

# The roles of fasting blood glucose to HDL-cholesterol ratio and monocyte to HDL-cholesterol ratio on coronary slow flow in non-diabetic patients

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## Abstract

**Aim:** This study aimed to evaluate the relationship between coronary slow flow (CSF) with fasting blood glucose/high-density lipoprotein cholesterol ratio (GHR) and monocyte/high-density lipoprotein cholesterol ratio (MHR) in patients without overt diabetes and to reveal the effects of hyperglycemia and inflammation on CSF development.

**Material and methods:** In this retrospective study, a total of 237 patients who underwent coronary angiography were enrolled and were divided into two groups according to CSF presence. 109 of them had CSF and 128 of them had coronary normal flow (CNF). The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was calculated for each coronary artery and the values above the normal range were defined as CSF.

**Results:** GHR and MHR were significantly higher in CSF patients compared to those without ( $p < 0.001$ ,  $p < 0.001$ ). In correlation analysis, total TFC showed a statistically significant relation with these markers (for both  $r = 0.745$ ,  $p < 0.001$ ). In multivariate logistic regression analysis, GHR and MHR were independent predictors for CSF presence ( $p < 0.001$ ,  $p < 0.001$ ). The receiver operating characteristic (ROC) curve analysis showed the best cut off values of GHR and MHR as 2.105 and as 12.93, respectively (AUC=0.861,  $p < 0.001$ ; AUC=0.849,  $p < 0.001$ ).

**Conclusion:** In this study, there was a strong relationship between CSF with GHR and MHR. In addition, elevated values of GHR and MHR supported the roles of hyperglycemia and inflammation in CSF etiopathogenesis.

**Key words:** coronary slow flow, fasting blood glucose, high-density lipoprotein cholesterol, monocyte counts

## Introduction

Coronary slow flow (CSF) is characterized by delayed perfusion of distal vessels in the absence of significant epicardial coronary stenosis [1]. Although the underlying etiopathogenic mechanisms have been the focus of many researchers for years, these mechanisms are still not clearly understood. It has been proposed that microvascular disorders, endothelial dysfunction, systemic inflammation, blood cell abnormalities, and occult atherosclerosis may play a role in the pathogenesis [2].

Diabetes is a well-known risk factor for coronary artery disease (CAD) and there is growing evidence on the relationship between fasting blood glucose (FBG) and microvascular complications. However its effect on macrovascular complications such as CAD is relatively less clear [3-5]. While it has been debated whether elevated FBG levels may be a risk factor for CAD in non-diabetic patients, some studies have revealed that hyperglycemia has negative effects on CAD in this population [6,7]. As with CAD, few studies reported the association of

CSF considered as early stage of CAD with hyperglycemic conditions other than diabetes. Hence, it has been assumed that hyperglycemic states such as insulin resistance (IR) may impair the coronary microvascular circulation due to endothelial damage before overt diabetes manifests [8,9]. However, more data are needed to support the effects of hyperglycemia on CSF.

Dyslipidemia, like diabetes, is a traditional cardiovascular risk factor and related to adverse cardiovascular outcomes [10]. The previous studies demonstrated the relationship between CSF with high-density lipoprotein cholesterol (HDL-C) and triglyceride levels [11,12]. Recently, as a novel marker, the FBG/HDL-C ratio (GHR) has been reported as an independent predictor for all-cause mortality in non-diabetic patients undergoing percutaneous coronary intervention (PCI) [13]. To our best knowledge, the role of this novel marker in non-diabetic patients has not yet been investigated.

Monocyte count to HDL-C ratio (MHR) is a marker associated with inflammation and the studies have reported that MHR may predict cardiovascular disease (CVD), stent thrombosis and adverse cardiovascular outcomes [14-16]. However there are few data on the relationship between MHR and CSF [17]. Thus, in this study, we aimed to evaluate the effect of hyperglycemia and inflammation on CSF etiopathogenesis using GHR and MHR.

## Material and methods

### Patients and clinical data

In this single-center study, a total of 237 patients, including 128 coronary normal flow (CNF) and 109 coronary slow flow (CSF) patients who applied to our cardiology outpatient clinic with stable angina and/or equivalent symptoms and underwent coronary angiography for suspected CAD, were retrospectively analyzed. The patients with a history of CAD or revascularization, left ventricular dysfunction (ejection fraction < 50%), congenital heart disease, overt diabetes, cerebrovascular disease, malignancy, acute or chronic inflammation, autoimmune disorders, severe kidney or liver disease were excluded. In addition, patients receiving drugs that affect glycolipid metabolism were also excluded from the study.

The clinical, laboratory and angiographic data of each patient were obtained from the hospital registry system. From fasting blood, GHR was calculated by dividing the glucose level by the HDL-C level, and MHR was calculated by dividing the monocyte cell count by the HDL-C level. The study was approved by the Ethics Committee of the Pamukkale University, Faculty of Medicine in accordance with the Helsinki declaration (protocol No E-60116787-020-56171).

### Coronary angiography

The recorded views on the digital system were examined by two experienced cardiologists who were blind to the clinical data of the study population. The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was calculated as described by Gibson et al. [18]. TFC was obtained by calculating the difference between the frame where the contrast enters the coronary artery and the last frame where the contrast reaches the distal coronary landmark. The distal bifurcation for left anterior descending artery (LAD), the distal bifurcation of the longest branch for left circumflex artery (LCx), and the first side branch of the posterolateral artery for right coronary artery (RCA) were defined as the distal ends. The normal range of CNF was accepted for LAD as a  $36.2 \pm 2.6$  frames, for LCx as a  $22.2 \pm 4.1$  frames and for RCA as a  $20.4 \pm 3.0$  as previously defined by

Gibson et al. [18]. The greater than 2 standard deviations from these thresholds were considered CSF. The cine frames were recorded at a 15 frames/second in this study so the values were multiplied by 2. Since, LAD was longer, the frame count was divided by 1.7 to calculate the corrected TFC.

### Statistical analysis

All data were analyzed using SPSS version 21.0 software (SPSS, Inc., Chicago, Ill., USA). The normality of the distribution was checked using Kolmogorov-Smirnov test. Continuous and categorical variables were presented as the mean  $\pm$  standard deviation (SD) and as the number (percentage). In comparison of continuous variables, the independent-sample t test or Mann-Whitney U test was used. The Chi-squared test was performed to compare the categorical variables. The variables with significant relationship ( $p < 0.05$ ) in univariate analysis, which were considered to be risk factors for CSF and did not show multicollinearity, were included in multivariate logistic regression analysis. GHR and MHR were taken place in different regression models due to the multicollinearity. The relation between total TFC with GHR and MHR was revealed using the Spearman correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive power of GHR and MHR for CSF presence. In determining the best cut off values of these parameters, the Youden Index, which overlaps with the point closest to the upper left corner of the ROC curve graph and reflects the value with the highest sum of sensitivity and specificity, was used. A 2-sided  $p$  value of  $< 0.05$  was considered significant.

### Results

This study was conducted with a total of 237 patients. The mean age of the whole population was  $56.84 \pm 11.42$  years and the male sex ratio was 60.8%. The demographic and clinical data of the patients according to having CSF are summarized in Table 1. There was no significant difference in demographical data such as smoking, hypertension and hyperlipidemia between the groups. CSF patients showed significantly higher levels of white blood cells (WBC), monocytes, FBG, glycated hemoglobin (HbA1c), creatinine, triglycerides (TG), C-reactive protein (CRP) and significantly lower levels of HDL-C. However, ejection fraction, hemoglobin, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were similar. The total TFC was higher in CSF patients compared to CNF patients as expected ( $93.04 \pm 17.56$  vs  $54.90 \pm 6.91$ ,  $p < 0.001$ ). Of the CSF, 73.4% was associated with the LAD artery, 50.5% with the LCx artery, 66.1% with the RCA. In addition 43 patients (39.4%) had CSF in a single vessel and 66 patients (60.6%) had CSF in two or three vessels on angiographical views. GHR was calculated as  $2.61 \pm 0.47$  and  $1.84 \pm 0.54$  in patients with and without CSF, respectively, and there was a strong statistical significance ( $p < 0.001$ ). MHR was significantly higher in CSF patients compared to those without ( $18.33 \pm 7.34$  vs  $10.61 \pm 3.83$ ,  $p < 0.001$ ) (Table 1, Figure 1).

Total TFC was significantly associated with GHR and MHR in correlation analysis (for both  $r = 0.745$ ,  $p < 0.001$ ) (Figure 2). Then GHR and MHR were evaluated in terms of whether that they may be independent markers for CSF presence using multivariate logistic regression analysis. However two models were performed in regression analysis because of multicollinearity. In model 1, MHR ( $p < 0.001$ ), HbA1c ( $p < 0.001$ ) and CRP ( $p = 0.023$ ) were identified as independent predictors for CSF presence. In model 2, only GHR was an independent

Table 1

Baseline characteristics and clinical data of the study population

Variables	All population (n=237)	CNF group (n=128)	CSF group (n=109)	p-value
<b>Demographics</b>				
Age (years)	56.84±11.42	57.34±10.57	56.25±12.37	0.308
Male gender, n (%)	144 (60.8)	75 (58.6)	69 (63.3)	0.459
Hypertension, n (%)	123 (51.9)	67 (52.3)	56 (51.4)	0.882
Hyperlipidemia, n (%)	44 (18.6)	23 (18)	21 (19.3)	0.798
Smoking, n (%)	85 (35.9)	44 (34.4)	41 (37.6)	0.604
Ejection fraction (%)	58.66±3.51	58.98±3.15	58.28±3.88	0.108
<b>Laboratory</b>				
Hemoglobin, g/dL	14.34±6.94	14.07±1.40	14.66±10.14	0.115
WBC, 10 <sup>3</sup> /μL	9.12±5.12	8.08±1.81	10.35±6.96	<0.001
Monocyte, (10 <sup>9</sup> /L)	567.93±190.90	477.03±97	674.68±217.43	<0.001
FBG, mg/dL	90.34±11.75	83.98±9.43	97.81±9.64	<0.001
HbA1c (%)	5.63±0.54	5.33±0.45	5.99±0.40	<0.001
Creatinine, mg/dL	0.82±0.15	0.78±0.13	0.85±0.16	<0.001
Tchol, mg/dL	187.76±39.88	186.62±41.90	189.09±37.51	0.635
TG, mg/dL	158.22±63.52	132.21±55.98	188.75±58.20	<0.001
LDL-C, mg/dL	111.88±34.36	112.70±33.73	110.92±35.22	0.691
HDL-C, mg/dL	43.56±10.22	48.05±10.80	38.28±6.23	<0.001
CRP, mg/dL	0.64±0.56	0.43±0.28	0.89±0.69	<0.001
GHR	2.19±0.63	1.84±0.54	2.61±0.47	<0.001
MHR	14.16±6.88	10.61±3.83	18.33±7.34	<0.001
<b>Corrected TIMI frame count</b>				
LAD	25.22±9.02	19.31±2.08	32.17±9.08	<0.001
Lcx	23.07±8.46	17.89±3.58	29.16±8.50	<0.001
RCA	24.03±9.26	17.78±3.37	31.36±8.57	<0.001
Total TFC	72.44±23.02	54.90±6.91	93.04±17.56	<0.001
<b>Slow flow related artery</b>				
LAD, n (%)	80 (73.4)	-	80 (73.4)	-
Lcx, n (%)	55 (50.5)	-	55 (50.5)	-
RCA, n (%)	72 (66.1)	-	72 (66.1)	-
Single vessel, n (%)	43 (39.4)	-	43 (39.4)	-
Multi vessel, n (%)	66 (60.6)	-	66 (60.6)	-
<b>Medications</b>				
RAS blocker, n (%)	89 (37.6)	49 (38.3)	40 (36.7)	0.802
CCB, n (%)	45 (19)	29 (22.7)	16 (14.7)	0.119
Diuretics, n (%)	28 (11.8)	10 (7.8)	18 (16.5)	0.039
Statin, n (%)	32 (13.5)	18 (14.1)	14 (12.8)	0.784

CNF- coronary normal flow; CSF- coronary slow flow; FBG- fasting blood glucose; TG- triglycerides; Tchol- total cholesterol; LDL-C- low-density lipoprotein cholesterol; HDL-C- high-density lipoprotein cholesterol; WBC- white blood cells; CRP- C-reactive protein; LAD- left anterior descending artery; LCx- left circumflex artery; RCA- right coronary artery; TIMI- thrombolysis in myocardial infarction; TFC- "thrombolysis in myocardial infarction" frame count; RAS- Renin-angiotensin system; CCB- calcium channel blockers; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

Figure 1a - The comparison of GHR values between the groups

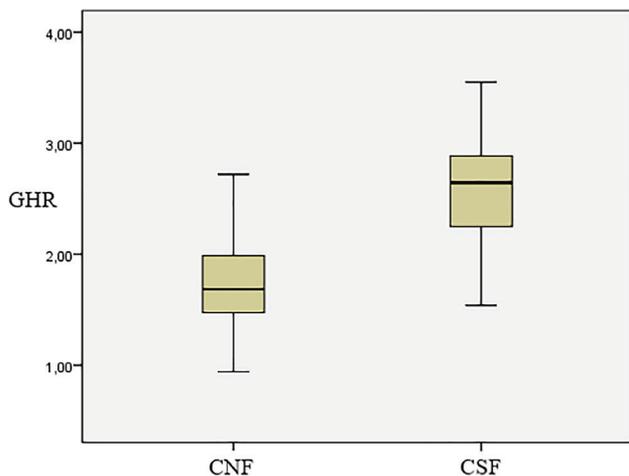
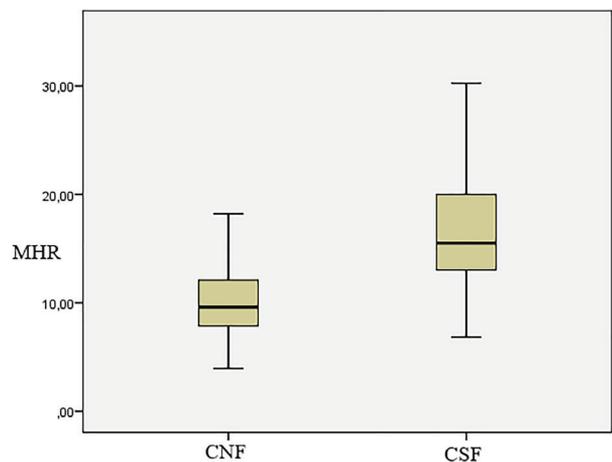
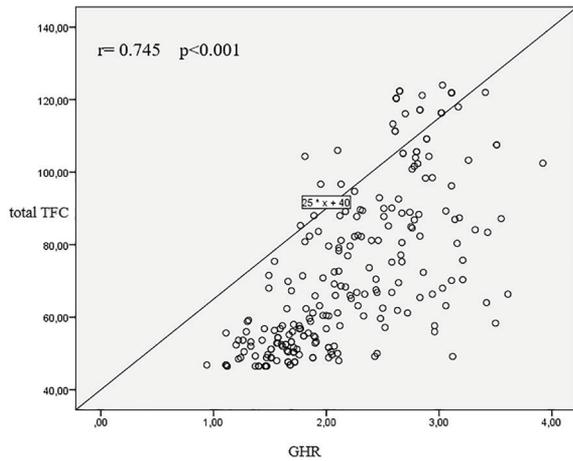


Figure 1b - The comparison of MHR values between the groups

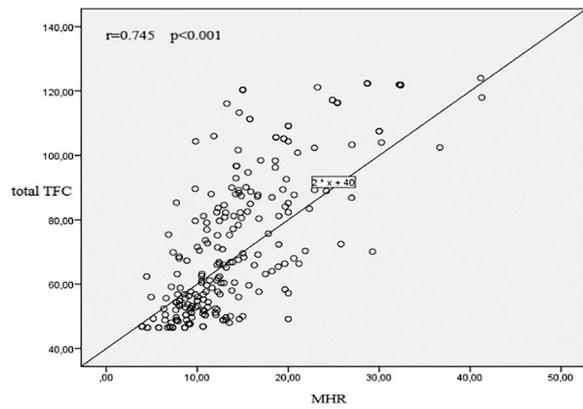


Abbreviations: GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio; CNF- coronary normal flow; CSF- coronary slow flow

**Figure 2a** - The relationship between total TFC and GHR



**Figure 2b** - The relationship between total TFC and MHR



Abbreviations: TFC- “thrombolysis in myocardial infarction” frame count; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

**Table 2** The multiple logistic regression analysis in predicting of CSF presence

**Model 1**

Variables	OR	95% CI	p-value
WBC	1.059	0.972-1.154	0.192
HbA1c	15.804	6.144-40.601	<0.001
Creatinine	0.096	0.006-1.577	0.101
CRP	0.263	0.083-0.831	0.023
MHR	1.320	1.184-1.471	<0.001
Constant	.000	-	<0.001

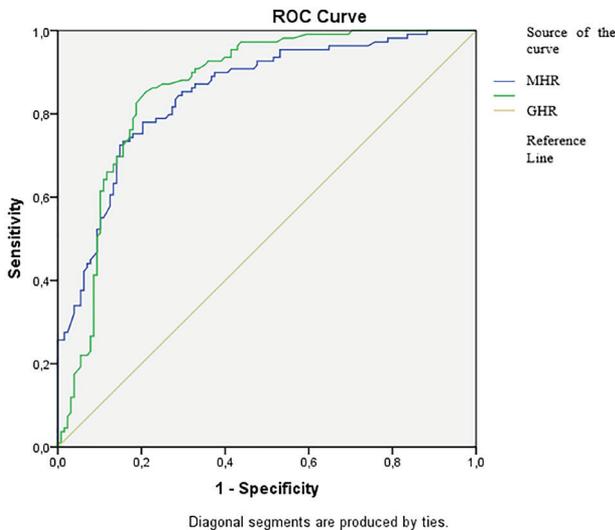
CSF- coronary slow flow; WBC- white blood cells; CRP- C-reactive protein; MHR- monocyte to HDL-C

**Model 2**

Variables (Model 2)	OR	95% CI	p-value
WBC	1.144	0.970-1.350	0.109
TG	1.003	0.995-1.010	0.485
Creatinine	0.732	0.061-8.774	0.805
CRP	0.733	0.573-4.149	0.392
GHR	8.773	3.906-19.704	<0.001
Constant	0.001	-	<0.001

CSF- coronary slow flow; WBC- white blood cells; TG- triglycerides; CRP- C-reactive protein GHR- glucose to HDL-C ratio

**Figure 3** - The receiver-operator characteristic (ROC) curve to determine the best cut-off values of GHR and MHR in predicting of CSF presence



Abbreviations: CSF- coronary slow flow; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

predictor for CSF presence ( $p < 0.001$ ) (Table 2). The receiver operating characteristic (ROC) curve analysis showed the GHR and MHR best cut off values as 2.105 at 78.91% specificity and 85.32% sensitivity, and as 12.93 at 79.69% specificity and 77.98% sensitivity, respectively (GHR, AUC=0.861, 95% CI=0.813-0.910,  $p < 0.001$ ; MHR, AUC=0.849, 95% CI=0.800-0.898,  $p < 0.001$ ) (Figure 3).

**Discussion**

In this study, we evaluated the relationship of CSF with GHR and MHR and revealed that these markers were increased in CSF presence regardless of all-causes. In addition, these markers were strongly correlated with total TFC, which indicates CSF severity.

CSF is an angiographic entity detected at a rate of 1-7% in patients with suspected CAD. It should be recognized without delay due to risk of hypotension, acute coronary syndrome, life-threatening arrhythmia and sudden death [19,1]. Although the etiopathogenesis of CSF remains unclear, there is increasing data suggesting the role of hyperglycemia and inflammation in this process. Elevated FBG levels are often related to IR and trigger oxidative stress, protein C kinase activation and non enzymatic protein glycosylation, resulting in acceleration of atherosclerosis by impairment of endothelial cell function, the decrease of NO release and inducing of procoagulant [20,21]. Several studies have demonstrated that increased FBG may lead to an increase risk of cardiovascular risk factors and CAD [22,23]. As in CAD, hyperglycemia may be responsible for CSF pathogenesis due to its adverse effects on endothelial function. Indeed, some data have confirmed this relation by showing the impairment of flow-mediated dilatation in the brachial artery and the decrease of endothelin-1, NO, homocysteine and diethyl methyl arginine responsible for vasomotor tonus [1]. Moreover, endothelial dysfunction may be accepted as an early stage of atherosclerosis, and a higher TFC may reflect the microvascular resistance of coronary arteries [24,25]. One study demonstrated that the impairment glucose tolerance was common in patients with CSF even if absence of overt diabetes and another study revealed the

effects of hyperglycemia on non-diabetic CSF patients [26,27]. Moreover Ozan et al. [28] and Arslan et al. [29] found a higher TFC in patients with IR compared to those without.

HDL-C is one of the lipid parameter related to CAD and mortality independently from other cardiovascular risk factors. It is also known that HDL-C particles protect the endothelial cells by preventing LDL-C oxidation [30]. Lower HDL-C levels were found to be an independent predictor for CSF in some studies and Sezgin et al. reported that low HDL-C levels may play a role in endothelial dysfunction in CSF [11,12]. However, Kalayci et al. [31] failed to show the relationship between CSF with HDL-C and attributed these contradictory findings to smoking, insufficient exercise time, and use of lipid-lowering drugs. GHR is a novel marker derived from the FBG and HDL-C, and one study showed that GHR may be an independent predictor for adverse cardiovascular outcomes in non-diabetic patients [13]. GHR may be considered as a marker indicating IR. Because IR is not only associated with hyperglycemia but also the impairment of lipid metabolism including elevated of triglycerides and LDL-C levels, and lower of HDL-C levels [32]. For the first time, we investigated the relationship between GHR with CSF in this study. We showed that GHR was elevated in non-diabetic CSF patients and was an independent predictor for CSF presence. We also confirmed that, as in previous studies, IR may play a role in CSF pathogenesis [24-29]. Furthermore, Yilmaz et al. [33] found a higher prevalence of metabolic syndrome associated with impairment of glycolipid metabolism in CSF patients. Another finding of our study was higher levels of HbA1c in CSF patients, similar to previous studies [34,35]. However some data have reported that CSF may not be related to hyperglycemia [36]. The inconsistencies between the studies may be linked to size of the sample, the characteristics of study population, inclusion and exclusion criteria, measurement technique differences, and drug use.

Monocytes and macrophages are blood cells associated with immunity, and circulating monocytes migrate to atherosclerotic plaques, differentiate into macrophages, and contribute to atherosclerosis by forming foam cells [37]. On the other hand, HDL-C particles exert an anti-atherosclerotic and anti-inflammatory effects by inhibiting macrophage migration, activation and adhesion [38]. MHR is a novel marker for

inflammation and several studies have shown its relationship with CAD and adverse cardiovascular outcomes [16,14]. However, the role of MHR in CSF pathogenesis is not clearly elucidated. Canpolat et al. [17] published a study that MHR may be an independent predictor of CSF presence and supported our findings. Another remarkable point in our study was the higher CRP levels in patients with CSF. Previous studies found a relationship between elevated CRP levels and CSF. In addition, it has been suggested that CSF is not only localized coronary artery pathology but also a systemic vascular disorder in which many local and systemic inflammatory factors contribute to its development [39,17,1].

Our study had some limitations. First, the study was a single-center study and had a relatively small sample. Due to a more homogeneous sample, the study findings cannot be generalized to the whole population and different ethnic groups. In addition, we cannot ignore the potential risk of bias and relative overestimation in single-center studies. Second, we measured FBG, HDL-C levels and monocyte cell counts only once at admission. Therefore, we may not exclude possible laboratory errors. Third, in the evaluation of endothelial dysfunction, we did not use advanced methods such as intravascular ultrasound or computed tomography, that present more reliable information on atherosclerosis.

## Conclusion

As a result, in this study, we confirmed that both hyperglycemia and inflammation play a role in CSF etiopathogenesis by demonstrating elevated GHR and MHR in CSF, independent from all-causes. Our findings also provide a new evidence that endothelial dysfunction may develop without overt diabetes manifests. However, our findings need to be confirmed by larger-scale prospective studies.

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