Covid-19: monitoring of patients' laboratory data during a 90-day length of hospital stay

Covid-19: acompanhamento de dados laboratoriais de pacientes durante 90 dias de internação

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ABSTRACT
Background: In March 2020, COVID-19 was declared a pandemic. In this study, patients were selected through the chest HRCT diagnosis. Laboratory tests such as blood count, fibrinogen, D-dimer, AST, ALT, troponin, LDH, albumin, CRP, electrolytes and ferritin were analyzed. Aims: To monitor the laboratory evolution of COVID-19 in patients during hospitalization. Method: Of 115 patients, 93 were selected and analyzed every three days for 90 days. Data were analyzed using the IBM, SPSS, Statistics for Windows, 23.0 software. Results: 34.4% were female, and 65.6% male; Hct and Hb dropped after the 13th day of hospitalization; leukocyte levels remained up to 15,000, increasing to >20,000 after the 55th day of hospitalization; lymphopenia occurred in 10 to 15% of the patients, with increased eosinophils; platelet levels decreased at the end of hospitalization. Fibrinogen, D-dimer, LDH, CRP and ferritin levels increased throughout the hospitalization period. Urea and creatinine increased slightly from the 30th day onwards. There were no alterations in PTA, troponin, chlorine, potassium and albumin levels, with a decrease throughout the hospitalization period. Conclusion: Knowledge of the behavior of laboratory tests together with the disease evolution give support to the clinical and therapeutic management of COVID-19.

Keywords: SARS Coronavirus, laboratory testes Covid-19, biochemical analysis

RESUMO
Introdução: Em março de 2020 a COVID-19 foi declarada como uma pandemia. Neste estudo, pacientes foram selecionados através do diagnóstico por TCAR de tórax. Exames laboratoriais como hemograma, plaquetas, fibrinogênio, D-dímero, TGO, TGP, troponina, LDH, albumina, PCR, eletrólitos e ferritina foram coletados e analisados. Objetivo: Acompanhar a evolução laboratorial da COVID-19 dos pacientes ao longo da internação. Metodologia: De 115 pacientes, foram selecionados 93 e analisados a cada três dias durante 90 dias. Os dados foram analisados por software IBM, SPSS, Statistics for Windows, 23.0. Resultados: 34,4% são do sexo feminino, 65,6% do sexo masculino; Hct e Hb caíram após o 13°dia; Leucócitos mantiveram-se até 15.000, sendo maior de 20.000 a partir do 55° dia de internação; linfopenia entre 10 a 15%; com aumento de eosinófilos; as plaquetas reduziram no final da internação. Fibrinogênio, D-dímero, LDH, PCR e ferritina aumentaram durante todo o período da internação. Uréia e creatinina aumentaram discretamente a partir do 30° dia. Não houve alterações de TAP, troponina, cloro, potássio e albumina com diminuição em todo o período da internação. Conclusão: O conhecimento do comportamento dos exames laboratoriais junto a evolução da doença, trazem segurança no manejo clínico e terapêutico da COVID-19.

Palavras-chave: Coronavírus SARS, testes laboratoriais Covid-19, análises bioquímicas.

1 INTRODUCTION

The first case of COVID-19 infection appeared in late December, 2019. Cases of pneumonia of unknown etiology were reported early in the spread of the virus. Some patients

were diagnosed with severe symptoms of acute respiratory infection, others with rapidly developing acute respiratory distress syndrome (ARDS), acute respiratory failure and other severe complications, similar to the symptoms observed in the aforementioned outbreaks [1].

On January 30, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as the sixth public health emergency of international concern, after H1N1 (2009), Poliomyelitis (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019). On March 11, 2020, the coronavirus outbreak was declared a pandemic [2}. The challenges faced by China, where COVID-19 started, would quickly be faced by European countries, with epicenters in Italy and Spain, and subsequently by countries such as the United States, Canada and Brazil [3].

Transmission can occur through contact with people carrying the virus, symptomatic, asymptomatic or individuals in the incubation period, which makes it difficult to control the infection and makes it a disease with a high transmission rate and pandemic risk. The most common symptoms are fever, cough and fatigue, headache, hemoptysis, diarrhea, and dyspnea [4].

The time between COVID-19 symptom onset and death showed a median of 14 days, depending on the patient's age and immune response [5]. The case fatality rate ranged from 8 to 14.8% in patients aged 70 to 79 years and over 80 years of age [6], showing that the elderly might be more affected due to the immune function impairment. This study found that elderly patients with comorbidities were more susceptible to COVID-19. Moreover, other risk factors include older age, male gender, and high body mass index. Adverse prognostic factors include lymphopenia and increase in the levels of transaminases, lactate dehydrogenase, D-dimers and ferritin. These laboratory measurements represent a state of hyperinflammation, which largely increases the risk of COVID-19-related Acute Respiratory Syndrome, multiple-organ failure, and mortality [7].

The laboratory diagnosis associated with the clinical characteristics of COVID-19 plays an important role in the early detection, diagnosis and assistance in the treatment of patients. Some abnormalities more frequently found in the literature were: low serum albumin (98%); increased values of C-reactive protein (86%); lactate dehydrogenase (76%) and ferritin (63%), anemia (51%); neutrophilia (38%); increased D-dimer values (36%); lymphopenia (35%) and increased values of aminotransferases (35%). The clinical characteristics disclosed by the computed tomography of the chest presented as pneumonia; however, there were abnormal characteristics, such as acute respiratory distress syndrome, acute cardiac lesion, and the occurrence of ground-glass opacity leading to death [8]. With a long incubation period,

prolonged duration and affecting people of all ages, this disease generates long-term hospital bed occupation [9]. In addition to the occurrence of mutations in the SARS-CoV-2, with the emergence of new variants already disseminated in several countries [10].

The emergence of new variants raises concerns regarding vaccination and people who were previously infected or vaccinated, due to the risk of reinfection. It is important to increase the capacity for diagnosis and systematic sequencing of SARS-CoV-2, as well as sharing these sequencing data on international research platforms [10].

Analyzing the disease pathogenicity and evolution is essential for the adequate control, clinical and therapeutic management of the patient. This study aims to expand information on laboratory parameters in hospitalized patients with COVID-19.

2 METHODOLOGY

2.1 STUDY DESIGN AND PLACE

This is a documental, cross-sectional, retrospective and quantitative study based on secondary data, carried out at Hospital de Messejana Dr. Carlos Alberto Studart Gomes, a tertiary public state hospital, specialized in heart and lung diseases of high complexity, in which heart transplantation procedures are performed in adults and children, as well as lung transplantation. It was used as a referral hospital for the care and hospitalization of patients with COVID-19.

2.2 POPULATION AND SAMPLE

This study analyzed a total of 115 patients. Of these, 93 were selected, aged over 18 years, from July to December 2020, with a long period of hospitalization at Hospital de Messejana Dr. Carlos Alberto Studart Gomes. The analysis of the results of laboratory parameters was performed every three days, throughout 90 days of hospitalization and confirmed for COVID-19 through chest computed tomography, of which all images were analyzed by a single radiologist. Patients not diagnosed with COVID-19 by the chest computed tomography analysis were excluded.

2.3 VARIABLES

The complete blood count was run in whole blood through automatic cell analysis using the Beckman Coulter DHX 800 equipment, including red blood cell count, as well as measurements of erythrocyte parameters, hematocrit, hemoglobin and red cell distribution

width (RDW), leukocyte populations (neutrophils, lymphocytes, eosinophils, basophils and monocytes), in addition to platelet count.

The measurement of prothrombin activity time, activated partial thromboplastin time and fibrinogen were performed in citrated plasma samples in the automated ACL Top 550 Werfen equipment, the same performing D-Dimer analysis using the latex immunoassay methodology in citrated plasma.

Serum levels of urea, creatinine, magnesium and albumin were measured by the colorimetric method; the alanine aminotransferase (ALT)/ and lactate dehydrogenase (LDH) measurements were performed in serum using the enzymatic methodology, whereas chlorine, potassium and sodium levels were measured in serum using the Indirect ISE (Ion Selective Electrode) method; serum calcium was measured using the Arzenazo III method, all using the AU 480 Beckman Coulter equipment. The measurements of highly-sensitive troponin T and serum ferritin were performed in serum by electrochemiluminescence using the Cobas 6000 Roche equipment, and the C-Reactive Protein measurement was performed in serum, using the nephelometry method in the BN II Systems equipment.

Moreover, sociodemographic data were collected from the participants, such as age and gender.

2.4 STATISTICAL ANALYSIS

The categorical quantitative results were presented as percentages and counts and the numerical ones as measures of central tendency. Kolmogorov-Smirnov normality tests were performed for numerical variables. One-way ANOVA repeated measures were used with the day variable used to signal the repetitions aiming to assess the variations in the results of each measurement over time. P values < 0.05 were considered significant. The data obtained at the collection were tabulated and analyzed using the IBM SPSS Statistics for Windows, Version 23.0 software. Armonk, NY: IBM Corp. IBM Corp. Released 2015.

3 RESULTS

The total number of analyzed patients was 115. Of these, 93 who had a long period of hospitalization were selected, which allowed analyzing the results of laboratory parameters every three days, over the course of 90 days of hospital length of stay. All patients analyzed in the present study were confirmed through computed tomography and those who showed patterns of viral infection by COVID-19 were selected.

Regarding gender, 32 (34.4%) were female and 61 (65.6%) were male. The most affected age group in this study was 65 years.

Throughout the 90 days of patients' hospitalization, there was a significant reduction in the levels of hemoglobin and hematocrit, with the decline beginning approximately on the 13th day (Figures 1.a and 1.b, respectively). The RDW, another altered parameter of the erythroid series, was shown to be increased in the second half of the assessed hospital length of stay (Figure 1.c).

There was no significant change in total leukocytes, but they remained between 10,000 and 15,000 leukocytes/mm³, with an increase ≥20,000 between approximately the 55th day and the 65th day of hospital admission, returning to normal values in the last 25 days of hospitalization. The relative neutrophil values in the studied patients were significantly elevated during practically the entire first half of the hospital length of stay, with a return to normality after this period (Figure 1.d). Another parameter related to the leukocyte series that showed a significant change was the relative number of lymphocytes, with a reduction during practically the entire hospitalization period, with relative values between 10% and 15%, for the most part (Figure 1.f). In relation to eosinophils, there was a significant increase in the relative values during approximately 10 days of hospital stay, the period after the 43rd day, continuing until the 53rd day (Figure 1.e).

The platelets of the analyzed patients remained at normal levels, with values ranging from 250,000/mm³ to 400,000/mm³, with a tendency to decrease in the last days of hospitalization (Figure 1.g).

The prothrombin activity time of the analyzed patients showed no significant alterations, but the activated partial thromboplastin time was elevated during the entire hospitalization period. In this study, fibrinogen and D-dimer were significantly elevated in patients during hospitalization (Figures 2.a and 2.b, respectively).

There was a slight increase in urea levels until approximately the 30th day, with a greater increase in the values in the final phase, between approximately the 50th and 70th days of hospitalization; in this last period, there was also a significant increase in creatinine levels (Figure 2.f).

Regarding the AST levels, there was no significant change; however, alanine aminotransferase (ALT) levels showed an increase between the 25th and 30th days, and also between the 45th and 50th days, approximately (Figure 2.g).

There was no significant change in troponin levels in the assessed patients (Figure 2.e)

The analyzed patients showed a significant increase in lactate dehydrogenase (LDH) levels during the entire period of hospitalization.

The measurements of the levels of chlorine, potassium and calcium electrolytes did not show any significant changes. Although there were no significant alterations, sodium levels showed a tendency to decrease in the final phase of hospitalization. Similarly, the magnesium measurements, without significant values, showed a tendency to decrease after the 20th day of hospitalization (Figure 2.h).

Serum albumin levels were reduced during almost the entire hospital stay (Figure 2.d).

In this study, CRP (C-reactive protein) values were significantly elevated during the entire hospital stay (Figure 2.c).

Serum ferritin levels remained elevated almost throughout the entire hospitalization phase, with the highest levels observed between approximately the 15th day and the 30th day (Figure 1.h).

Figure 1. Laboratory tests of patients with COVID-19 performed during a 3-day period, throughout 90 days of hospitalization. Reference values: 1.a) Hemoglobin: Male sex: 13 - 18 g/dL/ Female sex: 11.5 - 16.4 g/dL; 1.b)Hematocrit: Male sex: 40 - 54 g/dL / Female sex: 35 - 38 g/dL); 1.c) Red Cell Distribution Width (RDW): 10 - 16%; 1.d) Neutrophils: 45 - 75%; 1.e) Eosinophils: 1 - 6%; 1.f) Lymphocytes: 20 - 45%; 1.g) Platelets: 140,000 - 500,000/mm^3; 1.h) Ferritin: Male sex: 30 - 400ng/mL/ Female sex: 13 - 150 ng/mL.

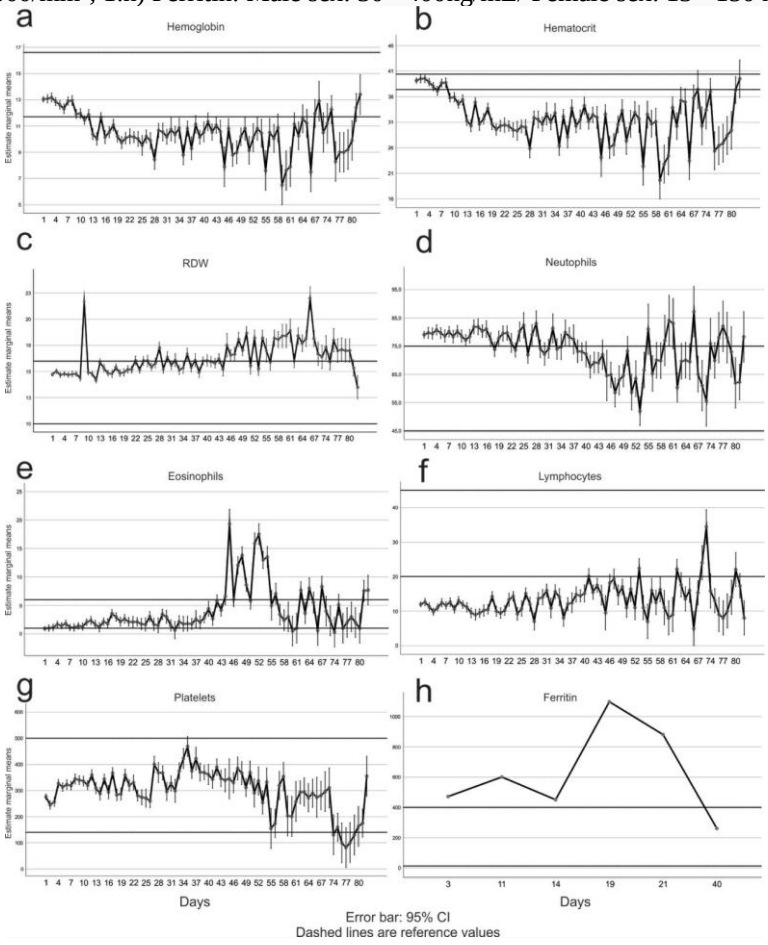
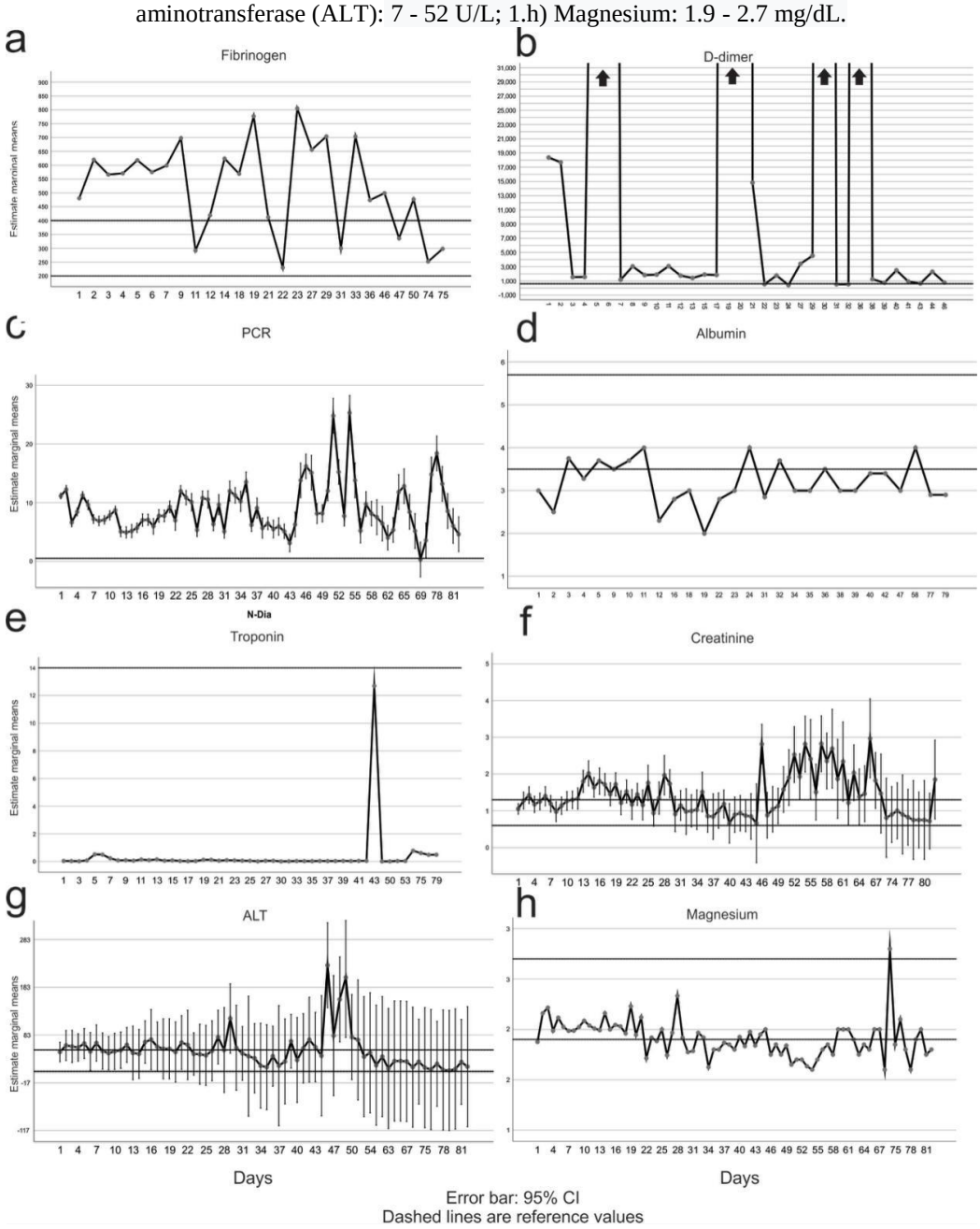


Figure 2. Laboratory tests of patients with COVID-19 performed during a 3-day period, throughout 90 days of hospitalization. Reference values: 1.a)Fibrinogen: 200 - 400 mg/dL; 1.b) D-Dimer: <0.6 µg/mL; 1.c) CRP: <0.5 mg/dL; 1.d) Albumin: 3.5 - 5.7 g/dL; 1.e) Troponin: ≤14 ng/L; 1.f) Creatinine: 0.6 - 1.3 mg/dL; 1.g) Alanine aminotransferase (ALT): 7 - 52 U/L; 1.h) Magnesium: 1.9 - 2.7 mg/dL.



4 DISCUSSION

According to the 2020 WHO guidelines, in areas where the COVID-19 virus is widely spread, RT-PCR screening is considered sufficient [11]. However, one or more negative results do not exclude the possibility of infection by the virus. Several factors can lead to a negative result in an infected individual, including poor sample quality, insufficient collected content, collection performed late or early in the course of the infection, or the sample not being handled and shipped adequately. Due to possible failures in the performance of the RT-PCR test, the

National Health Commission of China recommended computed tomography (CT) as the main type of diagnostic screening, emphasizing that radiological examinations would be important for the early detection of the disease [12, 13]. The criteria used in the selection of patients assessed in this study, related to computed tomography, were based on the standards duly recognized in the literature as characteristics of viral infection for COVID-19 [8, 14].

As far as gender is concerned, the reported cases of COVID-19 vary in different countries. In Brazil, in relation to cases of Severe Acute Respiratory Syndrome (SARS) by COVID-19, 55% of those affected are male. In this study, there was a predominance of 65.6% of males. In absolute numbers, China had more cases reported in men, while in South Korea there is a higher frequency in women. In Spain, the frequency of cases is similar for both genders. Initially, it was more frequent in men, but later, the magnitude of the numbers ranged from equal to increasing in women [15]. Based on published studies, the mean age of patients was 56 years, ranging from 55-65 years, with men being the most often affected. This fact would probably be related to the high levels of Angiotensin-Converting Enzyme II (ACE2) [16]. Data from the Ministry of Health of Brazil, in 2021 [17], reported that the most affected age group was 60 to 69 years old, with 22.2% of cases. In this study, the mean age of the assessed patients was 65 years.

The pandemic situation has boosted science to a better understanding of the mechanisms of SARS-CoV-2 virulence factors, aiming to identify them and develop barriers to their transmission and development in the human body, as well as to know their pathogenicity and clinical evolution of the patients in the different phases of this disease, through the employed tests, with the objective of providing safer and more successful therapeutic approaches in controlling the virus spread.

The knowledge about the course of the disease is very important when correlating the obtained results and the hospitalization period of the assessed patients. According to the literature, initially, SARS-CoV-2 binds to the host's ACE2 receptor with the help of transmembrane serine protease-2 (TRMPSS2), a co-receptor, cleaving the viral protein. In the asymptomatic phase, infection of the host cell, viral diffusion in the human body and the production of virions predominate. The innate immunity, mediated by natural killer cells, neutrophils and monocytes/macrophages, reacts to viral replication, causing cytopathic effects with the release of pro-inflammatory mediators, triggering the onset of signs and symptoms. Cell immunity, mediated by B cells, CD4 and CD8 T cells, develops, increasing the intensity of these symptoms. There is an imbalance between effective and hyperactivated immune responses that can result in a cytokine storm, increasing lung injury, leading to respiratory

failure. In this phase, protective neutralizing antibodies can enhance the activation of the antibody-dependent response and activate the complement system classical pathway, with an increase in viral replication and release of pro-inflammatory cytokines. The imbalance between inflammation and coagulopathy, as well as the SARS-CoV-2 infection of blood vessel walls cells determine thrombotic events causing organ damage. These uncontrolled processes trigger a strong pathological cycle, which eventually lead to systemic and organic cell dysfunction [7]. The patients in the present study were assessed from the onset of the first symptoms, during which time they were admitted for hospitalization.

In general, in the initial days after SARS-CoV-2 infection, clinical or laboratory markers do not demonstrate a severity factor. Approximately 5 days after the development of viral pneumonia, the cytokine storm can occur, which represents the period of greatest inflammatory stress and severity in the patient's clinical status. Therefore, the need for serial measurements of inflammatory and thrombotic markers when monitoring the disease evolution would be justified [18].

COVID-19 has shown to be an infectious and inflammatory disease that mainly affects the lungs, but which also involves damage to multiple organs with different injury pathways. Hemoglobinopathy, hypoxia and iron overload play an additional role in these injuries. Hemoglobin dysfunction can occur due to hemoglobin denaturation and deregulation of iron metabolism [19]. The observed alterations regarding the RDW (red cell distribution width) indicate the variability in the sizes of the erythrocytes of the assessed patients, which may provide complementary information for the etiological diagnosis of anemia, even before iron deficiency is identified [20]. In this study, a significant reduction in hemoglobin levels was observed, as well as in hematocrit, in addition to an increase in RDW throughout 90 days of hospitalization.

A meta-analysis showed that increased neutrophil and decreased lymphocyte levels are persistent findings in patients hospitalized with COVID-19 [8], similar to the data found in this study with 90 days of hospitalization. Another study showed a significant relationship between the increase in total leukocytes, about 1.5-fold greater, higher neutrophil levels, with an approximately 1.7-fold greater count, and reduction in the number of lymphocytes, 0.9-fold lower in patients who showed disease worsening, requiring intensive care [21]. The abovementioned meta-analysis showed as predictive values of worsening for patient admission at the ICU an increase in leukocytes of about 2-fold, an increase in neutrophils of up to 4.4-fold, and the reduction of lymphocytes, of 0.4-fold [8]. In this study, although in the beginning of the second half of the hospitalization period the total leukocyte levels were high, the analysis

of the 90 days of hospitalization showed no significant change in these levels. Eosinophils are circulating leukocytes found in tissues that have potent pro-inflammatory effects on several diseases. The patients assessed here had increased levels of eosinophils during the second half of the hospitalization period (from the 43rd to the 53rd day), for about 10 days. It was demonstrated that these cells have several other functions, including immunoregulation and antiviral activity. Their granules contain cytotoxic proteins, eosinophil peroxidase and two RNAses (the eosinophil cationic protein and the eosinophil neurotoxin). There is little indication that eosinophils have a protective role during SARS-CoV-2 infection; however, eosinopenia seems to be a prognostic indicator for more severe COVID [22].

Some authors discuss the association between critically-ill patients with COVID-19 and their specific coagulation profile, particularly D-dimer elevation, prolonged prothrombin time, and low platelet counts. According to the authors, these changes reflect the hypercoagulable state observed in critically-ill patients, which can promote microthrombi in the lungs or other organs [23]. More studies are necessary to improve the understanding between the hematological function of platelets and Covid-19, and different stages of the disease, gender, age, and preexisting comorbidities should be considered.

The increase in the activated partial thromboplastin time of the patients analyzed in this study is mostly due to the heparin anticoagulant therapy (low molecular weight) required by patients with COVID-19. The thrombotic complications of these patients seem to resemble systemic coagulopathies in severe infections, such as sepsis-induced coagulopathy or disseminated intravascular coagulation. Data in the literature show that patients with COVID-19 have elevated D-dimers and fibrinogen levels, similar to what was found in this study. There were no significant changes in prothrombin activity time in the patients studied herein. Patients with disseminated intravascular coagulation usually have prolonged prothrombin time and thrombocythemia [24].

Many patients with COVID-19 have characteristic coagulation alterations, such as high fibrinogen levels, as well as increased D-dimer levels, which can help in the screening for the identification of hypercoagulable patients. Increased D-dimer occurs in parallel with fibrinogenemia in many patients [25], as shown in this study. There are reports of an increase in these parameters in non-severe patients [26], whereas other authors have reported worsening with increased values of D-Dimer, of around 2.5-fold; similarly, other authors have shown significantly higher values of D-Dimer (2-fold increase) in more severe cases, when compared to milder cases [21, 27].

In this study, the values of serum urea levels showed a slight increase, without statistical significance; however, serum creatinine levels, especially after the 50th day of hospitalization, showed a significant increase. There are reports of altered creatinine values, of around 1.1-fold lower [21]. Reports point to a direct relationship between high creatinine levels and other markers of renal function with severity and mortality in patients with COVID-19 [28].

There is a study that shows an increase in both transaminases, aspartate aminotransferase (AST), with an increase of about 1.8-fold, and ALT, with an increase of about 1.5-fold [21]. In another study, an increase of 1.8-fold in the ALT levels was observed in the patients [8]. This study observed that between approximately 25 and 30 days of hospitalization, there was an approximately 2-fold increase in the ALT levels, and an increase of approximately 4-fold between days 45 and 50 of hospitalization.

The presence of elevated troponin in hospitalized patients was associated with higher mortality in patients with COVID-19 [29, 30]. Authors showed a 2.2-fold increase in the troponin levels of the assessed patients [21]. In this study, there was no significant change in troponin levels during the 90 days of hospitalization.

Similarly to the high levels of lactate dehydrogenase (LDH) observed in the patients in this study during their 90 days of hospitalization, other authors also found high levels of LDH, around 2.1-fold higher [21, 26]. Elevated LDH values are associated with worsening of the disease, need for hospitalization and mortality in patients [31].

Studies have shown a significant reduction in serum levels of sodium, potassium and calcium in patients with COVID-19, although chlorine levels did not show any significant changes [32]. In the patients analyzed in this study, although the serum levels of sodium and calcium showed a certain decrease in their values, it was not significant. Moreover, serum chloride and potassium levels did not show any significant changes. The patients showed a reduction in serum magnesium levels as of the 22nd day of hospital admission, but without significance, differently from what was reported by other authors [33]. It is important to evaluate the patients' electrolyte levels so that corrective therapeutic actions can be carried out quickly and effectively.

This study showed a reduction in the patients' albumin levels analyzed throughout the 90 days of hospitalization. Authors have shown a reduction of approximately 0.8-fold in the albumin values of their assessed patients [8].

The C-reactive protein levels of the patients assessed in this study showed an elevation of approximately 10-fold or higher in their serum levels. The data obtained in the present study

are in agreement with other studies; however, some of them evaluated patients with non-severe COVID 19 [26, 27].

When directly destroyed by the virus, the hemoglobin releases iron into the circulation, which can lead to a loss of the hemoglobin's capacity to bind to oxygen, causing tissue hypoxia and organ failure. Additionally, the increased free iron can cause oxidative damage to the lungs and other organs, leading to inflammation and immune dysfunction. Excess iron causes blood hyperviscosity, leading to thrombotic phenomena and a state of circulatory hypercoagulation. On the other hand, in a compensatory way, there is an increase in ferritin, a protein that stores iron. This is a predictor of COVID-19 severity, as it contributes to immune dysfunction, inflammation and hypercoagulation [34]. In this study, an increase in serum ferritin levels was observed in the assessed patients.

5 CONCLUSION

The COVID-19 pandemic remains one of the biggest challenges faced in recent decades. The understanding of the pathophysiological mechanisms through laboratory data obtained during the hospitalization of patients with COVID-19 is an important contribution to the implementation of effective therapeutic actions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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