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D-Dimer, platelets and C-reactive protein in patients with COVID-19: Correlations in deceased and surviving patients

Dímero D, plaquetas y proteína C reactiva en pacientes con COVID-19: correlaciones en pacientes fallecidos y sobrevivientes

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SUMMARY

Introduction: *COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with activation of the inflammatory process.* **Objective:** *This study aims to determine D-Dimer, platelets, and C-reactive protein (CRP) in COVID-19 patients and controls and to determine these values in surviving and deceased COVID-19 patients.* **Method:** *Descriptive, retrospective, and cross-sectional research was conducted from March to June 2020. A total of 59 patients underwent SARS-CoV-2 testing and were diagnosed with COVID-19. They were classified into two groups according to their evolution (survivors: 49 and deceased: 10). A healthy control group (N=20) was also analyzed.* **Result:** *In general, during COVID-19, the values of D-Dimer and CRP were found to increase significantly compared to control individuals. The highest values were found in patients who died during the disease. Likewise, it was appreciated that during the disease, there were more positive correlations between the different parameters studied in surviving patients than in controls and deceased patients. From a clinical point of view, high CRP and D-Dimer values may be useful as predictors of severity and mortality; therefore, high levels of CRP and D-Dimer are alarm signs. Loss of association observed in deceased patients may constitute another alarm sign.* **Conclusion:** *This study shows the importance of D-Dimer and CRP in the pathophysiology of COVID-19 and a possible predictive value for severe disease progression.*

Keywords: *D-Dimer, platelet, C-reactive protein, COVID-19, deceased patients; survivor's patients.*

RESUMEN

Introducción: *COVID-19 es una enfermedad causada por el síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) asociado a la activación del proceso inflamatorio.* **Objetivo:** *Este estudio tiene como objetivo determinar el Dímero D, las plaquetas y la*

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proteína C reactiva (PCR) en pacientes y controles de COVID-19 y determinar estos valores en pacientes sobrevivientes y fallecidos de COVID-19. **Método:** *Se realizó una investigación de tipo descriptiva, retrospectiva y de corte transversal, en el período comprendido desde marzo a junio 2020. Un total 59 pacientes sometidos a pruebas de SARS-CoV-2 y diagnosticados con COVID-19. Fueron clasificados en dos grupos según su evolución; (sobrevivientes: 49 y fallecidos: 10). También se analizó un grupo de control sano (N=20).* **Resultado:** *En general, durante la COVID-19 se encontró que los valores de Dímero D y PCR aumentaron significativamente en comparación con los individuos de control. Los valores más altos se encontraron en pacientes que fallecieron durante la enfermedad. Asimismo, se apreció que durante la enfermedad existen más correlaciones positivas entre los diferentes parámetros estudiados en pacientes sobrevivientes en comparación con controles y pacientes fallecidos. Desde el punto de vista clínico, los valores elevados de PCR y Dímero D pueden ser útiles como predictores de gravedad, incluso de mortalidad; por tanto, los niveles elevados de PCR y Dímero D son señales de alarma. La pérdida de asociación observada en pacientes fallecidos puede constituir otra señal de alarma.* **Conclusión:** *Este estudio muestra la importancia del Dímero D y la PCR en la fisiopatología de COVID-19 y un posible valor predictivo para la evolución grave de la enfermedad.*

Palabras clave: *Dímero D, plaquetas, proteína C reactiva, COVID-19, pacientes fallecidos; pacientes supervivientes.*

INTRODUCTION

The current pandemic affecting the world is caused by a new type of coronavirus (SARS-CoV-2). This virus affects different organs and tissues through the induction of exacerbated inflammatory processes (1-3). These inflammatory processes are due to the interaction of the virus with its enzyme ACE2 (angiotensin-converting enzyme 2) receptor, inducing a decreased activity and expression of this enzyme and leaving the Angiotensin II (Ang II) overexpressed with increased proinflammatory activity, creating an inflammatory state called "cytokine storm" (3-6). Previous reports have pointed to Ang II as an inducer of pro-inflammatory cytokines, and among those cytokines, C-reactive protein (CRP), which is not only an indicator of inflammation but induces severe effects during COVID-19 (SARS-CoV-2 induced disease) (3). Previous studies have demonstrated the presence of predictive factors for the severity of COVID-19, including age, CRP, D-Dimer, albumin, Lactate Dehydrogenase, ferritin, procalcitonin, and diabetes (7-10). One of the alterations that occur during COVID-19 most closely related to the severity of the disease is the effect of proinflammatory cytokines on coagulation factors, an alteration that leads to venous thromboembolism and disseminated intravascular coagulation (11-13). Previous studies have reported the association between D-Dimer and CRP as a predictive factor of COVID-19 severity (14). Platelet count and CRP have also been associated with the severity of COVID-19 (12,15). In this retrospective study, we aimed to evaluate the potential of CRP, D-Dimer, and platelet counts in the outcome prediction of patients with COVID-19 and determine the behavior of these parameters in patients with COVID-19 who died and survived.

MATERIALS AND METHODS

This retrospective study was conducted on patients from several clinical institutions in Portoviejo, Manabí, Ecuador, from March to June 2021. N=59 COVID-19-positive patients were included and evaluated for SARS-CoV-2, and 20 uninfected individuals were used as a control population. The study included data from the clinical histories of patients who attended different health centers in Portoviejo, Ecuador, survivors, deceased, and people without a diagnosis of COVID-19 as a control. There was no follow-up study; it was limited to observing the behavior of selected parameters in patients who survived and died from COVID-19. The Inclusion criteria were Clinical data of patients positive for SARS-CoV-2 virus infection. As a control, the non-positive individuals free of infectious diseases, chronic diseases, immune disorders, and neoplastic disorders. Exclusion criteria were medical histories of individuals outside the study period who had incomplete or illegible information and patients with organic alterations mentioned in the inclusion criteria.

A nasopharyngeal swab sample was taken from each patient to detect SARS-CoV-2 RNA by RT-

PCR using the cobas® SARS-CoV-2 Qualitative assay from Roche Molecular Systems INC. The collected samples were taken using a standard technique in viral culture medium and sent to molecular biology laboratories for processing in hospitals authorized by the National Institute of Public Health Research (INSPI) of Ecuador, which met the requirements in time and form for the study. The patients were classified into two groups according to their results (survivor: 49 and deceased: 10). A healthy control group (N=20) was also analyzed. Data such as age and sex, complete blood count with differential count (platelets), and C-reactive protein levels were collected from each patient's medical records. To determine D-Dimer from each patient, 3 mL of blood with Calcium Citrate was taken to obtain plasma. It was done by indirect agglutination technique with latex particles (Diagnostica Stago) with reference value < 0.5 μg/mL (16). A venous blood sample with EDTA anticoagulant (3 mL) was taken to perform a Complete Hematology, which was processed by the electrical impedance method for the count and the SFT method for hemoglobin in a BC-2600 Auto Hematology Analyzer (Vitalab Distributor). To determine C-reactive protein (CRP), blood without anticoagulant (5 mL) was taken from each patient to obtain serum. PCR was assessed using an Azmoon PARS CRP immunoturbidimetry kit on a HITACHI 7600-020 automated biochemical analyzer.

The study was reviewed and approved by the Bioethics Committee of the Faculty of Health Sciences of the Technical University of Manabí in compliance with the Ethical Standards and Principles. Statistical analysis was performed using GraphPad Prism, version 7.0 (GraphPad Software, In San Diego, USA). Measurement data with normal distribution are represented as mean ± standard deviation. For continuous variables that were normally distributed, differences between the two groups were compared using Welch's t-test. Correlation analysis was calculated using the Pearson correlation test. A p-value < 0.05 was considered statistically significant.

RESULTS

This study reports 59 patients infected by the SARS-CoV-2, of which 57.63 % were male and 42.37 % were female. The controls were 20 healthy individuals not infected by SARS-CoV-2, where 40 % were male and 60 % were female. Table 1 compares gender and age values in the groups of individuals with COVID-19 and controls. As shown in the Table 1, patients who died from COVID-19 were older than that of survivors, showing a statistically significant difference of p = 0.001 in both groups. As shown in Figure 1, patients with COVID-19 presented higher values of D-dimer (p=0.004) and CRP (p=0.01) compared to healthy individuals. No significant differences were found when comparing platelet values and age. It was found that D-dimer (p<0.001) and CRP (p<0.001) values were elevated in patients who died compared to those who survived COVID-19. Older age was found in the deceased patients (p<0.001). There was no statistical significance in the platelet values (Figure 2).

Table 1. Gender, age and number of the different groups studied

Parameters	COVID-19: Survivors	COVID-19: Deceased	Controls
Male	27	7	8
Female	22	3	12
Age (years)	51.10 ± 2.02	73.70 ± 5.58*	58.40 ± 2.66
N	49	10	20

Welch t-test was used for all pairwise comparisons. *p = 0.001 vs. COVID-19: Survivors and Controls. Data: mean ± Standard Error.

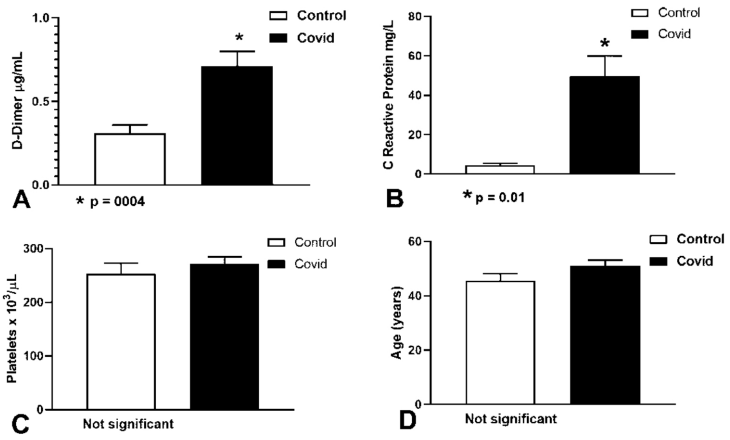

Figure 1. Comparison of the parameters studied between COVID-19 patients and controls. Increased expression of D-Dimer (A) and C-reactive Protein (B) in COVID-19 patients was found. No differences between platelet values (C) and age (D) were observed.

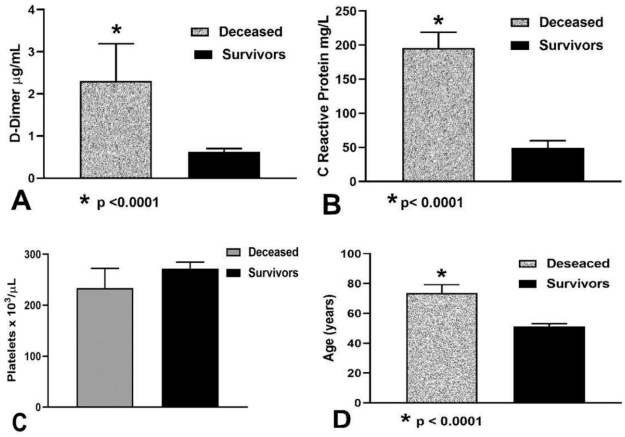

Figure 2. Comparison of the parameters studied between COVID-19 deceased patients and survivor patients. Increased expression of D-Dimer (A) and C-reactive Protein (B) in COVID-19 deceased patients was found. No differences in platelet values (C) between groups were found. Higher age in deceased patients (D) than in survivor patients was observed.

Table 2 and Figure 3 show the correlations in the group of patients who survived COVID-19. Positive correlations were observed between the values of CRP and D-Dimer, CRP and age, platelets and D-Dimer, and D-Dimer and age.

When the Pearson test was applied to analyze the values of the group of patients with COVID-19 and the group of controls to assess the trend of correlations between the different parameters studied, the correlations in the group of patients who survived COVID-19 showed positive correlations between the values of CRP and D-dimer, CRP and age, platelets and D-dimer, and D-dimer and age (Table 2 and Figure 3). A positive correlation was only found between platelet and D-dimer values in patients who died from COVID-19 (Table 3, Figure 4). Table 4 and Figure 5 show the correlations of the parameters studied in the control group. The controls show a significant positive correlation only between age and D-Dimer.

Table 2. Correlations between the different parameters in surviving COVID-19 patients.

Correlation	r square	p-value	f
D-Dimer-CRP	0.3949	**0.0004**	14.27
Platelets- CRP	0.007438	0.5557	0.3522
Age-CRP	0.1512	**0.0058**	8.370
Platelet-D-Dimer	0.1190	**0.0152**	6.347
Age-D-Dimer	0.1511	**0.0058**	8.365
Platelets-Age	0.01270	0.4407	0.6048

C-reactive protein. Data. mean ± Standard Error. Survivors. N=49

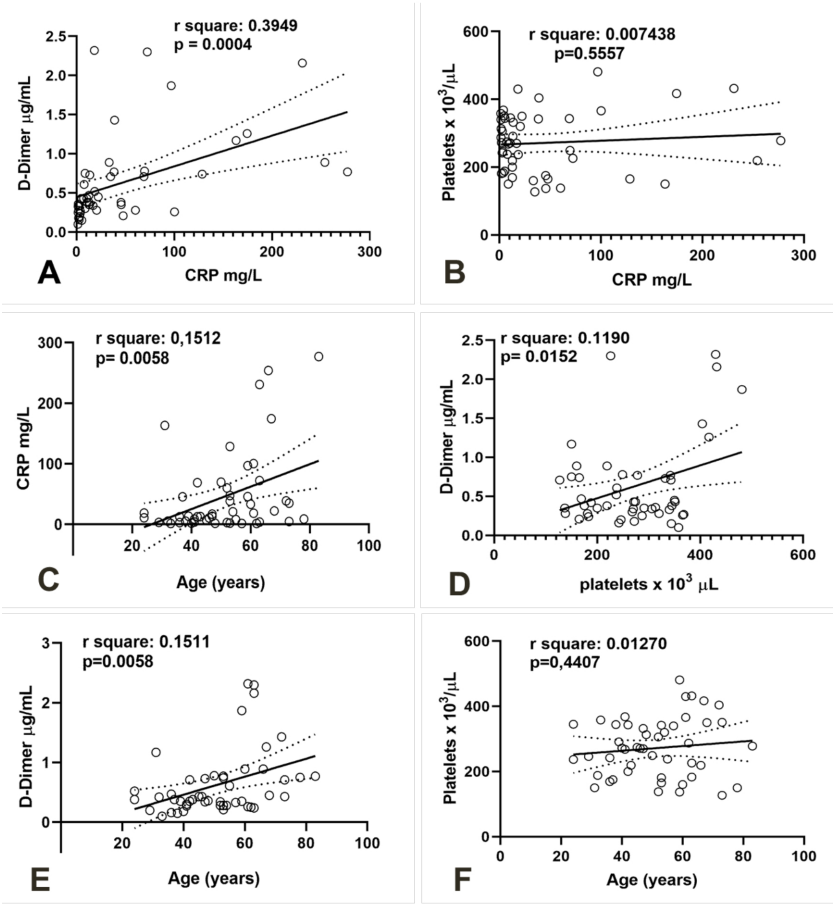

Figure 3. Correlations between the different parameters studied in surviving COVID-19 patients. High positive correlations between C reactive protein (CRP) / D-Dimer (A), CRP / Age (C), platelet / D-Dimer (D), and Age / D-Dimer (E) were observed.

Table 3. Correlations between the different parameters in deceased COVID-19 patients.

Correlation	r square	p-value	f
D-Dimer-CRP	0.03280	0.6410	0.2364
Platelets- CRP	0.03878	0.5856	0.3227
Age-CRP	0.01060	0.7771	0.08572
Platelet-D-Dimer	0.9678	**<0.0001**	210.2
Age-D-Dimer	0.09447	0,4211	0.7303
Platelets-Age	0.1178	0.3317	1.068

CRP: C-reactive protein; Data: mean ± Standard Error; N= 10

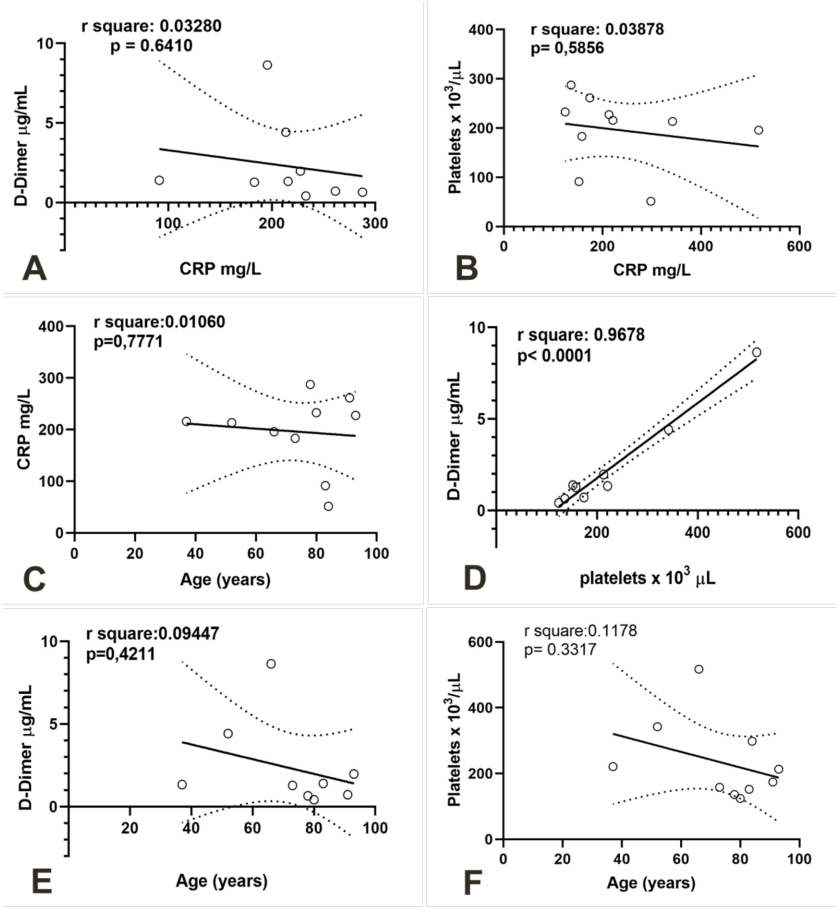

Figure 4. Correlations between the different parameters studied in deceased COVID-19 patients. A high positive correlation was observed between platelets and D-dimer values (D).

Table 4. Correlations between the different parameters in control individuals.

Correlation	r square	p value	f
D-Dimer-CRP	0.08182	0.2828	1.247
Platelets- CRP	0.02088	0.5934	0.2985
Age-CRP	0.02708	0.5425	0.3897
Platelet-D-Dimer	0.02417	0.5654	0,3467
Age-D-Dimer	0.4972	**0.0023**	13.85
Platelets-Age	3.621e-005	0.9824	0.0005070

CRP: C-reactive protein; Controls: N=20. Results: mean ± Standard Error

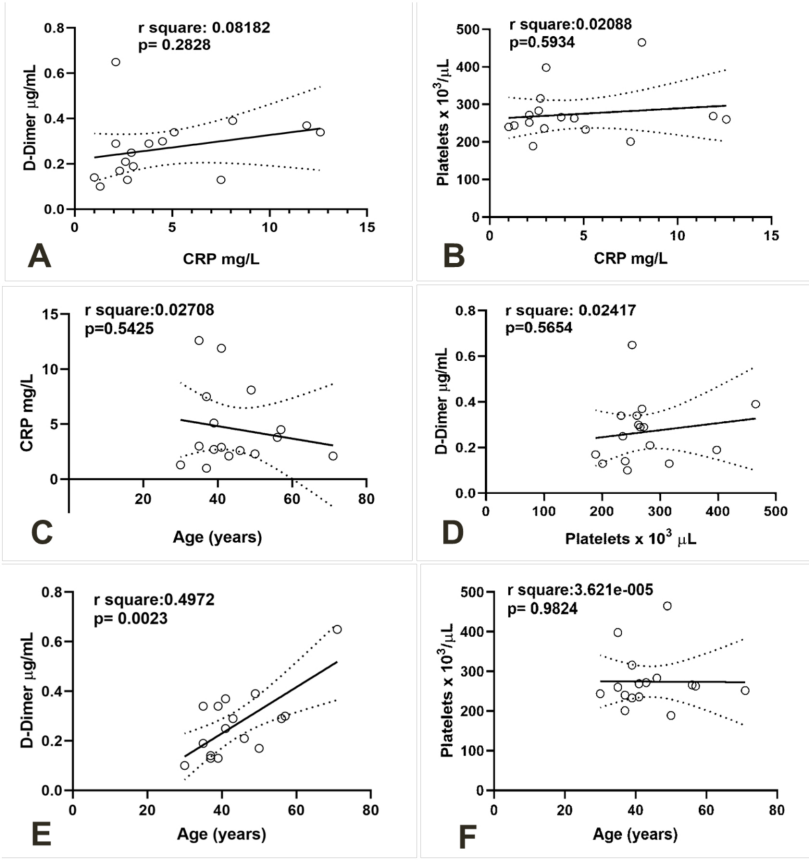

Figure 5. Correlations between the different parameters studied in control individuals. A high positive correlation was observed between age and D-Dimer values (E).

DISCUSSION

This study shows that patients with COVID-19 have elevated serum D-Dimer and CRP values when compared to healthy controls. Analogously, the values of these two molecules from patients who died were highly increased when compared with the values of patients who survived this disease. Previous studies (3,17-20) have demonstrated increased D-Dimer and CRP during COVID-19. This study reflects this finding in both surviving and deceased patients, with the latter having higher values than the surviving group of patients, suggesting that the intensity of the response of these molecules is a predictive factor in causing severity and death in COVID-19 patients. A salient fact in this study is related to the increased age of the patients who died. It has been reported that advanced age is a predisposing factor for severity in patients with COVID-19 (21), a fact that is reflected in the deceased patients in this study. In the hyperinflammatory state (cytokine storm) during COVID-19, elevated amounts of proinflammatory cytokines and biomarkers are produced, which are responsible for cardiopulmonary collapse and systemic failure of various organs (22,23).

In this study, three parameters were analyzed to measure their predisposing factor to the severity of SARS-CoV-2 infection. D-Dimer, CRP, and platelets. CRP is an acute-phase inflammatory protein produced by the liver that can be elevated in various conditions including systemic inflammation (24). This protein indicates inflammation and can cause deleterious effects during COVID-19. Thus, its elevation may be directly related to the reported damage in COVID-19 or by inducing the production of other effector molecules (3). There is a discrepancy regarding serum CRP values as a predictor of severity in COVID-19. Studies are based on the cutoff point value to establish a predictive value of the severity of CRP levels. Meta-analysis studies report that a cutoff of ≥10 mg/L has a diagnostic value for the severity of COVID-19 (18). However, there are inconsistencies according to the cutoff used in the analyses (25-28). A wide range of cutoffs has been reported to relate to COVID-19 severity (1000 to > 3 mg/L) (18,25,28,29), reflecting the need to obtain an optimal range of CPR cutoff value for severity prediction in COVID-19. In our study, the CRP values in patients who survived had a mean of 49.62 mg/L, well above the values of healthy individuals (4.59 mg/L). In patients who died, they had a mean of 196.1 mg/L, well above the values of survivors (49.62 mg/L), suggesting that high CRP values are related to the mortality rate. However, several factors can alter CRP levels even during COVID-19. These factors include age, sex, smoking, obesity, lipid levels, blood pressure, and liver damage (24). Related to this, the highest values found in this study were in patients who died of COVID-19 and who were the oldest, suggesting that the combination of advanced age and high CRP levels are predictive of mortality in this disease. Previous studies have reported that older age is a condition for increased severity of COVID-19. Studies of the immune system in older individuals found alterations in both the adaptive and innate immune systems. During old age, the adaptive immune system is depressed in its functions. However, the innate system is proinflammatory, producing a state of chronic inflammation. This inflammatory state may be related to the severity of SARS-CoV-2 disease. In addition, elderly people may be deficient in vitamin D, an anti-inflammatory agent important against the inflammation present in COVID-19 (21,30,31).

In this study, D-Dimer was also elevated and associated with the severity of COVID-19. Overall, patients who survived COVID-19 presented a mean of 0.71 μg/mL compared to the mean of healthy individuals (0.30 μg/mL). However, the highest values were found in patients who died (2.55 μg/mL), suggesting the severity predictive value of high levels of D-Dimer. This further supports the hypothesis that SARS-CoV-2 infection induces alterations in the coagulation system that may lead to hypercoagulability, inducing thromboembolic phenomena and disseminated intravascular coagulation (17,19). The D-Dimer cutoff is not fully established in COVID-19; however, the International Society of Thrombosis and Hemostasis (ISTH) guideline suggests that a 3- to 4-fold elevation of D-Dimer may imply increase thrombus production (20). In the findings of this study, patients with COVID-19 had a 2.36-fold increase over the values of healthy individuals.

Still, patients who died had an 8.50-fold increase over normal values and a 3.59-fold increase over those who survived. These data suggest that in the death of patients with COVID-19 in this study, coagulation abnormalities may have played an important role. Our findings are similar to previous reports where high values of D-Dimer, CRP, and leukocytes were found in patients who died of the disease compared to survivors (32).

Platelets, which represent an important element in coagulation, did not vary significantly in the different groups studied.

The association of the studied parameters (CRP, D-Dimer, platelets, and age) in surviving patients, deceased patients, and healthy controls were measured by correlation studies (Pearson). Interestingly, the surviving patients presented a higher number of positive correlations (4 out of 6) compared to the deceased patients (1 out of 6) and healthy controls (1 out of 6). Thus, CRP production is related to D-Dimer production and age to CRP and D-Dimer production in COVID-19 survivors. These possible associations have been previously reported in COVID-19 (7,8,18,33). However, inexplicably, they are not present in patients who died or in normal controls. This discrepancy in the presence of correlations has been reported by others, who report high positive correlations between CRP and circulating leukocytes in patients who survived the disease compared to the lack of correlation with those who died (32). Despite the importance of age in patients who died (older), there was no correlation between age and any of the parameters studied, except for the correlation between D-Dimer and platelets. The reason for this lack of correlation between patients who survived and those who died is not known. However, discrepancies between CRP and D-Dimer in patients with pulmonary thromboembolism have been reported, suggesting that these two parameters may lose their association (34).

From the clinical point of view, high CRP and D-Dimer values may be useful as predictors of severity, even mortality. It is difficult to define the cutoff of these parameters since a wide range of them has been reported, but generally, high levels of CRP and D-Dimer are alarm signs. The finding of loss of association between CRP and D-Dimer that can be observed in surviving patients but not in deceased patients may constitute another alarm sign. Both D-Dimer and CRP levels, in addition to being predictive biomarkers of severity, can also be used to monitor the improvement of COVID-19.

This study has several limitations, some of which correspond to the sample size examined and chosen, which limits the ability to apply the conclusions to other populations. The information collected retrospectively was consistent with the digital medical records, although they were exposed to biases in data entry. The research was conducted at the beginning of the pandemic, when the behavior of the virus variants that impacted the population was not yet known, making it difficult to monitor and supervise each indicator, considering the emergency circumstances in which they occurred. These patients were hospitalized. Although significant associations with disease severity were found, a multicenter study with a larger number of participants is needed to replicate our findings in a large national territory.

CONCLUSIONS

In conclusion, patients with COVID-19 had elevated serum D-Dimer and CRP values compared to healthy controls, especially in patients who died. This study shows the importance of D-Dimer and CRP in the pathophysiology of COVID-19 and a possible predictive value for severe disease progression.

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