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Evaluation of Clinical Characteristics and Plasma Cortisol Concentrations in Individuals with COVID-19 and Post-COVID Syndrome

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Abstract

COVID-19 generates systematic alterations in humans both in active stages of infection and over time, called post-COVID syndrome. Cortisol is a hormone that is overexpressed in inflammation and cellular stress processes. Its main function is to return to physiological homeostasis, so its evaluation together with other clinical parameters can allow us to determine the degree of systemic affectation by COVID-19. **Objective:** To evaluate changes in clinical parameters and plasma cortisol concentrations in patients with active COVID-19 and post-COVID syndrome. **Material and Methods:** Healthy patients, in stages of mild infection, critical and with post-COVID syndrome, were recruited, obtaining, through clinical diagnoses and interviews, their main clinical characteristics, in addition to plasma, in which cortisol concentrations were determined using competitive ELISA. **Results:** The critical stage group had higher frequencies of comorbidities, clinical symptoms, as well as more altered laboratory parameters compared to the other subgroups. In the post-COVID syndrome group after the initial infection, most laboratory parameters recovered, however, several clinical symptoms remained latent over time. The determination of cortisol showed an increase in its concentration, being higher in patients in critical stage and with post-COVID syndrome. **Conclusion:** COVID-19 disease generates clinical alterations that trigger an increase in plasma cortisol. These alterations increase as the stages of infection become more severe and some of them remain altered in patients with post-COVID syndrome.

Keywords

COVID-19, Cortisol, Post-COVID Syndrome

1. Introduction

Coronaviruses belong to the Coronaviridae family. They are divided into four genera: alpha, beta, gamma and delta. Seven coronaviruses have been identified in humans that fall into the alpha and beta genera. In the latter, there are the coronaviruses SARS-1, SARS-2 and MERS (Middle East Respiratory Syndrome). Alphacoronaviruses normally cause the common cold, while betacoronaviruses in some cases can cause respiratory distress in adults. These viruses arise from the mutation of viruses from animals such as bats, which serve as reservoirs before passing to the host (humans). SARS-2 has been related to the genome of a virus found in the horseshoe bat of the species Rhinolophus, with a similarity of 96%, which was located in Yunnan province. At first, the idea was postulated that the intermediate host or even the first reservoir was the pangolin (Pangolin-Cov), but it has not been confirmed [1].

COVID-19 is a disease caused by the SARS-CoV-2 virus, which is a mutant strain of SARS-2. They are enveloped, pleomorphic or spherical viruses, which have RNA as their genome, with a size between 80 to 120 nm in diameter. Superficially, they have projections of the spike (S) glycoprotein, and like most betacoronaviruses, they have hemagglutinin-esterase (HE) protein dimers. Its viral envelope consists of two proteins that stand out: protein M and protein E, the first being the most abundant, while the second is characterized by its hydrophobic character; both proteins are fused with lipid membranes obtained from the host cell [2].

SARS-CoV-2 can be transmitted through microdroplets and fomites. It has affinity for the respiratory tree, generating an abnormal inflammatory immune response. Of its surface proteins, S is the one that binds to the host cell through receptors for angiotensin-converting enzyme II (ACE II). These receptors are present in type II pneumocytes of the lung, although they can also be found in smaller numbers in the kidney and adrenal walls. Once the virus binds to the cell membrane, it enters through a mechanism of endocytosis, where the viral RNA genome is released into the cytoplasm for replication. Genomic RNA acts on the endoplasmic and Golgi reticulum, making nucleocapsids form intracellular virons and new viral particles that leave the cell by exocytosis, altering the cells in a functional and structural way, leading to cell death by apoptosis [3].

The most frequent symptoms of COVID-19 are fever, cough, fatigue, anosmia, ageusia, anorexia, myalgia, nasal congestion, headache, diarrhea, vomiting, respiratory distress. There are also neurological manifestations such as seizures, speech problems, agitation, weakness, Sensory loss and balance problems, com-

monly in immunosuppressed people, atypical symptoms such as decreased alertness, reduced mobility, diarrhea, loss of appetite, confusion, and absence of fever sometimes occur. This disease can be classified according to its severity. After recovery, some patients may present persistent symptoms typical of an active stage of infection. This post-stage of the disease is known as post-COVID syndrome, which is a series of both subjective and objective clinical manifestations that last more than 8 weeks after 3 months of the original clinical picture [3]. The first case of this disease was described on December 8, 2019 in Hubei province (Wuhan city) [2].

When the virus enters the body, immune cells recognize its viral markers, generating non-specific antiviral activity of the innate system such as macrophages, neutrophils, and dendritic cells that are activated to eliminate the virus and activate the adaptive immune response; in the adaptive response, T lymphocytes recognize cells that are infected by the virus and rapidly increase in number to combat the infection. T4 helper cells attract other cells of the immune system and stimulate B cells to produce specific antibodies against the virus. IgM antibodies are the first to be made and disappear after several weeks. IgG antibodies are produced at the same time or a couple of days later, and their values usually remain for months or years. Cytotoxic T lymphocytes kill the cells in which the virus is multiplying and help slow or stop the infection [4].

To strengthen autoimmunity, vaccines such as Janssen, Astra-Zeneca, Sputnik-V, CanSino, among others, have been used, which are manufactured with human and primate adenovirus vectors. Pfizer-BioNTech, Moderna and CureVac are mRNA vaccines. A third type are SARS-CoV-2 inactivated whole virus vaccines from Bharat Biotech, Sinopharm and Sinovac [5]. Current variants of these vaccines incorporate mutations in the spike glycoprotein gene that COVID-19 vaccines target [4].

Physiological stress is generated by multiple factors, including any disease that modifies the state of comfort or homeostasis of an organism, like the viral disease COVID-19. During this event, a hormone known as cortisol is secreted, which acts on all tissues as a warning signal. Cortisol, also called hydrocortisone, is the glucocorticoid found in greatest quantity in the body. It is secreted in the adrenal glands in the zona fasciculata and perhaps also in the zona reticularis. Cortisol secretion is stimulated by adrenocorticotropic hormone (ACTH) from the anterior part of the pituitary gland. ACTH secretion occurs as part of the general adaptation syndrome in response to stress. Cortisol and other glucocorticoids have many effects on metabolism; they stimulate gluconeogenesis, and inhibit the utilization of glucose in non-essential tissues, which helps to increase blood glucose concentration, and promote lipolysis (fat breakdown) and the consequent release of free fatty acids into the blood, therefore which guarantees access to essential nutrients and obtaining energy in tissues with physiological conditions, likewise they have the ability to regulate the immune system, promoting anti-inflammatory processes, among other functions. Chronic stress can

promote oversecretion of cortisol, which can cause atrophy of the hippocampus, possibly due to inhibition of neurogenesis. Likewise, a correlation has been made between the overexpression of cortisol in inflammatory processes, cellular stress and in some physiological functions. A procedure to measure cortisol in the blood is the ELISA technique, it is a quantitative, sensitive, versatile and accessible method, it is based on the use of specific antibodies to detect a protein of interest [6] [7].

Since the first case of COVID-19 recorded, this disease has caused the death of millions of humans due to the systemic alterations it generates in the active infection, as well as in the post-COVID syndrome [3]. Therefore, it is important to evaluate the clinical effects, as well as some plasma stress markers such as cortisol in different stages of active infection, as well as in the post-COVID syndrome to contribute to knowledge about the behavior and severity of this disease. It is postulated that COVID-19 disease generates alterations in some clinical parameters, as well as in plasma cortisol concentrations depending on the stage of severity during active infection, as well as in the post-COVID syndrome stage. Therefore, the objective of the present investigation was to evaluate the clinical parameters and plasma concentrations of cortisol in patients who had COVID-19 disease in different stages of severity and in some with post-COVID syndrome.

2. Material and Methods

2.1. Patients

Between March 15 and November 1, 2020 (first epidemiological wave of COVID-19 in Mexico), patients with clinical symptoms associated with COVID-19 were recruited in the Respiratory Triage Unit of the Zacatecas General Hospital No. 1. from the Mexican Social Security Institute (IMSS), after undergoing RT-qPCR tests for SARS-CoV-2. For this project, 30 patients with a confirmatory RT-qPCR test of the disease were selected and after analyzing their clinical histories from the IMSS databases, they were classified as follows: 15 patients in Mild Stage (MS) because they are ambulatory with mild symptoms, treated with conventional antipyretics and 15 patients in Critical Stage (CS) due to being intubated with a qSOFA value ≥ 2 at the time of admission, with severe Acute Respiratory Distress Syndrome (ARDS) based on arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) ratio < 100 mmHg at the moment of admission and having reports of life-threatening organ dysfunction (kidney, liver injury, vascular or CNS complications).

The different patients who participated in the project during the first epidemiological wave, two years after their recovery and discharge from the hospital, were contacted through telephone calls and invited to participate in this project, assisting 15 individuals with persistent clinical symptoms associated with the initial infection, which were classified in the Post COVID Syndrome (PCS) group.

As a Negative Control (NC), 10 healthy patients with a negative RT-qPCR test for SARS-CoV-2 were recruited, who attended the Metabolomics and Proteomics

laboratory of the Academic Unit of Biological Sciences, UAZ, Zacatecas, Mexico.

Blood samples were collected from the different experimental groups, blood counts and blood chemistry were performed within the IMSS biochemical laboratory. A portion of the blood was transferred to the UAZ Metabolomics and Proteomics laboratory, where the blood plasma was isolated by centrifugation and stored at −80˚C for the determination of cortisol.

The clinical information of these individuals (sex, age, comorbidities, symptoms) was obtained from the clinical records of the hospitalized patients using the IMSS databases, as well as through interviews in the Negative Control and Post COVID individuals.

This project was carried out in accordance with the Declaration of Helsinki [8]. The experimental protocols were reviewed and approved by the Research and Ethics Committees of the IMSS, registration number R-2022-3301-038.

Informed consent was obtained from all participants in this project and they were informed in writing about the collection of their samples for research purposes and were given the right to decline participation.

2.2. Determination of Plasma Cortisol Concentrations

Using the Competitive Immune Assay for the In Vitro Determination of Total Cortisol in Human Plasma (Cortisol ELISA RE52611 from IBL INTERNATIONAL GMBH, Hamburg, Germany) the plasma cortisol concentrations of each experimental unit were determined.

The procedure of this assay consisted of making 1:50 dilutions of each plasma sample with a standard solution A supplied in the kit, then 50 µL of standards A to F with known concentrations of cortisol 0.0, 0.015, 0.04, 0.17, 0.7 and 3.0 µg/dL respectively were added to generate a concentration curve, as well as two internal quality controls (0.052 - 0.109 and 0.37 - 0.69 µg/dL) and each sample in duplicate in the different respective wells of a microtiter plate, then 100 µL of an enzyme conjugate containing cortisol conjugated with HRP was added to each well in order to compete with plasma cortisol for the binding sites of each well. The plates were incubated for 2 h at room temperature in orbital shaking at 50 rpm to subsequently discard the incubation solutions and wash the wells 4 times with a diluted Wash Buffer, followed by this, 100 µL of TMB Substrate Solution was added to each well, incubating again under the same conditions for 30 min for the interaction with the HRP conjugate, triggering a blue colorimetric reaction. Once the incubation was completed, the progress of the reaction was stopped. By adding 100 µL of TMB stop solution, which turned the coloring to a yellow hue, in which its optical density was evaluated using a Thermo Scientific MULTISKAN GO ELISA plate reader at 450 nm.

Once the optical densities were obtained, a calibration curve was generated by an automatic method using the ©MyCurveFit 2022 software with a 4 Parameter Logistics setting, which calculated the plasma cortisol concentrations of each sample, which were multiplied by the dilution factor to obtain the total concen-

tration of this analyte.

2.3. Statistical Analysis

Means ($\bar{X}$ ± SD) or medians (M with interquartile ranges [IQR]), as well as frequencies (%) were used to describe the clinical characteristics of the patients who made up the different study groups, for continuous and nominal data, respectively. The normality of the continuous data was evaluated using the Shapiro-Wilk test and depending on the normality of the data, we analyzed whether there were differences between their means or medians using one-way ANOVAs or Kruskal-Wallis, respectively, followed by comparisons between groups with Welch's t tests. Trends in nominal variables such as; sex, symptoms, comorbidities, among others, were evaluated using chi-square tests. Values of $P \leq 0.05$ were considered statistically significant. These analyses, as well as the tables and figures of the different variables, were carried out using the statistical software GraphPad Prism version 8.0.1 for Windows (GraphPad Software, La Jolla California USA), as well as Excel, Microsoft Office Professional Plus 2019.

The plasma cortisol concentrations of the different groups were represented graphically through $\bar{X}$ ± SD and asterisks represented whether there was a statistical difference between groups, as well as its degree.

3. Results

3.1. Clinical Features

3.1.1. Age and Gender

Of the 10 individuals in the negative control (NC) group, 60% were men with a mean age of 50.3 ± 6.4 years; of the 15 individuals in the mild stage (MS) group, 53% were men with ages of 57.6 ± 5.7 years; in the critical stage (CS) group with 15 individuals, 33% were men with an age of 57.9 ± 10 years; finally, in the post-COVID syndrome (PCS) group with 15 individuals, 60% were men and the age was 57.3 ± 7.4 (Table 1).

Table 1. Age, gender and comorbidities by study group. Negative Control (CN), Mild Stage (MS), Critical Stage (CS), Post COVID Syndrome (PCS).

Variable	NC (n = 10)	MS (n = 15)	CS (n = 15)	PCS (n = 15)	P-value
Age, $\bar{X}$ ± SD	50.3 ± 6.4	57.6 ± 5.7	57.9 ± 10	57.3 ± 7.4	0.0716
Male gender, n (%)	6 (60)	8 (53)	5 (33)	6 (40)	0.5129
Comorbidities (self-reported), n (%)					
Mellitus diabetes	1 (10)	4 (26)	5 (33)	3 (20)	0.5729
Hypertension	4 (40)	2 (13)	8 (53)	6 (40)	0.1418
Obesity	2 (20)	2 (13)	7 (46)	0 (0)	**0.0127*f**

*a = NC vs MS, *b = NC vs CS, *c = NC vs PCS, *d = MS vs CS, *e = MS vs PCS, *f = CS vs PCS.

3.1.2. Comorbidities

Taking the previous order, there were 10%, 26%, 33% and 20% of cases with Diabetes mellitus, respectively; 40%, 13%, 53% and 40% with Hypertension; and 20%, 13%, 46% and 0% with Obesity. Although there was only a significant statistical difference with a higher percentage of cases with obesity in the EC group (P = 0.0127), it is notable that this group always had a higher frequency of comorbidities (Table 1).

3.1.3. Clinical Symptoms

Fever, cough, headache and dyspnea were statistically different between the groups, giving higher frequencies in the groups with active disease. It was remarkably observed that cough, dyspnea, diarrhea, chest tightness, myalgia, arthralgia and anosmia had higher frequencies in the PCS group, compared to the NC group, possibly indicating symptomatologic prevalence (Table 2).

3.1.4. Laboratory Data

Lymphocytes, monocytes, neutrophils and glucose were altered parameters in the CS group, showing a significant statistical difference (Table 3).

3.2. Unit

Plasma Cortisol Concentrations

After evaluating the plasma concentrations of cortisol in the different study groups, means of 4.4 ± 2 μg/dL were obtained in the NC group, 11.6 ± 8 μg/dL in the MS group, 20.6 ± 9.2 μg/dL in the CS and 15.8 ± 7.1 μg/dL in the PCS group.

Table 2. Clinical symptoms by study group. Negative Control (NC), Mild Stage (MS), Critical Stage (CS), Post COVID Syndrome (PCS).

Variable	NC (n = 10)	MS (n = 15)	CS (n = 15)	PCS (n = 15)	P-value
Clinical symptoms, n (%)					
Fever	0 (0)	6 (40)	10 (66)	0 (0)	**<0.0001*b, e, f**
Cough	0 (0)	10 (66)	13 (86)	4 (26)	**<0.0001*a, b, f**
Headache	4 (40)	13 (86)	9 (60)	6 (40)	**0.0381*a, e**
Dyspnoea	1 (10)	3 (20)	12 (80)	6 (40)	**0.0010*b, d**
Diarrhea	0 (0)	1 (6.7)	3 (20)	1 (6.7)	0.3376
Chest tightness	1 (10)	3 (20)	3 (20)	6 (40)	0.324
Pharyngalgia	2 (20)	6 (40)	6 (40)	2 (13)	0.2684
Myalgia	4 (40)	10 (66)	9 (60)	10 (66)	0.5276
Arthralgias	4 (40)	10 (66)	8 (53)	10 (66)	0.4953
Anosmia	0 (0)	6 (40)	2 (13)	2 (13)	0.0577

*a = NC vs MS, *b = NC vs CS, *c = NC vs PCS, *d = MS vs CS, *e = MS vs PCS, *f = CS vs PCS.

Table 3. Laboratory data of the different study groups. Negative Control (NC), Mild Stage (MS), Critical Stage (CS), Post COVID Syndrome (PCS).

Variable	NC (n = 10)	MS (n = 15)	CS (n = 15)	PCS (n = 15)	P-value
Laboratory data					
Erythrocytes (1×10^6/mL), $\bar{X}$ ± SD	5.2 ± 0.5	5.3 ± 0.4	4.9 ± 0.7	5.3 ± 0.6	0.3986
Hemoglobin (g/dL), $\bar{X}$ ± SD	15.2 ± 1.4	15.6 ± 1	14.3 ± 2	15.9 ± 1.7	0.1677
Platelets (1×10^6/mL), M (Q1 - Q3)	290.5 (246.8 - 342.5)	251 (208 - 384)	251.5 (191.3 - 280)	238 (222 - 265)	0.2893
Leukocytes ($\times 10^3$), M (Q1 - Q3)	7.5 (6.4 - 9.2)	6.6 (5.4 - 8.7)	9.4 (5.7 - 13)	7.3 (6.2 - 8.7)	0.2783
Lymphocytes (%), M (Q1 - Q3)	36 (27.3 - 38.7)	31.6 (18 - 34.9)	10.8 (6 - 13.9)	36.4 (31.2 - 39)	**<0.0001*b, d, f**
Monocytes (%), M (Q1 - Q3)	6 (4.6 - 8.5)	8.6 (5.7 - 10.9)	3.85 (2.5 - 7.5)	7.1 (6.4 - 8.7)	**0.0467*d, f**
Neutrophils (%), M (Q1 - Q3)	55.3 (50.5 - 63.3)	59.2 (55.1 - 71.1)	84.8 (75 - 89.9)	52.7 (50.9 - 59.7)	**<0.0001*b, d, e, f**
Glucose (mg/dL), M (Q1 - Q3)	93 (85 - 102.8)	120 (97.5 - 144.5)	134.5 (109.8 - 322.3)	111.7 (100.9 - 147.6)	**0.0080*a, b, c,**
Creatinine (mg/dL), M (Q1 - Q3)	0.95 (0.7 - 1.2)	0.9 (0.7 - 1.1)	0.9 (0.7 - 1.5)	0.8 (0.7 - 0.9)	0.1685

*a = NC vs MS, *b = NC vs CS, *c = NC vs PCS, *d = MS vs CS, *e = MS vs PCS, *f = CS vs PCS.

The CS group had a higher plasma concentration of cortisol, which was statistically different from the NC and MS groups, indicating a greater increase in cortisol compared to healthy individuals or those in mild stages of COVID-19. The PCS group showed a considerable increase in plasma cortisol compared to the NC group, practically triple and comparing this value with the MS and CS group, there were no statistical differences, indicating that the plasma concentrations of the PCS group are similar to those of the active stages of COVID-19 infection (Figure 1).

4. Discussion

The present investigation evaluated the clinical parameters and plasma concentrations of cortisol in patients who had COVID-19 disease in different stages of severity and in some with post-COVID syndrome.

When analyzing the frequencies of comorbidities such as hypertension, diabetes mellitus and obesity in the different study groups, it was possible to distinguish that the highest number of frequencies of these variables occurred in the critical stage group. The above agrees with the meta-analysis by Salazar, *et al.*

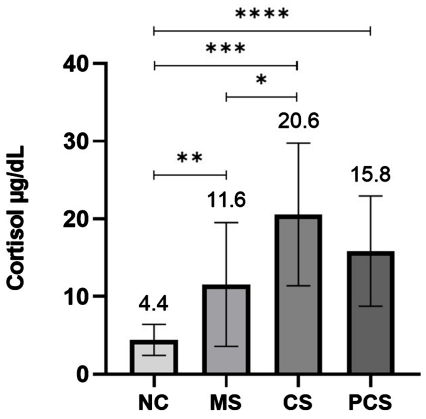

Figure 1. Means ± SD of plasma cortisol concentrations by study group. Negative Control (NC), Mild Stage (MS), Critical Stage (CS), Post COVID Syndrome (PCS).

[9] in which they analyzed a population of 46,248 individuals from various regions of China, Italy, and the United States of America, whose main comorbidities associated with severe forms of COVID-19 were hypertension, cardiovascular diseases, diabetes mellitus, and obesity; likewise, Loarce-Martos *et al.* [10] found in a population of 101 individuals, these comorbidities including heart disease that led infected individuals to critical stages of infection or even death. These associations may be due to the fact that when an individual presents metabolic and physiological alterations derived from these comorbidities, systemic homeostasis is altered and this can aggravate the physiological damage generated by COVID-19 infection.

Regarding clinical symptoms such as fever, cough, headache and dyspnea, the groups with active disease presented higher frequencies. Fever and cough agree with what was reported by Gökmen *et al.* [11], as well as by Loarce-Martos *et al.* [10], who analyzed 1607 individuals from different regions of the world. In the PCS group, it was observed that cough, dyspnea, diarrhea, chest tightness, myalgia, arthralgia and anosmia remained latent compared to the NC group, coinciding with Bozua *et al.* [3] who carried out a meta-analysis in various populations (Italy, Great Britain, and the United States) in which individuals commonly presented dyspnea, cough, and chest pain.

In the case of laboratory data: in the CS group, lymphocytes and monocytes were found to be decreased, while neutrophil and glucose values increased. This agrees with the research by Herrera-Van *et al.* [12] in which different populations in Mexico that suffered from the disease were analyzed, presenting both leukocytes, neutrophils, lymphocytes, monocytes, and glucose with the same pattern of alteration; Likewise, Cáceres-Bernaola *et al.* [13], in an Asian population, described similar alterations at least in lymphocytes, neutrophils, and glucose; and with Fernández-Pérez *et al.* [1], which found alterations in lymphocytes in Latin American populations. These alterations in cell populations can occur as happens in other respiratory viruses such as influenza, due to the infection and destruction of lymphocytes by the virus, in addition to the fact that when viral

multiplication accelerates, the integrity of the alveolar-capillary barrier is compromised and the cells of the pulmonary capillaries are affected, accentuating the inflammatory response with greater accumulation of neutrophils, monocytes and exacerbation of capillary endothelitis [14]. Regarding the glucose alteration, it may be due to the action of cortisol itself, as well as the pancreatic damage caused by the virus. The islet cells of the pancreas express ACE2 on their membrane, where the virus binds to the extracellular domain of ACE2 and enters the cells, inducing cellular dysfunction that can lead to a decrease in insulin secretion, resulting in hyperglycemia [15].

Regarding cortisol, when evaluating its plasma concentrations in the different study groups, means of 4.4 ± 2 μg/dL were obtained in the NC group, increasing to 11.6 ± 8 μg/dL in the MS group, then to 20.6 ± 9.2 μg/dL in the Cs group and finally 15.8 ± 7.1 μg/dL in the PCS group.

In general, it was observed that plasma cortisol concentrations increased as the severity of the disease increased, reaching a peak concentration in the CS group, where they were at least 4 times more than those in the NC group, this indicates that the Patients being in a critical stage of infection with greater cellular and tissue damage, as well as greater stress and inflammation, their body tries to return to organic homeostasis through various mechanisms, specifically in this case through greater synthesis of cortisol. Remarkably, it was observed that in the PCS group the elevated concentrations of this hormone were similar to those of the group in the active infection stage and with respect to the NS group the increase in cortisol remained elevated at least 3 times more, this despite that more than two years passed after the initial infection, which indicates, together with the presence of persistent clinical symptoms, that the organisms affected by this disease do not fully recover from the initial systemic alterations and continue to suffer altered physiological processes. These results agree with the study by Tan *et al.* [16], where they evaluated 535 patients diagnosed with COVID-19, the patients who had the disease more severely, with greater clinical alterations and more comorbidities, presented a greater increase in plasma cortisol; likewise, Ahmadi *et al.* [17], in an analysis of 154 individuals with COVID-19, observed that cortisol increased when the severity of the disease increased in patients who died, which is why this metabolite was considered a predictor of severity and survival; Similarly, Tomo *et al.* [18] evaluated cortisol in 79 healthy individuals and 76 Rt-PCR positive SARS-COV2, and found that cortisol levels were higher in infected individuals, increasing progressively with the severity of the disease, in addition that these values were higher in patients who died compared to those who survived.

It is relevant to consider the trends in plasma cortisol concentrations in the different groups, considering that sampling for the PCS group was carried out two years after the initial infection. These data contrast with the research of Chua *et al.* [19] and Yavropoulou *et al.* [20] where cortisol was evaluated in patients with SPC 3 months after the initial infection, obtaining hypocortisolemia. This could be explained because the adrenal glands suffer acute damage in viral

infections, making them go through a stress process combined with that of the infection, which can even induce adrenal infarctions, causing the loss of their functions and with it a drop in the synthesis of cortisol. Another mechanism includes the increase of proinflammatory cytokines, such as TNF-α, which leads to a decrease and impairment in the release of ACTH by altering the production of angiotensin-2 and cortisol in the glands. The difference in results is probably due to the fact that two years after the initial infection, glandular function can be restored to a certain extent along with cortisol concentrations and since there are still stress and inflammatory processes after the initial infection, the levels of cortisol would rise as in an acute infection; it is worth mentioning that in a previous project, the work team evaluated inflammation, through the plasma determination of Interleukins in patients with PCS belonging to Zacatecas and Chihuahua, Mexico, in the same time periods, finding that some of these molecules remained elevated compared to healthy patients suggesting chronic inflammation [21], which reinforces the idea that together with persistent clinical symptoms, high concentrations of cortisol and interleukins, patients with PCS after 2 years of the initial infection would continue to have important clinical repercussions derived from this disease.

5. Conclusions

COVID-19 disease generates clinical alterations that trigger an increase in plasma cortisol. These alterations increase as the stages of infection become more severe and some of them remain altered in patients with post-COVID syndrome.

Therefore, it is of utmost importance to go to the doctor in a timely manner in case of infection with this disease, as well as provide clinical follow-up in the case of any clinical manifestations that indicate post-COVID syndrome, in order to maintain a good quality of life in the affected population.

Conflicts of Interest

The authors declare there are no conflicts of interest regarding publication of this manuscript.

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