Biochemical changes in patients with COVID-19

Alterações bioquímicas de pacientes com COVID-19

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Abstract

Objective: To identify the biochemical alterations of patients with moderate and severe COVID-19 and the predictors of severity in those who progressed from the moderate to the severe stage.

Methods: This is a prospective cohort study with 709 patients hospitalized with a confirmed diagnosis of COVID-19 and moderate and severe illness. It was carried out in a university hospital of medium and high complexity, in the state of São Paulo, from April 2020 to December 2021. Data collected from medical records were laboratory tests and clinical progression of patients. In the descriptive analysis, absolute frequency, percentage, mean and standard deviation were used. Pearson's chi-square, Fisher's exact, Mann-Whitney or Student's t tests were used to compare the differences between the moderate and severe groups. The significance level adopted was 0.05.

Results: The mean age was significantly higher in severe patients than in moderate ones ($p<0.001$). Hemoglobin and platelet values were statistically lower upon admission in the group of critically ill patients, C-reactive protein and D-dimer higher ($p<0.001$). The number of deaths was significantly higher in patients who were hospitalized in a serious condition ($p<0.001$) and we also found that hemoglobin and platelets were below the reference values at hospitalization in this group. Of the 533 patients who were hospitalized in a moderate condition, 38 progressed to a severe condition.

Conclusion: The results show the importance of clinical assessment of biochemical variables at the time of admission as predictors of severity. The findings reported in this investigation corroborate data from the literature and can elucidate early interventions for better management of patients from the moment of hospitalization.

Resumo

Objetivo: identificar as alterações bioquímicas dos pacientes com apresentação moderada e grave da doença Covid-19 e as preditivas de gravidade nos que evoluíram do estagio moderado para o grave.

Métodos: Estudo de coorte prospectivo com 709 pacientes internados com diagnóstico confirmado de COVID-19 e apresentação moderada e grave da doença. Foi realizado em um hospital universitário de média e alta complexidade do estado de São Paulo, no período de abril de 2020 a dezembro de 2021. Os dados coletados dos prontuários foram exames laboratoriais e evolução clínica dos pacientes. Na análise descritiva, foi utilizado frequência absoluta, percentual, média e desvio padrão. Os Testes do Qui-Quadrado de Pearson, Exato de Fisher, Mann-Whitney ou t de Student foram utilizados para comparar as diferenças entre os grupos dos moderados e graves. O nível de significância adotado foi de 0,05.

Resultados: A média de idade foi significantemente maior nos pacientes graves em relação aos moderados ($p<0,001$). Os valores da hemoglobina e plaquetas foram estatisticamente menores na internação no grupo

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dos pacientes graves, proteína C-reativa e D-Dímero, maiores (p<0,001). O número de óbitos foi significantemente maior nos pacientes que foram internados em estado grave (p<0,001) e verificamos também que a hemoglobina e plaquetas estavam abaixo dos valores de referência na internação deste grupo. Dos 533 pacientes que internaram em estado moderado, 38 evoluiram para quadro grave.

Conclusão: Os resultados mostram a importância da avaliação clínica das variáveis bioquímicas no momento da internação como preditivas de gravidade. Os achados reportados nesta investigação corroboram com dados da literatura e podem elucidar intervenções precoces para melhor manejo dos pacientes desde o momento da internação.

Resumen

Objetivo: Identificar las alteraciones bioquímicas de los pacientes con cuadro moderado y grave de la enfermedad de COVID-19 y las predictivas de gravedad en los que evolucionaron de nivel moderado a grave.

Métodos: Estudio de cohorte prospectivo con 709 pacientes internados con diagnóstico confirmado de COVID-19 y cuadro moderado y grave de la enfermedad. Fue realizado en un hospital universitario de complejidad mediana y alta en el estado de São Paulo, durante el período de abril de 2020 a diciembre de 2021. Los datos obtenidos a partir de las historias clínicas fueron pruebas de laboratorio y evolución clínica de los pacientes. En el análisis descriptivo se utilizó frecuencia absoluta, porcentaje, promedio y desviación típica. Para comparar las diferencias entre los grupos de los moderados y graves se utilizaron las pruebas χ^2 de Pearson, exacta de Fisher, Mann-Whitney o t de Student. El nivel de significación adoptado fue de 0,05.

Resultados: El promedio de edad fue considerablemente más alto en los pacientes graves en relación con los moderados (p<0,001). Los valores de la hemoglobina y de las plaquetas fueron estadísticamente inferiores en la internación en el grupo de los pacientes graves, proteína C reactiva y dímero D, superiores (p<0,001). El número de defunciones fue considerablemente más alto en los pacientes que ingresaron en estado grave (p<0,001) y verificamos también que la hemoglobina y las plaquetas estaban por debajo de los valores de referencia en la internación de este grupo. De los 533 pacientes que ingresaron en estado moderado, 38 evolucionaron hacia cuadros graves.

Conclusión: Los resultados muestran la importancia de la evaluación clínica de las variables bioquímicas en el momento de la internación como predictivas de gravedad. Los resultados informados en esta investigación confirman los datos de la literatura y pueden esclarecer intervenciones tempranas para un mejor manejo de los pacientes desde el momento de la internación.

Introduction

Research in several countries was carried out with the aim of seeking answers from the natural history of COVID-19, for the rapid confrontation and monitoring of cases of SARS-CoV-2 infection, which devastated different peoples and cultures around the world.[1]

In Brazil, the first case of COVID-19 was reported on February 26, 2020, with the first death recorded in March of the same year. Since then, the disease numbers, according to official data, add up to 659,227 deaths and 29,857,641 confirmed cases until March 29, 2022, with a lethality rate of 2.2%, as disclosed by Johns Hopkins University.[2]

The Brazilian National Contingency Plan, released by the Ministry of Health, has provided guidelines for controlling the pandemic, based on the World Health Organization (WHO) recommendations, which considers the scientific evidence generated in countries' publications, in addition to the experience accumulated with previous public health emergencies.[3]

Several studies have described sociodemographic data, clinical and biological characteristics of patients with COVID-19 and radiological or pathological findings associated with COVID-19.[4]

People infected with the new human coronavirus (severe acute respiratory syndrome coronavirus 2 [(SARS-CoV-2]) may present signs and symptoms in different degrees of intensity. The disease may present three distinct phases: mild, characterized by initial infection; moderate, in which pulmonary involvement occurs; and severe, which is when systemic hyperinflammation occurs.[5]

COVID-19 clinical management assessment is guided by disease severity. If findings at initial assessment suggest moderate or severe illness, hospitalization is required. Testing in hospitalized patients should include a complete blood count, a comprehensive metabolic panel, C-reactive protein (CRP) testing, and lung computed tomography (CT). However, it is worth mentioning that, according to the Brazilian Society of Pulmonology and Tisiology recommendations, CT should not be used in screening of COVID-19 in asymptomatic patients, and should only be considered in symptomatic and hospitalized patients or in very specific clinical situations.[6]

Faced with such an abrupt pandemic, the prognostic factors of the disease are still being investigated. Although most of published studies were conducted with isolated samples and a small number, initially,

perspectives and steps for consensus on risk factors for fatal outcomes are already being outlined.[7]

Recent studies have shown that, in addition to dyspnea, hypoxemia and acute respiratory distress, lymphopenia and cytokine storm are also important clinical features in patients with severe SARS-CoV-2 infection.[8]

A study published in 2021 looked at the relationship between cytokine storm and disease progression. Rapid viral replication in the early stages of infection results in an exacerbated pro-inflammatory response, with increased release of cytokines, generating a severe condition of hyperinflammation secondary to COVID-19 infection, often associated with a worse prognosis. The exacerbated response with pro-inflammatory hypercytokinemia, in the so-called cytokine storm, can progress with acute respiratory distress syndrome (ARDS) and multiple organ failure.[9]

Laboratory findings in hospitalized patients may include lymphopenia and elevated D-Dimer, lactate dehydrogenase, CRP, and ferritin levels. Findings associated with poor outcomes in some series include increased white cell count with lymphopenia, prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, D-Dimer, interleukin-6, CRP, and procalcitonin.[10-12]

Given the above on SARS-CoV-19 infection severity, in a pandemic scenario, we were motivated to investigate, through a prospective cohort, biochemical alterations that contributed to progression of mild to severe illness and with the survival or death outcomes. The results of this study aim to contribute to knowing the factors of disease progression, its prognosis, enabling better clinical management and care to control the disease seriousness.

This study aimed to identify the biochemical alterations in patients with moderate and severe illness and predictors of severity in those who progressed from moderate to severe.

Methods

This is a prospective cohort study, carried out between April 2020 and December 2021, in a university hospital of medium and high complexity in the state of São Paulo, a reference in teaching and research. It was suitable for the treatment of patients with positive diagnoses for COVID-19 during the pandemic and treated around 1,500 patients with a positive diagnosis for the disease.

The population consisted of all patients who were hospitalized during the study period with a diagnosis confirmed by Reverse Transcriptase reaction tests followed by positive Polymerase Chain Reaction (RT-CRP) for COVID-19, with moderate and severe illness. Thus, the sample consisted of 709 patients.

Data from patients admitted to Intensive Care Units or medical clinic units were prospectively collected by two previously trained researchers, which allowed double-checking at all stages of data collection.

The biochemical variables analyzed were hemoglobin, leukocytes, platelets, creatinine, D-Dimer and CRP on the first and seventh day of hospitalization. This time interval limit was adopted due to the fact that the studied population had records of the variables in this period. For this study, the need for endotracheal intubation during hospitalization was defined as a criterion for the transition from moderate to severe state, and 100% of patients classified as severe were those who required mechanical ventilation soon after hospitalization.

Patients, aged ≥18 years, with positive CRP for COVID-19 and moderate or severe illness were included. Patients under 18 years of age, those who had a negative CRP for the disease and medical records with insufficient data for the variables of importance to the study were excluded from the sample. Approximately 5% of a total of 747 medical records were not included in data collection.

Moderate illness: flu-like illness that presents dyspnea or severe signs and symptoms that require some ventilatory support, and may or may not present comorbidities that contraindicate home isolation, requiring hospitalization.[4]

Severe illness: flu-like syndrome that presents signs and symptoms of severity, such as deficit in the respiratory system, severe sub/intercostal retraction or central cyanosis, deficit in the cardiovascular sys-

tem, signs and symptoms of hypotension (arterial hypotension with systolic below 90 mmHg and/or diastolic below 60 mmHg) or decreased peripheral pulse with indication for treatment in the Intensive Care Unit (ICU), due to the high risk of mortality they present.[4]

The chosen biochemical variables of all patients with moderate and severe COVID-19 and those who progressed from moderate to severe illness with the discharge or death outcome were analyzed and stored in a Microsoft Excel 2003 spreadsheet. In the descriptive analysis, the data were presented using absolute frequencies and percentages, means and standard deviations.

Pearson's chi-square test or Fisher's exact test was used to compare differences between patients with and without progression to severe illness. The Mann-Whitney or Student's t test was used for quantitative variables to compare the differences between the group with moderate and severe illness. The significance level established was 5%. For data analysis, the results of laboratory tests were compared according to the state of health they were in and whether they suffered a moderate or severe alteration.

This study was approved by the Research Ethics Committee (REC) of the *Universidade Federal de São Paulo* (UNIFESP), under Opinion 4.077.381 and CAAE (*Certificado de Apresentação para Apreciação* Ética - Certificate of Presentation for Ethical Consideration) 32381120.6.0000.5505, in compliance with the regulations of the Brazilian National Health Council (CNS).[13]

Results

We analyzed 709 medical records of patients over 18 years of age with positive Polymerase Chain Reaction for COVID-19. Of these, 571 (80.5%) had moderate illness at the time of admission and 138 (19.4%) had severe illness. The transition time from moderate to severe status of the 38 patients who required intubation was 4.9 days (± 2.3). In Table 1, we presented and compared the differences between moderate and severe patients using demographic characteristics, days of hospitalization and outcomes of patients admitted with moderate conditions and those admitted with severe conditions. The mean age of moderate patients was 56 (±15.27) years and most were male. In the group of severely obese patients, the mean age was 61 (±14.45) years, and the majority was male (65.22%).

Table 1. Demographic characteristics, days of hospitalization and outcomes of groups of patients with moderate or severe conditions hospitalized with COVID-19 (n=709)

	Moderate n=571(80.5)	Severe n=138(19.4%)	p-value
Age (years)			
Mean (SD)	56.16(15.27)	61.99(14.45)	<0.001***
Sex			
Male n (%)	307(57.60)	90(65.22)	0.105*
Female n (%)	226(42.40)	48(34.78)	
Length of stay			
Mean (SD)	8.12(5.09)	16.08(12.27)	<0.001****
Outcome, n (%)			
Outcome	523(98.12)	86(62.32)	<0.001*
Death	10(1.88)	52(37.68)	

*Chi-square test; ***Student's t test; ****Mann-Whitney; SD: standard deviation

The mean age of severe patients was significantly higher than that of moderate patients (p<0.001). Males were more prevalent in both groups studied. It is observed that the average number of days spent in hospital in the severe group was twice as long as in the moderate group. The prevalent comorbidities in the severe and moderate group were hypertension and diabetes mellitus. The number of deaths was statistically significant in patients who were hospitalized in severe condition (p<0.001). In Table 2, we present the values of the biochemical analyzes of moderate and severe patients on the 1st and 7th day of hospitalization.

It is observed that hemoglobin values decreased by 7th day in both groups, with the statistically significant difference being lower in the group of severe compared to moderate (p<0.001). Leukocyte values were statistically significant on the 1st (p<0.001) and 7th day (p<0.001) in the group of hospitalized in severe condition. Regarding platelet values, the group of severe were statistically significant (p<0.001) in both 1st and 7th day of hospitalization when compared to the moderate group. Creatinine values were significant in the group of severe patients in both 1st and 7th days (p<0.001). It is noteworthy that in

Table 2. Distribution of biochemical analyses on the 1st and 7th day of hospitalization of moderate and severe patients with COVID-19 (n=709)

	Moderate n(%) 571(80.5)	Severe n(%) 138(19.4)	p-value
Hemoglobin (g/dL)/Normal range: 12 to 15.5 g/dL			
Day 01, Mean (SD)	13.11 (2.13)	12.67 (2.86)	0.082****
Day 07, Mean (SD)	12.11 (2.16)	11.32 (2.52)	<0.001****
Leukocytes (cell/mm³)/Normality range: 3,500 to 10,500 cell/mm³			
Day 01, Mean (SD)	8618 (9874.88)	9990(5788.29)	<0.001****
Day 07, Mean (SD)	8257 (4810.59)	12784 (8439.72)	<0.001****
Platelets (cell/mm) /Normality range: 150.000 to 450,000 cell/mm			
Day 01, Mean (SD)	224240 (95579.36)	190276 (87865.66)	<0.001****
Day 07, Mean (SD)	306565 (126416.90)	237816 (117697.80)	<0.001****
Creatinine (mg/dL)/Normal range: 0.5 to 0.9 mg/dL			
Day 01, Mean (SD)	1.689(1.91)	2.401 (2.63)	<0.001****
Day 07, Mean (SD)	1.409 (1.49)	3.212 (2.73)	<0.001****
CRP (mg/L) /Normality value: ≤ 1 mg/L			
Day 01, Mean (SD)	105.65 (78.35)	161.01 (123.95)	<0.001****
Day 07, Mean (SD)	50.67 (53.31)	155.01 (139.75)	<0.001****
D-Dimer Normality range: < 0.5			
Day 01, Mean (SD)	2.254 (3.19)	3.675 (4.72)	<0.001****
Day 07, Mean (SD)	2.486 (3.38)	5.807 (5.66)	<0.001****

***Student's t test; ****Mann-Whitney; SD: standard deviation; CRP: C-reactive protein

Table 3. Distribution of biochemical analyses on the 1st and 7th day of hospitalization of moderate and severe patients with COVID-19 (n=571)

	Moderate n(%) 533(93.3)	Moderate-severe n(%) 38(6.6)	p-value
Hemoglobin (g/dL)/Normal range: 12 to 15.5 g/dL			
Day 01, Mean (SD)	13.11 (2.13)	12.69 (2.54)	0.299****
Day 07, Mean (SD)	12.11 (2.16)	11.59 (1.90)	0.057****
Leukocytes (cell/mm³)/Normality range: 3,500 to 10,500 cell/mm³			
Day 01, Mean (SD)	8618 (9884.21)	8640 (4230.65)	0.265****
Day 07, Mean (SD)	8261 (4816.35)	13402 (16089.57)	<0.001****
Platelets (cell/mm) /Normality range: 150.000 to 450,000 cell/mm			
Day 01, Mean (SD)	224240 (95579.36)	182671 (77235.45)	0.006****
Day 07, Mean (SD)	306565 (126416.90)	276529 (123494.10)	0.139****
Creatinine (mg/dL)/Normal range: 0.5 to 0.9 mg/dL			
Day 01, Mean (SD)	1.68 (1.91)	1.50 (1.11)	0.915****
Day 07, Mean (SD)	1.40 (1.49)	2.33 (2.20)	0.158****
CRP (mg/L) /Normality value: ≤ 1 mg/L			
Day 01, Mean (SD)	105.65 (78.35)	133.47 (94.98)	0.101****
Day 07, Mean (SD)	50.67(53.31)	126.20 (97.57)	<0.001****
D-Dimer Normality range: < 0.5			
Day 01, Mean (SD)	2.25 (3.19)	3.40 (4.23)	0.001****
Day 07, Mean (SD)	2.48 (3.38)	4.41 (4.38)	<0.001****

***Student's t test; ****Mann-Whitney; SD: standard deviation; CRP: C-reactive protein

both groups, creatinine values were already high at the time of admission in relation to the reference values (0.5 to 0.9 mg/dl), which could suggest renal impairment right at the beginning of SARS-CoV-2 infection. CRP (p<0.001) and D-Dimer (p<0.001) test values showed statistical significance in the group of critically ill patients both on the 1st and 7th day of hospitalization in relation to the reference values. It is also worth mentioning here that both CRP and D-Dimer values were already high on the day of admission, in relation to the reference values (≤ 1 mg/L) and (<0.5), respectively. Table 3 shows the values of the biochemical analyzes carried out on the 1st and 7th day of hospitalization of patients in a moderate state who progressed to severe illness, according to the criteria established in the protocol of this study, are presented.

Hemoglobin values were statistically and significantly lower on the 7th day in patients who went from moderate to severe (p=0.05). Leukocyte values were significantly higher in patients who worsened on the 7the day of hospitalization (p<0.001). Platelet values were statistically significantly lower in patients who went from moderate to severe illness on the 1st day of hospitalization (p=0.006). Although creatinine values were high in relation to the reference value, no statistical difference was detected between the 1st and 7the day of hospitalization. CRP values were statistically and significantly higher in patients who worsened on the 7the day (p<0.001), and it is observed that on the 1st and 7th day, values were above the reference value (≤ 1 mg/L). D-Dimer values were statistically significantly higher in patients who worsened, both on the 1st and 7th day of hospitalization (p=0.001 and p<0.001, respectively). Patients who progressed from moderate to severe presented leukocytosis, thrombocytopenia, elevated CRP and D-Dimer levels upon admission. Table 4 presents the distribution of biochemical analyzes performed on the 1st and 7th day of hospitalization, comparing moderate patients with discharge and death.

Hemoglobin values were statistically and significantly lower in patients who died, on the 7th days,

Table 4. Distribution of biochemical analyzes of patients with COVID-19, on the 1st and 7th day of hospitalization in the moderate and severe phases with discharge or death outcome (n=571)

	Survival n(%) 553(96.8)	Deaths n(%) 18(3.1)	p-value
Hemoglobin (g/dL)/Normal range: 12 to 15.5 g/dL			
Day 01, Mean (SD)	13.16(2.10)	12.32(2.49)	0.152****
Day 07, Mean (SD)	12.00(2.22)	9.94(2.98)	0.053****
Leukocytes (cell/mm³)/Normality range: 3,500 to 10,500 cell/mm³			
Day 01, Mean (SD)	8527(9558.03)	12177(10363.66)	0.068****
Day 07, Mean (SD)	8384(4922.90)	18256(22260.26)	0.001****
Platelets (cell/mm) /Normality range: 150.000 to 450,000 cell/mm			
Day 01, Mean (SD)	222230 (94537.59)	171875 (80698.31)	0.020****
Day 07, Mean (SD)	308003 (129246.6)	180700 (66179.97)	<0.001****
Creatinine (mg/dL)/Normal range: 0.5 to 0.9 mg/dL			
Day 01, Mean (SD)	1.667(1.88)	2.035(1.42)	0.079****
Day 07, Mean (SD)	1.624(2.03)	2.818(1.68)	0.003****
CRP (mg/L) /Normality value: ≤ 1 mg/L			
Day 01, Mean (SD)	106.38(79.79)	104.23(75.34)	0.896****
Day 07, Mean (SD)	49.25(52.51)	185.24(128.84)	0.003****

****Mann-Whitney; : Mean; SD: standard deviation; CRP: C-reactive protein

and below the normal reference value (12 to 15.5 g/dl). Leukocyte values were statistically and significantly higher in patients who died, when compared to those who were discharged on the 7th day of hospitalization (p=0.001). Platelet values were statistically significantly lower in patients who died on the 1st and 7th day of hospitalization (p<0.02 and p<0.001). Creatinine values were statistically and significantly (p=0.003) higher in the group of patients who died on the 7th day of hospitalization. CRP values were statistically and significantly higher in patients who died on the 7th day (p=0.003), but both on the 1st and 7th day, the values are above the reference value (≤ 1 mg/L).

Discussion

SARS-CoV-2 transmission occurs mainly through contact with respiratory droplets from infected patients, and the disease mainly affects the respiratory, cardiovascular, gastrointestinal and neurological systems.[14,15]

Laboratory tests provide critical support for the proper clinical management of COVID-19 from screening to diagnosis, prognosis and monitoring. There is increasing evidence of significant differences in clinical, pathologic, and radiologic patterns between COVID-19 and non-COVID-19 viral interstitial pneumonias.[16]

In the present study, patients admitted to Hospital São Paulo with a diagnosis of SARS-CoV-2 (COVID-19) infection, confirmed by RT-CRP tests, classified as moderate or severe according to their clinical status upon admission. In this study, it was possible to observe the possibilities of aggravation for the disease, making the transition from moderate to severe or the improvement of clinical condition, and it was also possible to verify the predictive variables for the outcomes of discharge or death in the two groups analyzed.

The mean age of patients who presented the disease, initially classified as moderate, was 56 (±15.27) years. In the group of patients who were hospitalized as serious, the mean age was 61 (±14.45) years, with male prevalence in both groups. The mean age of severe patients was significantly higher than that of moderate patients (p<0.001). In a study carried out in Brazil, with an analysis of 250,000 hospitalizations due to COVID-19, the mean age was 60 years (SD17); however, in northeastern Brazil, the authors found a higher proportion of patients aged 80 years or older affected by SARS-CoV-2 infection.[17]

In our series, important complications observed in patients infected with SARS-CoV-2 mainly included signs and symptoms affecting the respiratory system, such as respiratory failure and ARDS.[18,19] In this scenario, which suggests an increase in the length of hospital stay, there is mainly mechanical ventilation support therapy, especially in ICUs, which demand high-cost maintenance of the system.[19] For this study, the need for intubation was defined as a criterion for the transition from moderate to severe status; thus, 100% of patients classified as severe required mechanical ventilation.

In this study, the length of hospital stay observed in the group of severely ill patients was twice as long as the length of stay in the group of moderate patients. Such data are corroborated with the findings found in a study carried out in the United Kingdom, to estimate the length of stay of patients

with COVID-19, whose results showed a permanence rate of 17.3 days in the ICU to 9.1 days for those who did not need intensive care.[20]

The outcome of death was significantly higher among the group of patients who were hospitalized with the most severe form of the infection (p<0.001), possibly due to late diagnosis and treatment. Most deaths occurred in accordance with data in the literature, in which a higher incidence is observed in the adult population, however, mortality is higher in older adults.[21]

In the biochemical analyses, we observed that the hemoglobin values decreased between the 1st and 7th day in the moderate and severe groups. Furthermore, the difference was statistically smaller on the 7th day in the severe group compared to the moderate group (p<0.001). In patients who went from moderate to severe, hemoglobin values were statistically significantly lower on the 7th day (p=0.05). In patients who died on the 7th day, the values were statistically and significantly lower (p=0.05).

Another study, which compared the results of laboratory tests on blood samples from patients with COVID-19 and influenza, revealed that low levels of hemoglobin and hematocrit were strongly associated with severe COVID-19.[21] In this regard, a significant decrease in hemoglobin values in patients with COVID-19 may indicate progression to a more severe illness, since the drop was more intense in patients who required intensive care.[22]

In this study, leukocyte values were significantly higher on the 1st (p<0.001) and 7th day (p<0.001), comparing moderate and severe patients and were also statistically and significantly higher in patients who worsened on the 7th day of hospitalization (p<0.001) and statistically and significantly higher in patients who died when compared to those who were discharged on the 7th day of hospitalization (p<0.001).

Leukocytosis became more evident in both groups throughout the hospital stay, suggesting that the white blood cell count upon admission has the potential to be used as a prognostic indicator. This observation seems to be in line with other studies, especially when lymphocytes are reduced.[23, 24]

Leukocyte levels upon admission of a patient with COVID-19 may indicate illness severity, and may be associated with bacterial infection, and it may be useful to monitor hemoglobin, LDH and D-Dimer levels during hospitalization to assess disease progression.[25]

The identified value of platelets was statistically significant, being lower (p<0.001) in the group of critically ill patients both on the 1st and 7th day of hospitalization. In patients who went from moderate to severe, values were statistically significantly lower on the 1st day of hospitalization (p=0.006) and we found significantly lower values in patients who died on the 7th day of hospitalization (p<0.001). Consistent with the findings of a meta-analysis conducted in 1,779 patients with COVID-19, in which the authors revealed that a low platelet count was associated with a five-fold increased risk of severe illness, and an even lower platelet count, it was associated with mortality in these patients.[26]

Another study indicates that, in severe acute respiratory syndrome (SARS), the combination of viral infection and mechanical ventilation causes endothelial damage, triggering platelet activation, aggregation and thrombosis in the lung, causing high consumption of platelets;[27] however, the same mechanism has yet to be defined in COVID-19. Thrombocytopenia is thought to have multifactorial causes. The literature reports that, among the hematological alterations present in COVID-19, disseminated intravascular coagulation was more observed in patients who died when compared to survivors (71.4% x 0.6%).[17]

Creatinine values were statistically significantly higher in the group of critically ill patients, both on the 1st and 7th day (p<0.001). In the group of patients who made the transition from moderate, no statistical difference was detected between the 1st and 7th day, although values are higher than reference values and were statistically significantly (p=0.003) higher in the group of patients who died on the 7th day of hospitalization. In both groups, the values were already high upon admission in relation to reference values (0.5 to 0.9 mg/dl).

Creatinine is a waste product from the breakdown of phosphocreatine from muscle metabolism.

About 98% of creatine remains in the muscle, and 1.6% to 1.7% of this is converted to creatinine daily, which is excreted by the kidney.[28] Therefore, creatine release and production by the muscle is basically constant.

This creatinine generation rate is directly proportional to muscle mass, varies according to sex, ethnicity, and age, and is affected by circumstances that cause muscle loss.[29] Creatinine is freely filtered by the glomerulus, and is not metabolized or absorbed by the kidney. However, the amount of urinary creatinine that comes from tubular secretion is approximately 25%, being more expressive the lower the glomerular filtration rate (GFR). The amount secreted depends on the serum concentration and the individuals, which is inconstant and can be altered by drug effects.[28]

Patients with elevated baseline serum creatinine showed increased levels of procalcitonin, aspartate aminotransferase and lactose dehydrogenase, higher white blood cell counts and lower lymphocyte and platelet counts, in addition to developing some abnormalities of coagulation pathway, such as prolonged activated partial thromboplastin time and higher D-Dimer.[30]

CRP values were statistically significantly higher in the group of critically ill patients on the 1st and 7th day ($p<0.001$). Values were statistically significantly higher on the 7th day in patients who worsened ($p<0.001$), statistically significantly higher in patients who died on the 7th day ($p=0.003$). In all groups, the values were already high upon admission in relation to reference values (≤ 1 mg/L).

One of the central features of severe COVID-19 is the host's hyperinflammatory response, due to the so-called cytokine storm, defined as a systemic and uncontrolled inflammatory response, resulting from the release of large amounts of pro-inflammatory cytokines resulting from the activation of natural cellular immunity. Increased levels of several inflammatory biomarkers, including CRP and LDH, have been reported in patients with COVID-19.[31] Among inflammatory biomarkers, CRP levels significantly increase in the early stage of the disease, and a positive correlation between increased CRP levels and disease severity has also been described.[8] Overall, the available evidence suggests that, in the early stage of COVID-19, CRP levels may reflect disease severity.[31]

D-Dimer values were statistically significantly higher in the group of critically ill patients on the 1st and 7th day ($p<0.001$). They were also statistically significantly higher in patients who worsened, both on the 1st and 7th day of hospitalization ($p=0.001$ and $p<0.001$, respectively). In both groups, they were higher in relation to reference values (<0.5).

Increased D-Dimer levels found in patients with severe COVID-19 reflect changes in coagulation[32] as well as being associated with an increased risk of ICU admission and mortality.[33] When D-Dimer values were more altered during patients' hospitalization, the severe group had significantly higher values, suggesting that increased D-Dimer levels may be associated with the trend of clinical worsening and the need for ICU admission.

The fact that the study was carried out based on data from electronic medical records, the loss was only 5% of the total number of medical records due to lack of information necessary for the completeness of the eligible variables. Data entry was double checked and, in the event of typing errors, they were corrected. In this way, we consider the reliability of the results obtained in this research carried out in a secondary source.

Some limitations should be pointed out: Data collection should receive special attention both in an attempt to obtain data in a more complete way and with greater standardization, as errors arising from the notes of this collection are important to be scored. We also highlight the completion of medical records by health professionals who were not part of the study.

For the health and nursing areas, we highlight that the study shows the importance of early assessment of biochemical changes that may suggest predicting severity and possible disease progression. Monitoring these changes would facilitate better management of care such as the need for intensive care, respiratory support and adequate forecast of human resources.

Conclusion

This study showed that age was predictive of severity. Length of stay was determined according to disease severity. Upon admission, D-Dimer levels were elevated even though the infection was in the early stages. With disease progression, there was a significant increase in this marker. For the health and nursing areas, we emphasize that the early assessment of biochemical alterations can suggest a prediction of severity and possible disease progression, which would facilitate better care management. The most significant alterations found that suggest severity were hemoglobin, leukocytes, platelets, creatinine, CRP and D-Dimer.

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Collaborations

Barbosa DA, Zanão PL, Higino GS, Grandi JL, Belasco AGS and Fonseca CD collaborated with the study design, data analysis and interpretation, article writing, relevant critical review of the intellectual content and approval of the final version to be published.

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