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Relation between Hematological and Biochemical Parameters per Days of Symptoms in Hospitalized Patients with flu-like syndrome and COVID-19

Relação entre Parâmetros Hematológicos e Bioquímicos por dias de Sintomas em Pacientes Internados com síndrome gripal e COVID-19

Relación entre parámetros hematológicos y bioquímicos por días de síntomas en pacientes internados síndrome gripal y COVID-19

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Djalma Alexandre Alves da Silva
ORCID: https://orcid.org/0000-0003-1295-981X
Federal University of Triangulo Mineiro, Brazil
E-mail: djalma.bio2@gmail.com
Leonardo Eurípedes de Andrade e Silva
ORCID: https://orcid.org/0000-0002-0485-229X
Federal University of Triangulo Mineiro, Brazil
E-mail: leonardoeuripedes@gmail.com
Chamberttan Souza Desidério
ORCID: https://orcid.org/0000-0003-4399-0633
Federal University of Triangulo Mineiro, Brazil
E-mail: chamberttan_sd@hotmail.com
Thais Soares Farnesi-de-Assunção
ORCID: https://orcid.org/0000-0003-3415-9004
Federal University of Triangulo Mineiro, Brazil
E-mail: thaisfarnesi@gmail.com
Ana Carolina de Morais Oliveira
ORCID: https://orcid.org/0000-0002-1353-5683
Federal University of Triangulo Mineiro, Brazil
E-mail:anacarolm@yahoo.com.br
Rafael Obata Trevisan
ORCID: https://orcid.org/0000-0002-4509-9142
Federal University of Triangulo Mineiro, Brazil
E-mail: rafael_obata1@hotmail.com
Malu Mateus Santos
ORCID: https://orcid.org/0000-0002-6849-1702
Federal University of Triangulo Mineiro, Brazil
E-mail: malumateus26@gmail.com
Fernanda Rodrigues Helmo
ORCID: https://orcid.org/0000-0003-2621-6611
Federal University of Triangulo Mineiro, Brazil
E-mail: fernandahelmo@gmail.com
Laís Milagres Barbosa
ORCID: https://orcid.org/0000-0003-4674-3494
Federal University of Triangulo Mineiro, Brazil
E-mail: laism.bio@gmail.com
Juliana Cristina Costa-Madeira
ORCID: https://orcid.org/0000-0001-7232-7297
Federal University of Triangulo Mineiro, Brazil
E-mail: julianamadeiravet@gmail.com
Rafaela Miranda Barbosa
ORCID: https://orcid.org/0000-0002-0052-4416
Federal University of Triangulo Mineiro, Brazil
E-mail: rafaelamirandabarbosa98@gmail.com
Anna Victória Bernardes e Borges
ORCID: https://orcid.org/0000-0003-0453-0394
Federal University of Triangulo Mineiro, Brazil
E-mail: annab.borges@outlook.com
Andrezza Cristina Cancian Hortolani Cunha
ORCID: https://orcid.org/0000-0001-8800-4783
Federal University of Triangulo Mineiro, Brazil
E-mail: andrezzaccunha@gmail.com

Loren Queli Pereira
ORCID: https://orcid.org/0000-0003-2891-443X
Federal University of Triangulo Mineiro, Brazil
E-mail: lorenbiomedica@gmail.com
Weslley Guimarães Bovi
ORCID: https://orcid.org/0000-0002-7737-1737
Federal University of Triangulo Mineiro, Brazil
E-mail: weslley_guim@hotmail.com
Giovanna Ferreira Bueno
ORCID: https://orcid.org/0000-0001-8744-4349
Federal University of Triangulo Mineiro, Brazil
E-mail: gifebueno@gmail.com
Fabiano Vilela Mundim
ORCID: https://orcid.org/0000-0003-4870-6064
Federal University of Triangulo Mineiro, Brazil
E-mail: fabianouftm@gmail.com
Ivan Borges Monteiro
ORCID: https://orcid.org/0000-0002-4985-5507
UNIMED São Domingos Hospital, Brazil
José de Alencar Gomes da Silva Regional Hospital, Brazil
E-mail: ibmonteiro05@yahoo.com.br
Yulsef Moura Ferreira
ORCID: https://orcid.org/0000-0002-7285-4780
José de Alencar Gomes da Silva Regional Hospital, Brazil
E-mail: yulsef@gmail.com
Guilherme Henrique Machado
ORCID: https://orcid.org/0000-0002-6272-1511
Mário Palmério Universitary Hospital, Brazil
E-mail: guilhermehm7@hotmail.com
Kennio Ferreira Paim
ORCID: https://orcid.org/0000-0002-6035-8392
Federal University of Triangulo Mineiro, Brazil
E-mail: kennio.paim@uftm.edu.br
Hélio Moraes-Souza
ORCID: https://orcid.org/0000-0001-8049-348X
Federal University of Triangulo Mineiro, Brazil
E-mail: helio.morais@.uftm.edu.br
Carlo José Freire Oliveira
ORCID: https://orcid.org/0000-0003-2211-7333
Federal University of Triangulo Mineiro, Brazil
E-mail:carlo.oliveira@uftm.edu.br
Marcos Vinicius da Silva
ORCID: https://orcid.org/0000-0002-2966-7621
Federal University of Triangulo Mineiro, Brazil
E-mail: marcosuftm@gmail.com
Virmondes Rodrigues
ORCID: https://orcid.org/0000-0001-8706-4223
Federal University of Triangulo Mineiro, Brazil
E-mail: virmondes.rodrigues@uftm.edu.br

Abstract
Beside the acute respiratory syndrome caused by COVID-19, the exacerbated inflammatory process leads to systemic coagulation disorders, acute cardiovascular disorders, acute renal failure, metabolic changes and other clinical manifestations, increasing the mortality of patients with severe forms of the disease. The development of effective vaccines and drugs for the adequate treatment of severe forms of the disease has become a priority for the scientific and medical community. Likewise, the discovery of possible predictors for the early identification of severe cases with a high risk of death are constantly being sought. Laboratory tests, such as blood count, coagulation tests, hormonal and biochemical tests, are performed on a daily basis in the hospital environment and have proved to be very useful in the search for these indicators. In our study, we evaluated the laboratory tests of 398 positive and negative patients for COVID-19 admitted to hospitals in Uberaba, from the Macroregion of Triângulo Sul, state of Minas Gerais, with a population of 800,000 inhabitants. In our results, it was observed that the patients who died presented anemia, neutrophilic leukocytosis, increased CRP, urea and creatinine from the 5th, 6th day of symptoms, and with lymphopenia on the 1st day. In blood gas analysis, pH, SaO_2 and PO_2 were reduced since the 1st day of symptoms in patients who died, and the pH remained reduced until the clinical outcome. Changes were also found in the dosage of LDH, aPTT, albumin and electrolytes. Given these results, laboratory tests can be useful as predictive signs of severity in the early days of symptoms.
Keywords: COVID-19; *SARS-CoV-2*; Clinical laboratory techniques; Biomarkers.

Resumo

Além da síndrome respiratória aguda causada pela COVID-19, o processo inflamatório exacerbado acarreta distúrbios sistêmicos de coagulação, distúrbios cardiovasculares agudos, insuficiência renal aguda, alterações metabólicas e outras manifestações clínicas, aumentando a mortalidade de pacientes com as formas graves da doença. O desenvolvimento de vacinas e medicamentos, bem como de biomarcadores eficazes no diagnóstico e tratamento adequado das formas graves da doença se tornaram prioridade para a comunidade científica e médica. O monitoramento de parâmetros hematológicos e bioquímicos realizados diariamente em pacientes acometidos pela COVID-19, fornecem informações sobre as condições de saúde dos pacientes, sendo de grande importância na evolução da doença. Diante disso, avaliamos os exames laboratoriais de 398 pacientes positivos e negativos para COVID-19 internados em hospitais de Uberaba, provenientes da Macrorregião do Triângulo Sul, estado de Minas Gerais, com população de 800 mil habitantes. Em nossos resultados observamos que os pacientes que foram a óbito apresentaram anemia, leucocitose com neutrofilia, aumento de PCR, ureia e creatinina a partir do 5°, 6° dia de sintomas, e linfopenia no 1° dia. Na gasometria, o pH, SaO_2 e PO_2 estavam reduzidos desde o 1° dia de sintomas nos pacientes que foram a óbito, sendo que o pH se manteve reduzido até o desfecho clínico. Alterações também foram observadas na dosagem de DHL, TTPa, albumina e eletrólitos. Nossos resultados evidenciam que os exames laboratoriais podem ser úteis como biomarcadores de gravidade já nos primeiros dias de sintomas.
Palavra-chave: COVID-19; *SARS-CoV-2*; Exames e diagnósticos laboratoriais; Biomarcadores.

Resumen

Además del síndrome respiratorio agudo causado por la COVID-19, el proceso inflamatorio exacerbado provoca trastornos sistémicos de la coagulación, trastornos cardiovasculares agudos, insuficiencia renal aguda, alteraciones metabólicas y otras manifestaciones clínicas, aumentando la mortalidad de los pacientes con formas graves de la enfermedad. El desarrollo de vacunas y fármacos eficaces para el tratamiento adecuado de las formas graves de la enfermedad se ha convertido en una prioridad para la comunidad científica y médica. Asimismo, constantemente se evalúa el descubrimiento de biomarcadores para la identificación temprana de casos graves con alto riesgo de muerte. Las pruebas de laboratorio, como el hemograma, las pruebas de coagulación, las pruebas hormonales y bioquímicas, se realizan a diario en el ámbito hospitalario y han demostrado ser de gran utilidad en la búsqueda de estos biomarcadores. En nuestro estudio, evaluamos los exámenes de laboratorio de 398 pacientes positivos y negativos para COVID-19 ingresados en hospitales de Uberaba, de la Macrorregión del Triângulo Sur, estado de Minas Gerais, con una población de 800.000 habitantes. En nuestros resultados observamos que los pacientes que fallecieron presentaban anemia, leucocitosis con neutrofilia, aumento de PCR, urea y creatinina desde el 5°, 6° día de síntomas, y linfopenia el 1° día. En el análisis de gases en sangre, el pH, el SaO_2 y la PO_2 se redujeron desde el primer síntoma en los pacientes que fallecieron, y el pH se mantuvo reducido hasta el resultado clínico. Se observaron cambios en la dosificación de LDH, aPTT, albúmina y electrolitos. Nuestros resultados muestran que las pruebas de laboratorio pueden ser útiles como biomarcadores de gravedad en los primeros días de síntomas.
Palabras clave: COVID-19; *SARS-CoV-2;* Técnicas de laboratorio clínico; Biomarcadores.

1. Introduction

In December 2019, was diagnosed in Wuhan, province of Hubei (China), a severe acute respiratory syndrome caused by a virus, named in January 2020 as novel coronavirus 2019 *SARS-CoV-2* (Y.-H. Jin et al., 2020), and the disease caused by this coronavirus named as COVID-19 (Y. Jin et al., 2020) being declared a global pandemic in March 2020 (Adil et al., 2021). The diagnosis of COVID-19 was initially performed by polymerase chain reaction (PCR) techniques, considered the gold standard test for viral detection. Another way was detecting the presence of IgA, IgM and IgG antibodies produced against the virus (Guo et al., 2020; Lu et al., 2020). Nowadays, the detection of the *SARS-CoV-2* viral antigen by immunochromatographic rapid test device, expedited the screening and detection of symptomatic, oligosymptomatic, and asymptomatic patients (Fenollar et al., 2021; Rai et al., 2021).

Early diagnosis proved to be an extremely useful epidemiological tool, in the identification of mild and asymptomatic cases. Which helped social isolation politics and the controlling of viral spread. Extensive testing also provides medical personnel to appropriate treatment of patients with moderate and severe disease (Sreepadmanabh et al., 2020). In severe diseased patients, laboratory tests become an extremely useful tool, as they are easy to perform and inexpensive (Acar et al., 2021). In this study, it was analyzed the correlation between hematological and biochemical parameters with the different outcomes of hospitalized patients due to *SARS-CoV-2* infection divided by groups and per day of symptoms.

2. Methodology

Study Design

The study was conducted from March 25 to October 21, 2020. It was a retrospective and observational study, carried out in hospitalized patients of four hospitals in Uberaba-MG. They were responsible for caring for patients with COVID-19 from the entire macro-region of the Southern Triangle. The Southern Triangle region covers 27 municipalities with a population of approximately 800 thousand, mostly urban inhabitants (91.67%) (IBGE, 2019). This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the Hospital de Clínicas from Universidade Federal do Triângulo Mineiro with approval n° **3.957.676.** Patients who agreed to participate in the study signed an informed consent form. Patients who could not sign were included only after the consent of their legal guardian. The free and informed consent gave our team access to the medical and laboratory data records necessary for the study.

Patients and data gathering

Patients who, prior to or during hospitalization, underwent serology, Nasal Swab Antigen Search Test, or Nasal Swab RT-qPCR with a positive result for COVID-19 were included in the study. Patients hospitalized with influenza-like illness and a negative diagnosis for COVID-19 were included as a negative control for the disease. The following exclusion criteria were adopted: patients who refused to participate in the study.

All the demographic data of these patients, such as age, sex, hospital of admission, outcome, symptoms, testing for SARS-CoV-2, days of symptoms prior to admission, length of hospital stay, medications, as well as hematological, biochemical, and coagulation parameters were extracted from the medical records. These data were organized in an electronic data sheet. Entries that did not show some of the variables selected for the study were excluded from this analysis. Patients were divided into groups according to clinical outcome (COVID-19 Negative, COVID-19 Recovered, and COVID-19 Death).

Statistical Analysis

For statistical tests, data were tabulated in Microsoft® Excel and analyzed using GraphPad Prism 8.0, (La Jolla, CA, USA). For descriptive analyses, absolute (N) and relative frequencies were used with 95% confidence levels. The chi-square test was used to verify associations of proportions in the different categories of the variables analyzed. To evaluate hematological and biochemical parameters, normal distribution and homogeneous variance were tested for all study variables using the Shapiro-Wilk test. When the distribution was considered normal and the variance homogeneous, one-way analysis of variance (ANOVA) with Tukey's post-hoc test was used. In cases where the distribution was not Gaussian, Kruskal-Wallis with Dunns' post-hoc test and the unpaired multiple t test were used. The differences observed were considered significant when $p \leq 0,05$.

3. Results

Clinical and epidemiological data

The study consisted of 398 patients who had a positive test confirmation for COVID-19 and also patients who had flu syndrome and were used as a negative control for evaluation. We had a total of 157 female patients (39.4%) and 241 male patients (60.6%). From these, 341 (85.7%) had a positive diagnostic test for COVID-19, while 57 (14.3%) had only flu syndrome with a negative diagnostic test for COVID-19. The positive COVID-19 group had a follow-up during hospitalization and was divided into patients who were discharged and patients who died. From the 341 COVID-19 positive patients, 219 patients (64.2%) were discharged, while 122 patients (35.8%) died.

The COVID-19 Negative group consisted of 57 patients, with a predominance of males with 59.6% (34 patients) and with 40.4% females (23 patients), the group had a mean age of 57 .8 (± 20.8) years. The recovered COVID-19 group had 219 patients with 61.2% male (134 patients) and 38.8% female (85 patients), the group had a mean age of 53.2 (± 14.9) years old. The recovered COVID-19 group had 219 patients with 61.2% male (134 patients) and 38.8% female (85 patients), the group had a mean age of 53.2 (± 14.9) years old. The COVID-19 Death group was composed of 113 patients, also with a predominance of males representing 64.6% of the group (73 patients) and with 35.4% of female patients (49 patients), the average age of the group was 64.7 (± 15.8) years, as shown in table 1.

Table 1 - Distribution of the study population for COVID-19 positivity in relation to males and females. Where, N = number of individuals and SD = standard deviation.

Covid-19 Test	Gender	Death	N	Mean (Years)	Median (Years)	SD (Years)	Minimum (Years)	Maximum (Years)
Negative	Female	No	23	56.5	53	23.9	15	97
	Male	No	34	58.6	56.0	18.8	19	91
Positive	Female	No	85	53.5	54	17.8	14	92
		Yes	49	64.2	65	16.7	23	98
	Male	No	134	53.0	53.0	12.8	26	88
		Yes	73	65.0	66	15.2	31	100

Source: Authors (2022).

Hematological and Biochemical Parameters

The results of the hematological and biochemical tests, requested by the clinical staff during the patient's hospitalization, taking into account the onset of symptoms, were collected from the electronic medical records and grouped according to the diagnosis for COVID-19 (negative or positive) associated with the clinical outcome (discharge or death).

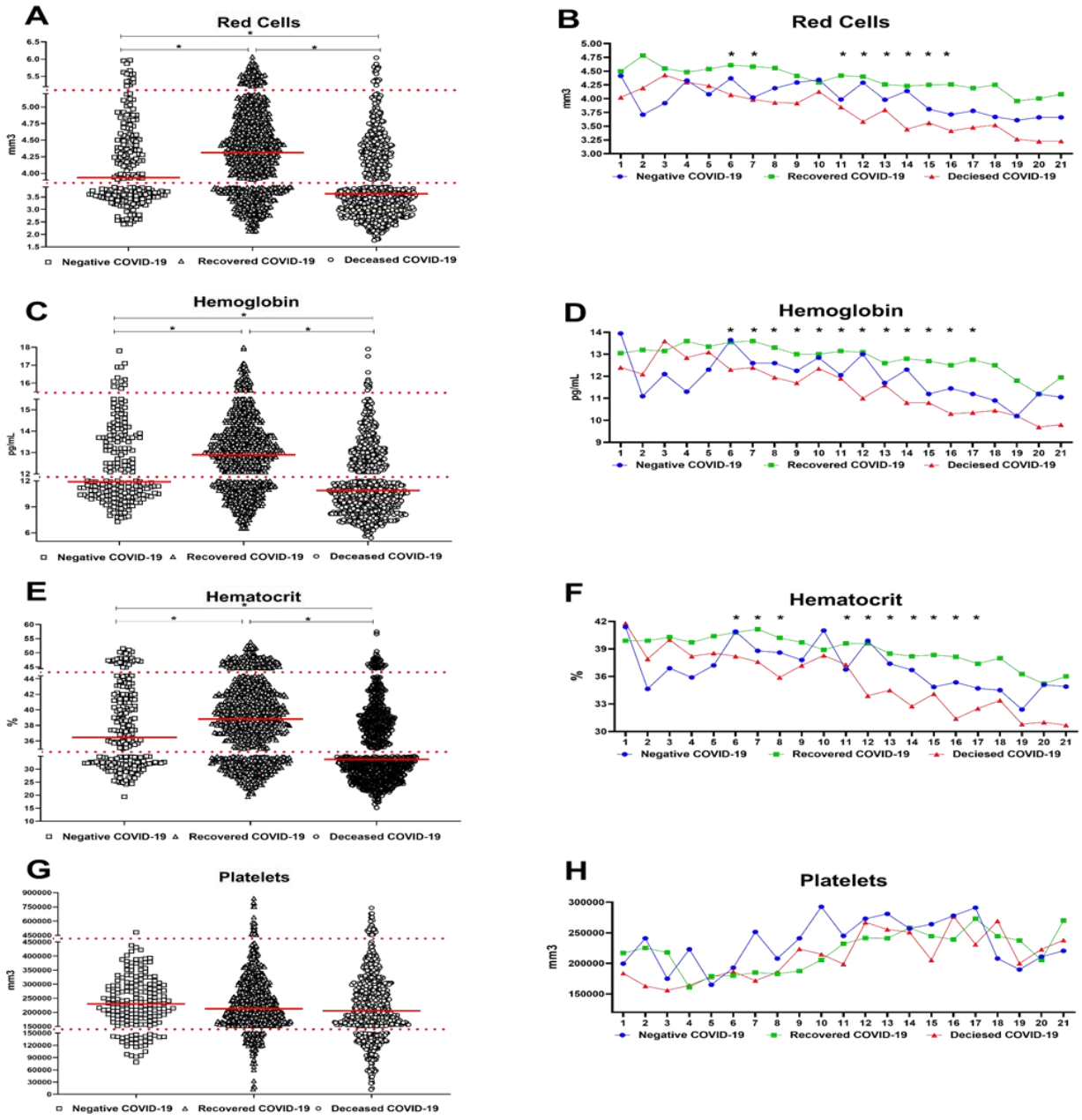
Red cells analysis (Figure 1A, C and E) showed a reduction in erythrocyte count, hemoglobin dosage and hematocrit calculation in the COVID-19 Death group when compared to the recovered COVID-19 group ($p<0,05$ respectively) and to the COVID-19 Negative group ($p<0,05$ respectively), indicating that these patients present a considerable anemic picture. The Recovered COVID-19 group, on the other hand, had better red cell parameters when compared to patients in the negative COVID-19 group ($p<0,05$ respectively).

In order to understand the hematological dynamics of those affected by COVID-19, it was analyzed the daily average of laboratory tests per day of symptoms, reported by patients included in the study from the moment of hospital admission to the 21st day of symptoms after hospitalization. And it was observed that patients in the COVID-19 Death group had lower erythrocyte counts since hospital admission, with a significant difference from the 6th to the 7th and from the 11th to the 16th day of symptoms ($p<0,01$ respectively). They also presented lower hemoglobin concentration from the 6th to the 17th day of symptoms ($p<0,01$ respectively), and lower hematocrit levels from the 6th to the 8th and from the 11th to the 17th days of symptoms ($p<0,01$ respectively) when compared to the Recovered COVID-19 group (Figure 1B, D and F).

Due to several reports of changes in platelet functions in patients affected by COVID-19, platelet count data was analyzed. Although patients in the COVID-19 Negative group visually presented a better count compared to patients affected

by *SARS-CoV-2* during the hospitalization period, the present work did not demonstrate any statistical difference between the groups studied (Figure 1G and H).

Figure 1 - Hematological parameters of the red and platelet series in diferente groups.



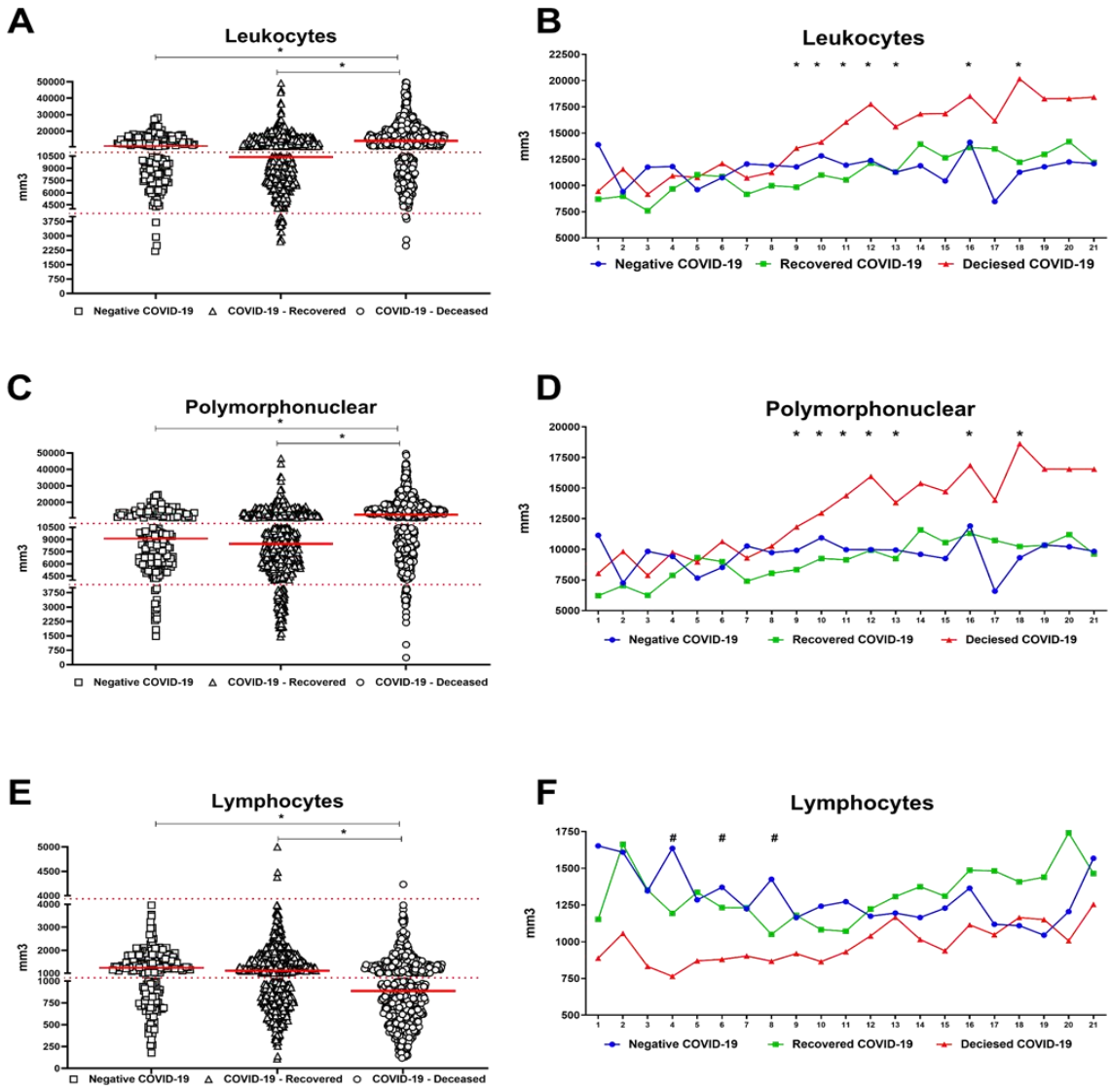
Hematological parameters of the red and platelet series of patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19 (57), Recovered COVID-19 (219) and Deceased COVID-19 (122). In A, C, E and G the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D, F and H show the values per symptom day in the different groups. The * indicate statistical differences between Deceased COVID-19 versus Recovered COVID-19 groups according to symptom days (Multiple unpaired t tests, values <0,01). p values were described in the text. Source: Authors (2022).

In addition to the findings above, it is extremely important to evaluate white blood cells, as it allows us to assess the evolution of the infectious/inflammatory condition of patients affected by the disease. In (Figure 2A), we noticed that the patients in the COVID-19 Death group presented leukocytosis when compared to the Recovered COVID-19 group and the

negative COVID-19 group (p<0,05 respectively). In (Figure 2C) we observed that the leukocytosis was predominantly of polymorphonuclear cells and in the same way the COVID-19 Death Group presented neutrophilia when compared to the Recovered COVID-19 group and the negative COVID-19 group (p<0,05 respectively).

We evaluated the daily mean of leukocytes (Figure 2B and D) and demonstrated a significant increase in leukocytes and polymorphonuclear cells in the COVID-19 Death group compared to the COVID-19 Recovered group, on the 9th to 13th, 16th and 18th days of symptoms (p<0,01 respectively). In (Figure 2E) it reveals that despite the leukocytosis existing in the COVID-19 Death group, they had lymphopenia in relation to the Recovered COVID-19 group (p<0,01) and the negative COVID-19 group (p<0,01). In the dynamics of this change (Figure 2F), it was noticed that in patients in the COVID-19 Death group, lymphocyte reduction occurred significantly on the 4th, 6th and 8th days of post-hospitalization symptoms when compared to the COVID-19 Negative group (p<0,01 respectively).

Figure 2 - Assessment of white leukocytes, by groups and by day of symptoms.



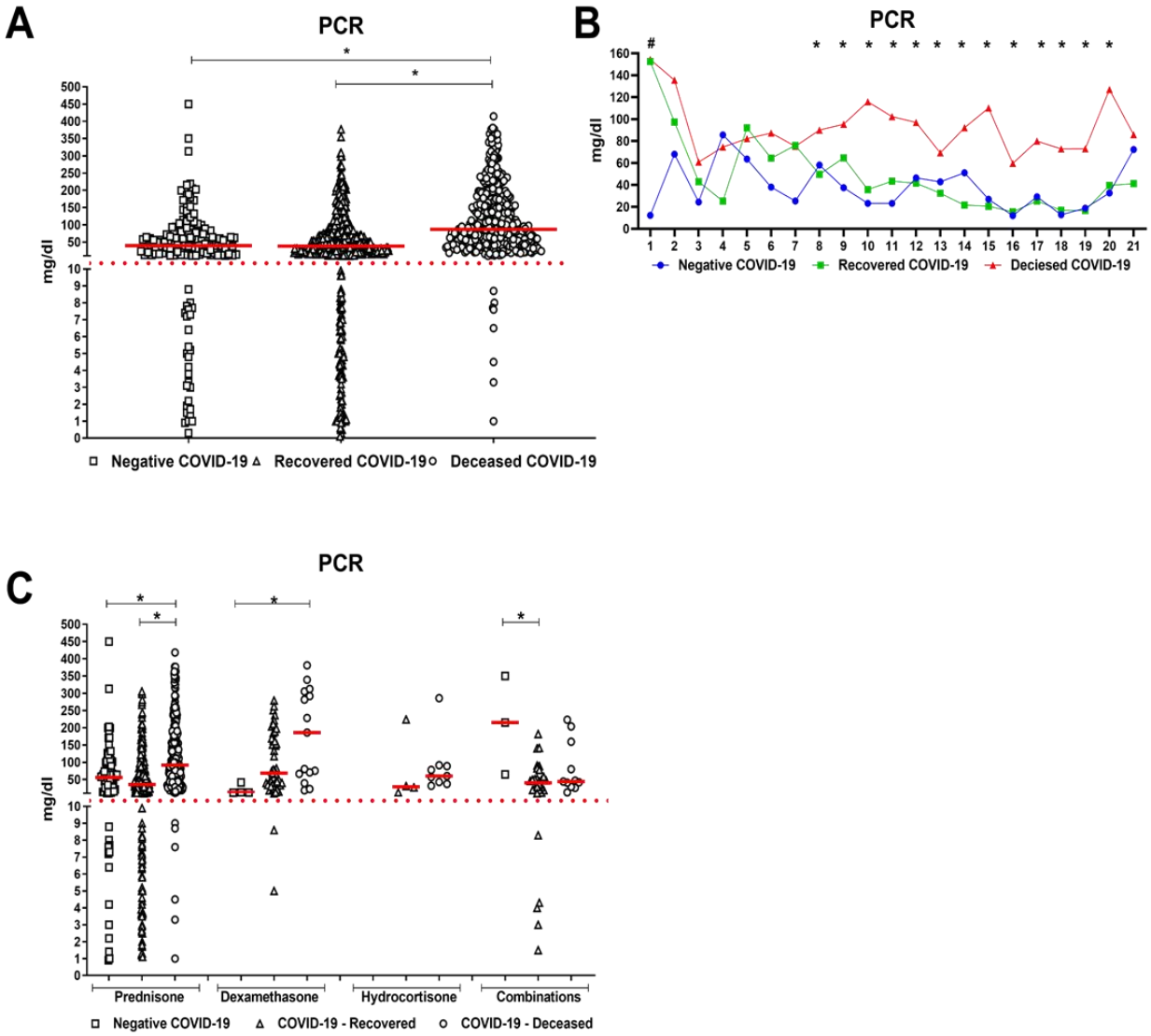
Hematological parameters of the white series of patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. In A, C and E the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D and F show the values per symptom day in the different groups. The * and # indicate statistical differences between Deceased CODIV-19 versus Recovered COVID-19 and Deceased CODIV-19

versus negative COVID-19 groups according to symptom days, respectively (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

PCR analysis (Figure 3A) showed that patients in the COVID-19 Death group had an increase in this protein compared to the Recovered COVID-19 group ($p<0,01$) and the COVID-19 Negative group ($p<0,01$). In (Figure 3B), it is noteworthy that both patients in the Recovered COVID-19 group and the COVID-19 Death group had higher CRP values on the 1st day of post-hospitalization symptoms compared to the group hospitalized with flu-like syndrome, indicating that they already arrive with a significant inflammatory condition ($p<0,01$), COVID-19 Death vs. COVID-19 Negative group. The CRP values practically equaled on the 3rd day, remaining so until the 8th day of symptoms. From the 8th to the 20th day of post-hospitalization symptoms, there was an increase in protein in the COVID-19 Death group compared to the Recovered COVID-19 group and the COVID-Negative group, but the statistical differences occurred only between the two first groups ($p<0,01$ respectively).

In (Figure 3C) it shows that the median of all groups is above the reference value of this analyte, regardless of the type of corticosteroid used. In addition, we noted that the COVID-19 Death group of patients had significantly higher plasma levels of CRP compared to the Recovered COVID-19 group and the negative COVID-19 group, with the use of prednisone ($p<0,05$ respectively), regarding the use of dexamethasone, there was an increase in CRP in the COVID-19 Death group compared to the COVID-19 Negative group ($p<0,05$). The use of hydrocortisone did not promote statistical difference between the different groups. When two or more corticosteroids were administered, a reduction in CRP levels was observed in the Recovered COVID-19 group compared to the negative COVID-19 group, the COVID-19 Death group was also lower, but without statistical difference.

Figure 3 - Assessment of C-reactive protein (CRP), by groups, by day of symptoms and use of corticosteroids.



C-reactive Protein (PCR) of patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. In A, the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, show the values per symptom day in the different groups. The * and # indicate statistical differences between Deceased CODIV-19 versus Recovered COVID-19 and Deceased CODIV-19 versus negative COVID-19 groups according to symptom days, respectively (Multiple unpaired t tests, p values <0,01). In C, shows CRP values versus the type of corticosteroid administered during hospitalization (Kruskal-Wallis test, P VALUE <0,05). p values were described in the text. Source: Authors (2022).

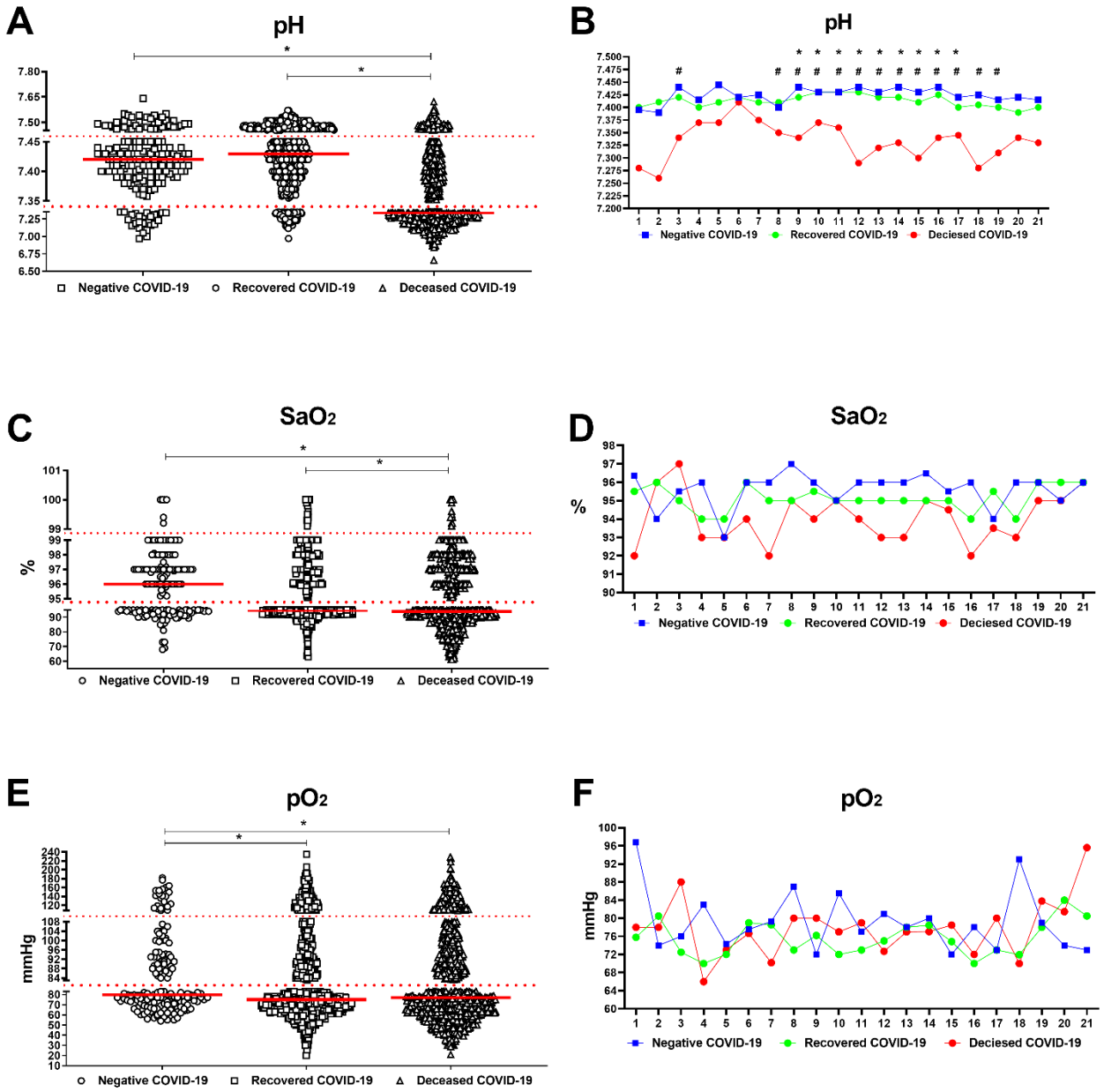
In (Figure 4A) a reduction in the pH dosage was noticed in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group (p<0,05 respectively). In (figure 4C) a lower SaO2 was observed in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group (p<0,05 respectively). In (Figure 4E) the oxygen concentration was evaluated and a reduction in pO2 was seen in the Recovered COVID-19 and in the Death COVID-19 groups compared to the negative COVID-19 group (p=<0,05 respectively). In order to understand the blood gas parameters, we evaluated the measurements daily, and it was found that in the COVID-19 Death group the blood pH was lower since the onset of symptoms when compared to the other groups (Figure 4B).

In the same group, an increase in pH was perceived after the first days of symptoms after hospitalization, and from the 7th day onwards, the values decreased again and remained low until the 21st day of post-hospitalization symptoms. When comparing the COVID-19 Death group in relation to the COVID-19 Recovered group, the difference was observed from the 9th to the 17th day of symptoms ($p<0,01$ respectively). In the comparison between the COVID-19 Death group and the COVID-19 Negative group, we saw that the differences occur on the 3rd day and from the 8th to 19th days of post-hospitalization symptoms ($p<0,01$ respectively).

In (Figure 4D) the daily SaO2 average was evaluated, and as in the pH measurements, a lower concentration of SaO2 was observed in the COVID-19 Death group on the first day of post-hospitalization symptoms. In the next 2 days, an increase in saturation was observed and from the 4th day onwards it decreased again, remaining lower until the 21st day in relation to the other groups. Despite the lower concentration in SaO2, there were no differences between the groups.

In (Figure 4F) we evaluated the daily mean of pO2 and saw a variation in the COVID-19 Death group until the 4th day of symptoms, and after that day the pO2 concentrations were similar to the other groups, with no differences between them.

Figure 4 - Assessment of hydrogen potential (pH), oxygen saturation (SaO2) and oxygen pressure (pO2), by groups and by day of symptoms.

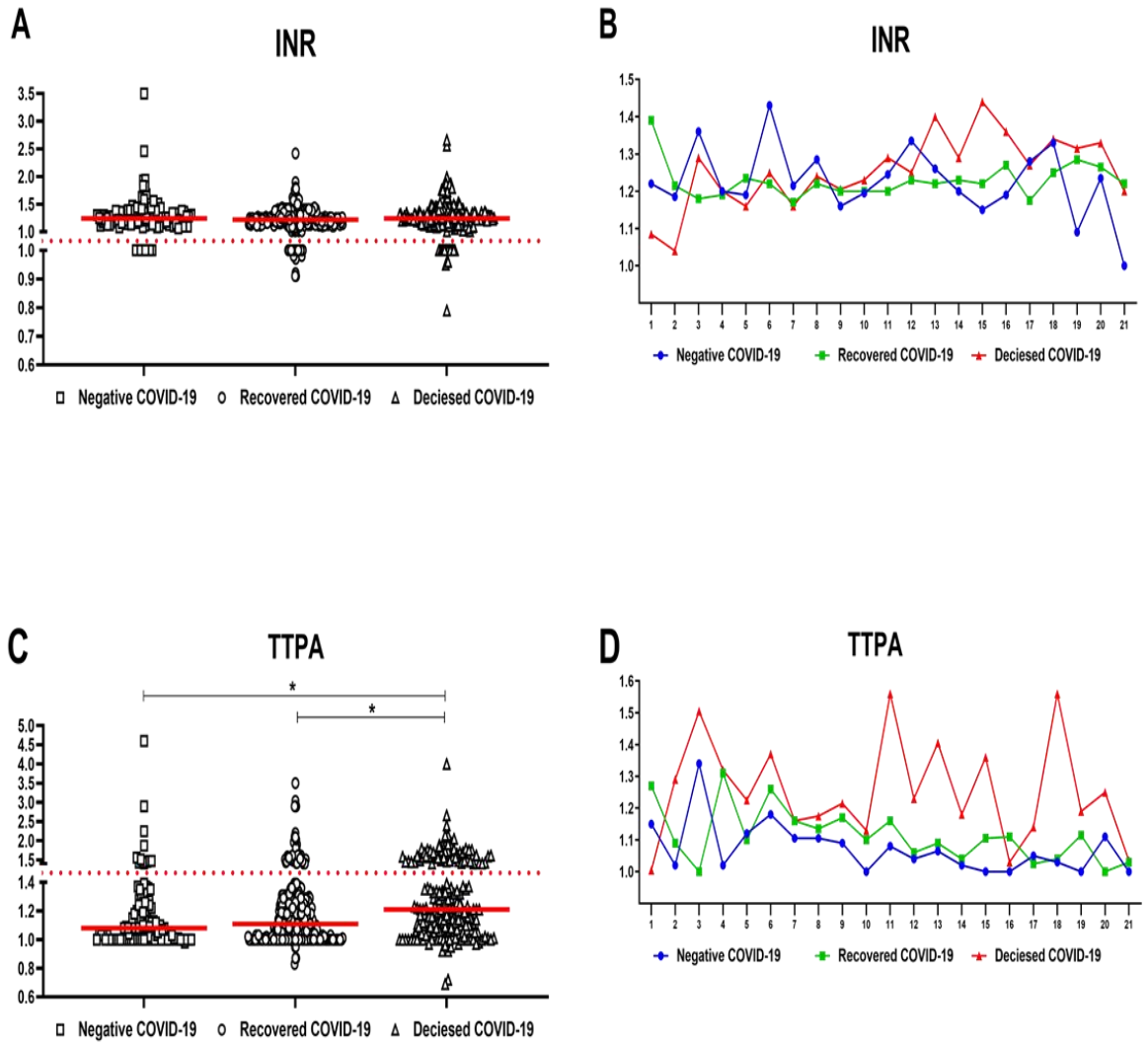


Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. In A, C and D, show potential hydrogen (pH), oxygen saturation (SaO2) and oxygen pressure (pO2), respectively and the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D and F, show values of potential hydrogen (pH), oxygen saturation (SaO2) and oxygen pressure (pO2) per symptom day in the different groups. The * and # indicate statistical differences between Deceased COVID-19 versus Recovered COVID-19 and Deceased COVID-19 versus Negative COVID-19 groups according to symptom days, respectively (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

In (Figure 5A and C) the international normalized ratio (INR) of (PT, Prothrombin Time) and the Index of (aPTT-Activated Partial Thromboplastin Time) were evaluated in the 3 groups and an increase in the APTT Ratio was observed in the COVID- 19 Death in relation to the Recovered COVID-19 group and the negative COVID-19 group ($p<0,05$ respectively). In (figure 5B and D) the daily mean of INR and the aPTT Ratio per day of symptom were evaluated and no difference was

noticed between the groups, despite the aPTT ratio being increased in the COVID-19 Death group in relation to the other groups.

Figure 5 - Evaluation of the INR of (PT, Prothrombin Time) and the Index of (aPTT-Activated Partial Thromboplastin Time), by groups and by day of symptoms.



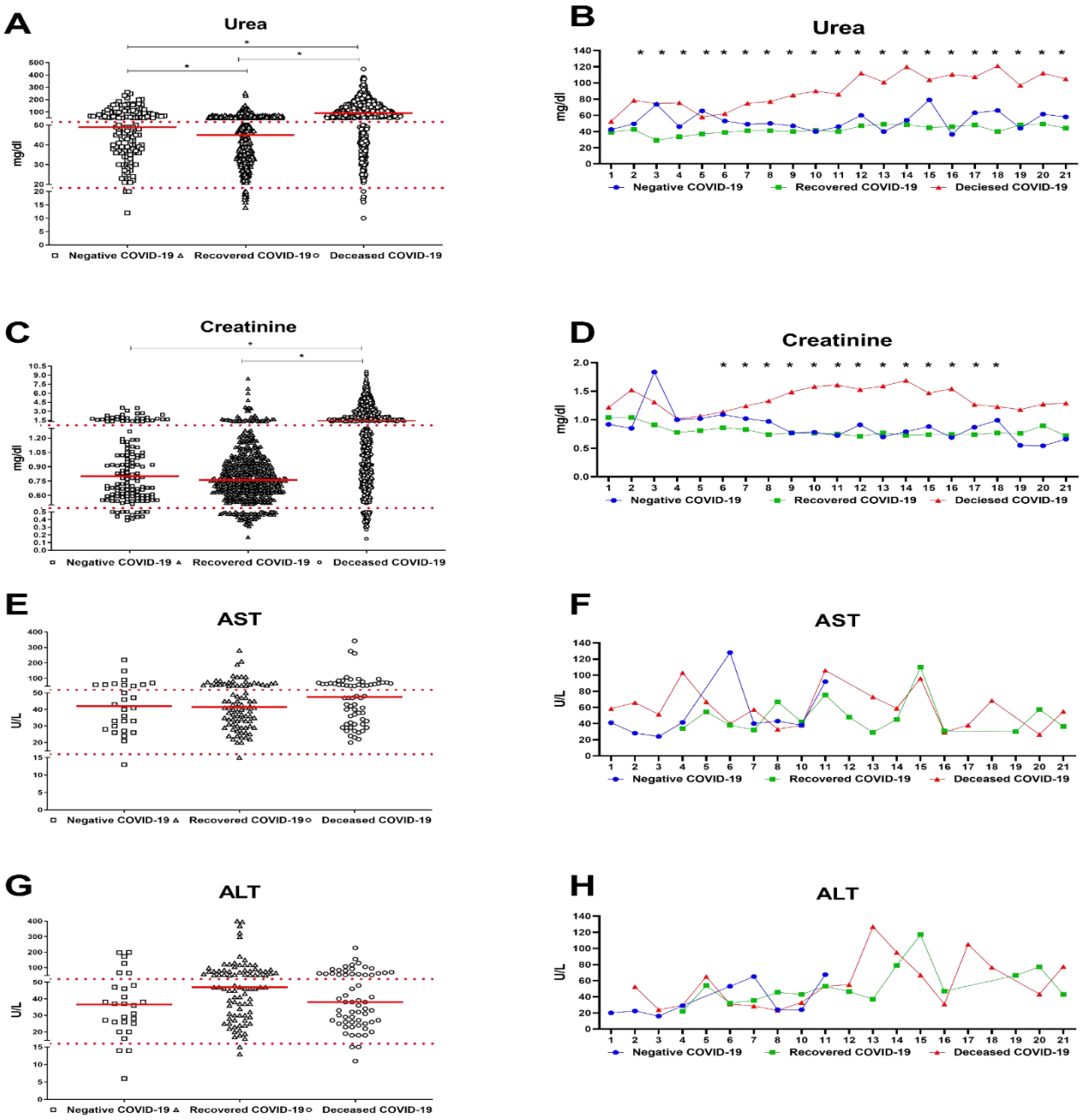
Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19, and INR (international normalized ratio) (A and B) and APTT-activated ratio (C and D) were measurement. In A and C, the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B and D, show the values per symptom day in the different groups. p values were described in the text. Source: Authors (2022).

When evaluating the biochemical parameters, in (figure 6A), an increase in urea was observed in the COVID-19 Death group compared to the Recovered COVID-19 group and the Negative COVID-19 group ($p<0,05$ respectively), and a lower concentration of the analyte in the Recovered COVID-19 group compared to the Negative COVID-19 group ($p<0,05$). In (figure 6C), higher levels of creatinine was found in the Death COVID-19 group compared to the Recovered COVID-19 group and the negative COVID-19 group ($p<0,05$ respectively). The averages of the biochemical parameters were evaluated daily. In (figure 6B) a rise in urea was observed in the COVID-19 Death group compared to the recovered COVID-19 group on the 2nd day, persisting until the 21st day of post-hospitalization symptoms ($p<0,01$ respectively). In (figure 6D) it was observed that

the increase in creatinine in the COVID-19 Death Group occurred from the 6th day onwards, remaining until the 18th day of symptoms compared to the Recovered COVID-19 group (p<0,01 respectively).

In (Figure 6E and G) the dosages of liver enzymes Aminotransferase de Aspartate (AST) Aminotransferase de Alanine (ALT), showed no significant difference between the groups analyzed. In (figure 6F and H) we show the daily mean of enzymes per day of symptoms, and similarly, no differences were noticed between the analyzed groups.

Figure 6 - Evaluation of Urea, Creatinine Aminotransferase de Aspartate (AST) Aminotransferase de Alanine (ALT), by groups and by day of symptoms.

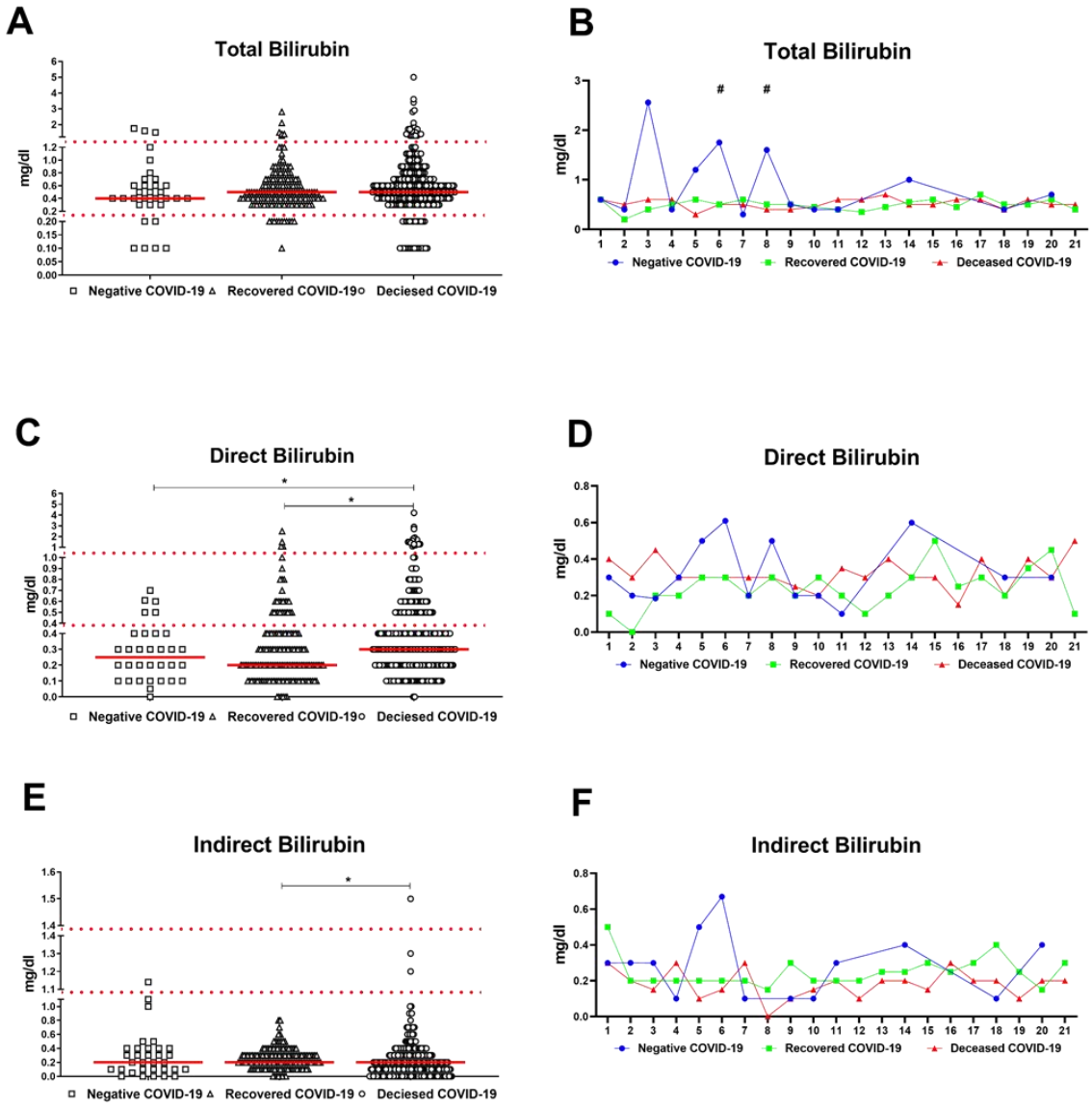


Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. A, B, C and D show urea and creatinine measurement and E, F, G and H show AST and ALT measurement. In A, C, E and G the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D, F and H, show the values per symptom day in the different groups. The * and # indicate statistical differences between Deceased CODIV-19

versus Recovered COVID-19 and Deceased CODIV-19 versus Negative COVID-19 groups according to symptom days, respectively (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

Bilirubin dosages were evaluated, in (figure 7A) the amount of total bilirubin showed no difference between the groups. In (figure 7C) an increase in direct bilirubin was observed in the Death COVID-19 group compared to the Recovered COVID-19 group and the negative COVID-19 group (p<0,05 respectively). In (figure 7E) an increase in indirect bilirubin was observed in the COVID-19 Death group compared to the recovered COVID-19 group (p<0,05). In the daily averages (figure 7B, D and F) there was only an increase in total bilirubin in the Negative COVID-19 group compared to the COVID-19 group Death on the 6th and 8th days of symptoms (p<0,01 respectively). In the other dosages, there was no difference between the analyzed groups.

Figure 7 - Bilirubin assessment by groups and by day of symptoms.

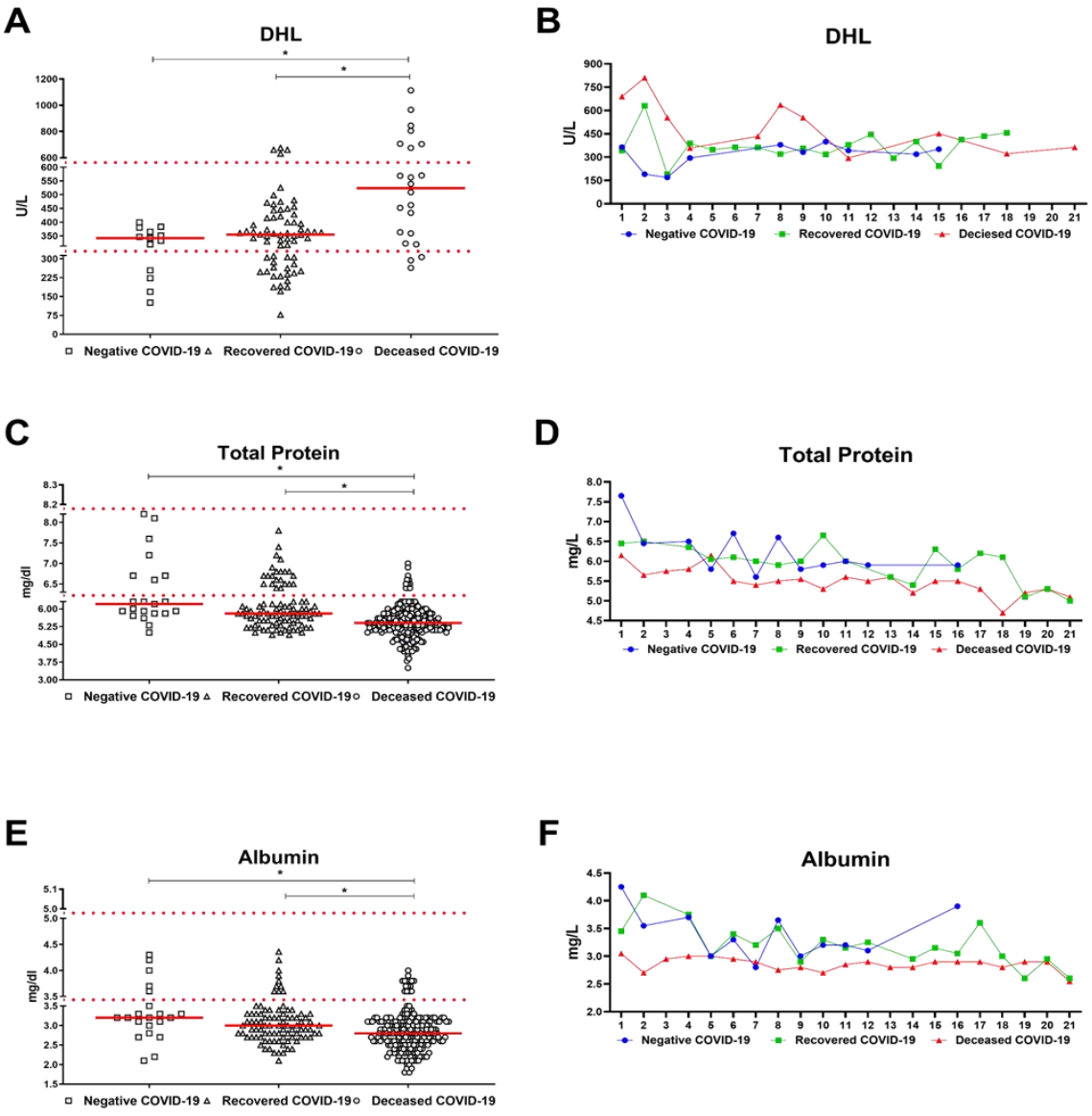


Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. A, C and E show total bilirubin, direct bilirubin and indirect bilirubin, respectively. In these pictures, the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D and F show the values per symptom day in the different groups. The # indicate statistical differences between Deceased CODIV-19 versus Negative COVID-19 groups according to symptom days (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

When evaluating cell injury markers such as lactate dehydrogenase (DHL), in (figure 8A), an increase in the enzyme was observed in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group. ($p<0,05$ respectively). In (figure 8B), as in the previous parameters, the daily behavior of the enzyme per day of symptoms was demonstrated and there was no difference between the groups analyzed. In (Figure 8C and E) the total protein and albumin dosages were evaluated, and a decrease in proteins was seen in the COVID-19 Death group compared to the Recovered COVID-19 and Negative COVID-19 group ($p<0,05$ respectively).

In the Figure (8D and F) as previously done in the other analyzed parameters, the daily behavior of proteins was evaluated by day of symptoms and even without statistical difference, lower concentrations of both total protein and albumin can be observed in the COVID-19 Death group in relation to the other groups.

Figure 8 - Assessment of lactate dehydrogenase (DHL), total protein and albumin by groups and by day of symptoms.



Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. A, C and E show DHL, total protein and albumin, respectively. In these pictures, the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D and F show the values per symptom day in the different groups (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

In the electrolyte dosages, higher levels of sodium (Na) was observed (figure 9A) in the COVID-19 Death group compared to the Recovered COVID-19 group and the Negative COVID-19 group ($p<0,05$ respectively). An increase in Na was also seen in the Recovered COVID-19 group compared to the Negative COVID-19 group ($p<0,05$). When evaluating the daily mean of Na per day of symptoms (figure 9B), a higher concentration of Na was observed in the COVID-19 Death group compared to the COVID-19 Recovered group, with a difference on the 7th day and the 11th to the 20th day ($p<0.01$ respectively).

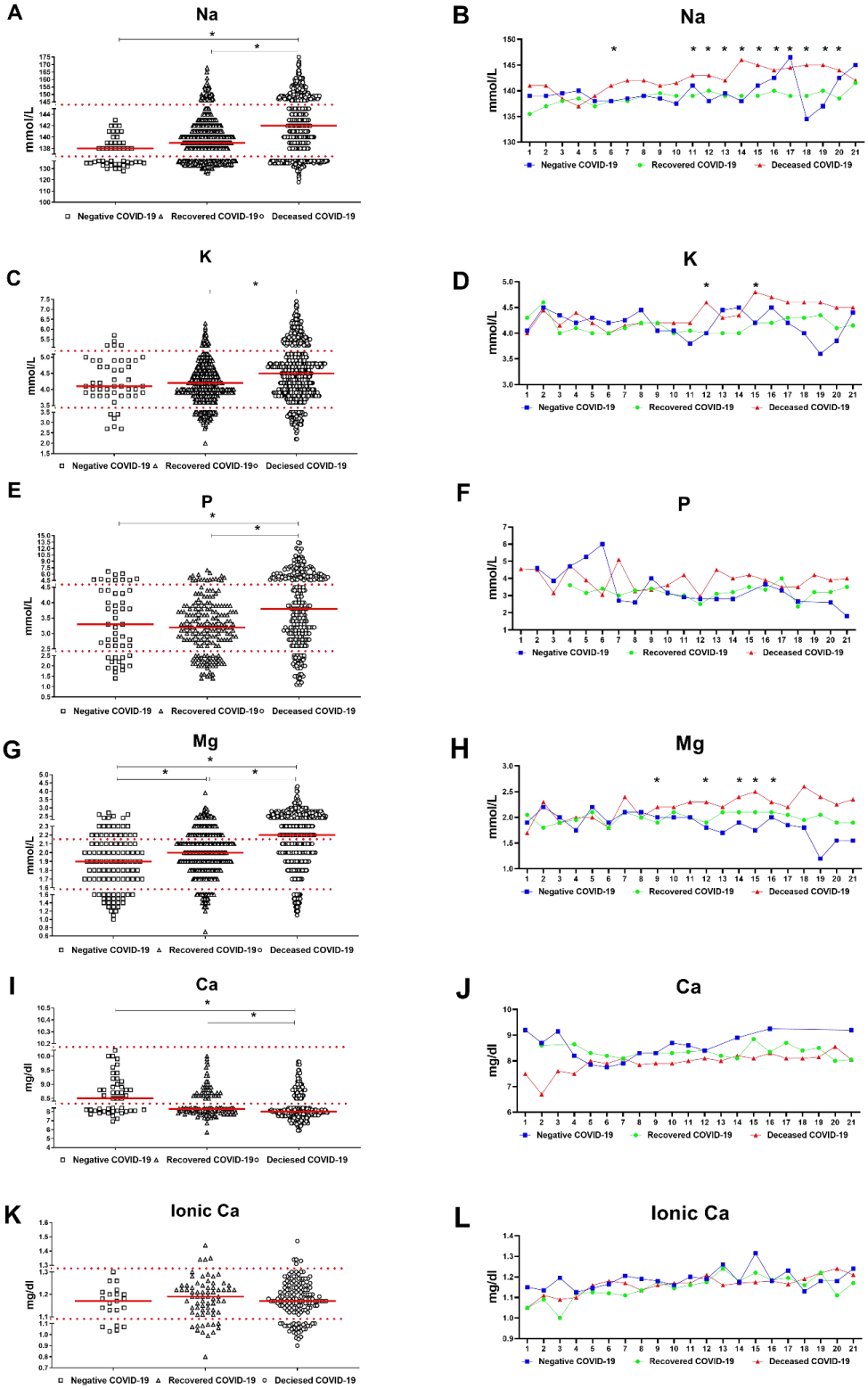
In (figure 9C) an increase in potassium (K) was found in the COVID-19 Death group compared to the recovered COVID-19 group ($p<0,05$). When evaluating the daily averages of K per day of symptoms (figure 9D), it was observed that the highest concentration of K in the COVID-19 group occurred on the 12th and 15th days of symptoms compared to the Recovered COVID-19 group ($p<0,01$ respectively).

In (figure 9E) a rise in phosphorus (P) was seen in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group ($p<0,05$ respectively). In (figure 9F) no differences were observed in the daily averages of P in the evaluated groups.

In (figure 9G) higher levels of magnesium (Mg) were noticed in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group ($p<0,05$ respectively). An increase in Mg was also seen in the Recovered COVID-19 group compared to the negative COVID-19 group ($p<0,05$). In (figure 9H) when evaluating the daily averages per day of symptoms, an increase in Mg was observed in the COVID-19 Death group compared to the recovered COVID-19 group from the 9th day to the 21st day of symptoms, with a difference on the 9th, 12th, 14th, 15th and 16th day after hospitalization ($p<0,01$ respectively).

In (figure 9I) a reduction in calcium (Ca) was noticed in the COVID-19 Death group compared to the Recovered COVID-19 group and the negative COVID-19 group ($p<0,05$ respectively). In (figure 9J) no differences were seen in the daily averages of Ca in the evaluated groups. In (figure 9K-L) no differences were observed in the dosages of ionic calcium in the analyzed groups and also by day of symptoms.

Figure 9 - Assessment of electrolytes (sodium (Na), potassium (K), phosphorus (P), magnesium (Mg), total calcium (Ca), and ionic calcium (ionic Ca), by groups and by day of symptoms.



Patients with flu syndrome were classified according to COVID-19 positivity and clinical outcome and divided into the following groups: Negative COVID-19, Recovered COVID-19 and Deceased COVID-19. In A, C, E, G, I and K show sodium (Na), potassium (K), phosphorus (P), magnesium (Mg), calcium (Ca) and ionic calcium (ionic Ca) per group, respectively. In these pictures, the dashed line and the solid horizontal line represent the reference values and the median, respectively. The * indicates statistical differences between groups (Kruskal-Wallis test, post Dunn's test, p values <0,05). In B, D, F, H, J and L show the values of electrolytes measurement per symptom day in the different groups. The * indicates statistical differences between Deceased COVID-19 versus

Recovered COVID-19 groups according to symptom days (Multiple unpaired t tests, p values <0,01). p values were described in the text. Source: Authors (2022).

4. Discussion

SARS-COV-2 infections showed that the elderly population is one of the most affected by the virus, in addition to being more susceptible to infection, with a greater number of more severe cases. However, severe cases are also correlated with associated comorbidities, not just age (Nikpouraghdam et al., 2020; Zheng et al., 2020). In our study, a higher mean age was observed in the COVID-19 group that died, and also a greater number of male patients in this group, this distribution may be related to the increase in the production of inflammatory markers demonstrated in elderly men (ten-Caten et al., 2021). Since the declaration of a pandemic status, a higher incidence, greater severity and greater number of deaths have been seen in men, and this relationship may occur due to the function of sex hormones, which are related to the mediation of the functional immune response against different viral respiratory tract infections (Kadel & Kovats, 2018).

A positive diagnosis for COVID-19 is the first step towards isolating, monitoring, and caring for patients with the infection. Biochemical and hematological laboratory tests are simple, inexpensive, easy to perform, and extremely important for monitoring hospitalized patients, as well as for identifying severe cases (Guo et al., 2020; Horvath, Lind, Frece, Wurzer, & Stadlbauer, 2021). Daily blood count, clotting factors, C-reactive protein (CRP), blood gas analysis, renal, hepatic and nutritional predictors are fundamental in medical management and in the appropriate treatment of patients with the disease (Yuan et al., 2020; Zheng et al., 2020).

Hematological changes in patients with COVID-19 are associated with anemia, occasional mild thrombocytopenia, leukocytosis with increased polymorphonuclear cells, and lymphopenia. Direct infection of the virus in the bone marrow, hemophagocytosis in the spleen, lymph nodes, liver and bone marrow may explain anemia in patients with the disease, which in most cases present with fusion anemia, and more evidently in critically ill patients (Yuan et al., 2020; Zheng et al., 2020). Neutrophilic leukocytosis is common in COVID-19, as they are the first innate immune cells to be recruited. The effector mechanisms of these cells such as phagocytosis, cytokine production and activation of NETs are used to fight viral infections (Barr et al., 2018; Borges et al., 2020; Lamichhane & Samarasinghe, 2019; Rosales, 2020). The cause of lymphopenia caused by *SARS-CoV-2* infection is not very clear, and may occur by apoptosis caused by direct infection of the virus in lymphocytes (Panesar, 2008), in other studies, necrosis of lymph nodes, spleen, other lymphoid tissues, and reduced hematopoiesis may explain the low peripheral blood lymphocyte count (Xu et al., 2020).

In our study, a lower concentration of erythrocytes, hemoglobin and hematocrit was observed in patients in the COVID-19 Death group compared to the other groups, and surprisingly high levels of red blood cell parameters in patients in the COVID-19 Recovered group compared to others. Our results demonstrate that anemia can be an important factor in the worsening of the disease, and as a consequence, the increase in mortality (Yuan et al., 2020), in critically ill patients, a reduction in hemoglobin was found from the 7th day of post-hospitalization symptoms, and can be used as a prognosis of disease severity. There were no significant differences in platelet counts, however daily analyzes showed a lower number of platelets in patients in the COVID-19 group Death in the first days of infection, but within normal limits, with more evident thrombocytopenia occurring in patients with systemic hypercoagulability syndrome (Wool & Miller, 2021).

In our analysis of white blood cell parameters, neutrophilic leukocytosis and lymphopenia were observed in patients in the COVID-19 Death group compared to the others, corroborating data in the literature, where severe patients with the disease have this profile (Liu et al., 2020). When analyzing the daily averages per day of symptoms, it was found that neutrophilic leukocytosis becomes evident in critically ill patients who died from the 6th day of post-hospitalization symptoms,

while lymphopenia in this same group of patients is reduced since the 1st day of symptoms. This data can be used as a severity predictor for COVID-19.

C-reactive protein (CRP), is a widely used inflammation biomarker, was described by Tillet and Francis in 1930 as an acute phase protein (Tillett & Francis, 1930), its synthesis occurs in the liver by stimulation of interleukin-6 (IL -6) (Morley & Kushner, 1982). Increased CRP is found in several pathologies, renal and cardiovascular diseases, surgical procedures, chronic inflammatory diseases, venous thromboembolism, sepsis and virais pneumonias (Folsom et al., 2009; Murashima et al., 2019; Vasileva & Badawi, 2019). Recently, higher concentrations of CRP and COVID-19 are associated with high severity and mortality in patients with the disease (Luo et al., 2020; Petrilli et al., 2020).

Our data agree with the literature, where CRP levels are high in all patients involved in the study, however a higher concentration was found in patients in the COVID-19 Death group. When analyzing the daily averages of symptoms per day, it was observed that patients with COVID-19 had higher concentrations of the protein on the 1st day compared to patients in the COVI-19 Negative group. After hospitalization, CRP levels fall until the 3rd day in patients with the disease, and rise again, remaining high in the patients of the COVID-19 Death group until the 21st day. In critically ill patients with COVID-19, the highest concentration of CRP on admission is associated with high mortality (Luo et al., 2020).

The exacerbated increase in CRP in patients with COVID-19 is associated with complications in patients with the disease, such as acute respiratory syndrome, acute cardiovascular injury, acute kidney injury, venous thromboembolism, and increased mortality (Murashima et al., 2019). One of the treatments indicated to reduce the inflammatory process in the disease was the use of corticosteroids, where the use of dexamethasone was the most suitable for the treatment of severe pneumonia in COVID-19 (Luo et al., 2020). In our study, the use of different corticosteroids was evaluated in isolation in the treatment of hospitalized patients with COVID-19, and unlike published studies, the corticosteroids used did not reduce CRP levels in patients with the severe form of the disease. However, when used in association, regardless of the corticoid class, we observed a reduction in CRP in patients with the disease, but without interfering with the mortality of patients with the severe form of COVID-19.

Blood acid-base balance is fundamental for the adaptation and maintenance of the body, and this balance is measured by pH and blood gases through arterial and venous blood gas analysis (Nechipurenko et al., 2021). Changes in pH lead to acidosis or alkalosis, which can be of respiratory, metabolic or mixed origin. Acidosis is directly associated in patients with the severe form of COVID-19, with metabolic acidosis being the most common (Chhetri et al., 2020; Shevel, 2020), manifesting as lactic acidosis, ketosis, and diabetic ketoacidosis COVID-19 induced (Chee et al., 2020).

In our study, a reduction in blood pH was demonstrated, resulting in acidosis in the COVID-19 Death group compared to the other groups. Several factors may contribute as risk factors for the development of severe pneumonia and consequently metabolic acidosis in patients with COVID-19, elderly over 65 years, obesity, diabetes, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary diseases, cancer and pregnancy (Andersen et al., 2013; Kraut & Madias, 2014; Ma et al., 2020; Newington et al., 2013). It is suggested that metabolic acidosis acts as a worsening factor for patients with COVID-19, especially in patients with the aforementioned comorbidities (Nechipurenko et al., 2021).

When evaluating the blood gases daily in our study, it was observed that in the patients of the COVID-19 Death group, the blood pH was lower since the first day of symptoms reported by the patient, this pH improves until the 6th, returning to fall from the 7th day, remaining in acidosis until the 21st of post-hospitalization symptoms. Respiratory acidosis with high levels of CO2 can act synergistically with metabolic acidosis when natural buffers are depleted. We believe that at the onset of symptoms, the acidosis presented by patients in the COVID-19 Death group was of respiratory origin, since acidosis of metabolic origin in the disease occurs later, after the consumption of body resources (Nechipurenko et al., 2021). In

contrast, respiratory and metabolic alkalosis in hospitalized patients with COVID-19 are associated with survival (Bezuidenhout et al., 2021).

Respiratory failure caused by COVID-19 is responsible for the large number of hospitalized patients (Grasselli et al., 2020), Most of these patients need non-invasive ventilatory support, however, the worsening of the clinical status, or the failure of non-invasive support, leads to the need for intubation, and consequently to an increase in the mortality of patients with severe forms of COVID-19 (Ji et al., 2020). In our study, a lower oxygen saturation (SaO2) was observed in patients in the COVID-19 Death group compared to the other groups, and a lower oxygen pressure (pO2) in patients in the COVID-19 Death and Recovered groups compared to the COVID-19 Negative group, respiratory failure being one of the factors responsible for the hospitalization of patients with COVID-19. In the same way as blood pH, SaO2 and pO2 improved after hospitalization, probably due to the oxygen support offered to patients. However, SaO2 falls again from the 4th, remaining stable in the COVID-19 Death group until the 21st day of symptoms, even though there are no differences between the groups. The same was observed in pO2, and in the daily average of symptoms, patients who died had a similar or even higher pO2 than patients who recovered from the disease, this fact can be explained by the different types of ventilatory support used in the patients (Gattinoni et al., 2020).

Among the clinical manifestations of COVID-19, coagulopathies and disseminated intravascular coagulation (DIC) are associated with a higher rate of ICU admissions, the need to use mechanical ventilation and, consequently, the death of patients with the disease (Boccia et al., 2020), D-dimer increase and thrombocytopenia are the most common homeostatic alterations in this group of patients (Levi et al., 2020). The inflammatory process in the lungs caused by the uncontrolled increase in cytokines is related to the deterioration of gas exchange and pulmonary fibrinolysis, and this factor leads to an increase in D-dimer (Vivas et al., 2020), in addition to an increase in tissue factor, fundamental part of the homeostasis process (Lillicrap, 2020).

In our study, the D-dimer dosages were not evaluated, due to infrastructure, cost and logistical reasons for carrying out the test. However, the PT INR and the aPTT index were routinely evaluated in the three groups of patients in the study, and we found no differences in the INR in the evaluation by group, nor in the evaluation by day of symptom. The fact that we express our results in INR needs to be analyzed with caution, as slight changes in prothrombin time in critically ill patients can be a predictor of severity (Tang et al., 2020).

In the analysis of the aPTT index, an increase in the index was observed in the patients who died in the analyzes by groups, however these differences were not seen in the analyzes by day of symptoms, even with the aPTT index from the 10th increased day in the group of patients with COVID-19 Death. But we cannot say whether this increase is directly related to some coagulopathy caused by the disease, or whether the cause is the use of high molecular weight heparin to prevent clotting. According to Gómez-Mesa 2021, the increase above 5 seconds in the APTT assessment may be a marker of poor prognosis in patients with severe COVID-19 occurring from the 4th to the 10th day of hospitalization (Gómez-Mesa et al., 2021) and in our study a similar result was observed.

Acute kidney injury is one of the complications found in patients with severe forms of COVID-19 (Murugan & Kellum, 2011) especially in patients with acute respiratory syndrome who require invasive mechanical ventilation, comorbidities such as diabetes, hypertension and cardiovascular diseases (Izcovich et al., 2020). Several situations contribute to acute kidney injury in COVID-19, direct virus infection in the kidney parenchyma with cytokine production and exacerbated inflammation, obstruction of glomerular and peritubular capillaries by erythrocyte aggregation, fibrin thrombi or fibrinoid necrosis, glomerular ischemia due to the presence of fibrin in glomerular capillaries evidencing activation of coagulation,

nephrotoxic drugs, nosocomial sepsis, hypovolemia and hemodynamic changes (Gabarre et al., 2020; Su et al., 2020; F. Zhou et al., 2020).

In our study, a higher concentration of urea and creatinine was found in patients in the COVID-19 Death group compared to the other groups, unlike patients in the COVID-19 Recovered group, where urea levels were lower than the others. When evaluating the daily mean of urea and creatinine per day of symptoms, a higher concentration of the two analytes was already observed on the first day in the patients of the COVID-19 Death group, becoming permanent from the 6th, 7th day until the 21st of symptoms from post-hospitalization. In most cases, acute kidney injury (AKI) is identified between the 5th and 9th day after admission (Fei Zhou et al., 2020) and our findings corroborate the data described in the literature. However, the slightly increased values in our data, in the first days of symptoms, demonstrate the importance of establishing a time criterion for the increase in urea and creatinine and the onset of an acute kidney injury as early as possible, given that that few cases are discovered on hospital admission (Huang et al., 2020; L. Wang et al., 2020).

Liver involvement in COVID-19 has been reported in patients infected with COVID-19 due to damage caused by the direct presence of the virus in hepatocytes (Ding et al., 2004; Tan et al., 2004) however the low expression of angiotensin converting enzyme 2 (ACE2) makes the liver a less likely target for infection (Cha et al., 2020). Studies performed at the beginning of the pandemic showed that about 14% to 53% of COVID-19 patients had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) alterations (Zhang, Shi, & Wang, 2020).

Our data show that in some patients with COVID-19 Death and Recovered COVID-19, AST and ALT levels were increased, but without differences with patients in the COVID-19 Negative group, who also showed changes in some patients. These data show mild hepatic impairment in patients with COVID-19 (Zhang et al., 2020). In the analysis of daily averages per day of symptoms, AST and ALT levels were shown to increase later, around the 11th and unstable until the 21st of post-hospitalization symptoms in the positive groups for COVID-19. Our data corroborate the literature, where liver dysfunction in COVID-19 is associated with a longer period of hospitalization, and aggravated by the cytotoxicity of drugs used in the treatment of the most severe forms of the disease (Fan et al., 2020).

In terms of total bilirubin in our study, the results were similar to those of AST and ALT, with no differences between the groups evaluated. In the evaluations of the fractions, we observed a slight increase in direct and indirect bilirubin in the COVID-19 Death group in relation to the others. Bilirubin elevations are reported in COVID-19, but less frequently in the analysis of the daily averages per day of symptoms, there were no differences even at a late stage, as demonstrated in the averages of AST and ALT enzymes. Out-of-normal liver enzymes are more evident in critically ill patients, as most patients have lower levels and resolve with clinical improvement (Bangash et al., 2020).

Several parameters were used as indicators to determine prognosis in patients with COVID-19, lactate dehydrogenase (DHL) was one of them, as it has been associated with viral infections in patients in the past (Tao et al., 2018). However, in our study, the use of LDH occurred in less quantity than other indicators such as CRP. In any case, an increase in the enzyme was observed in the COVID-19 Death group, showing a difference between patients in the other groups. Our data agree with the literature where increased LDH is associated with high mortality (Ruan et al., 2020). When evaluating the daily averages per day of symptoms, an increase in LDH was noticed in patients in the COVID-19 groups, and more evidently in the COVID-19 Death group, although there were no statistical differences. Elevated levels of LDH on admission may be related to high mortality with shorter hospital stays (Wu et al., 2020).

Several risk factors for COVID-19 have been identified and well defined, such as advanced age, diabetes, hypertension and other comorbidities, among which malnutrition or pre-malnutrition should be considered (D. Wang et al., 2020). The relationship between other virais pneumonias and the nutritional status of critically ill patients has been reported in

current epidemics as well as the 1918 pandemic (Moser et al., 2019; Short et al., 2018). The risk of malnutrition in patients with COVID-19 may be related to food reduction, inflammatory processes leading to catabolism and reduced mobility due to prolonged hospitalization, in addition to other factors mentioned above. Protocols for assessing nutritional status are defined by the Global Leadership Initiative on Malnutrition (GLIM) where weight, body mass index BMI and body mass loss are considered (Pironi et al., 2021).

In our study, total protein and albumin dosages were evaluated and a reduction in both parameters was observed in patients in the COVID-19 Death group compared to the others, showing that malnutrition is common in critically ill patients (Li et al., 2020). An important finding of the study is the fact that patients in the COVID-19 Death group had lower levels of total protein and albumin from the 1st day of symptoms, assessed from hospital admission and remaining low until the 21st day, even without differences between the groups. In hospitalized patients, whether due to infectious disease or surgery, malnutrition is associated with longer hospital stays, higher mortality and readmissions (Agarwal et al., 2013; Hudson et al., 2018). In patients in the Recovered COVID-19 group, we observed that the reduction in protein levels occurs later and nutritional replacement in these patients is necessary even after hospital discharge (Bedock et al., 2021).

The expression of angiotensin-converting enzyme-2 (ACE2) is regulated by electrolytes present or absent in the body (Cole-Jeffrey et al., 2015). The low supply of electrolytes in the body can affect the immune system, favoring various infections (Gombart et al., 2020). Therefore, the electrolytes requested in the clinical routine of hospitalized patients with or without COVID-19 were evaluated.

Sodium significantly regulates the expression of ACE2, and studies have shown a low concentration of the ion in patients with COVID-19, and that this low concentration was more evident in patients with the severe forms of the disease (Habib et al., 2020). Our data show the opposite, patients with COVID-19 have a higher concentration of sodium compared to patients negative for the disease, and more evidently in patients in the COVID-19 Death group. When analyzing the daily averages of symptoms per day, it was observed that in patients who died, sodium concentrations became elevated later.

Potassium reduction (hypokalemia) is associated with the risk of acute cardiac injury and acute respiratory syndrome in COVID-19, and this reduction is linked to low expression of ACE2 after *SARS-CoV-2* binding (Tirotta et al., 2020). Similar to sodium, lower potassium levels were found in patients with the severe form of COVID-19 (Lippi et al., 2020), and similarly, our data show the opposite, a higher concentration of potassium in the COVID-19 Death group in relation to the others. In the daily averages for days of symptoms, the increase in potassium also occurs later.

Phosphorus is involved in various functions in organisms such as protein production, cell repair and maintenance Previous studies have shown that hypophosphatemia is related to severe forms of COVID-19, as are sodium, potassium and calcium (Izcovich et al., 2020; Lippi et al., 2020) In our results, a higher concentration of phosphorus was observed in patients in the COVID-19 Death group, differing from the data in the literature. In the analysis of the daily averages per day of symptoms, a slight increase was seen in patients who died, as seen in the dosages of sodium and potassium.

Magnesium plays an important role in the immune response, regulating immune functions such as cell adhesion, immunoglobulin synthesis, macrophage and cytokine response (Williams et al., 2020), studies suggest that magnesium plays an important role against viral infections (Jayawardena et al., 2020). Our data show an increase in magnesium in patients with COVID-19 in relation to patients negative for the disease, and likewise a higher concentration in daily averages per day of symptoms in patients in the COVID-19 Death group also in a later fashion.

Calcium has a fundamental role in bone metabolism, and in immunity it acts to eliminate viruses from cells (Rodriguez-Morales et al., 2020). In our study, a lower concentration of total calcium was observed in patients in the COVID-19 Death group compared to the others, in agreement with other studies, however this decrease needs to be evaluated with

other parameters such as albumin and ionized calcium (Lippi et al., 2020). In our work, the low concentration of albumin in patients with COVID-19 Death may be the cause of the low concentration of total calcium, since there were no differences in the ionic calcium dosages between the groups analyzed.

Studies suggest that the reduction in minerals at hospital admission was associated with severe forms of COVID-19 (Wang et al., 2021), However, our data showed a late rise in the levels of these minerals. We believe that these increases are linked to the change in renal function observed in urea and creatinine measurements in critically ill patients who died from COVID-19.

5. Conclusion

The early identification of severe forms of COVID-19 in hospitalized patients represents a challenge for the medical community. In our study, we demonstrated that hematological and biochemical parameters may be used as predictors of severity. Anemia, leukocytosis with neutrophilia and lymphopenia, increase in CRP, urea and creatinine after 5 days of post-hospitalization symptoms in patients who died suggest that such tests are good predictors of severity assessment. Early and constant monitoring is crucial to choose the intervantions that may prevent an unfavorable outcome for the patient.

Declarations of interest

The authors declare no conflicts of interest.

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