No	9 (47.4)	10 (52.6)	
Yes	53 (59.5)	36 (40.4)	
Diabetes mellitus			0.335
No	39 (54.2)	33 (45.8)	
Yes	23 (63.9)	13 (36.1)	
Dyslipidemia			0.732
No	17 (54.8)	14 (45.2)	
Yes	45 (58.4)	32 (41.6)	
Chronic renal failure			0.025
No	53 (63.1)	31 (36.9)	
Yes	9 (37.5)	15 (62.5)	
History of CAD			1.000
No	57 (57.0)	43 (43.0)	
Yes	5 (62.5)	3 (37.5)	

p-value calculated by Student's t-test/Mann-Whitney, or Fisher Chi-squared/exact test.
Results expressed as average ± standard deviation or n (%).
rSS: residual SYNTAX score; ECHO: echocardiogram; CAD: coronary artery disease.

There was a significant association between rSS and CIN (p=0.04). Patients with CIN were more associated with rSS ≥8 than those without CIN. There is a significant association between rSS and MACE (p=0.01) – patients with MACE were more associated with rSS ≥8, according to table 6.

Table 6. Residual SYNTAX score in follow-up

Variables	rSS <8 (n=62)	rSS ≥8 (n=46)	p-value
Cardiac death			0.310
No	61 (58.6)	43 (41.3)	
Yes	1 (25.0)	3 (75.0)	
Non-fatal MI			0.074
No	62 (59.0)	43 (40.9)	
Yes	0	3 (100.0)	
TVR			-
No	62 (57.4)	46 (42.6)	
Yes	0	0	
TLR			-
No	62 (57.4)	46 (42.6)	
Yes	0	0	
CABG			0.179
No	62 (58.5)	44 (41.5)	
Yes	0	2 (100.0)	
Major bleeding			1.000
No	60 (57.1)	45 (42.9)	
Yes	2 (66.7)	1 (33.3)	
CIN			0.040
No	61 (60.4)	40 (39.6)	
Yes	1 (14.3)	6 (86.7)	
MACE			0.010
No	61 (61.0)	39 (39.0)	
Yes	1 (12.5)	7 (87.5)	

p-value calculated by the Chi-squared/exact Fisher test.
Results expressed as n (%).
rSS: residual SYNTAX score; MI: myocardial infarction, TVR: target vessel revascularization; TLR: target lesion revascularization; CABG: coronary artery bypass graft; CIN: contrast-induced nephropathy; MACE: major adverse cardiac event.

Independent predictors of high rSS included smoking (p=0.04) and patients with CRF (p=0.01). Patients with a high rSS had a 9.69-fold higher incidence of MACE than patients with a low rSS (p=0.02), and patients with a low ejection fraction (≤40) had an incidence of MACE occurrence 3.14-fold higher than patients with a preserved ejection fraction (>40) (p=0.04).

DISCUSSION

The present study showed that anatomical residual coronary artery disease (rSS≥8) helped to predict worsen prognosis in patients with STEMI and undergoing pharmacoinvasive strategy. This was also shown in many trials,

such as DANAMI-3 PRIMULTI, PRAMI (Preventive Angioplasty in Myocardial Infarction) and CvLPRIT (Complete *versus* Lesion-Only Primary PCI Trial), where the authors demonstrated occurrence of MACE was positively correlated with higher residual coronary artery disease, which is objectively assessed using rSS.[4-6]

The importance of systematizing a risk angiographic score in patients with STEMI has been previously evaluated.[2,3] Although the SYNTAX score has been described and validated in patients with multivessel CAD and left main artery disease, it has also been shown to be an independent predictor of MACE and mortality in STEMI patients. However, the impact of residual coronary disease (rSS) after pharmacoinvasive strategy was poorly explored.

Some studies have shown that about 30 to 50% of patients with STEMI have multiple coronary lesions. Revascularization of the infarction-related artery is associated with lower mortality rates, reinfarction and development of heart failure.[7,8] Therefore, it is important to systematically evaluate the real impact of residual coronary disease through rSS in these patients.

The mean baseline SYNTAX score was approximately 14, despite the low mean age, conferring to our population a similar profile of the ACUITY study.[9] One of the possible causes of the prognostic accuracy of the rSS for in-hospital mortality was the small number of patients and the short follow-up period. Probably, the incidence of CIN was a confounding factor for increased number of MACE.

In the short, medium- and long term, the Brazilian Unified Health System (SUS, acronym from the Portuguese) has several challenges, mainly because it needs more resources and the optimization of the use of public funds. Currently, twice as many resources are invested in diseases (hospitalizations, surgeries, transplants) than in basic health actions (vaccines and consultations), which prevent cardiovascular diseases. In fact, these are chronic public health problems in Brazil, largely due to a logic that experts define as short-sighted and hospital-centered approach. It must be replaced by a system that prioritizes Primary Care, early diagnosis, and prevention work.

Our total mortality rate was lower than 4% conferring an optimal metric for pharmacoinvasive strategy in our country, where there is still shortage of an organized infarction network. In-hospital deaths were associated with left ventricular dysfunction with mixed shock (one case with bacterial pneumonia associated with mechanical ventilation, and two cases of coronavirus infection). Follow-up deaths were associated with heart failure and sudden death and one case with lung cancer complications. Our stroke rate was lower than 3%, demonstrating safety of pharmacoinvasive strategy, although our mean age was less than 60 years. In the STREAM study, the total stroke rate was 1.6% in the pharmacoinvasive group, *versus* 0.5% in the primary PCI group.[10]

In the multivariate analysis, the group with rSS ≥8 had a higher incidence of CIN (p=0.036). Renal and cardiac problems are more common in those with atherosclerosis in other vascular structures. To corroborate this fact, we found higher rates of renal dysfunction and multivessel involvement in CIN. The prevalence of coronary artery disease may cause multiple coronary artery involvement and extensive atherosclerosis in the renal arterial bed by a similar mechanism. Based on this theory, and in the light of the results we obtained, multiple coronary artery involvement in STEMI patients may cause high rSS, diffuse atherosclerosis in the renal arterial bed, and indirectly renal dysfunction and consequently an increase in CIN tendency, by a similar mechanism. CIN is associated with a worse prognosis after PCI. It is associated with a high risk of renal failure and length of hospital stay with increased mortality rates.[11] There was no significant association between the rSS with other outcomes, including in-hospital mortality, perhaps due to the small sample and short follow-up period.

In our study, patients with a high rSS had a 9.69-fold higher incidence of MACE than patients with a low rSS (p=0.027). It could be explained by the fact that patients with high rSS had a large extent of myocardium that is jeopardized or ischemic, and overall vascular burden, which is high in these patients. In contrast, patients who had complete anatomical revascularization as evidenced by a lower rSS had excellent prognosis at follow-up. Généreux et al. had already proposed this association between the rSS as an independent predictor of MACE in patients with STEMI with incomplete revascularization after primary PCI.[2]

Revascularization of infarct-related artery is associated with decreased mortality, reinfarction and development of heart failure in patients with STEMI.[9] The question is whether pharmacological treatment and secondary prevention are sufficient to stabilize other plaques, because roughly 30 to 50% of patients with STEMI have more than one coronary lesion. Many compared the outcomes between complete revascularization *versus* culprit-lesion-only revascularization after PCI. A metanalysis presented by Atti et al., with more than 7,000 patients, showed lower risk of cardiovascular mortality and reinfarction with complete revascularization *versus* culprit-lesion-only revascularization.[12] Another study investigated the impact of complete *versus* culprit-lesion-only revascularization on 3-year patient outcomes in the SYNTAX trial, who declared that complete revascularization group had less number of MACE on follow-up.[13] Another meta-analysis from nine studies, by Aggarwal et al., showed less residual plaque burden following PCI was in line with a lower rate of death, myocardial infarction, and need for coronary artery bypass grafting, at a mean follow-up of 29 months.[14]

The rSS adds information to the STEMI scenario regardless of whether pharmacoinvasive strategy is used

as revascularization. The use of this tool is fundamental to identify high-risk patients (rSS ≥8) for adverse cardiovascular events and, thus, we can optimize the treatment strategy, trying to reduce the impact of residual coronary disease with complete revascularization, when it is feasible.

The limitations of our study were the small number of patients, the short follow-up period, and the experience of a single center.

CONCLUSION

The residual SYNTAX score ≥8 in the context of patients diagnosed with ST-segment elevation myocardial infarction and undergoing pharmacoinvasive strategy was associated with worsen prognosis. The development of contrast-induced nephropathy was more frequent in patients with a high residual SYNTAX score (≥8), probably due to multifactorial causes. Independent predictors of residual SYNTAX score include smoking, chronic renal failure, and ejection fraction ≤40%; other risk factors for cardiovascular disease were not associated with increased residual SYNTAX score.

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None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: RRF and FA; data collection: RRF and TF; data interpretation: RRF, TF and FA; text writing: RRF, TF and FA; approval of the final version to be published: RRF, TF and FA.

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