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**Original Research Article**

# A study of serum calcium level in cases of malaria in a tertiary care hospital

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## ABSTRACT

**Background:** Malaria is a tropical disease caused by *Plasmodium* species, commonly *P. falciparum* and *P. vivax*. Carpopedal spasm has been noted in many patients presenting with malarial fever. Most of the patients are later found to have hypocalcaemia. Hypocalcaemia associated with malaria can cause many clinical manifestations, including life threatening conditions such as arrhythmias, convulsions etc.
**Methods:** A cross-sectional study was conducted with the aim to determine the prevalence and clinical profile of hypocalcaemia in different types of malarial fever. 88 patients of malarial fever were studied. Patients were stratified according to the species of plasmodium and into complicated and uncomplicated malaria. Total serum calcium level and QTc interval were analysed in each patient. Data collected were analysed.
**Results:** Prevalence of hypocalcaemia in malaria was found to be 54.45% in our study. Hypocalcaemia was more prevalent in complicated malaria than uncomplicated malaria. Complicated falciparum malaria showed highest prevalence of hypocalcaemia. Status of complexity of malaria was not found to be related to occurrence of hypocalcaemia in any types of malaria. Prevalence of QTc prolongation in malaria was found to be 48.46%. Prevalence of QTc prolongation was found to be more in complicated malaria than uncomplicated malaria. QTc prolongation was most prevalent in complicated falciparum malaria. 83.3% of those with QTc prolongation had hypocalcaemia.
**Conclusions:** Hypocalcemia and QTc prolongation were more prevalent in complicated malaria than in uncomplicated malaria. Both Hypocalcaemia and QTc prolongation were most prevalent in complicated falciparum malaria.

**Keywords:** Serum calcium, *Plasmodium falciparum, Plasmodium vivax*

## INTRODUCTION

Malaria is a tropical Disease caused by protozoa *Plasmodium. P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi* are known to cause malarial infections in humans. Malaria is transmitted by female anopheles mosquito.[1]

Initial symptoms of malaria are mostly non-specific including headache, fatigue, abdominal discomfort, myalgia and arthralgia which is followed by fever. High grade fever occurring at regular intervals with chills and rigors is seen. Fever spikes occur every second day in *P. vivax* and *P. malariae* malarial infections and is known as tertian fever. Quartian fever (fever spikes on every third day) is seen in *P. falciparum* and *P. malariae* infection. In *P. knowlesi* infection fever spike is seen in every 24 hours. Mild jaundice and hepatosplenomegaly are often seen in malaria. Severe normocytic normochromic anaemia, renal failure, acidemia/acidosis, unarguable coma, pulmonary edema/adult respiratory distress syndrome, hypoglycaemia, hypotension/shock, bleeding/ disseminated intravascular coagulation, convulsions,

haemoglobinuria are manifestations of complicated malaria.

Normal serum calcium level is 8.5-10.2 mg%. Of this 50% is bound to serum protein 50% remains free in circulation. Serum calcium level <8.5 mg% is taken as hypocalcemia. Patients remain asymptomatic in mild and chronic hypocalcemia or they may directly present in life threatening complications. Moderate hypocalcemia presents with paresthesia especially over fingers and circumoral areas. Carpopedal spasm, Chvostek's sign and Trosseau's sign can be elicited on clinical examination of these patients. Severe hypocalcemia presents with seizures, carpopedal spasm, bronchospasm, laryngospasm, prolongation of QT interval and arrythmias.[1] Ca++ based signalling pathway used by plasmodium parasites results in reduced calcium status, especially intracellular calcium, but not Ca++ found in body fluids. Environment of the host cell cytoplasm is disturbed by this.[2] Also, *Plasmodium falciparum* infected red blood cells show increased permeability for calcium. The magnitude of the increase is greater than that normally require activating the Ca++ dependent K+ channel. Some studies showed that Falciparum infection increases the influx of Ca++ to over 1mmol which is much higher than the normal values. The pathway responsible for the enhanced influx was expressed at approximately 30 hrs post invasion.[3] Calcium dependent Transglutaminase activity that reduces the calcium level is found increased, in some studies. This decrease is found simultaneous with maturation of the parasite. The effect is maximum when the trophozoites are 48 hrs old and at that time most of the calcium is found in the parasite.[4] Also, Ionized calcium "set point" for basal PTH secretion is decreased in malaria. But a normal PTH response to acute hypocalcaemia in malaria skeletal resistance may attenuate the effect of the PTH response but patients with malaria appear relatively resistant to the calcium chelating effects of citrated blood products. Disturbed Parathyroid hormone profile has also contributed to the lowered Calcium status.[5] 'Sick euparathyroid syndrome' is defined as a state in which the parathyroid response to hypocalcemia remains depressed during active infection, with recovery of the glandular function as the parasitemia gets cleared.[6] Mild asymptomatic hypomagnesemia is seen in malaria. Hypomagnesemia impairs the release of parathormone by the parathyroid gland and blunt the tissue response to parathormone.[7] This in turn results in hypocalcemia. Many studies found out that hypocalcemia has prognostic value in malaria as it may indicate complicated malaria or heavy parasitemia and its return to normal serum level may indicate clinical recovery and parasite clearance.[8]

## METHODS

A cross sectional study was conducted at Surat Municipal Institute of Medical Education and Research (SMIMER) Hospital from April 2020 to July 2021. All indoor patients that were slide positive cases of malaria and that gave consent to participate were enrolled for the study. Patients <18 years of age, known case of hypo/hyperparathyroidism, known case of chronic kidney disease or known case of chronic liver disease were excluded from the study. Patients that have undergone thyroid surgery or patients with hypoalbuminemia were excluded from the study. Also, patients on treatment with drugs like diuretics, phenytoin, barbiturates, calcitonin or calcium supplements were excluded from the study.

After approval from the Institutional Ethics Committee. Informed written consent for allowing the use of clinical data of the patients was taken. No harm to any subject was done and the method of blood collection and advantages and disadvantages of the study were explained to the patient. If any patient was found with altered serum calcium, he was given immediate appropriate treatment under the guidance of the consultant of the treating unit.

A total of 88 patients were included for the study. Both thick and thin smear were done for diagnosing malaria. Thick smear gives a diagnosis of malaria whereas thin smear was done to identify the species of malaria. Serum calcium was measured in all the patients at the time of admission. No patient was included more than once. A detailed proforma was filled up for each patient.

History and detailed clinical examination was done with special emphasis on signs and symptoms of complicated malaria and hypocalcaemia. Convulsions, carpopedal spasms, numbness, Trousseau's sign and Chvostek's sign were considered as the clinical manifestation of hypocalcemia in this study. Patients were also stratified into different groups according to sex and age. Sex and age wise distribution of hypocalcemia in malarial patients was also analyzed. Those with peripheral smear positivity for malaria was taken as the cases of malarial fever and enrolled for the studies.

Patients were stratified into 3 groups according to the species of *plasmodium* parasite causing the disease. Patients with *P. falciparum* infection, *P. vivax* infection and mixed infection (*P. falciparum*+ *P. vivax*) constituted the 3 groups. Cerebral malaria (Glassgow comma scale <11, convulsions), acute renal failure (Serum creatinine >3 mg/dl, serum urea >40 mg/dl), ARDS, shock (systolic BP <80 mmHg), severe anemia (Hb <7 g/dl, HCT <20%), hypoglycemia (RBS <40 mg/dl), Abnormal bleeding, jaundice (serum bilirubin >3 mg/dl) and pulmonary edema were considered as complicated malaria for this study. Malarial patients were stratified into 2 groups according to the severity of the disease- complicated and uncomplicated malaria.

Blood was collected from the patient for serum calcium at the time of admission. Serum calcium was measured in central lab by Arsenazo method (reference range- 8.5- 10.2 mg/dl). Total serum calcium level was analyzed in each patients. Total calcium level of <8.5 mg% was taken as hypocalcemia for this study. ECG was taken for all patients at the time of admission. QT segment was

analyzed in each patients. Normal QTc in an ECG is equal to less than 0.44 sec. QTc of duration >0.44 sec was considered as prolonged QTc for this study. To analyze the data OpenEPI software (version 3.1, released 2013) was used and Chi Square and Fischer Exact tests were used.

## RESULTS

A total of 88 malarial fever patients were included in the study. 48 patients were males and 40 patients were females. Out of 88 malarial cases 36 patients were infected with *plasmodium falciparum*. Out of 36 *falciparum* malaria 11 patients presented with complicated malaria while 25 patients had uncomplicated malaria. 39 out of 88 patients were having vivax malaria. Nine out of 39 had complicated vivax malaria whereas 30 patients had uncomplicated vivax malaria. 13 out of 88 patients presented with mixed infection. Six patients with mixed infection had complicated malaria while five patients had uncomplicated malaria.

**Table 1: Comparison of prevalence of hypocalcaemia in malaria in males and females.**

| Gender | Serum calcium level | | | | | |
|---|---|---|---|---|---|---|
| | Hypocalcaemia | | Normal | | Total | |
| | N | % | N | % | N | % |
| **Male** | 29 | 60.42 | 19 | 39.58 | 48 | 100.00 |
| **Female** | 19 | 47.50 | 21 | 52.50 | 40 | 100.00 |
| **Total** | 48 | 54.55 | 40 | 45.45 | 88 | 100.00 |

**Table 2: Comparison of prevalence of hypocalcaemia in different age groups.**

| Age group (in years) | Serum calcium level | | | | | |
|---|---|---|---|---|---|---|
| | Hypocalcaemia | | Normal | | Total | |
| | N | % | N | % | N | % |
| **11-20** | 10 | 62.50 | 6 | 37.50 | 16 | 100.00 |
| **21-30** | 14 | 51.85 | 13 | 48.15 | 27 | 100.00 |
| **31-40** | 12 | 50.00 | 12 | 50.00 | 24 | 100.00 |
| **41-50** | 5 | 55.56 | 4 | 44.44 | 9 | 100.00 |
| **51-60** | 2 | 40.00 | 3 | 60.00 | 5 | 100.00 |
| **61-70** | 5 | 71.43 | 2 | 28.57 | 7 | 100.00 |
| | 48 | 54.55 | 40 | 45.45 | 88 | 100.00 |

**Table 3: Prevalence of hypocalcaemia in complicated and uncomplicated malaria.**

| Type of malaria | Serum calcium level | | | | | |
|---|---|---|---|---|---|---|
| | Hypocalcaemia | | Normal | | Total | |
| | N | % | N | % | N | % |
| **Complicated** | 18 | 69.23 | 8 | 30.77 | 26 | 100 |
| **Uncomplicated** | 30 | 48.39 | 32 | 51.61 | 62 | 100 |
| **Total** | 48 | 54.55 | 40 | 45.45 | 88 | 100 |

**Table 4: Correlation between hypocalcaemia and QTc prolongation in different species of malaria.**

| Type of malaria | Serum calcium level | QTC Status | | | | | |
|---|---|---|---|---|---|---|---|
| | | Prolongation | | Normal | | Total | |
| | | N | % | N | % | N | % |
| **Complicated falciparum** | Hypocalcaemia | 10 | 83.33 | 1 | 50.00 | 11 | 78.57 |
| | Normal | 2 | 16.67 | 1 | 50.00 | 3 | 21.43 |
| | Total | 12 | 100.00 | 2 | 100.00 | 14 | 100.00 |
| **Uncomplicated falciparum** | Hypocalcaemia | 10 | 71.43 | 5 | 45.45 | 15 | 60.00 |
| | Normal | 4 | 28.57 | 6 | 54.55 | 10 | 40.00 |
| | Total | 14 | 100.00 | 11 | 100.00 | 25 | 100.00 |
| **Complicated vivax** | Hypocalcaemia | 4 | 100.00 | 0 | 0.00 | 4 | 57.14 |
| | Normal | 0 | 0.00 | 3 | 100.00 | 3 | 42.86 |

Continued.

| Type of malaria | Serum calcium level | QTC Status | | | | | |
|---|---|---|---|---|---|---|---|
| | | Prolongation | | Normal | | Total | |
| | | N | % | N | % | N | % |
| | Total | 4 | 100.00 | 3 | 100.00 | 7 | 100.00 |
| Uncomplicated vivax | Hypocalcaemia | 8 | 72.73 | 5 | 22.73 | 13 | 39.39 |
| | Normal | 3 | 27.27 | 17 | 77.27 | 20 | 60.61 |
| | Total | 11 | 100.00 | 22 | 100.00 | 33 | 100.00 |
| Complicated mixed | Hypocalcaemia | 2 | 100.00 | 2 | 50.00 | 4 | 66.67 |
| | Normal | 0 | 0.00 | 2 | 50.00 | 2 | 33.33 |
| | Total | 2 | 100.00 | 4 | 100.00 | 6 | 100.00 |
| Uncomplicated mixed | Hypocalcaemia | 1 | 50.00 | 0 | 0.00 | 1 | 20.00 |
| | Normal | 1 | 50.00 | 3 | 100.00 | 4 | 80.00 |
| | Total | 2 | 100.00 | 3 | 100.00 | 5 | 100.00 |

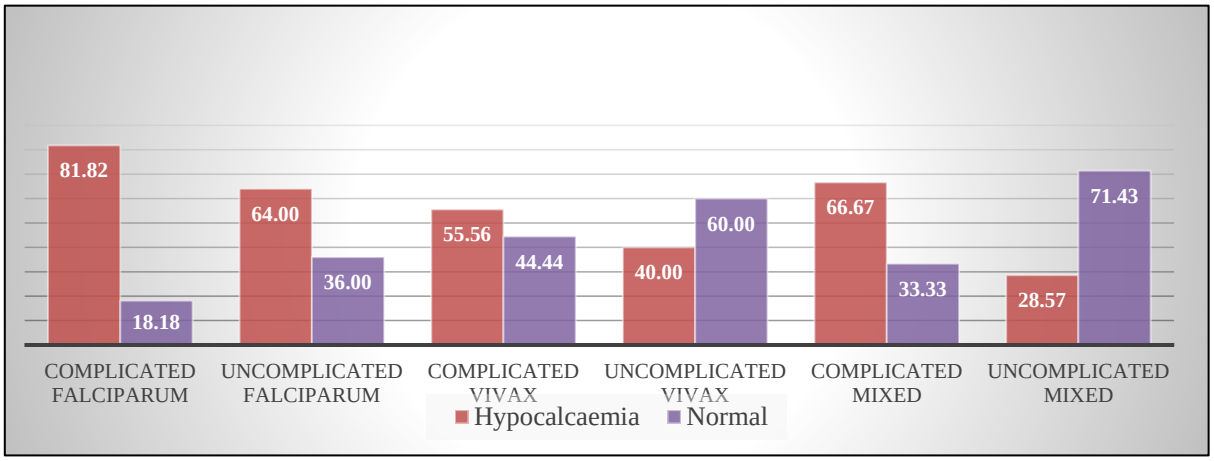


**Figure 1: Prevalence of hypocalcaemia in different types of malaria.**

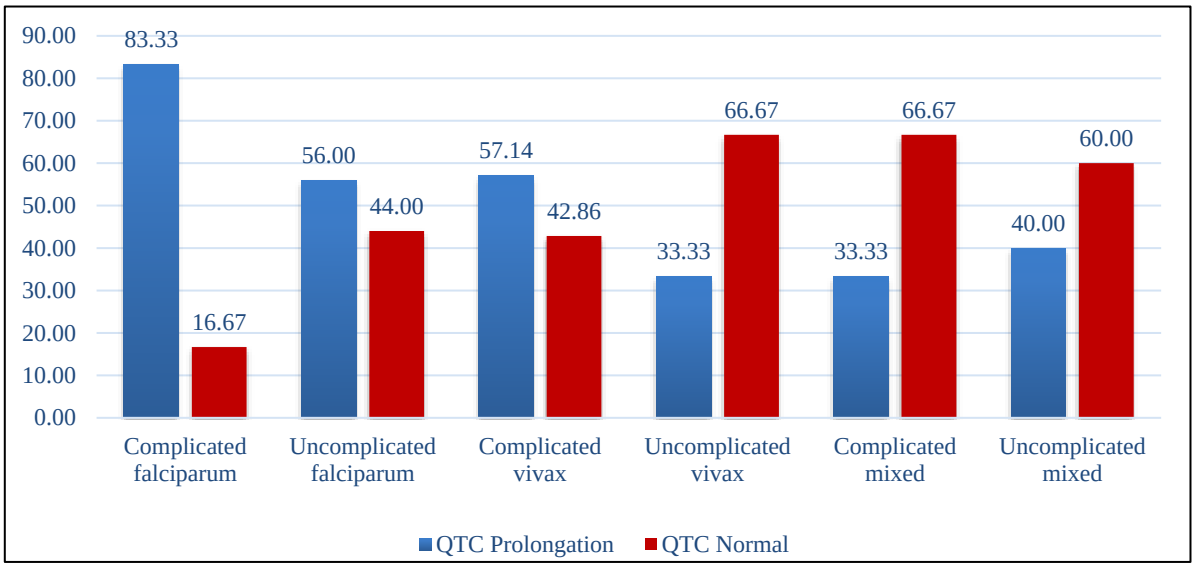


**Figure 2: Comparison of prevalence of QTc prolongation in different species of complicated and uncomplicated malaria.**

Out of 88 malarial cases 48 patients (54.45%) were found to have hypocalcemia. 40 patients (45.45 %) presented with normal serum calcium level. Out of 48 males with malaria 29 patients (60.4%) have hypocalcemia while 19 patients (39.58%) didn't have hypocalcemia. 19 out of 40 female patients (47.5%) developed hypocalcemia while 21 patients (52.5%) had normocalcemia. There was no statistically significant difference of prevalence of

hypocalcemia in malaria between males and females. (Table 1)

Patients were divided according to their age groups. Out of 16 patients from age group 11 to 20 years, 10 patients (62.5%) had hypocalcemia. Out of 27 patients from age group 21 to 30 years, 14 patients (51.85%) had hypocalcemia. Out of 24 patients from age group 31 to 40 years, 12 patients (50.0%) had hypocalcemia. Out of 9 patients from age group 41 to 50 years, 5 patients (55.56%) had hypocalcemia. Out of 5 patients from age group 51 to 60 years, 2 patients (40.0%) had hypocalcemia. Out of 7 patients from age group 61 to 70 years, 5 patients (71.4%) had hypocalcemia. There was no statistically significant difference of prevalence of hypocalcemia in malaria patients of different age groups (p=0.802). (Table 2)

Out of 88 malarial cases 26 patients were having complicated malaria. 18 patients (69.23%) out of 26 complicated malaria had hypocalcemia while 30 patients (48.39%) out of 62 uncomplicated malaria presented with hypocalcemia. 8 patients (30.77%) with complicated malaria had normal serum calcium. 32 patients with uncomplicated malaria (51.61%) had normal serum calcium. Hypocalcemia was found to be more prevalent in complicated malaria than uncomplicated malaria. The results were analyzed with Pearson chi square test and p-value was found to be significant (p value-0.040). (Table 3)

81.82% (9 patients) of complicated *falciparum* malaria cases had hypocalcemia. Only 18.18% (2 patients) of complicated falciparum malaria patients had normocalcemia. 64% of patients with uncomplicated falciparum malaria presented with hypocalcemia whereas 36% patients had normocalcemia. 55.56% of those with complicated vivax malaria had hypocalcemia. Normocalcemia was noted in 44.44% of patients with complicated hypocalcemia. 40% of patients with uncomplicated vivax malaria were having hypocalcemia whereas normocalcemia was reported in 60% patients with uncomplicated vivax malaria. Hypocalcemia was detected in 66.7% of those with complicated mixed infection while 33.3% of them had normocalcemia. Only 28.57% patients with uncomplicated mixed infection developed hypocalcemia. 71.43% of those with uncomplicated mixed infection had normocalcemia. Prevalence of hypocalcemia was found to be highest in those with complicated falciparum malaria. There was a statistically significant difference in the prevalence of hypocalcemia between the different types of malaria (p value- 0.004). (Figure 1)

43 (48.86%) out of 88 malarial cases were found to have prolonged QTc. QTc was normal in 45 patients (51.14%).

83.33% of patients with complicated falciparum malaria patients had prolonged QTc. Prevalence of QTc prolongation in complicated vivax malaria and complicated mixed malarial infection were 57.14% and 33.3% respectively. QTc was normal in 44%, 66.67% and 60% patients with uncomplicated *falciparum* malaria, uncomplicated vivax malaria and uncomplicated mixed malarial infection respectively. Complicated *falciparum* malarial patients were found to have the highest prevalence of QTc prolongation. It was found to be statistically significant. (p=0.027) (Figure 2)

Both QTc prolongation and hypocalcemia were noted in 83.3%, 71.43%, 100%, 72.73%, 100% and 50% of patients with complicated falciparum malaria, uncomplicated *falciparum* malaria, complicated vivax malaria, uncomplicated vivax malaria, complicated mixed infection and uncomplicated mixed infection. The association between QTc prolongation and hypocalcemia was found to be statistically significant only in complicated (p=0.005) and uncomplicated vivax (p=0.001) malaria. (Table 4)

## DISCUSSION

In our study, hypocalcemia was found to be more prevalent in complicated malaria than uncomplicated malaria. This result concurs with most of the literature we reviewed. Prabha et al in her study observed that 27 (45%) out of 60 malarial cases were having hypocalcemia. 88.24% of complicated malarial patients developed hypocalcemia while only 27.19% patients with uncomplicated malaria had hypocalcemia. So, she concluded that hypocalcemia is not uncommon in malaria and found to be more prevalent in complicated malarial cases.[9] Mishra et al detected hypocalcemia in 44 (62.86%) out of 70 cases of malaria. She concluded that hypocalcemia is a feature of severe/ complicated malaria as it had a good correlation with parasite load and complications.[10] Agarwal et al in their study found that 155 (63%) out of 246 malarial patients studied developed hypocalcemia.[11] In our study, prevalence of hypocalcemia was found to be highest in those with complicated falciparum malaria. It is also observed that complexity/severity of any type of malaria doesn't seem to have any influence on serum calcium level. Agarwal et al in their study found that 94 (65.28%) out of 144 falciparum malarial cases were having hypocalcemia.[12] 50% cases of vivax malaria (43 out of 86 cases) had hypocalcemia. 18 out 28 patients with mixed malarial infection developed hypocalcemia. Hypocalcemia was found to be prevalent in falciparum and mixed malarial infection.[13,14]

In our study, it is found that prevalence of QTc prolongation was higher in complicated malaria than that in uncomplicated malaria. Prevalence of QTc prolongation was highest in falciparum malarial fever. Complicated *falciparum* malaria was found to have highest prevalence of QTc prolongation. The association between QTc prolongation and hypocalcemia was found to be statistically significant only in complicated and uncomplicated vivax malaria. Prabha et al noted significant correlation between degree of hypocalcemia and QTc prolongation. Mishra et al noted that all 44 malarial patients with hypocalcemia had QTc prolongation. Sony et al in their study found that all 26

cases of malaria with hypocalcemia had QTc prolongation. She concluded that QTc prolongation was significant in complicated *falciparum* and mixed malarial infection as compared to uncomplicated falciparum and *vivax* malaria.

Prevalence of hypocalcemia in malaria was found to be 54.45% in our study. There was no statistically significant difference of prevalence of hypocalcemia in malaria between males and females, and between different age groups. Hypocalcemia was more prevalent in complicated malaria than uncomplicated malaria. Among different types of malaria, prevalence of hypocalcemia was highest in falciparum malaria. Complicated falciparum malaria showed highest prevalence of hypocalcemia. Prevalence of QTc prolongation in malaria was found to be 48.86%. Prevalence of QTc prolongation was found to be more in complicated malaria than uncomplicated malaria.[15]

***Limitations***

In this study limited number patients were evaluated. It was a cross sectional study. Serum calcium and QTc at the time of admission was evaluated. Development of hypocalcemia or QTc prolongation during treatment was not considered. Other electrolyte abnormalities (example-hypokalemia) that can cause QTc prolongation were not considered.

## CONCLUSION

Prevalence of hypocalcemia in malaria was found to be 54.45% in our study. Hypocalcemia was more prevalent in complicated malaria than uncomplicated malaria. Among different types of malaria, prevalence of hypocalcemia was highest in falciparum malaria. Complicated falciparum malaria showed highest prevalence of hypocalcemia. Prevalence of QTc prolongation in malaria was found to be 48.86%. 72.1% of patients with hypocalcemia had prolonged QTc. Prevalence of QTc prolongation was found to be more in complicated malaria than uncomplicated malaria. 83.33% of complicated malarial patients with QTc prolongation were found to have hypocalcemia.

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