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ASSOCIATION OF HYPERGLYCEMIA WITH NO-REFLOW OR SLOW REFLOW IN PATIENTS WITH STEMI UNDERGOING PPCI

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ABSTRACT

Background: Primary percutaneous coronary intervention (PPCI) is associated with no-reflow and slow-reflow phenomena in patients with ST-elevation myocardial infarction (STEMI) which is associated with larger infarct size, ventricular dysfunction and mortality. Patients with hyperglycemia at admission have poor outcomes, but there are limited data in people with diabetes, particularly in the region of South Asia.

Objective: To assess the association between admission hyperglycemia and no-reflow/slow-reflow in diabetic STEMI patients undergoing primary percutaneous coronary intervention.

Methods: A prospective cohort study with consecutive sampling of 116 diabetic STEMI patients (58 hyperglycemic, 58 normoglycemic) in NICVD Karachi over a period of six months. Hyperglycemia was considered as admission glucose level ≥180 mg/dL. The coronary flow was evaluated using TIMI grading, and the adjusted relative risk for no-reflow/slow flow was estimated by Modified Poisson Regression.

Results: Hyperglycemic patients were more likely to experience no-reflow/slow-flow than were normoglycemic patients (63.8% vs 19.0%, $p < 0.001$). Unadjusted RR = 3.36 (95% CI: 1.92 – 5.88). With adjustment, hyperglycemia was still emerged as an independent predictor (ARR = 2.98; 95% CI: 1.68 – 5.28; $p < 0.001$). Time of ischemia (ARR = 1.12 per 10 min; $p = 0.003$) and time from door-to-balloon (ARR = 1.08 per 10 min; $p = 0.028$) were significantly associated. Patients with hyperglycemia experienced more arrhythmias (20.7% vs. 3.4%; $p = 0.004$), stent thrombosis (12.1% vs. 1.7%; $p = 0.032$), and death rate (20.7% vs. 1.7%; $p = 0.001$).

Conclusion: Admission hyperglycemia is an independent predictor of no-reflow/slow-flow in diabetic STEMI patients. The routine measurement of glucose levels at presentation will allow for early risk stratification and may lead to more intensive management to achieve better outcomes.

KEYWORDS: Hyperglycemia, Slow-reflow, No-reflow, STEMI, Primary PCI, Diabetes mellitus, TIMI flow grade

INTRODUCTION

STEMI is the leading cause of mortality and morbidity worldwide [1]. Primary revascularization within the window period has been considered of significant value in terms of prognosis for patients with STEMI [2]. The aim is to restore epicardial coronary artery patency and improving chances of survival when performed in a given time interval. Even after reopening of culprit coronary artery with primary revascularization, some patients develop impaired myocardial perfusion a phenomenon called no-reflow or slow reflow which has been associated with larger infarct size, ventricular dysfunction and increased mortality [3] Angiographically, the Thrombolysis in Myocardial Infarction (TIMI) flow grading system is used to assess this phenomenon.

High blood glucose levels are often seen at the time of hospital admission in patients presenting with acute myocardial infarction, even in individuals without previously diagnosed diabetes mellitus. Greater the risk factors, greater the risk of major adverse cardiovascular outcomes is the rule [4]. Diabetes mellitus has significantly been associated as a major risk factor for causing acute MI [5]. However, the presenting levels of sugars irrespective of diabetic status is associated with poor outcomes for the patients with STEMI [6].

Patients with high levels of glucose in the blood (such as >180–200 mg/dL) are much more likely to have impaired coronary flow after a percutaneous coronary intervention (PCI) than those with a normal level of glucose in the blood.[7] Hyperglycemia has been found to be an independent risk factor for the no-reflow phenomenon, which is

found to be linked to worse clinical outcomes such as larger infarct size, left ventricular dysfunction, arrhythmias, cardiogenic shock and short term mortality. Thus, understanding modifiable factors like peak glycemia is crucial for early therapeutic interventions and better patient outcomes. [8].

Although there is increasing evidence regarding the association between hyperglycemia and adverse coronary microvascular outcomes, availability of local data is very limited. One out of every four individuals in Pakistan are affected by CAD[9].Considering this high burden of cardiovascular disease and diabetes, assessing admission glucose levels to be used as a simple and early predictor of the no-reflow or slow-reflow phenomenon in this population, holds great importance.

Therefore, this study aims to determine the association between admission glucose levels and the occurrence of no-reflow or slow-reflow in patients with STEMI undergoing primary percutaneous coronary intervention. This may contribute to identifying high-risk patients and improve peri-procedural management strategies.

MATERIALS AND METHODS

This is a prospective comparative cohort study that was conducted at the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan for 6 months with approval from the College of Physicians and Surgeons Pakistan and the Institutional Review Board. Written informed consent was obtained from all participants and data was anonymized. This study evaluated the relationship between hyperglycemia upon admission and no-reflow/slow reflow in diabetic patients with STEMI who underwent a primary percutaneous coronary intervention (PPCI).

Patients were adults aged 18-75 years, of both sexes, with confirmed STEMI, established diabetes mellitus before index admission, presenting within 12 hours of symptom onset, undergoing PPCI. Exclusions included previous CABG, cardiogenic shock upon admission, serum creatinine > 2 mg/dl, previous MI or PCI, and pre-PPCI thrombolysis. All eligible patients were recruited in consecutive non probability sampling during study period.

Sample size was calculated with WHO calculator using the no-reflow/slow-flow rate of 52.0% (hyperglycemic) vs. 14.1% (normoglycemic) from Iwakura et al [4]. With significance set at 5% and a power of 80%, 23 patients were needed in each group. A design factor of 2.5 inflated the requirement to 58 per group, which resulted in 116 diabetic patients (58 hyperglycemic, 58 normoglycemic).

Demographic data, smoking status, hypertension and symptom duration were reported after the informed consent was obtained. Venous blood samples were drawn for Admission random blood glucose before PPCI. Using standard institutional procedures, PPCI was performed through the femoral or radial artery and the culprit artery was identified by the ECG and angiography. An interventional cardiologist evaluated post-procedural flow using TIMI scale, grade 0/1 (no-reflow), grade 2 (slow-flow), and grade 3 (normal) [10]. No reflow was defined as TIMI 0/1 in absence of mechanical obstruction after successful mechanical reperfusion, slow flow as TIMI 2 with delayed opacification. Patients were divided into two groups: normoglycemia (random glucose <180 mg/dL) and hyperglycemia (≥180 mg/dL). Clinical outcomes (arrhythmias, stent thrombosis, length of stay, in-hospital mortality) and total ischemic time, door-to-balloon time, thrombus aspiration, and glycoprotein IIb/IIIa inhibitor use were documented. The quantitative variables were age, duration of symptoms, random glucose, ischemic time, and door-to-balloon time. Qualitative variables were sex, smoking, hypertension, location of infarct, TIMI flow grade, and clinical outcomes.

Data was analyzed using SPSS version 27.0. Continuous variables were checked for normality by the Shapiro-Wilk test and histograms, and normally distributed data were presented as mean ± SD and compared with the independent t-test. The Ordinal TIMI flow grades were compared by Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test (or Fisher's exact test for small expected cell counts, <5). The unadjusted Relative Risk (RR) was determined for the primary outcome. The Adjusted Relative Risk (ARR) was estimated by a Modified Poisson regression with robust estimated error variance (total ischemic time, door-to-balloon time, anterior infarct location, hypertension, smoking, thrombus aspiration, and glycoprotein IIb/IIIa inhibitor use). A two-tailed p value of less than 0.05 was taken as statistically significant.

RESULTS

Descriptive Statistics and Baseline Characteristics

A total of 116 diabetic patients with STEMI who were admitted to the hospital for primary PCI were included and classified into two groups: hyperglycemia (random blood glucose (RBG) ≥180 mg/dL, n=58) and normoglycemia (RBG <180 mg/dL, n=58). The overall mean age was 62.1 ± 6.5 years, with 66.4% (n=77) male patients. Baseline characteristics were similar between groups with the exception of admission glucose, total ischemic time, and door-to-balloon time. Normality testing by Shapiro-Wilk test revealed that age (W=0.974, p=0.083), ischemic time (W=0.981, p=0.111), and door-to-balloon time (W=0.976, p=0.068) were normally distributed and thus data are presented as mean ± SD. Admission blood glucose was normally distributed in each group, with a significantly higher mean glucose level in the hyperglycemic group (240.5 ± 36.2 mg/dL vs. 154.8 ± 14.6 mg/dL; p<0.001).

Table 1: Baseline Characteristics of Diabetic STEMI Patients Stratified by Admission Hyperglycemia

Variable	Total (N=116)	Hyperglycemia (≥180 mg/dL) (n=58)	Normoglycemia (<180 mg/dL) (n=58)	p-value
Age (years), Mean ± SD	62.1 ± 6.5	62.4 ± 6.8	61.9 ± 6.2	0.675†
Male Gender, n (%)	77 (66.4)	38 (65.5)	39 (67.2)	0.844‡
Hypertension, n (%)	62 (53.4)	33 (56.9)	29 (50.0)	0.453‡
Smoking, n (%)	45 (38.8)	24 (41.4)	21 (36.2)	0.565‡
Admission RBS (mg/dL), Mean ± SD	197.6 ± 50.6	240.5 ± 36.2	154.8 ± 14.6	**<0.001**†
Ischemic Time (mins), Mean ± SD	180.9 ± 36.8	198.6 ± 38.4	163.2 ± 22.6	**<0.001**†
Door-to-Balloon (mins), Mean ± SD	45.7 ± 10.7	49.8 ± 11.2	41.6 ± 8.4	**<0.001**†
Anterior Infarct, n (%)	52 (44.8)	29 (50.0)	23 (39.7)	0.262‡
Thrombus Aspiration Used, n (%)	42 (36.2)	20 (34.5)	22 (37.9)	0.700‡
GP IIb/IIIa Inhibitor Used, n (%)	26 (22.4)	19 (32.8)	7 (12.1)	**0.007**‡
†Independent t-test; ‡Chi-square test. RBS: Random Blood Sugar; GP: Glycoprotein.				

Prevalence and Primary Outcome of No-Reflow or Slow-Reflow

The overall no reflows or slow reflows rate of prevalence in this diabetic STEMI cohort was 41.4%, (48/116; 95% CI: 32.5% – 50.7%).

The primary outcome (no-reflow or slow-flow) occurred significantly more often in the hyperglycemia group than in the normoglycemia group (63.8% vs. 19.0%). Chi-square test revealed a significant association between admission hyperglycemia and impaired post-procedural coronary flow, ($\chi^2 = 23.84$; df = 1; $p < 0.001$).

Table 2: Prevalence of No-Reflow or Slow-Reflow (Primary Outcome)

Outcome	Total (N=116)	Hyperglycemia (n=58)	Normoglycemia (n=58)	Chi-square	p-value
No-Reflow or Slow-Reflow, n (%)	48 (41.4)	37 (63.8)	11 (19.0)	23.84	**<0.001**
Normal Flow (TIMI 3), n (%)	68 (58.6)	21 (36.2)	47 (81.0)		

Overall Prevalence rate of No-Reflow/Slow-Flow: 41.4% (95% CI: 32.5% – 50.7%).
Unadjusted Relative Risk = 3.36 (95% CI: 1.92 – 5.88).

Unadjusted Relative Risk

The unadjusted RR for developing no-reflow or slow flow in diabetic patients with admission hyperglycemic ≥180 mg/dL as in non-diabetic patients was 3.36 (95% CI: 1.92 – 5.88) suggesting that diabetic patients with admission hyperglycemia ≥180 mg/dL were more than three times as likely to experience impaired microvascular perfusion after PPCI.

Flow Grade Distribution & Complications (Secondary Outcomes)

Post-Procedural TIMI Flow Grade:

In the hyperglycemic group, severe impairment (TIMI 0-1, true no-reflow) was significantly more common (48.3%, n=28) than in the normoglycemic group (8.6%, n=5), as analyzed by the ordinal TIMI flow grades. In contrast, normal TIMI 3 flow was obtained in 36.2% (n=21) of hyperglycemic patients versus 81.0% (n=47) of normoglycemic patients. The Mann-Whitney U test showed a significant difference in the distribution of TIMI flow grades between the two groups ($Z = -5.12$; $p < 0.001$).

Clinical complications and mortality:

Patients in the hyperglycemia group had significantly worse clinical outcomes. The incidence of arrhythmias after the procedure was seen in 20.7% (n=12) versus 3.4% (n=2) (p=0.004), whereas stent thrombosis was noted in 12.1% (n=7) versus 1.7% (n=1) (p=0.032). Mortality in hospital was significantly high in hyperglycemia group (20.7%, n=12) compared to normoglycemia group (1.7%, n=1) (p=0.001). In addition, the percentage of hyperglycemic patients who needed long hospitalization (more than 48 hours) was significantly higher: 58.6% (n=34) versus 6.9% (n=4) (p<0.001).

Table 3: Distribution of Post Procedural TIMI Flow Grade

TIMI Flow Grade	Total (N=116)	Hyperglycemia (n=58)	Normoglycemia (n=58)	p-value*
TIMI 0 (No-Reflow)	17 (14.7)	15 (25.9)	2 (3.4)	
TIMI 1 (No-Reflow)	16 (13.8)	13 (22.4)	3 (5.2)	
TIMI 2 (Slow-Flow)	15 (12.9)	9 (15.5)	6 (10.3)	
TIMI 3 (Normal Flow)	68 (58.6)	21 (36.2)	47 (81.0)	
Total	100%	100%	100%	**<0.001**
Values are presented as n (%). Mann-Whitney U test (Z = -5.12).				

Table 4: Secondary Clinical Outcomes & Post Procedural Complications

Variable	Hyperglycemia (n=58)	Normoglycemia (n=58)	Chi-square	p-value
Post-Procedural Arrhythmia, n (%)	12 (20.7)	2 (3.4)	8.31	**0.004**
Stent Thrombosis, n (%)	7 (12.1)	1 (1.7)	4.64	**0.032†**
In-Hospital Mortality, n (%)	12 (20.7)	1 (1.7)	10.36	**0.001†**
Hospital Stay > 48 hours, n (%)	34 (58.6)	4 (6.9)	34.82	**<0.001**
†Fisher's Exact test applied as expected cell count was <5.				

Using Adjusted Relative Risk (Modified Poisson Regression)

To consider the potential influence of confounding factors, Modified Poisson Regression with robust error variance was used to calculate an Adjusted Relative Risk (ARR) for the primary outcome, accounting for each of the following; total ischemic time (minutes), door-to-balloon time (minutes), infarct location, hypertension, smoking status, and use of thrombus aspiration and GP IIb/IIIa inhibitors.

Admission hyperglycemia ≥ 180 mg/dL remained a strong independent predictor of no-reflow/slow-flow with an Adjusted Relative Risk (ARR) of 2.98 (95% CI: 1.68 – 5.28; $p < 0.001$) after the adjustment. Moreover, higher total ischemia time (ARR for a 10-min increase = 1.12; 95% CI: 1.04-1.21; $p = 0.003$) and higher door-to-balloon time (ARR for a 10-min increase = 1.08; 95% CI: 1.01-1.16; $p = 0.028$) turned out to be statistically significant independent predictors. There was a trend towards increased odds for anterior infarction although the result was not statistically significant (ARR = 1.42; 95% CI: 0.92 – 2.18; $p = 0.112$).

Table 5: Modified Poisson regression with independent predictors of No-Reflow or Slow-Reflow (Adjusted Relative Risk)

Predictor Variable	Adjusted RR	95% CI	p-value
Admission Hyperglycemia (≥180 mg/dL)	**2.98**	1.68 – 5.28	**<0.001**
Ischemic Time (per 10-min increase)	**1.12**	1.04 – 1.21	**0.003**
Door-to-Balloon Time (per 10-min increase)	**1.08**	1.01 – 1.16	**0.028**
Anterior Infarct Location	1.42	0.92 – 2.18	0.112
Hypertension	1.15	0.78 – 1.69	0.482
Smoking	1.08	0.72 – 1.62	0.698
Thrombus Aspiration Used	0.88	0.62 – 1.25	0.482
GP IIb/IIIa Inhibitor Used	0.92	0.65 – 1.30	0.641
Model adjusted for all variables listed. RR: Relative Risk; CI: Confidence Interval.			

DISCUSSION

Bloodstream infections continue to be a significant source of morbidity and mortality among neutropenic hematologic malignancy patients. Admission hyperglycemia (random blood glucose level >180 mg/dl) was strongly and

independently associated with no-reflow or slow reflow phenomenon among diabetic patients with STEMI who underwent PCI. The overall rate of impaired coronary microvascular perfusion in our patients was 41.4%, and the rate was quite different between the hyperglycemic (63.8%) and normoglycemic (19.0%) groups. This finding is consistent with the landmark study of Iwakura et al., where hyperglycemia (admission glucose ≥160 mg/dL) was associated with impaired microvascular reperfusion in 52.0% of patients as compared to 14.1% of patients without hyperglycemia ($p < 0.0001$), and was found in different populations across 20 years. [4]

The relative risk of 3.36 (95% CI: 1.92 – 5.88) in our study suggests that diabetic patients with hyperglycemia were over 3 times more likely to have no-reflow or slow-flow than those with normoglycemia. The adjusted relative risk was 2.98 (95% CI: 1.68 – 5.28; $p < 0.001$) after adjusting for potential confounders (total ischemic time, door-to-balloon time, infarct location, hypertension, smoking status, and the use of glycoprotein IIb/IIIa inhibitors or thrombus aspiration). This modified risk assessment is similar to the results of recent large scale studies. In a study of peak glycemia in 252 STEMI patients in 2026, the odds of no-reflow, at the OR of 8.16 (95% CI: 4.1 – 16.2, $p < 0.001$), were found to be independent of peak glycemia levels > 180 mg/dL. [8] In the same way, 480 patients with STEMI were selected and stress hyperglycemia was an independent predictor of the no-reflow phenomenon with an odds ratio of 3.247 (95% CI: 1.656 – 6.368, $p = 0.001$) by Khalfallah et al. [11] In addition, admission hyperglycemia was strongly associated with no-reflow (17.5% incidence; $p = 0.001$) as confirmed by Elkammash et al. [7].The uniformity of these results in different populations and study designs provide strong biological support for the hypothesis that hyperglycemia is a causal factor in microvascular dysfunction after reperfusion.

Distribution of TIMI flow grades in our study showed that TIMI 0-1 was seen in 48.3% of hyperglycemic patients and 8.6% of normoglycemic patients, whereas slow flow (TIMI 2) was seen in 15.5% and 10.3% respectively. Of note is that this pattern is seen not only in association with marginal flow reduction, but also when microvascular perfusion is completely or nearly completely stopped. A study in Pakistan at Armed Forces Institute of Cardiology, Rawalpindi, found that no-reflow (9.3%) or slow flow (55.8%) was significantly higher in patients with admission glucose level >200 mg/dL than in those with lower glucose level ($p = 0.01$). [12] In the previous study, more slow-flow was observed than in our study which could be explained by a different definition of slow-flow or different selection criteria for patients. However, both studies again confirm that high glucose levels at presentation are good predictors of post-procedural coronary flow impairment.

The relationship between hyperglycemia and no-reflow is a complicated and multi-factorial mechanism. It has been demonstrated that hyperglycemia induces expression of leukocyte adhesion molecule, which could cause microvascular obstruction and damage to endothelial cells by elastase. This enhances formation of the thrombus and a decrease in ischemic preconditioning. [7] Furthermore, hyperglycemia can cause oxidative stress, endothelial dysfunction, and platelet aggregation, which all play a role in the no-reflow phenomenon occurring in the microvasculature. [4, 13] This finding is consistent with the observation that no-reflow risk did not differ between glycosylated hemoglobin (GHb) levels of <6% and >6%, but was higher with hyperglycemia (23.2% vs. 1.5%). [8, 14] indicating that acute rather than chronic glycemic control is the most important factor in determining no-reflow risk. A study published in 2022 also found that no-reflow, after PPCI, was also linked to admission hyperglycemia, not diabetes. [7]

The relationship between total ischemic time and door-to-balloon time with no-reflow and slow-flow (ARR: 1.12, $p = 0.003$ and 1.08, $p = 0.028$, respectively) is consistent with the known importance of time-to-reperfusion in the treatment of STEMI. Myocardial injury becomes worse with prolonged ischemia, and reperfusion will make the heart more vulnerable to microvascular dysfunction, as revealed by recent studies which showed that the duration of ischemia is a strong predictor of no-reflow following primary PCI in STEMI patients. [15] This is especially relevant because our cohort had significantly longer ischemic times in the hyperglycemic patients than in the normoglycemic patients (198.6 ± 38.4 vs. 163.2 ± 22.6 minutes; $p < 0.001$), as well as longer door-to-balloon time (49.8 ± 11.2 vs. 41.6 ± 8.4 minutes; $p < 0.001$). This synergistic effect of these risk factors, hyperglycemia, prolonged ischemia and delayed reperfusion, greatly increases the risk of bad outcomes. In line with our results, a recent meta-analysis reported that the in-hospital mortality rate, reperfusion time and risk of reinfarction, heart failure and cardiogenic shock were all significantly higher among STEMI patients with hyperglycemia on admission. [16]

No reflow and slow flow had a clinical impact in our secondary outcomes. Patients with hyperglycemia demonstrated significantly higher rates of post-procedural arrhythmias (20.7% vs. 3.4%; $p = 0.004$), stent thrombosis (12.1% vs. 1.7%; $p = 0.032$), and in-hospital mortality (20.7% vs. 1.7%; $p = 0.001$). These results are similar to the mortality rates reported in the literature with no-reflow between 7.4% and 30.3%. [8, 17] The economic and resource utilization implications of the effect are further highlighted by the significantly longer hospital stay (>48 hours) seen in 58.6% of hyperglycemic patients and 6.9% of normoglycemic patients ($p < 0.001$). There is a consistent association between hyperglycemia and poor outcomes after STEMI in systematic reviews and meta-analyses; admission and fasting blood glucose levels have been demonstrated as predictors of short-term outcomes. [16, 18]

The results of our adjusted model for anterior wall infarction showed a trend toward increased risk of no reflow or slow flow (ARR = 1.42; 95% CI: 0.92 – 2.18; $p = 0.112$). The lack of significance could be due to the relatively small

population size in our study or may reflect that the prognostic significance of the site of the infarct might be altered in our study population of diabetic patients whose underlying microvascular disease might modify the impact of the site of the infarct. However, this is similar to Iwakura et al.'s finding of anterior AMI being an independent predictor for no-reflow. [4]

There are several limitations in this study. Generalizability may be limited as it was conducted in one single center in a tertiary-care facility in Pakistan. The number of patients in this sample may have been sufficient for the primary analysis but not for some secondary and subgroup analyses. [19] Additionally, the angiographic TIMI flow grading was utilized, and not more sophisticated techniques such as myocardial contrast echocardiography or cardiac MRI, which may underestimate microvascular dysfunction. [20] HbA1c levels were not estimated in all cases, which precluded an adequate evaluation of chronic glycemic control, and the intentional sampling of diabetic patients limited the ability to make generalizations to non-diabetic cases. [21]

Although limited, the prospective design and the use of sophisticated statistical analysis (Modified Poisson Regression) improve the validity of the results. [4] In clinical practice, admission random blood glucose is a good screening test that is easy to obtain, inexpensive, and is a useful indicator of diabetic STEMI patients with high risk of no-reflow. [22] Association of hyperglycaemia with longer door-to-balloon time highlights the importance of optimising reperfusion procedures. [23]

The following steps in research should include randomized controlled trials of intensive glucose-lowering treatments started in the emergency department and the incorporation of novel biomarkers or advanced imaging modalities for better risk stratification. [24, 25]

CONCLUSION

In diabetic patients with STEMI undergoing primary PCI, admission hyperglycemia (≥180 mg/dL) was a strong, independent predictor of no-reflow or slow-reflow phenomenon with an adjusted relative risk of 2.98. Patients with hyperglycemia have substantially increased risk of post-procedural complications such as arrhythmias, stent thrombosis, longer hospital stay, and in-hospital mortality. Door-to-balloon time and total ischemic time are further independent factors of poor microvascular perfusion. These results highlight the role of admission random blood glucose as a simple, easily accessed biomarker for risk stratification in diabetic STEMI patients. Minimizing ischemic time and early identification of hyperglycemia may help to achieve better procedural outcomes and decrease mortality in this high-risk population. The management of diabetic STEMI patients should focus on routine glucose measurement at admission and expedient reperfusion protocols.

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