Original Article

Association Between Systemic Immune- Inflammation Index and Severity of Coronary Artery Disease in Acute Myocardial Infarction Patients

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Abstract:

Background: Acute myocardial infarction is one of the leading causes of death across the world. Determination of severity is important in patients with acute myocardial infraction for the therapeutic decision making. Systemic immune-inflammation index (SII) has been proposed as a new prognostic marker in patients with acute MI. Several international studies have found to compare the relation between SII and severity of coronary artery disease. In these studies, they demonstrated that the SII is higher in severe CAD. In our country, no such study has been done yet to predict the severity of coronary artery disease by estimating SII in acute MI patients. Moreover, SII is cheap, easily available, non-invasive and routinely done procedure.

Objectives: This study was conducted to find out the association of SII to severity of CAD in acute MI patients.

Methods: This observational cross sectional analytical study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, SSMC and Mitford Hospital and NICVD, Dhaka from March 2021 to February 2022. Patients with acute MI (STEMI and NSTEMI) were approached for this study according to inclusion and exclusion criteria. Coronary angiogram was done during index hospitalization. The severity of coronary artery disease was assessed by Vessel score and Gensini score. According to Gensini score CAD severity detected as mild to moderate (d"50) , severe (>50). Patients were divided into two groups according to Gensini score: Group A, severe CAD (Gensini score >50) and Group B, mild to moderate CAD(Gensini score d"50). SII calculated from admission CBC report.

Results: Among 70 patients in our study 33 (47.1%) were in the high Gensini group (Group A) and 37 (52.85%) were in low Gensini group (Group B). Mean systemic immune inflammation index was found significantly higher in group A than group B, p value 0.001. We found strong positive correlation between SII and Gensini score (r= 0.7, p= 0.001). With the increase of SII, Gensini score increases demonstrating more severe CAD. In multivariate logistic regression analysis, after adjustment of confounding, hypertension (p=0.01, OR=4.84), NLR (P=0.004, OR=1.81) and SII (P=0.011. OR=1.002) remain independent predictor of severe CAD. In ROC curve analysis, the AUC of SII for predicting severity of CAD is 0.8 with p value < 0.001, 95% CI (0.71-0.91) and SII cut off value 686 can predict severe CAD with 78% sensitivity and 76% specificity. So, from this study, it is evident that SII is directly associated with coronary artery disease severity.

Conclusion: Increased SII was associated with angiographically severe coronary artery disease in acute Myocardial Infarction patients and this association is independent of conventional cardiovascular risk factors.

Key words: SII: Systemic immune inflammation index; CAD: Coronary Artery Disease

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Introduction:

Cardiovascular diseases (CVDs) are the leading cause of death globally and major contributor of disability. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global death, of these 85% due to heart attack and stroke. Three quarters of CVD death take place in low and middle-income countries. [1]

CAD is growing by epidemic proportion day by day in Bangladesh.[2] The exact prevalence of coronary artery disease in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available.[3] Recent data indicates CAD prevalence in Bangladesh is between 1.85% and 3.4% in rural and 19.6% in urban population.[4]

The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

ACS are further classified into ST-elevation MI (STEMI), Non-ST elevation MI (NSTEMI) and Unstable angina (UA).[5] Acute myocardial infarction is the most severe manifestation of coronary artery disease.

Atherosclerosis plays a dominant role in the pathophysiological process of CAD and atherosclerosis are closely associated with inflammation.[6] Atherosclerosis is primarily an inflammatory disease and the role of inflammation in the process of initiation, progression and plaque de-stabilization in atherosclerosis has been well studied.[7] Evidence from various studies has demonstrated that increased levels of inflammatory markers are associated with increased rates of cardiac events in patients with CAD.[8]

The role of inflammatory markers in cardiovascular diseases has been studied extensively and a consistent relationship between various inflammatory markers and cardiovascular diseases has been established in the past. Among these C reactive protein (CRP), Highly sensitive CRP, Fibrinogen, Interleukin -6 (IL-6), Monocyte/ Macrophage colony stimulating factor (MCSF), Tumor necrosis factor alpha, Lipoprotein associated phospholipase A2, and Interlukin-1 isoform are noteworthy.

Different white blood cell (WBC) subtypes play crucial role in the pathogenesis of atherogenesis and atherothrombosis.[9] Neutrophils are the most abundant subtype of WBC which play major role in mediating inflammatory response. Neutrophils have been shown to mediate tissue damage and inflammation in advanced stage of atherosclerosis. It has been positively associated with necrotic core area, lesion size and plaque vulnerability. On the other hand, lymphocyte play an important role in regulating the inflammatory response and atherosclerotic process. A low lymphocyte count is associated with progression of atherosclerosis. Lymphopenia is associated with a poor prognosis in various disease like stable CAD, acute coronary syndromes and heart failure. Platelets are one of the major determinants of prothrombotic potential in arterial thrombosis and they also participate in the inflammatory process and atherogenesis. Active platelets interact with the endothelium, leukocyte and inactivated platelets. So, platelets have role in development of CAD.[10]

Biomarkers derived from the counts of these three cell types have been widely investigated in

recent years like neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and they

have been found to be associated with severity of coronary artery disease. Systemic Immune-

Inflammation Index (SII) is a novel and intriguing marker of inflammation and immune system.[11]

SII is determined as absolute platelet count × absolute neutrophil count/absolute lymphocyte count. SII gathers neutrophil, lymphocyte and platelet and reflects the balance between inflammatory and immune status. It has been suggested that since SII includes 3 cell types, it may provide valuable information regarding inflammation. It is a potential biomarker for cardiovascular diseases.[12]

Coronary angiography is the gold standard for the clinical judgement of CAD whereas the Gensini score is a quantitative indicator for the estimation of the severity of coronary artery stenosis on the basis of coronary angiography.

Several international studies have shown the relationship between SII and severity of CAD. They showed that higher the SII, higher the severity of CAD. So, purpose of our study is to demonstrate relation between SII and severity of CAD in acute MI patients.

Methods: This cross-sectional observational study was carried out in the Department of Cardiology of DMCH, Sir Salimullah Medical College and Mitford Hospital and National Institute of Cardiovascular Diseases, Dhaka from March,2021 to February 2022. Patients with acute myocardial infarction who undergone coronary angiogram during the study period were selected by purposive sampling. Patients who underwent prior PCI and/or CABG, patients with heart failure - NYHA class III, IV,

hematological diseases, malignancy, chronic kidney disease, chronic liver disease, ongoing infection, chronic inflammatory disease, autoimmune disease, pregnancy were excluded from the study. Total 70 cases were included in the study and were divided into two groups on the basis of severity of coronary artery disease according to Gensini score: Group A (Severe CAD, Gensini score > 50) and Group B (Mild-Moderate CAD, Gensini score d" 50). After taking informed written consent from each patient, meticulous history was taken and detailed clinical examination was performed and recorded in predesigned structured proforma. Levels of hemoglobin, white blood cells, neutrophils, lymphocytes, other differentials of white blood cells and platelets were determined by automated hematology analyzer. Serum creatinine, random blood sugar, fasting lipid profile and other screening tests for coronary angiogram were done. Coronary angiogram was done by conventional method in the same hospital setting. Severity assessment was done by Gensini score and vessel score.

SII was calculated by multiplying the number of platelets with NLR (Neutrophil-Lymphocyte Ratio) obtained from peripheral blood sample. Angiographic pattern and severity of coronary artery disease were assessed by interpretation of coronary angiogram by visual estimation by two cardiologists. Severity of coronary stenosis was graded according to the number of major epicardial vessel with significant stenosis (vessel score) and Gensini score.

In vessel score, significant coronary artery disease was defined as > 70% stenosis in any of

the three major epicardial coronary arteries or a left main coronary artery stenosis > 50%. Angiograms revealing coronary artery stenosis < 70% in major epicardial coronary arteries were termed non-obstructive CAD. Extent of coronary artery disease was defined as significant single, double or triple vessel coronary artery disease. Score ranged from 0 to 3 depending on the number of vessels involve. Left main coronary artery was scored as single vessel disease.

i) Score 0 = no vessel involvement, ii) Score 1 = single vessel involvement, iii) Score 2 = double vessel involvement, iv) Score 3 = triple vessel involvement.

The Gensini score was developed by Gensini and takes into consideration the geometrical severity of lesions by angiography, the cumulative effects of multiple obstructions, and the significance of jeopardized myocardium. A nonlinear score was assigned to each lesion based on the severity of stenosis as indicated by the reduction of lumen diameter. A multiplier was applied to each lesion score based upon its location in the coronary tree depending on the functional significance of the area supplied by that segment. The final Gensini score was the sum of the lesion scores. The score assessed 14 coronary artery segments, which were scored according to their anatomical importance (ranging from 0.5 to 5) multiplied by the score regarding the maximum degree of obstruction. The points of the 14 segments were summed up to yield a final score.

Total Gensini score was calculated as:

% of stenosis	Score
1-25%	1
26-50%	2
51-75%	4
76-90%	8
91-99%	16
100%	32
Vessel (S) involved	Vessel multiplier score
Left Main	5
Proximal LAD / LCX	2.5
Mid LAD/Mid LCX	1.5
Distal LAD/ Distal LCX /First Diagonal/ First OM/RCA/PDA/PLV	1
Second Diagonal/Second OM	0.5

Total Gensini score = Sum of (Score for % of stenosis X Score for Vessel(s) involved)

Interpretation of coronary angiogram will be made as the Gensini score. According to Gensini score, CAD was categorized as mild-moderate CAD (d"50), severe CAD (>50).

SPSS 23 was used for data analysis. Continuous variables were expressed as mean ± SD and categorical variables as frequency and percentage. The Kolmogorov-Smirnov test was used to verify the normality of distribution of continuous variables. Quantitative variables were analyzed by student's t test and Man Whitney U test. Categorical variables were analyzed by Chi-square test. To test association between SII and coronary artery disease severity Spearman's rank order correlation test were used. Simple logistic and multivariate logistic regression analysis were done to evaluate the independent predictor of severe CAD and results are shown as odds ratio and 95 % confidence intervals. P

value < 0.05 was considered significant and p value <0.001 was considered as highly significant. ROC curve analysis was done to obtain a cut-off value of SII to predict severe CAD with maximum sensitivity and specificity.

Results:

This cross-sectional observational study was conducted in the department of cardiology, DMCH, SSMCH, NICVD from March 2021 to February 2022. The main objective of this study was to find out the association between systemic immune-inflammatory index (SII) and coronary artery disease severity in acute MI patients. Among the total 70 patients' group-A had 33 and group- B had 37 patients. Most of the patients are above 50 years of age (Figure 1). Among the sample populations 90% were male and 10 % were female (Figure 2). The mean age differences between the group were statistically significant (p=0.03). Male: Female ratio was 10.6:1. Among the conventional CVD risk factors, hypertension and dyslipidemia were significantly high in group-A (p<0.05). No significant difference (p>0.05) between two groups was found in case of diabetes, smoking and family history of CAD (Table 1).

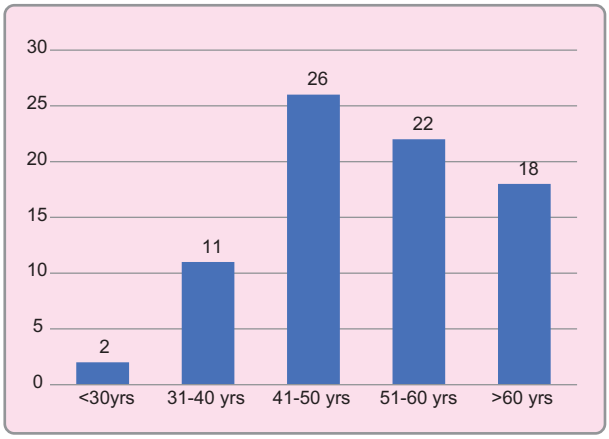

Fig.-1: *Distribution of age among sample populations (N=70)*

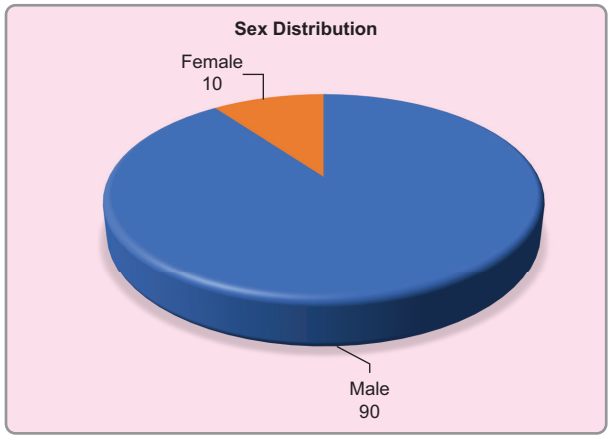

Fig.-2: *Distribution of sex among sample populations (N=70)*

Table-I

Demographic and risk factors variables of study patients (N=70)

Variables	Group A (n=33)	Group B (n=37)	P value
Age, mean ± SD,yrs	53.39±8.8	48.27±10.60	0.03^{S}
Sex			
Male	30(91%)	33(89%)	
Female	3(9%)	4(11%)	0.81^{NS}
Smoker, n (%)	17 (51.5%)	16(43.2%)	0.33^{NS}
Hypertension, n (%)	27 (81.8%)	19 (51.3%)	0.007^{S}
Diabetes Mellitus, n (%)	21 (63.6%)	15 (40.5%)	0.08^{NS}
Dyslipidaemia, n (%)	28 (84.8%)	19 (51.3%)	0.003^{S}
Family history of CAD, n (%)	3 (9%)	7 (19%)	0.31^{NS}

Group A= Severe CAD, Gensini score > 50
Group B= Mild -Moderate CAD, Gensini score d" 50
s =significant
ns = not significant
p value reached from Students t -test and Chi square test.

The differences in mean hemoglobin, RBS and serum creatinine levels between two groups were insignificant (p>0.05). In lipid profile study, HDL was significantly low in group A

(p<0.01). LDL and serum TG were significantly higher in group-A (p value 0.001). Patients of group-A showed significantly higher mean WBC counts (p<0.01). Mean count of neutrophil and lymphocyte were statistically significant (p<0.001) across the group. The Mean NLR was 4.43± 2.27 in group-A & 2.01±1.56 in group-B and the difference was statistically significant (p=0.001). Mean LVEF also showed statistically significant difference between two groups (p<0.001) (Table 2 & Table 3).

Mean systemic immune-inflammation index was significantly higher in group A than group B and p value <0.05 (Table 4). Mean systemic immune -inflammatory index was significantly higher among patients with vessel score 2 and 3 than vessel score 0 and 1, p value 0.002 (Table 5).

There was a positive correlation between SII and coronary artery disease severity in terms

of Gensini score (r =0.7). With the increase of SII, Gensini score also increases. It was found statistically significant (p=0.001) by Spearman rank order correlation test. (Figure 3).

In ROC curve analysis, the AUC of SII for predicting severity of CAD is 0.8 with p value< 0.001, 95% CI (0.71-0.91). SII cut-off value 686 can predict severe CAD with 78% sensitivity and 76% specificity (Figure 4).

In multiple logistic regression analysis hypertension, NLR and SII were found independent predictors of severe CAD with ORs being 4.84, 1.81 and 1.002 respectively. (Table 6).

Table-II
Comparison of haematological parameters between groups (N=70)

Parameters	Group A (n=33) mean±SD	Group B (n=37) mean±SD	P value
Hb (gm/dl)	12.40 ± 1.68	12.79 ± 1.54	0.32^{NS}
Total WBC count	10684.2±3244.7	8710.5±2266.5	0.004^{S}
Neutrophil count	73.87± 8.59	58.00± 8.33	0.001^{S}
Lymphocyte count	20.15±7.42	32.73±7.20	0.001^{S}
Platelet count, $\times10^3/mm^3$	254± 76	246± 87	0.232^{NS}
NLR	4.43± 2.27	2.01±1.56	0.001^{S}

Group A= Severe CAD, Gensini score > 50
Group B= Mild -Moderate CAD, Gensini score ≤50
s =significant; ns = not significant
p value reached from Students t -test / Man Whitney U test.

Table-II
Comparison of laboratory parameters between groups (N=70)

Parameters	Group A (n=33) mean±SD	Group B (n=37) mean±SD	P value
Total cholesterol (mg/dl)	231.54± 45.79	211.37±41.27	0.06^{NS}
LDL (mg/dl)	120.18±27.57	107.64±25.05	0.05^{S}
HDL (mg/dl)	34.69±5.9	37.75±5.4	0.02^{S}
TG (mg/dl)	175.09±58.25	143.29±50.80	0.01^{S}
RBS (mg/dl)	8.17±2.45	7.74±2.93	0.50^{NS}
Serum creatinine(mg/dl)	1.29±0.6	0.9±0.5	0.24^{NS}
LVEF (%)	47.45±4.95	52.27±5.95	0.001^{S}
Gensini score	73.27±26.10	20.29±14.10	0.001^{S}

Group A= Severe CAD, Gensini score > 50
Group B= Mild -Moderate CAD, Gensini score ≤50
s =significant; ns = not significant
p value reached from Students t -test / Man Whitney U test.

Table-IV

Comparison of SII between the groups (N=70)

Parameters	Group A (n=33) mean±SD	Group B (n=37) mean±SD	P value
Systemic immune inflammation index (SII),× 10^3	1064.11±365.57	706.55±399.73	0.001^S

Group A= Severe CAD, Gensini score > 50
Group B= Mild -Moderate CAD, Gensini score d" 50
s =significant; ns = not significant
p value reached from Man Whitney U test.

Table-V

Distribution of SII among the sample populations (N=70)

Parameter	Vessel score "0" n=7	Vessel score "1" n=23	Vessel score "2" n=18	Vessel score "3" n=22	P value
Systemic immune inflammation index (SII), × 10^3	590.67±75.89	790.91±510.67	863.83±339.93	1062.89±378.91	0.002^S

s =significant; ns = not significant
p value reached from Kruskal -Wallis test.

Table-VI

Multivariate logistic regression analysis of determinant of severe coronary artery disease

Variables of interest	β	S. E	P value	OR	95 % CI
Hypertension	1.57	0.652	0.01^s	4.84	1.35 – 17.38
Dyslipidaemia	0.512	0.623	0.412	1.66	0.492 – 5.66
LVEF	0.085	0.078	0.277	0.919	0.789 – 1.09
NLR	0.595	0.211	0.004^s	1.813	1.19 – 2.74
SII	0.002	0.001	0.011^S	1.002	1.001-1.004

Dependent variable: Severe CAD (Gensini score > 50)
Independent variables: Hypertension, Diabetes mellitus, Dyslipidaemia, LVEF, NLR and SII.
s =significant.

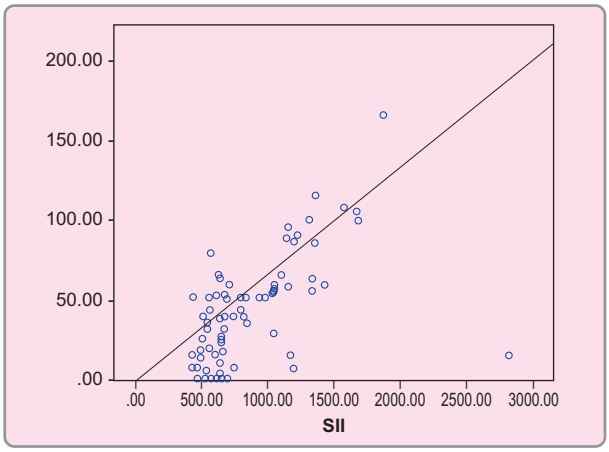

Fig 3: *Scatter diagram showing correlation between SII and Gensini score by Spearman's rank order correlation test.*

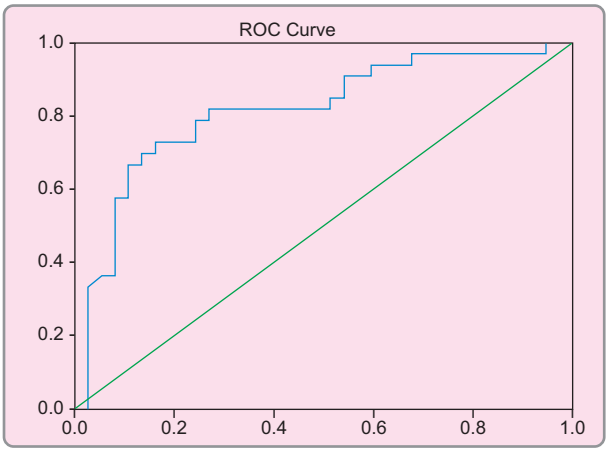

Fig 4: *The receiver-operating characteristics curve (ROC) analysis of SII for predicting severe CAD.*

Discussion:

The mean age of study patients was 50.16 ± 9.9 years ranging from 24 to 70 years. The mean age of group A patients was 53.39±8.8 years and that of group B was 48.27±10.6 years. The mean age of group A patients was significantly higher than group B. In a similar study conducted by Zhang et al,[13] mean age was significantly (p=0.001) higher in high Gensini score (>50) group.

The distribution of risk factors for coronary artery disease in the present study revealed that the most common risk factors, such as hypertension present in 81.8% (27) patients in group A and 51.3% (19) in group B, and the difference between two groups was statistically significant (p=0.007). Dyslipidemia was found in 84.8% (28) patients in group A and 51.3% (19) patients in group B and the difference between the groups was statistically significant (p value 0.03). Diabetes mellitus was found 63.6% (21) and 40.5% (15) patients in group A and B respectively and the difference was not statistically significant (p value=.08). Zhang et al, [13] also showed the similar findings. We didn't find any statistically significant difference of smoking and positive family history of premature CAD between the groups, which is consistent with previous study conducted by Kaya et al. [14]

In group A the mean WBC count was 10684.2±3244.7 (/ mm^3) and in group B mean WBC count was 8710.5±2266 (/mm^3) and this difference was statistically significant(p=.004). in a similar study conducted by Kaya et al [15]found mean WBC count 9.9 ± 3.1(K/μL) in higher Gensini score group and 8.3 ± 2.8 (K/μL) in lower Gensini score group and the difference was statistically significant. Mean neutrophil count was significantly higher and lymphocyte count was significantly lower in group A than group B. No significant difference in platelet count found between groups, which is similar with study done by kaya et al. [14] In our study,mean NLR significantly higher in group A than group B, which is consistent with study done by Zhang et al[13]

In case of Vessel score, mean SII was significantly higher in vessel score 2 and 3 group than vessel score 1 and 2 group, which p value is 0.002. In group A mean SII was 1064.11±365.57 and in group B mean SII was 706.55±399.73, the difference was statistically significant (p value 0.001) which is similar to study done by Liu et al. [16]

A positive correlation between SII and severity of CAD in terms of Gensini score was found in our study. Correlation co-efficient between SII and Gensini score was 0.7 (p=.001) which is statistically significant. With the increase of SII, Gensini score also increased, indicating more severe CAD.

In multivariate logistic regression analysis, after adjustment of confounding, NLR, hypertension and SII were found the independent predictor of severe coronary artery disease with OR 1.81, 4.84 and 1.002 & 95% confidence interval [1.19– 2.74], [1.35 -17.38] respectively. Zhang et al [13] & Candemir et al [10] also found NLR as an independent predictor of severe CAD.

By ROC curve analysis, our study found that SII > 686 can predict severe CAD in terms of Gensini score with 78% sensitivity, 76% specificity.

Conclusion:

From this study it may be said that increased systemic immune inflammation index is associated with angiographically severe coronary artery disease in acute myocardial infarction patients. So, this parameter might be useful for risk prediction of acute MI patients. Patients with acute MI, with SII level of more than 686, warrants more attention by the physicians and cardiologists in terms of more aggressive medical management and interventional treatment.

Limitations

Although the result of the study supports the hypothesis, there are some facts to be considered which might affect the results.

1. Relatively small sample size
2. The assessment of the severity of CAD was performed by coronary angiography, which has got its inherent limitations. Intravascular ultrasound may be more sensitive in the assessment of the severity of CAD.
3. The other synchronous inflammatory biomarkers of the patients were not evaluated in the study.
4. Cross-sectional study design was used in this study which was not ideal for proving cause or effect relationship between SII and severe CAD.

Conflict of Interest – None.

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