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Characteristics and Clinical Outcomes of COVID-19 Patients with Hyperglycemia: Retrospective Cohort Study from a COVID-19 Referral Hospital, Bandung, Indonesia

Hikmat Permana, Annisa Ikhsanawati, Evan Susandi, Nanny Natalia Mulyani Soetedjo, Bachti Alisjahbana

Department of Internal Medicine Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia

Abstract

Background: COVID-19 often causes severe complications in patients with metabolic disorders such as diabetes mellitus. Conversely, inflammation caused by infection may also trigger insulin resistance, resulting in hyperglycemia and is related to the disease severity. This study aimed to describe the characteristics and clinical outcomes of COVID-19 patients with hyperglycemia at one of the COVID-19 referral hospitals in Bandung, Indonesia.

Methods: This retrospective cohort study used secondary data from medical records of COVID-19 patients admitted to Dr. Hasan Sadikin General Hospital Bandung, Indonesia from March 2020 to March 2021. This study included all patients with confirmed COVID-19, aged >18 years, and had at least one blood glucose test at admission. Patients were grouped based on three possible types of hyperglycemia, namely diabetes mellitus, reactive hyperglycemia, and steroid-induced hyperglycemia; then their characteristics and disease outcomes were compared.

Results: This study identified 1,114 patients' medical records and included 1,013 data in the analysis. Hyperglycemia occurred in 45.1% of COVID-19 patients. The most common hyperglycemia types were diabetes mellitus (55.7%), reactive hyperglycemia (37.4%), and steroid-induced hyperglycemia (7%). The steroid-induced hyperglycemia group had similar characteristics as the diabetes group. The reactive hyperglycemia group exhibited a metabolic syndrome pattern resembling pre-diabetic conditions. The highest rates of severe disease and mortality were seen in the steroid-induced hyperglycemia group, followed by the diabetes group.

Conclusions: There is an elevated prevalence of hyperglycemia in COVID-19 patients with diabetes. The steroid-induced hyperglycemia group has the most unfavorable outcomes. These observations emphasize the importance of identifying hyperglycemic conditions to improve management and outcomes.

Keywords: COVID-19, characteristics, diabetes, hyperglycemia

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Correspondence:
dr. Annisa Ikhsanawati, Sp.PD, Department of Internal Medicine Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
E-mail:
annisa.ikhsanawati@yahoo.com

Introduction

The coronavirus disease (COVID-19) spreads very quickly, and the severity of this disease varies from flu symptoms, pneumonia, respiratory failure, arrhythmia, shock, multiple organ failure, and even death.[1,2] The SARS-CoV-2 virus has angiotensin-converting enzyme 2 (ACE2) receptors in various organs, including the lungs, cardiovascular system, kidneys, and pancreas.[3] This makes these organs the entry point for infection, direct viral replication, and inflammation.

A study in the United States that enrolled 1,122 COVID-19 patients in 88 hospitals has shown that patients with uncontrolled hyperglycemia have a higher length of stay and mortality than patients without hyperglycemia.[4] A meta-analysis of 18 studies reported that the prevalence of COVID-19 patients with diabetes

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was 14.5%. Diabetes patients have clinical manifestations similar to patients without diabetes, but the clinical symptoms are more severe.[5] Therapeutic approaches for COVID-19 continue to evolve, including antiviral therapy and anti-inflammatory drugs such as steroids administration and anti-IL6. Steroids are used in 45% of cases, especially in severe COVID-19 patients.[2] This medication can lead to steroid-induced hyperglycemia. Hence, it is crucial to closely monitor blood sugar levels in patients taking steroids to early identify the need for insulin therapy.[6]

SARS-CoV-2 infection often causes more severe diseases in patients with diabetes mellitus.[6] Conversely, inflammation caused by any infection may also trigger insulin resistance, which induces hyperglycemia and worsens disease severity.[6,7] Inflammation causes increased release of cytokines, chemokines, and apoptosis, which plays an important role in the pathogenesis of hyperglycemia. Therefore, hyperglycemia in COVID-19 patients can be caused by several mechanisms, including reactive processes due to inflammation, the selective higher proportion of diabetes mellitus patients hospitalized due to more severe disease, and induction of steroid drugs used in COVID-19 therapy.[8] Ability to identify the type of hyperglycemia is important to decide on the level of glycemic control necessary for the management of COVID-19.[2]

This study aimed to determine the proportion of the types of hyperglycemia managed among COVID-19 patients and to describe their characteristics and treatment outcomes. A comprehensive understanding of this information would help us develop appropriate management strategies and interventions to improve patient care.

Methods

This retrospective cohort study utilized COVID-19 patient information from a hospital register and medical records. Data was collected from patients with confirmed cases of COVID-19, aged ≥18 years, who had at least one random blood glucose test on admission. Exclusion criteria encompassed incomplete medical record data on age, gender, body mass index, and random blood glucose levels at hospital admission.

The hyperglycemia group was categorized as follows: a) Reactive hyperglycemia was defined as random blood glucose levels >140 mg/dl during hospitalization, not meeting the criteria for diabetes mellitus and steroid-induced hyperglycemia.[9] b) Type 2 diabetes mellitus was identified based on the American Diabetes Association criteria, namely having been previously diagnosed with diabetes or having classic diabetes symptoms with fasting plasma glucose (FPG) levels >126 mg/dl or a 2-hour plasma glucose levels >200 mg/dl; or random plasma glucose >200 mg/dl; or a hemoglobin A1c (HbA1c) level of >6.5%.[9,10] c) New-onset diabetes mellitus was referred to as having plasma glucose examination result resembling diabetes as in category b in individuals who had not previously suffered from the disease, d) Steroid-induced hyperglycemia condition was defined if the patient showed an increase in random blood glucose levels ≥200 mg/dl during treatment in patients receiving steroid therapy, previously had no symptoms or diagnosed as diabetes mellitus, and returned to normal when steroids were discontinued.[11] Patients without hyperglycemia were patients who did not meet the criteria for reactive hyperglycemia, diabetes mellitus, and steroid-induced hyperglycemia.

The clinical manifestations of COVID-19 were categorized into three levels of severity, namely mild, moderate, and severe. Mild condition was defined as symptoms that met the criteria for the COVID-19 case definition without any signs of hypoxia. Moderate condition was characterized by the presence of COVID-19 accompanied by clinical signs of pneumonia but without any signs of severe pneumonia, indicated by a SpO2 levels of 90% or higher in room air. The critical grade was assigned to patients with pneumonia who also had acute respiratory distress syndrome, sepsis, or septic shock.[12]

All data was processed using SPSS software version 25.0 (IBM corporation). Numerical data was tested for normality using the Kolmogorov-Smirnov test ($p>0.05$ indicated normal distribution). The unpaired t-test was used for normally distributed data, whereas the Mann-Whitney test was used to compare numerical data that was not normally distributed. Categorical data were analyzed using the Chi-Square test or Fisher's exact test. For more than two study groups, the ANOVA test was used for normally distributed data, and the Kruskal-Wallis test was used for non-normally distributed data. The significance level was set at $p\leq0.05$. The Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung approved this study with No. LB.02.01/X. 6.5/173/2021.

Table 1 Group Classification Based on History of Diabetes, Steroid Therapy, and Hyperglycemia Condition

Characteristics and Initial Laboratory Condition	Hyperglycemia Condition				
	Diabetes Mellitus n (%)	New Onset of Diabetes Mellitus n (%)	Reactive Hyperglycemia n (%)	Steroid-Induced Hyperglycemia n (%)	No Hyperglycemia n (%)
	n=139	n=115	n=171	n=32	n=556
History of diabetes mellitus					
Present	139 (100.0)	-	-	-	-
Not present	-	115 (100.0)	171 (100.0)	32 (100.0)	556 (100.0)
Steroid therapy					
Present	116 (83.5)	81 (70.4)	25 (14.6)	32 (100.0)	110 (19.8)
Not present	23 (16.5)	34 (29.6)	146 (85.4)	-	446 (80.2)
Random blood glucose level (mg/dl)					
≤ 140	22 (15.8)	16 (13.9)	9 (5.2)	8 (25.0)	556 (100)
141–199	33 (23.7)	22 (19.1)	147 (86)	10 (31.25)	-
≥200	84 (60.5)	77 (67.0)	15 (8.8)	14 (43.75)	-
Hba1c (%)	N=139	N=115	N=22	N=32	N=28
Median (min-max)	9 (5.4-25.2)	8.85 (6.5-14.3)	6 (4.5-6)	6 (5.5-6.1)	5.5 (4.9-5.96)
Hba1c, N (%)					
<7	8 (5.8)	-	22 (100.0)	32 (100.0)	28 (100.0)
7–7.9	23 (16.5)	38 (33.3)	-	-	-
8–8.9	43 (30.9)	22 (18.5)	-	-	-
>9	65 (46.8)	55 (48.2)	-	-	-

Results

Out of 1,114 COVID-19 patients, 1,013 patient's data were analyzed, which showed that 556 patients (54.9%) had no hyperglycemia and 457 patients had hyperglycemia (45.1%). The hyperglycemia group was further categorized as type 2 diabetes mellitus (n=139, 13.7%), new-onset diabetes mellitus (n=115, 11.3%), reactive hyperglycemia (n=171, 16.8%), steroid-induced hyperglycemia (n=32, 3.15%), and no hyperglycemia (n=556, 54.9%). (Table 1).

To validate the categories, the kinetics of random blood glucose levels during hospital admission were analyzed. The diabetes mellitus group consistently had higher blood glucose levels compared with the reactive hyperglycemia and steroid-induced hyperglycemia groups. The diabetes mellitus group showed a median blood glucose level of 200 mg/dl at admission, which remained unchanged throughout the hospitalization, but at week 4, some patients exhibited a decrease in blood glucose levels due to insulin therapy. The reactive hyperglycemia and steroid-induced hyperglycemia groups were discharged with similar median random blood glucose levels of 187 mg/dl and 188 mg/dl, respectively (Figure 1).

The characteristics and clinical outcomes of the hyperglycemia group showed that there were no gender differences between groups, however, the hyperglycemia groups had a higher age distribution than the non-hyperglycemia group. The steroid-induced hyperglycemia group had the highest body mass index, followed by the diabetes and reactive hyperglycemia groups. Hypertension, cardiovascular disease, and chronic kidney disease were more common in the diabetes group, followed by the steroid-induced hyperglycemia and reactive hyperglycemia groups. However, other comorbidities such as asthma, chronic obstructive pulmonary disease, liver disease, and malignancies were more common in the non-hyperglycemia group (Table 2).

Regarding severity and clinical outcomes, the steroid-induced hyperglycemia group exhibited the highest number of patients with severe illness and the highest mortality,

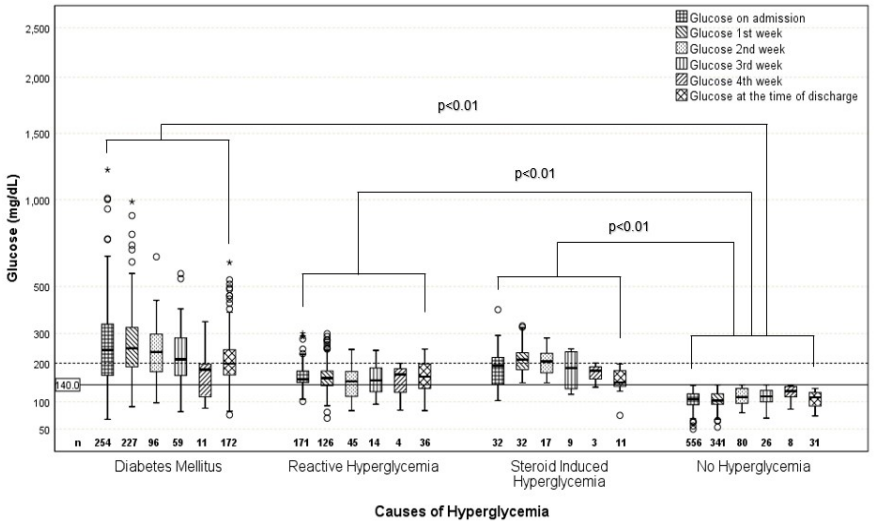

Figure 1 Kinetics of Random Blood Glucose Levels of Subjects during Treatment

followed by the diabetes group and then the reactive hyperglycemia group. Notably, the steroid-induced hyperglycemia group had nearly three times more occurrence of secondary bacterial infections and mortality than the diabetes group.

Furthermore, the findings of chest X-ray and laboratory examinations showed that steroid-induced hyperglycemia constituted the highest proportion of pulmonary infiltrates, followed by the diabetes group and the reactive hyperglycemia groups. Inflammatory markers, including leukocyte count, neutrophil lymphocyte ratio, C-reactive protein, and procalcitonin, were highest in the steroid-induced hyperglycemia group, followed by the diabetes group and then the reactive hyperglycemia group. Total cholesterol and HDL levels were lowest in the steroid-induced hyperglycemia group and similar in the other groups. Triglyceride levels followed the inflammation pattern, with the highest in the steroid-induced group, followed by the diabetes and reactive hyperglycemia groups (Table 3).

Discussion

This study found that approximately half of COVID-19 patients had hyperglycemia, with the main causes being diabetes mellitus (55.7%), reactive hyperglycemia (37.4%), and steroid-induced hyperglycemia (7%). This findings align with a report from Wuhan, China, which stated that hyperglycemia occurred in 50% of COVID-19 patients.[13] A previous study has reported lower rates of hyperglycemia during treatment.[14] Most of the subjects who experienced hyperglycemia had a history of diabetes mellitus, while the rest did not. Another study found that a higher percentage of SARS patients (46%) had reactive hyperglycemia compared to sepsis-induced hyperglycemia in medical ICUs, which is recorded at 20.33%.[15] These variations may be due to different study methods, patient populations, and geographic factors.

The random blood glucose kinetics during treatment confirmed the proper selection of the three hyperglycemia categories. Patients with diabetes mellitus showed the highest glycemic curve, followed by the reactive hyperglycemia and steroid-induced hyperglycemia groups. Hyperglycemia caused by the steroid returned to normal when the steroid was discontinued. It was observed that the glucose level dropped again in the fourth week or at the end of hospital admission. A previous study reported the kinetics of blood glucose levels in a cohort study of 19,694 patients admitted to the ICU at an academic medical center.[16] Currently, there is no study that specifically describes the kinetics of blood glucose levels in COVID-19 patients.

The age predominance in diabetes mellitus, reactive hyperglycemia, and steroid-induced hyperglycemia is ≥60 years. These results are consistent with previous research, where it was reported that a significant percentage of COVID-19 patients with hyperglycemia had a

Table 2 Characteristics and Outcomes of COVID-19 Patients with Different Types of Hyperglycemia

Characteristics	Total n=1,013	Group			
		Diabetes Mellitus n=254	Reactive Hyperglycemia n=171	Steroid-induced Hyperglycemia n=32	No Hyperglycemia n=556
Age (years), n(%)**					
18–29 years	114 (11.3)	2 (0.8)	13 (7.6)	1 (3.1)	98 (17.6)
30–39 years	177 (17.5)	17 (6.7)	22 (12.9)	1 (3.1)	137 (24.6)
40–49 years	194 (19.2)	45 (17.7)	36 (21.1)	6 (18.8)	107 (19.2)
50–59 years	225 (22.2)	71 (28.0)	41 (24.0)	3 (9.4)	110 (19.8)
≥60 years	303 (29.9)	119 (46.9)	59 (34.5)	21 (65.6)	104 (18.7)
Gender, n (%)					
Male	505 (49.9)	128 (50.4)	100 (58.5)	15 (46.9)	262 (47.1)
Female	508 (50.1)	126 (49.6)	71 (41.5)	17 (53.1)	294 (52.9)
Body mass index (kg/m^2), median (min-max)**	23.44 (16.05-47.06)	23.69 (17.30-42.61)	23.44 (17.01-41.80)	24.63(20.55-38.06)	23.07 (16.05-47.06)
Body mass index criteria (kg/m^2), n (%)*					
<18.5	30 (3.0)	6 (2.4)	2 (1.2)	0 (0.0)	22 (4.0)
18.5–22.9	433 (42.7)	99 (39.0)	74 (43.3)	5 (15.6)	255 (45.9)
23–24.9	304 (30.0)	82 (32.3)	52 (30.4)	15 (46.9)	155 (27.9)
25–29.9	198 (19.5)	55 (21.7)	34 (19.9)	8 (25.0)	101 (18.2)
≥30	48 (4.7)	12 (4.7)	9 (5.3)	4 (12.5)	23 (4.1)
Comorbidities, n (%)					
Hypertension **	306 (30.2)	108 (42.5)	64 (37.4)	15 (46.9)	119 (21.4)
Diabetes mellitus **	139 (13.7)	139 (54.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular disease *	93 (9.2)	35 (13.8)	15 (8.8)	4 (12.5)	39 (7.0)
Obesity	48 (4.7)	12 (4.7)	9 (5.3)	4 (12.5)	23 (4.1)
Chronic renal disease*	53 (5.2)	23 (9.1)	11 (6.4)	2 (6.3)	17 (3.1)
Asthma bronchiale	13 (1.3)	5 (2.0)	2 (1.2)	1 (3.1)	5 (0.9)
Pulmonary TB	3 (0.3)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
COPD	9 (0.9)	1 (0.4)	1 (0.6)	0 (0.0)	7 (1.3)
Chronic liver disease	12 (1.2)	2 (0.8)	0 (0.0)	10 (1.8)	10 (1.8)
Malignancy*	29 (2.9)	2 (0.8)	1 (0.6)	1 (3.1)	25 (4.5)
COVID-19 degree of severity, n (%)**					
Mild	273 (26.9)	18 (7.1)	30 (17.5)	0 (0.0)	225 (40.5)
Moderate	400 (39.5)	76 (29.9)	73 (42.7)	7 (21.9)	244 (43.9)
Severe, critically ill	340 (33.6)	160 (63.0)	68 (39.8)	25 (78.1)	87 (15.6)
Secondary infection, n (%)**	159 (15.7)	47 (18.5)	28 (16.4)	19 (59.4)	65 (11.7)
Outcome, n (%)**					
Recovered	857(84.6)	195(76.8)	143(83.6)	14(43.8)	505(90.8)
Death	156(15.4)	59(23.2)	28(16.4)	18(56.3)	51(9.2)

Note: *p<0.05, **p<0.01

median age of 69 years.[13] This study states that elderly patients and those with comorbidities have a higher risk of contracting moderate-to-severe COVID-19.

The study observed that the body mass index of patients in the hyperglycemia groups was mainly overweight. A previous study has suggested that overweight people, whether they have diabetes mellitus or not, may face a higher risk of developing severe COVID-19.[17] The theory underlying this association is related to impaired metabolism and organ function, leading to insulin resistance. Impaired cytokine and chemokine regulation,

Table 3 Chest X-ray and Laboratory Examination of COVID-19 Patients with Different Types of Hyperglycemia Admitted at Dr. Hasan Sadikin General Hospital

Characteristics	Total n=1,013	Group			
		Diabetes Mellitus n=254	Reactive Hyperglycemia n=171	Steroid-induced Hyperglycemia n=32	No Hyperglycemia n=556
Chest x-ray, n (%)**					
Presence of infiltrate	628 (62.0)	199 (78.3)	114 (66.7)	32 (100.0)	283 (50.9)
No infiltrate	385 (38.0)	55 (21.7)	57 (33.3)	0 (0.0)	273 (49.1)
Inflammation and cholesterol parameter, median (min-max)					
Leucocyte(/mm3)** n=1,008	7,800 (730-160,950)	8,260 (3,090-38,470)	8,730 (730-160,950)	10,820 (2,730-24,870)	7,320 (890-3,340)
NLCR ** n=1003	4.47 (0-96)	5.44 (1-96)	5.33 (0.1-48.42)	7.5 (0-46.76)	3.73 (0.18-48.47)
CRP (mg/l)** n=778	38.6 (0.1-408.5)	72 (1-380.3)	56.4 (0.1-373.3)	118.1 (10.6-408.5)	21.5 (0.1-291.2)
Procalcitonin (ng/ml)** n=771	0.25 (0.10-75)	0.30 (0.1-34.30)	0.28 (0.1-74.23)	0.7 (0.1-29.73)	0.2 (0.1-75)
Total cholesterol (mg/dl) n=322	172 (67-393)	172 (67-314)	173 (73-257)	167 (114-224)	171 (70-393)
HDL (mg/dl)** n=319	34 (10-177)	31 (11-177)	38 (10-117)	18 (16-37)	37 (12-94)
LDL (mg/dl) n=321	107 (19-265)	109 (30-224)	107 (19-189)	86 (40-131)	106 (25-265)
Triglyceride** (mg/dl) n=318	143 (36-650)	160 (36-650)	127 (38-534)	217 (178-471)	121 (44-471)

Note: *p<0.05, **p<0.01

increased apoptosis, and tissue fibrosis are observed in obesity and type 2 diabetes.[18]

Hypertension, cardiovascular diseases, and chronic kidney disease, as signs of metabolic disease, mostly occurred in the steroid-induced hyperglycemia and the hyperglycemia groups. Increased ACE2 expression results in more receptors in humans that can bind to SARS-CoV-2 as an entry point for infection.[19] In this study, the reactive hyperglycemia and steroid-induced hyperglycemia groups had similar metabolic syndrome patterns as the diabetes mellitus group, suggesting similarities in the pathophysiology and progression of metabolic disease among patients.

The severe COVID-19 proportion was highest in the steroid-induced hyperglycemia group, followed by the diabetes group. Various factors contribute to the increased risk and severity of SARS-CoV-2 infection in diabetes, including elevated ACE2 expression, furin, impaired T-cell function, and interleukin-6 (IL-6).[20] Secondary bacterial infections were the most common in the steroid-induced hyperglycemia group, followed by diabetes, reactive hyperglycemia, and non-hyperglycemic groups. Viral infection in a person who already has diabetes or hyperglycemia seems to be more prone to immune system disorders thereby inhibiting bactericidal activity. Steroid administration is believed to aggravate the infection.[21,22]

The steroid-induced hyperglycemia group exhibited the highest inflammatory parameters, consistent with their more severe condition, indicating a link between hyperglycemia and elevated inflammatory markers in COVID-19 patients.[23] Hyperglycemia is also associated with impaired leukocyte function, including phagocytosis and chemotaxis, leading to more severe disease. SARS-CoV-2 infections among diabetic patients often present with highly expressing IL-6 monocyte cells, indicating a heightened level of stimulation. Steroid-induced hyperglycemia has an added vulnerability to bacterial infection. The high dose of dexamethasone that the patients acquired partially paralyzed their immune defense system, which further increased the frequency of bacterial infections and was showed by overly increase in the values of inflammatory markers.[24,25]

Steroid-induced hyperglycemia and diabetes groups have the worst outcomes, as they are more likely to experience severe and critical COVID-19 symptoms.[26] In patients without previous diabetes, hyperglycemia predicts a poor prognosis along with elevations of other inflammatory biomarkers. This suggests a notion that hyperglycemia is associated with inflammation of pancreatic islet cells through binding of SARS-CoV to ACE2 present on islet cells, which will resolve with disease resolution.[27] Therefore, the outcome of patients in the hyperglycemia group is not better than that of patients without hyperglycemia.[14, 28–30]

The limitation of this study is that not all subjects had blood glucose and HbA1C levels checked during treatment. Blood

glucose measurements were tested on all patients admitted to hospital, however, follow-up glucose tests on all patients were not mandatory. There was no blood glucose check before the patient was diagnosed with COVID-19. In addition, there were no HbA1C test results before and after exposure to COVID-19. Although the sample size is not optimal, it sufficient to describe blood glucose levels in several groups.

In conclusion, hyperglycemia is a common condition associated with COVID-19, stemming from underlying diabetes, reactive hyperglycemia, or steroid-induced hyperglycemia. The worst outcomes and highest inflammation are observed in the steroid-induced hyperglycemia group, followed by diabetes and reactive hyperglycemia. This observation warrants increased attention from clinicians due to the higher risk of mortality. Further research is needed to understand the pathophysiology and mechanism of action of COVID-19 in hyperglycemia.

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