Musculoskeletal Symptoms in Individuals Afflicted by COVID-19

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Abstract
Objectives: The study aims to delineate the occurrence of musculoskeletal symptoms among COVID-19 patients admitted to hospitals and explore the relationship between interleukin levels and C-reactive protein (CRP).
Materials and Methods: A study involving the review of medical records was carried out on 109 patients aged 18 and above who were COVID-19 positive and hospitalized during treatment. Pregnant individuals with severe illnesses or insufficient data were excluded from the analysis. Demographic information and laboratory findings were extracted from a health database from earlier research conducted at the same hospital. The investigation focused on establishing the connection between musculoskeletal manifestations, CRP, and interleukin levels. P values less than 0.05 were accepted as statistically significant.
Results: A total of 109 individuals were assessed in this study. Among the patients, 34.86% (n = 38) reported arthralgia, 1.83% (n = 2) had arthritis, 41.28% (n = 45) experienced fatigue, and 32.11% (n = 35) encountered post-COVID-19 syndrome. Notably, no significant correlation was observed between musculoskeletal manifestations, CRP, and interleukin levels ($P > 0.05$). However, a positive correlation was identified between post-COVID-19 syndrome, fatigue, duration of O2 support, and duration of hospitalization ($P < 0.05$). Additionally, 54% of the patients were elderly, aged 65 years or older. Furthermore, CRP levels exhibited a positive correlation with the duration of hospitalization, O2 support, history of intensive care, and duration of intensive care ($P < 0.05$). Regarding interleukin levels, there was a positive correlation between interleukin-6 and CRP levels, duration of hospitalization, and O2 support duration ($P < 0.05$). No significant correlation was found between interleukin-6 and interleukin-10 levels ($P > 0.05$).
Conclusions: No correlation was observed between musculoskeletal symptoms and levels of CRP and interleukin. It is recommended to monitor individuals who have been hospitalized, elderly, experiencing unusual fatigue, or relying on oxygen support for the development of post-COVID-19 syndrome.
Keywords: Coronavirus, Findings, Muscular, SARS-CoV, Skeletal

Introduction

The typical presentation of a coronavirus disease 2019 (COVID-19) infection is characterized by upper respiratory tract symptoms, respiratory failure, and relatively rare complications (1). Additionally, musculoskeletal manifestations and the emergence of a post-COVID-19 syndrome are increasingly recognized outcomes of this infection. Myalgia, fatigue, arthritis, and arthralgia are accepted as the most commonly mentioned symptoms (2-5). Arthralgia was reported by 15.5–31% of COVID-19 patients, myalgia by 15.5–59%, arthritis by 5.7%, and fatigue by more than 50% (2-5). Intriguingly, some individuals may experience these symptoms at the beginning of the infection (6).

Following a COVID-19 infection, certain cases reveal the presence of positive autoantibodies and instances of reactive arthritis and rheumatoid arthritis (7-13). The post-COVID-19 syndrome is identified as a condition affecting individuals with a confirmed or probable history of COVID-19 infection, typically manifesting around 12 weeks after the initial infection. This syndrome entails symptoms persisting for at least eight weeks without explanation from an alternative diagnosis. Fatigue, shortness of breath, and cognitive dysfunction are the most common manifestations and may affect daily functions. These symptoms may also persist from the initial illness (14).

During illness, the abnormal activation of the immune system may result in the onset of autoimmunity and arthritis (7). Hence, the role of acute-phase reactants and cytokines in pathogenesis is noteworthy. It is believed that following immune activation, levels of C-reactive protein (CRP), interleukin 6 (IL6), and interleukin 10 (IL10) simultaneously rise and are indicative of prognosis. Numerous studies have established a correlation between elevated levels of CRP, IL6, and IL10 and the severity of the disease, along with musculoskeletal manifestations (15-18). As it was hypothesized that there might be an association between symptoms that occur after a coronavirus infection and lymphatic drainage dysfunction, the pathophysiology of prolonged symptoms has become a curiosity (19).

The primary objective of this research is to assess the occurrence of musculoskeletal issues among individuals admitted for COVID-19 treatment. Additionally, the study aims to establish connections and correlations between clinical characteristics and CRP, IL6, and IL10 levels. The hypothesis driving this investigation is the potential existence of a link between musculoskeletal complaints, post-COVID-19 syndrome, and various laboratory parameters, specifically IL levels.

Materials and Methods

The research was structured as a retrospective analysis of medical records. Inclusion criteria encompassed patients aged 18 and above, COVID-19 confirmed through real-time polymerase chain reaction (RT-PCR) of nasopharyngeal or throat swab specimens, and admittance to internal medicine or chest disease services between March 7 and December 31, 2020. The study specifically included individuals who received standard COVID-19 medications (oseltamivir + vitamin C + paracetamol) and underwent evaluation by the same internal medicine expert, pulmonologist, and physiatrist with consistent consultation during their hospitalization.

Exclusion criteria comprised pregnant patients, those with missing information, and individuals in the advanced stages of their illness (e.g., loss of consciousness, inability to articulate symptoms, or those who succumbed during hospital treatment). Additionally, patients with concomitant systemic conditions that could potentially influence outcomes, such as rheumatic illnesses or endocrine disorders, were omitted from the study. Demographic details of patients, including systemic illness, initial complaints, and history, as well as history of prolonged complaints, complications, hospitalization, intensive care, and oxygen support duration, were extracted from the hospital database. Information regarding COVID-19-related biochemical characteristics upon admission and during control (CRP, total white cell count, lymphocyte, neutrophil, platelet counts, and rheumatologic tests like rheumatoid factor, anti-CCP antibody, and anti-nuclear antibody) was also collected. Baseline CRP or blood test results indicate the tests conducted upon admission with PCR or swab samples, while control CRP or blood tests signify those administered before hospital discharge.

In a previous investigation involving COVID-19 patients with active disease, laboratory values for IL6 and IL10 were acquired from hospital records (20). Apart from routine blood tests, samples underwent centrifugation at 3000 rpm for five minutes. Following the division of serum samples, plasma samples were stored at -20 °C. To mitigate diurnal variations, sample collection occurred before 10 a.m. The determination of IL6 and IL10 levels employed the ELISA technique. The Immulite 2000XPI, an automated immunoassay tool from Siemens Healthcare GmbH, was utilized for measuring IL-6 levels. Quality control materials (ILCO10032 and ILCO20032) were applied at two levels. IL-10 levels in all serum samples were assessed using a sandwich ELISA technique with a DIA source ELISA kit (Belgium). Wells were filled with 100 l of standard and serum samples, sealed, and incubated for 2 hours at room temperature. Subsequently, 50 L of anti-IL10-HRP conjugate and 100 L of serum sample were added to the wells. Before rinsing the solutions, the mixture was incubated for 2 hours at room temperature with gentle stirring. In the final step, 50 L of the reaction stop buffer was applied to each well. A spectrophotometer was used to obtain data at 450 and 490 nm, considering the dilution factor while estimating IL10 levels. Ethics Committee approval was secured to gather IL6 and IL10 levels from the health database for the current study.

Additionally, control examination information after discharge from the hospital was obtained from the hospital database to determine which patients had prolonged (longer than 12 weeks) complaints such as fatigue, arthralgia, arthritis, sleep disorders, or fibrofog, which refers to the post-COVID-19 syndrome.

The study aimed to assess the prevalence of musculoskeletal issues and their correlation with post-COVID-19 syndrome, clinical characteristics, CRP, and IL6 and IL10 levels. Statistical significance was established at a P value of 0.05.

Statistical Analysis

Statistical analysis in this study utilized version 25.0 of the Statistical Package for the Social Sciences (SPSS) on the Windows platform, as provided by IBM Corp., located in Armonk, NY, USA. The normality of the values was assessed using the Shapiro-Wilk test. Given the non-normal distribution of values, medians (min-max) represented numerical data, while categorical variables were presented as frequency and percentage. The chi-square test was employed to examine the association between categorical variables. As for normally distributed categorical variables and age, the comparison was carried out using the t-test. The Mann-Whitney U test was implemented to assess the median values of two independent groups. Exploring the relationship between musculoskeletal manifestations (arthralgia, arthritis, and weariness), post-COVID-19 syndrome, clinical and laboratory variables, and IL6 and IL10 levels involved Spearman's correlation test. A

statistically significant threshold was set at $P < 0.05$ to determine the significance of the findings.

Results

This investigation included 140 hospitalized patients diagnosed with COVID-19 between March 7 and December 31, 2020. The analysis focused on 109 patients, excluding 15 individuals with missing data for control examinations after discharge from the hospital and 16 with end-stage disease who could not be discharged from the hospital and had no control data. The gender distribution revealed 39.45% female participants (n = 66) and 60.55% male participants (n = 43). Fatigue was reported by 41.28% of patients (n = 45), while arthralgia and arthritis in the metacarpophalangeal and proximal interphalangeal joints were noted in 34.86% (n = 38) and 1.83% (n = 2) of patients, respectively. Post-COVID-19 syndrome was observed in 32.11% (35) of patients, and a positive autoantibody was detected in a single patient. Additional clinical and laboratory details are presented in Table 1.

Notably, there was no discernible correlation among arthritis, arthralgia, fatigue, post-COVID-19 syndrome, baseline CRP, control CRP, IL6, or IL10 levels ($P > 0.05$). The only statistically significant correlation was found in the case of fatigue (r = 0.768, $P = 0.034$), which exhibited a positive correlation (r = 0.223, $P = 0.033$) with the IL6/IL10 ratio. The correlations between musculoskeletal manifestations and laboratory parameters are outlined in Table 2.

Post-COVID syndrome demonstrated a positive correlation (r = 0.438, $P = 0.001$) and an association ($\chi^2 = 17.44$, $P = 0.001$) specifically with symptoms of fatigue. A statistically significant association ($P = 0.026$) and a positive correlation (r = 0.235, $P = 0.025$) were observed between post-COVID syndrome and the duration of O2 support. Furthermore, a statistically significant association ($P = 0.005$) and a positive correlation (r = 0.297, $P = 0.004$) existed between post-COVID syndrome and the duration of hospitalization. Notably, no correlation was found between post-COVID-19 syndrome and anosmia (r = 1.000, $P = 0.664$). Additionally, there was no observed association between musculoskeletal manifestations, post-COVID-19 syndrome, and co-morbidities ($P > 0.05$). Patients with post-COVID-19 syndrome had a significantly higher mean age compared to those without post-COVID-19 syndrome (t = 2.112, $P = 0.012$). A substantial 54% of post-COVID-19 patients were elderly, aged over 65 years.

Baseline CRP levels exhibited positive correlations with control CRP levels (r = 0.505, $P = 0.001$), duration of hospitalization (r = 0.488, $P = 0.001$), and duration of O2 support (r = 0.544, $P = 0.001$). Furthermore, the history of intensive care (r = 0.279, $P = 0.007$) and duration of intensive care (r = 0.276, $P = 0.008$) were exclusively correlated with baseline CRP levels. Control CRP levels were significantly and positively correlated with the duration of hospitalization (r = 0.289, $P = 0.005$), duration

Table 1. Clinical and Laboratory Features of the Patients

Features	Value
Baseline CRP (mg/L), median (min-max)	30.62 (0.10-251.70)
Control CRP (mg/L), median (min-max)	13.25 (0-211)
Duration of hospitalization (days), median (min-max)	5 (0-30)
Duration of O2 support (days), median (min-max)	4.50 (0-31)
Duration of intensive care (days), median (min-max)	0 (0-16)
IL 6 levels (pg/mL), median (min-max)	9.18 (2.51-157.65)
IL 10 levels (pg/mL), median (min-max)	12.88 (0.13-178.57)

Table 2. Correlation Between Musculoskeletal Manifestations and Laboratory Parameters

	Baseline CRP	Control CRP	IL6	IL10	IL6/IL10 ratio
Arthralgia*					
r	0.177	0.001	0.022	-0.202	0.178
P	0.094	0.097	0.832	0.054	0.092
Arthritis*					
r	0.077	0.023	0.011	0.001	0.063
P	0.468	0.829	0.914	1.000	0.554
Fatigue*					
r	0.174	0.118	0.097	-0.175	0.223
P	0.100	0.265	0.362	0.097	0.033**
Post-COVID-19 syndrome*					
r	0.193	0.200	0.083	-0.036	0.160
P	0.067	0.058	0.437	0.734	0.130

*Spearman's correlation test; $P<0.05$ statistically significant.

of O2 support (r = 0.290, P = 0.005), baseline CRP levels (r = 0.505, P = 0.001), and fever (r = 0.278, P = 0.007).

The relationship between the length of hospital stay and fatigue exhibited a positive correlation (r = 0.212, P = 0.044). Likewise, a positive correlation was observed between the duration of hospitalization and baseline CRP levels (r = 0.488, P = 0.001), control CRP levels (r = 0.289, P = 0.005), fever (r = 0.298, P = 0.004), and the duration of oxygen support (r = 0.920, P = 0.001). Notably, the duration of oxygen support showed a significant positive correlation with baseline CRP (r = 0.544, P = 0.001) and control CRP (r = 0.290, P = 0.005).

A distinct contrast in the duration of hospitalization was evident between individuals with and without fatigue symptoms (P = 0.045). Furthermore, a notable discrepancy in baseline CRP levels was identified among patients monitored in the intensive care unit compared to those not (P = 0.008).

Examining IL6 levels, a positive correlation was identified with baseline CRP levels (r = 0.280, P = 0.007), control CRP levels (r = 0.231, P = 0.027), hospitalization duration (r = 0.278, P = 0.007), and the duration of oxygen support (r = 0.257, P = 0.013). Conversely, no correlation was observed between symptoms, clinical features, laboratory parameters, and IL10 levels (P > 0.05). The comprehensive details of the significant correlations between clinical features, post-COVID-19 syndrome, laboratory parameters, and their corresponding P and r values are provided in Table 3.

These results suggest that while there is no correlation between laboratory findings and fatigue symptoms following COVID-19, there is a correlation between the length of hospital stay and the duration of O2 support.

Discussion

COVID-19-related symptoms encompass musculoskeletal manifestations recognized in the literature to emerge within two weeks to one month following the diagnosis of COVID-19 (5). The prevalent musculoskeletal symptoms associated with the COVID-19 infection include myalgia, arthralgia, arthritis, and fatigue. Additional, albeit infrequent, possibilities include back pain, myositis, neuropathies, and myopathies (5,21-23).

The cause of muscle pain is connected to the reaction of cytokines, injury to muscle tissue, and increased lactate levels. Whether it appears as a symptom at the beginning or after COVID-19, joint pain is thought to be caused by an irregular immune response, activation of complements, and deposition of immune complexes (24-27). While less common than myalgia, arthralgia is characterized by more intense pain in affected patients (5). Although viral arthralgia has been associated with established viral infections, it has also been frequently reported in the context of the COVID-19 infection. Hoong et al found that among 294 COVID-19 patients admitted to the hospital, 5.7% experienced joint pain. Notably, joint pain was linked to levels of CRP rather than fever and lung inflammation (5). Another investigation with 38 hospitalized COVID-19 patients, where 34.8% experienced joint pain, revealed no significant connection between baseline CRP levels (r = 0.177, P = 0.094), control CRP (r = 0.001, P = 0.097), IL6 (r = 0.022, P = 0.832), and IL10 (r = 0-.202, P = 0.054). Arthritis may develop due to contracting COVID-19, arising from autoimmune

Table 3. Correlations Between Post-COVID-19 Syndrome, Clinical Features, Laboratory Parameters, and Interleukin Levels

	r	P
Post-COVID-19 syndrome- fatigue[*]	0.438	0.001[***]
Post-COVID-19 syndrome- O2 support duration[*]	0.235	0.025[**]
Post-COVID-19 syndrome- duration of hospitalization[*]	0.297	0.004[***]
Post-COVID-19 syndrome- anosmia[*]	1.000	0.664
IL6- duration of O2 support[*]	0.257	0.013[**]
IL6- basal CRP[*]	0.280	0.007[**]
IL6- control CRP[*]	0.231	0.027[**]
IL6- duration of hospitalization[*]	0.278	0.007[**]
Duration of hospitalization- fatigue[*]	0.212	0.044[**]
Duration of hospitalization- baseline CRP[*]	0.488	0.001[***]
Duration of hospitalization- control CRP[*]	0.289	0.005[**]
Duration of hospitalization- fever[*]	0.298	0.004[**]
Duration of O2 support - baseline CRP[*]	0.544	0.001[***]
Duration of O2 support - control CRP[*]	0.290	0.005[**]
History of intensive care- baseline CRP[*]	0.279	0.007[**]
Duration of intensive care- baseline CRP[*]	0.276	0.008[**]

*Spearman's correlation test; **P < 0.05 statistically significant; *** P < 0.001 statistically highly significant.

mechanisms such as molecular mimicry, loss of tolerance to self-peptides, proinflammation induced by antigen-presenting cell stimulation, and immunological activation (7). Following COVID-19, individuals may encounter discomfort in their joints, which could lead to conditions such as post-COVID-19 arthritis, rheumatic ailments, or the detection of autoantibodies within these patients (7,8). Although reactive arthritis emerges as the most prevalent rheumatic symptom post-COVID-19, indications of reactive arthritis or myositis are also plausible (13,21,22). Both single or limited joint inflammation and involvement of larger and smaller joints may manifest after a COVID-19 infection (5). As per Taha and colleagues' examination of 100 COVID-19 patients admitted to hospitals, arthritis was present in 37% of cases (17). However, in our current study, the prevalence of arthritis was notably lower, accounting for 1.83% (n = 2). Despite a statistically significant relationship observed between arthritis and CRP, as well as IL6 levels, our study did not find any correlation between arthritis and baseline CRP (r = 0.077, $P = 0.023$), control CRP (r = 0.023, $P = 0.829$), IL6 (r = 0.011, $P = 0.914$), or IL10 (r = 0.001, $P = 1.000$) levels.

The terms "post-COVID-19" and "persistent COVID" have surfaced because some individuals continue to experience symptoms even after the active phase of the infection has passed. Signs indicating post-COVID-19 syndrome, such as ongoing fatigue, muscle pain, feelings of sadness, and trouble with sleep, were noticed three months following the COVID-19 infection. A thorough investigation found that 80% of patients had symptoms a week after getting infected. Remarkably, studies in Switzerland and Italy found that 32% of patients treated outside hospitals and 83% of those hospitalized had lasting symptoms (28-31). A survey in the United Kingdom revealed that 20% of patients dealt with these symptoms for five weeks, and 10% had them for 12 weeks. Additionally, a survey based on Google, conducted around 6 ± 3 months post-COVID-19 infection (with 616 participants), showed that 30.7% of respondents fulfilled fibromyalgia criteria due to ongoing symptoms (32).

Although co-existing health conditions were identified as factors increasing the risk of post-COVID-19 syndrome, this research did not establish a clear link between post-COVID-19 syndrome and these health conditions. Laboratory tests revealed certain indicators, such as low lymphocyte and platelet counts, high levels of D-dimer, lactate dehydrogenase (LDH), troponin, CRP, ferritin, and IL-6, which were predictive of post-COVID-19 syndrome (31). Ortelli et al conducted a study comparing 12 COVID-positive patients with a control group. They found that the COVID-positive group exhibited higher levels of fatigue, cognitive impairment, lack of interest, and difficulty with decision-making. These patients also showed heightened inflammation and elevated IL6 levels (15). However, the current investigation did not find a significant relationship between post-COVID-19 syndrome and either normal or baseline CRP levels (r = 0.067, $P = 0.058$, and $P = 0.200$, respectively). Furthermore, there were positive connections noted between post-COVID-19 syndrome and fatigue (r = 0.438, $P = 0.001$), duration of hospitalization (r = 0.297, $P = 0.004$), and duration of oxygen therapy (r = 0.235, $P = 0.025$). A literature review indicated that abnormal inflammation and an imbalance in IL6 and IL10 levels contribute to post-COVID-19 syndrome (17). However, this study did not find any significant relationship between post-COVID-19 syndrome and IL6 (r = 0.083, $P = 0.437$), IL10 (r = 0-.036, $P = 0.734$), or the IL6/IL10 ratio (r = 0.160, $P = 0.130$).

Some theories propose a connection between COVID-19 infection, lymphatic obstruction, anosmia, and post-COVID-19 syndrome. However, the current investigation did not reveal any association between post-COVID-19 syndrome and anosmia (r = 1.000, $P = 0.664$) (17).

CRP, an acute-phase protein, is known for its non-specific response to tissue injury, infection, and inflammation. Furthermore, elevated CRP levels are observed in conjunction with IL6-induced inflammatory reactions, suggesting a parallel increase in both during acute-phase responses (33,34). Investigating the predictive role of procalcitonin, CRP, and IL6 in COVID-19 infection, Liu et al hypothesized their significance (35). Coomes et al found higher IL6 levels in severe COVID-19 patients (18). The current study revealed positive correlations between IL6 levels and basal CRP levels (r = 0.280, $P = 0.007$), control CRP levels (r = 0.231, $P = 0.027$), the duration of O2 support (r = 0.257, $P = 0.013$), and hospitalization duration (r = 0.278, $P = 0.007$). Baseline CRP levels were also positively correlated with O2 support duration (r = 0.544, $P = 0.001$), hospitalization duration (r = 0.488, $P = 0.001$), history of intensive care (r = 0.279, $P = 0.007$), and duration of intensive care (r = 0.276, $P = 0.008$). Control CRP levels exhibited positive correlations with O2 support duration (r = 0.290, $P = 0.005$) and hospitalization duration (r = 0.289, $P = 0.005$). These findings support the hypothesis that IL6 and CRP levels may serve as prognostic indicators in COVID-19 patients. Kappelmann et al identified IL6 levels as predictors for post-COVID-19 syndrome (36). However, in the present study, no correlation was observed between IL6 levels and post-COVID-19 syndrome (r = 0.083, $P = 0.437$).

IL10, renowned for suppressing immune responses, is produced by various cell types, including monocytes, macrophages, dendritic cells, mast cells, eosinophils, neutrophils, natural killer cells, B cells, and T cells. Prior investigations have suggested a simultaneous elevation in IL10 and IL6 levels amidst the COVID-19 infection, hinting at a plausible connection with cytokine storms, unfavorable prognoses, and complications (37). However, the current study has uncovered no significant correlation between IL10 levels and IL6 levels (r= 0.180, P= 0.085),

past intensive care history (r = 0.063, P = 0.550), duration of intensive care (r = 0.061, P = 0.564), duration of hospitalization (r = -0.129, P = 0.221), or duration of O2 support (r = -0.148, P = 0.158).

Limitaions and Directions for Future Research

Given the absence of correlations among musculoskeletal manifestations, post-COVID-19 syndrome, baseline or control CRP, IL6, and IL10 levels, there is a need for further studies to unravel the mechanisms underlying the symptoms of COVID-19 infection. Noteworthy limitations of this study include a small sample size and the exclusive focus on hospitalized patients. Future investigations should encompass larger sample sizes and diverse populations, including those from multiple centers and outpatient settings. Including a diverse range of participants from different demographic backgrounds can help better understand the prevalence and impact of post-COVID-19 syndrome. Longitudinal studies are needed to investigate the trajectory of post-COVID-19 syndrome symptoms and their persistence over time. Understanding the long-term outcomes and potential recovery patterns can provide valuable insights into managing and treating this condition. Another significant limitation of the study is the lack of a control group. Including control groups matched for demographic and clinical characteristics is essential to accurately assess the associations between post-COVID-19 syndrome and various symptoms, laboratory parameters, and comorbidities. This can help control for confounding factors and provide a clearer understanding of the specific effects of post-COVID-19 syndrome. The standardization of diagnostic criteria and assessment tools for post-COVID-19 syndrome is necessary to facilitate comparability across studies. Consensus guidelines can help ensure consistent evaluations and improve the accuracy of prevalence estimates and symptom profiles. Investigating the efficacy of different interventions and treatment approaches for managing post-COVID-19 syndrome is crucial. These findings could pave the way for the development of new follow-up strategies.

Conclusions

Based on the findings, no association was observed between musculoskeletal symptoms such as arthralgia, arthritis, fatigue, and post-COVID-19 syndrome. Additionally, no significant correlation was identified between baseline or control levels of CRP, IL6, and IL10 and the IL6/IL10 ratio. Further investigations are required to unravel the underlying mechanisms responsible for musculoskeletal manifestations and the development of post-COVID-19 syndrome in individuals with COVID-19. On the other hand, a noteworthy correlation was identified between fatigue and the duration of O2 support, hospitalization duration, and post-COVID-19 syndrome. Consequently, it is recommended to closely monitor individuals who fall into categories such as being hospitalized, elderly,

reliant on O2 support, or experiencing fatigue, as they may be more susceptible to developing post-COVID-19 syndrome.

Authors' Contribution

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