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Persistently elevated uric acid in post-COVID-19 syndrome

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Persistently elevated uric acid in post-covid-19 syndrome

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SUMMARY

When a person contracts COVID-19, the symptoms do not disappear once the virus leaves the body. Some symptoms persist for months after diagnosis, and elevated levels of metabolites resulting from respiratory disorders, such as uric acid, also persist. Uric acid can be used as a marker of severity and endothelial damage. To characterize the behavior of

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uric acid in post-COVID-19 syndrome during the first year of follow-up at the clinic located in Polyclinic 2 Ángel Ortiz Vázquez in Manzanillo, from January 2021 to December 2022, an analytical case-control study was conducted with 50 cases and 75 controls using theoretical, empirical, and statistical methods. The average age in cases and controls was similar; most admitted cases were reported as requiring care; at 6 and 12 months of follow-up, the predominant symptom was fatigue; the uric acid change in cases was higher than in controls; and the most frequent disease related to hyperuricemia in cases was gouty arthritis. There is an association between elevated uric acid and post-COVID-19 syndrome.

Keywords:COVID-19; Uric acid; Endothelial damage; Post-COVID syndrome.

ABSTRACT

When a person becomes ill with COVID-19, symptoms do not disappear once the virus leaves the body; some symptoms persist for months after the disease is diagnosed. There is also a persistent increase in metabolites resulting from respiratory disorders, such as uric acid, which can be used as a marker of severity and endothelial damage. In order to characterize the behavior of uric acid in post-COVID-19 syndrome during the first year of follow-up in the consultation office enabled at Polyclinic 2 Ángel Ortiz Vázquez in Manzanillo, an analytical case-control study was conducted from January 2021 to December 2022, including 50 cases and 75 controls, using theoretical, empirical, and statistical methods. The average age of cases and controls was similar; most admitted cases were reported as requiring care. At 6 and 12 months of follow-up, the predominant symptom was fatigue; the uric acid delta in the cases was higher than in the controls, and the most frequent disease related to hyperuricemia among the cases was gouty arthritis. There is an association between elevated uric acid and post-COVID-19 syndrome.

Keywords:COVID-19; Uric acid; Endothelial damage; Post-COVID syndrome.

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SUMMARY

When a person suffers from COVID-19, the symptoms do not disappear when the virus leaves the body; Some symptoms persist for months after diagnosis. There is also a persistent increase in metabolites resulting from respiratory disorders, such as uric acid, which can be used as a marker of pregnancy and endothelial damage. With the objective of characterizing the behavior of uric acid in the post-COVID-19 syndrome during the first year of support in an authorized consultation at Polyclinic 2 Ángel Ortiz Vázquez, in Manzanillo, an analytical study was carried out, both cases and controls, from January 2021 to December 2022, with 50 cases and 75 controls, using theoretical methods. empirical and statistical. The average cases and controls were similar; The majority of two hospitalized cases were classified as care. After 6 and 12 months of support, the predominant symptom was fatigue; The delta of uric acid in our cases was higher than that of two controls, the most frequent condition related to hyperuricemia, in our cases, was to gouty arthritis. There is an association between elevated uric acid and post-COVID-19 syndrome.

Key words:COVID-19; uric acid; Endothelial damage; Post-COVID syndrome.

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Introduction

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 epidemic a pandemic. (1-4) It then launched a strategy aimed at strengthening preparedness to rapidly identify, diagnose, and treat cases; identify and monitor contacts; prevent and control outbreaks in healthcare settings; implement health measures for travelers; and

raise public awareness through risk communication and community engagement.

The clinical picture varies constantly, (5,6) from the absence of symptoms to mild or severe manifestations, and a large number of patients present with a critical cascade, which can be complicated by acute respiratory distress syndrome and shock, leading to death. (6,7)

When a person contracts COVID-19, the debilitating symptoms of SARS-CoV-2 infection do not disappear after the virus leaves the body (3). Shortness of breath, extreme fatigue, and chest pain are some of the symptoms that persist for months after the illness. However, the authors of their study identified fatigue, musculoskeletal pain, and hair loss as the most persistent symptoms.

This situation can make returning to normal life extremely difficult, which can become a real challenge. Some current studies suggest that between 14% and 30% of COVID-19 patients suffer from at least one symptom of long COVID in the 90 days following infection. (6,8)

Disability associated with the symptoms of post-COVID-19 syndrome is one of its main characteristics, and therefore its impact on healthcare and rehabilitation units is considerable. The chronic neurological symptoms and fatigue associated with post-COVID-19 syndrome differ from the neurological complications of the acute phase. The impact on mental health and cognition is significant; at least 30% may experience symptoms of anxiety, depression, or both after recovering from the acute phase. (8,9)

Some reports indicated that during COVID-19, there was an increase in metabolites such as uric acid due to respiratory disorders, especially in the presence of hypoxia and systemic inflammation. Amenta et al. demonstrated that, in patients with respiratory illnesses, a serum uric acid level ≥ 6.9 mg/dL (approximately 410 µmol/L) is an independent predictor of mortality within 30 days of admission to the Intensive Care Unit. (10)

Serum uric acid concentration is influenced by several factors such as overproduction, decreased glomerular filtration or renal hypoperfusion, enhanced tubular absorption or

decreased elimination. (11,12) In the literature reviews carried out by the authors, no association between elevated uric acid and post-COVID-19 syndrome has been reported.

Although different studies have shown that the total antioxidant capacity of blood serum can be associated with increasing levels of uric acid, and that the relevance of this fact depends on the underlying pathophysiological mechanism which includes detrimental factors such as kidney injury. (13)

Serum uric acid levels have been associated with endothelial dysfunction and increased oxidative stress. High levels of this metabolite in the blood are associated with systemic inflammation and hypoxia. Changes in oxygen transport parameters and the concentration of metabolites obtained from purine degradation, including uric acid, can be useful for evaluating peripheral circulation. (14) In light of this accumulated knowledge, there is no evidence regarding the behavior of uric acid levels in post-COVID-19 syndrome and what clinical implications the possible elevation of this metabolite has in relation to persistent manifestations of the disease.

Disability associated with the symptoms of post-COVID-19 syndrome is one of its main characteristics, and therefore the impact it can have on healthcare and rehabilitation units is considerable. (5) The chronic neurological symptoms and fatigue associated with post-COVID-19 syndrome differ from the neurological complications of the acute phase. The impact on mental health and cognition is significant, and at least 30% may experience symptoms of anxiety and/or depression after recovery from the acute phase. (4,5)

In the last year, a profusion of terms has emerged in the literature to define this new entity (persistent or prolonged COVID-19, subacute COVID-19 syndrome, ongoing COVID-19, post-COVID-19 syndrome, etc.). This article uses the term post-COVID-19 syndrome. (3,6,7,15,16)

There is no universally agreed definition of the post-acute period of COVID-19. Some authors (10,17) suggest that the subacute period begins three weeks after the onset of

symptoms, since the average duration of positivity in the polymerase chain reaction (PCR) technique in symptomatic subjects has been estimated at 24 days. (11,18)

According to the National Institute for Health and Care Excellence (NICE), a diagnosis of Post-COVID-19 Syndrome can be considered before 12 weeks, while evaluating the possibility of an alternative underlying disease. (11,12,14)

Based on evidence that points to uric acid as a marker of severity and endothelial damage during the acute phase of COVID-19, and given the lack of studies exploring its long-term behavior, this study proposed the following hypothesis: there is an association between persistently elevated uric acid and the development of post-COVID-19 syndrome.

To verify this hypothesis, the research aimed to characterize the behavior of uric acid in patients with post-COVID-19 syndrome during the first year of follow-up in the outpatient clinic, comparing their levels with a control group and evaluating the appearance of clinical manifestations and diseases associated with hyperuricemia.

Methods

An analytical, case-control study was conducted in the "red zone" created for the isolation and care of positive cases of COVID-19 at the Celia Sánchez Manduley Hospital and continued in the outpatient follow-up consultation for these patients enabled at the Ángel Ortiz Vázquez Polyclinic 2, both in Manzanillo, Granma, Cuba, in the period between January 2021 and December 2022.

Fifty cases and 75 controls were included. Cases were defined as those who had suffered from COVID-19, confirmed by clinical and radiological manifestations, positive SARS-CoV-2 rapid test, and positive real-time PCR (RT-PCR), who had no history of gout or hyperuricemia, hypertension, or diabetes mellitus, no neoplasms, normal renal function, and were not obese (body mass index between 18 and 24). All these cases were hospitalized

with varying degrees of severity during the acute phase of the disease and received the treatment established by the Cuban protocol.

Patients were considered post-COVID-19 when, after 28 days from the initial diagnosis of the disease, they had two negative RT-PCR tests and persistent COVID-19 symptoms, as well as some sequelae of the disease. Seventy-five controls were selected; these were people who had not suffered from COVID-19, demonstrated by the absence of disease symptoms, and who had two negative rapid tests and two negative RT-PCR tests. They had similar age ranges (±5 years) and sex to the cases, lived in the same household or on the same block as the patient, and had no history of gout, hyperuricemia, hypertension, diabetes mellitus, neoplasms, normal renal function, and were not obese.

All participants (cases and controls) were thoroughly evaluated by the same research team during follow-up visits every three months until one year post-diagnosis (3, 6, 9, and 12 months). This evaluation included interviews, physical examinations, and tests such as chest X-rays, complete blood count with erythrocyte sedimentation rate, creatinine, blood glucose, and uric acid levels. At each visit, existing clinical manifestations and potential sequelae of the disease were recorded using conventional methods. Some of these tests were not part of the research study but were necessary to monitor for disease sequelae.

The study defined and measured its variables as follows to ensure accuracy and replicability:

Main dependent variable Uric acid levels were measured quantitatively in µmol/L from blood samples. Levels exceeding 420 µmol/L in men and 357 µmol/L in women were classified as "elevated".

Independent variable Condition (Case/Control). Cases were defined as patients with confirmed COVID-19 (clinical, radiological, and positive PCR) who, after 28 days and with two negative PCR tests, presented persistent symptoms (post-COVID-19 syndrome). Controls were individuals with no history of COVID-19, with negative tests, and matched for age, sex, and location.

Clinical outcome variables:

Persistent clinical manifestations: They were recorded through questioning and physical examination as nominal qualitative variables (e.g., Fatigue: Yes/No).

Diseases related to hyperuricemia: They were operationally defined as follows:

Gouty arthritis: clinical diagnosis of classic gouty arthritis (qualitative, Yes/No).

Renal and ureteral lithiasis: confirmed by the presence of renal colic and diagnosis by ultrasound (qualitative, Yes/No).

Type 2 Diabetes Mellitus:defined by the presence of classic symptoms and a fasting blood glucose > 7.8 mmol/L (qualitative, Yes/No).

Control Variables:included age (continuous quantitative, in years), sex (nominal qualitative: male/female) and the degree of severity during admission (nominal polytomous qualitative: severe ventilated, severe not ventilated, care).

The following scientific methods were used:

- From the theoretical level: analytical synthetic and hypothetical-deductive.
- From the empirical level: the survey, the interview and the case study.
- Statistical methods: descriptive and analytical.

Statistical analysis:

Descriptive statistics: measures of central tendency and dispersion for quantitative variables; frequencies and percentages for qualitative variables.

Inferential statistics:

Bivariate analysis: The Odds Ratio (OR) with its 95% confidence interval (95% CI) was calculated to assess the association between delta uric acid (dichotomized variable) and case/control condition.

Multivariate analysis: To control for possible confounding factors, a logistic regression

analysis was performed, introducing variables such as age, sex, and initial severity into the model.

Statistical hypotheses for the association relationship:

H0: There is no association between elevated uric acid and post-COVID-19 syndrome.

H1: There is an association between elevated uric acid and post-COVID-19 syndrome.

For a confidence level = 95%

For the collection of information, a data collection form was developed, which was previously validated through a pilot test and which collects all the variables necessary to achieve the objectives set out; it is an instrument that collects closed and open questions and is structured in several blocks.

The collected information was used to create a database using SPSS version 22.0, called "Uric Acid in Post-COVID-19 Syndrome." This database was protected, evaluated, and previously validated through a pilot test to ensure its usefulness in data processing. Tables were created to facilitate the understanding of the results.

Results

Table 1 describes the baseline characteristics of the study groups (50 cases and 75 controls), demonstrating that both groups are comparable in terms of key sociodemographic variables. The mean age was similar between cases (44.3 years) and controls (46.2 years), suggesting adequate age matching. The sex distribution showed a male majority in both groups (64% in cases and 64% in controls), and the population was predominantly urban (84% in cases and 80% in controls). The skin color distribution was also comparable, with a majority of individuals self-identifying as white in both groups. This homogeneity in baseline characteristics is crucial, as it reduces the possibility of these factors acting as confounding variables when analyzing the association between uric acid and post-COVID-19 syndrome,

thus strengthening the internal validity of the study.

Table 1 Sociodemographic description of the cases and controls studied.

Variables	Cases (N=SO)	Controls (N=7S)
Average age (years)	44.3 years	46.2 years
Sex	Male: 32 Female: 18	Male: 48 Female: 27
Origin	Urban: 42 Rural: 8	Urban: 60 Rural: 15
Skin color:	White: 33 Mestizos: 13 Blacks: 4	White: 47 Mestizos: 19 Black: 9

When evaluating the clinical manifestations at 12 months of follow-up (table 2), it was found that fatigue persisted in 16 cases for 32.0%, osteomyoarticular pain in 12 cases for 24.0%, hair loss (22.0%), depression (14.0%) and anxiety (12.0%).

Table 2. Persistent clinical manifestations in post-COVID-19 syndrome at 12 months of follow-up.

Clinical manifestations	No.	%
Fatigue	16	32.0
Osteoarticular pain	12	24.0
Hair loss	11	22.0
Depression	7	14.0
Anxiety	6	12.0

Source: Annex 2. Data collection form.

The differences in mean uric acid levels between cases and controls were analyzed during follow-up (Table 3). Cases had persistently higher values in all measurements.

Table 3 Average uric acid value (µmol/L) of cases and controls at the start of the study, at 3, 6, 9 and 12 months of follow-up.

Patients	Start of study	3 months	6 months	9 months	12

					months
Cases	480.6	492.3	462.5	438.1	430.9
Controls	324.5	322.7	325.6	325.6	319.4

Source: Annex 2. Data collection form.

The uric acid delta (difference between baseline and 12 months) showed a significant difference of 49.7 µmol/L for cases and 13.7 µmol/L for controls. In bivariate analysis, this difference was significantly associated with case status, with an OR of 4.6 (95% CI: 2.1–5.3), as shown in Table 4. Logistic regression analysis confirmed that this association remained independent after adjusting for confounding variables (adjusted OR = 4.4; 95% CI: 2.0–5.1).

Table 4. Delta of uric acid at baseline and at 12 months, OR and CI (95%) of cases and controls at 12 months of follow-up.

Patients	Delta of uric acid (µmol/L)	OR (95% CI)
Cases	49.7	4.6 (2.1 - 5.3)
Controls	13.7	1.0 (Reference)

Source: Annex 2. Data collection form.

In this investigation, the diseases that appeared in the cases, presumably related to persistent hyperuricemia, were predominantly acute gouty arthritis (36.0%), renoureteral lithiasis (30.0%), type 2 diabetes mellitus (16.0%) and ischemic heart disease (12.0%), as shown in Table 5.

Table 5. Diseases that appeared in the cases, presumably related to hyperuricemia.

Diseases in the cases	No.	%
Gouty arthritis	18	36.0
Renal and ureteral lithiasis	15	30.0
Type 2 Diabetes Mellitus	8	16.0
Ischemic heart disease	6	12.0

Source: Annex 2. Data collection form.

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Discussion

The path followed by this study always encounters the problem that many protocols and guidelines mention uric acid as one of the complementary tests to be indicated in the follow-up of these patients, but in reality there are no studies that give evidence of what its value is and what clinical significance it has, for that reason many of the assertions made here are hypothetical assumptions that will need future demonstration.

The clinical spectrum of this disease was highly variable. (1,4,6,9) The acute phase is characterized by headache, fever, dyspnea, non-productive cough, anosmia/ageusia, and myalgia, although a considerable proportion of patients may present with mild symptoms or be asymptomatic. (15,19) The severe form can be complicated by severe acute respiratory distress syndrome, hypoxia, respiratory failure, and multiple organ failure. (7,8,15) Various neurological complications have been described in the acute phase: encephalopathy, delirium, inflammatory syndromes of the central nervous system, encephalitis, Guillain-Barré syndrome, and stroke, among others. (9,10) Few studies have described uric acid levels only at the initial stage of the epidemic, during the hospitalization phase, and no study has done so during follow-up.

Severe acute respiratory syndrome coronavirus (SARS-CoV) caused an epidemic outbreak in 2002 that began in Guangdong, southeastern China, with more than 8,000 cases and 774 deaths. (13) Follow-up studies of survivors of this epidemic revealed that 50% of survivors experienced fatigue and sleep disturbances at 12 months. (20) Most studies addressing this issue report that 50% of SARS-CoV survivors experienced fatigue and sleep disturbances at 12 months, which is consistent with reviews such as that by Rogers et al. in The Lancet, (21) which highlights chronic fatigue as a common sequela in 60% of post-SARS/MERS patients. The association between >5 symptoms in the first week and long COVID (OR = 3.53) is

consistent with studies such as that by Sudre et al. in Nature Medicine, (22) which identified the initial symptom burden as a key predictor.

Clinical sequelae of multi-organ dysfunction have been described in a systematic review and meta-analysis of survivors of SARS-CoV and Middle East Respiratory Syndrome-associated coronavirus (MERS-CoV) (20) from previous pandemics. At 12 months, one-third of the patients had persistent symptoms of anxiety or depression, and 39% had post-traumatic stress disorder. The authors note that there is no evidence of altered uric acid levels in the SARS or MERS epidemics.

The COMEBAC study (19), conducted at Bicêtre Hospital in Paris, analyzed post-COVID-19 sequelae four months after hospital discharge. In this cohort, 57% of survivors (478/834) were assessed via telephone survey. Fifty percent reported at least one new symptom of a physical, emotional, or cognitive nature, the most frequent being fatigue (31%), cognitive difficulties (21%), and dyspnea (16%). Additionally, 174 patients were examined in person, and in this subgroup, 54% suffered from sleep disorders and 38% from cognitive impairment. The COMEBAC study (19) and data from the Zoe cohort reinforce this trend, with 31–54% affected, suggesting a similar pattern among betacoronaviruses.

Lam et al. (20) had already documented anxiety, depression, and PTSD in SARS/MERS survivors in 2009, in line with the 39% reported in the article. For COVID-19, meta-analyses such as that of Taquet et al. in The Lancet Psychiatry (23) confirm an increased risk of mental disorders (33% at 6 months).

An analysis of the prospective observational cohort of 4,182 subjects with COVID-19 who prospectively recorded their symptoms in the 'Zoe' digital application of the 'Covid Symptom Study' has shown that experiencing more than five symptoms of COVID-19 during the first week of illness is associated with a higher risk of persistent COVID-19 (odds ratio = 3.53; confidence interval: 2.76-4.5). (4)

Recent studies suggest that hyperuricemia may be linked to the severity of COVID-19 due

to its inflammatory role, opening avenues for future comparisons. The results presented in this research, which show a significant association and persistent elevation of uric acid in cases, support this hypothesis and extend it to the context of post-COVID-19 syndrome.

Conclusions

Uric acid levels remained persistently elevated during the year of follow-up in the studied cases compared to the controls, so it is possible to state that there is an association between elevated uric acid and post-COVID-19 syndrome, supported by a significant OR and a logistic regression analysis.

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Conflicts of interest

The authors declare no conflict of interest.

Authorship contribution

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