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SEÇÃO: ARTIGO ORIGINAL

Effect of the SARS-CoV-2 viral load on hematological and biochemical parameters

Efeitos da carga viral do SARS-CoV-2 nos parâmetros hematológicos e bioquímicos

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Abstract

Objective: the viral load is determined by the cycle threshold (Ct), which is inversely proportional to the amount of target sequences present in the sample. In various viral diseases, the induction of inflammatory cytokines is strongly correlated with the viral load. However, the viral kinetics of SARS-CoV-2 remain poorly characterized, and its association with disease progression remains controversial. This study aimed to understand the correlation between the SARS-CoV-2 viral load and the biochemical and hematological markers in COVID-19-positive patients.

Methods: data from patients with detectable viral load for SARS-CoV-2 treated between March 2020 and May 2021 were collected between Jan/2023 and Jan/2024. Data were analyzed using Qui-square test, Student's t-test, and analysis of variance.

Results: the mean Ct values for the N and ORF1AB genes were 26.73 (±3.95) and 25.93 (±4.75), respectively. A Ct value below the mean for the N and ORF1AB genes, suggesting a higher viral load, was observed in 17.8% (n=152) and 18.4% (n=157) of the patients. The monocyte-to-lymphocyte ratio (MLR) was below the reference value for COVID-19-negative patients (P<0.0001). The C-reactive protein and ferritin levels were higher in patients with COVID-19 (P<0.05). Leucopenia (P<0.001), lymphocytopenia (P<0.001), neutropenia (P<0.001), and thrombocytopenia (P=0.003) were observed more frequently in patients with COVID-19.

Conclusion: the MLR below the reference value was more frequent observed in patients with a higher Ct value (lower viral load).

Keywords: COVID-19, RT-qPCR, biomarkers.

Resumo

Objetivo: a carga viral é determinada pelo *cycle threshold* (Ct), que é inversamente proporcional à quantidade de sequências-alvo presentes na amostra. Em várias doenças virais, a indução de citocinas inflamatórias está fortemente correlacionada com a carga viral. No entanto, a cinética viral do SARS-CoV-2 permanece pouco caracterizada e sua associação com a progressão da doença ainda é controversa. Este estudo teve como objetivo entender a correlação entre a carga viral do SARS-CoV-2 e os marcadores bioquímicos e hematológicos em pacientes positivos para COVID-19.

Métodos: os dados de pacientes com carga viral detectável para SARS-CoV-2 atendidos entre março de 2020 e maio de 2021 foram coletados entre janeiro de 2023 e janeiro de 2024. Os dados foram analisados utilizando o teste qui-quadrado, o teste t de Student e a análise de variância.

Resultados: os valores médios de Ct para os genes N e ORF1AB foram 26,73 (±3,95) e 25,93 (±4,75), respectivamente. Um valor de Ct abaixo da média para os genes N e ORF1AB, sugerindo uma carga viral mais alta, foi observado em 17,8% (n=152) e 18,4% (n=157) dos pacientes. A razão monócito-linfócito (MLR) estava abaixo do valor de referência para pacientes negativos para COVID-19 (P<0,0001). Os níveis de proteína C-reativa e ferritina encontravam-se mais altos em pacientes posi-

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tivos para COVID-19 (P<0,05). Leucopenia (P<0,0001), linfocitopenia (P<0,0001), neutropenia (P<0,0001) e trombocitopenia (P=0,003) foram observadas com mais frequência em pacientes positivos para COVID-19.

Conclusão: uma MLR abaixo do valor de referência foi observada com mais frequência em pacientes com um valor de Ct mais alto (carga viral mais baixa).

Palavras-chave: COVID-19, RT-qPCR, biomarcadores.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19 and is responsible for more than six million deaths worldwide (1). In the acute phase of the disease, alterations in the hematological and inflammatory profiles occur, which is characterized by an increase in the levels of C-reactive protein (CRP), erythrocyte sedimentation rate, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, ferritin, and D-dimer, as well as evident lymphopenia (2). Biomarkers related to COVID-19 tend to gradually increase as the clinical condition worsens (3).

The association of disease progression with the viral kinetics of SARS-CoV-2 can aid in identifying high-risk patients and improving treatment strategies (4). Viral kinetics can be observed through reverse transcription quantitative polymerase chain reaction (RT-qPCR), where the viral load is established in the exponential phase of the reaction and is determined by the cycle threshold (Ct) (5). Ct represents the point at which the emitted fluorescence corresponds to the initial RNA quantity in the sample analyzed (6). Thus, the Ct value is inversely proportional to the number of target sequences present in the sample (viral load); in other words, the more copies, the lower the Ct value (7).

There is some correlation between the viral load and the clinical evolution of the disease in hospitalized patients with COVID-19; the viral load is higher in severe cases than in non-severe cases (8). Conversely, a study conducted in New York City determined that a higher viral load at the time of hospital admission was independently associated with mortality (9).

This study aimed to understand the association between the SARS-CoV-2 viral load and the hematological and biochemical markers in COVID-19-positive patients.

Materials and methods

A retrospective study was conducted using data from the clinical laboratory database of the Military Police Hospital of the State of Goiás. The requirement for obtaining informed consent was waived due retrospective nature of the study and it was used deidentified data. The study was approved by the National Research Ethics Commission (No: 4.272.030).

The study included data collected from March 2020 to May 2021, a period of exponential increase in the number of COVID-19 cases in Brazil (10). Of the 12,648 individuals tested for SARS-CoV-2 using RT-qPCR at the Military Police Hospital of the State of Goiás, 853 were included in the study because they had undergone tests to determine complete blood count and CRP, ferritin, and D-dimer levels on the same date.

Ferritin, CRP and D-dimer were realized by Immunoturbidimetry (Mindray North America, Mahwah, NJ, USA). Reference values (RV) for ferritin were: children, 7.0–140.0 µg/L; men, 30.0–220.0 µg/L; and women, 20.0–110.0 µg/L, for CRP ≤ 8.5 mg/L and for D-dimer ≤ 600.0 ng/mL. All of them were categorized as normal or abnormal based on the RV.

Leukocyte and platelet counts were determined by impedance. The leukocytes were differentiated by optical flow cytometry and counted using a hematological counter (Celltac/MEK-7300; Nihon Kohden do Brasil). RV: Total leukocytes, 3,500–11,000/µL; lymphocytes, 800–4,000/µL; monocytes: 100–1,000/µL; neutrophils: 1,500–7,000/µL; platelets: 150,000–450,000/µL. Absolute counts were categorized as normal, if within the RV. The abnormal values were further subdivided into high (>RV) and low (<RV). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and MLR were calculated.

RNA extraction and RT-qPCR were performed for the ORF1ab and N target genes using the XG--CV19-MB-96-Mobius kit (Pinhais, Paraná, Brazil). Ct value <40 was considered RT-PCR/COVID-19 positive. Ct values were classified as "high viral load" when below the mean Ct value and "low viral load" when above the mean Ct value.

Data were tabulated and analyzed using Graph Prism (version 7 by Dotmatics), quantitative variables were analyzed using measures of central tendency. Qualitative variables were presented as absolute numbers and percentages. The chi-square test was used to verify if there was a significant association between categorical variables and analysis of variance (ANOVA) was performed to compare Ct values according to the hematological and biochemical parameters. A P-value<0.05 was considered statistically significant. Hypothesis testing was conducted using R Studio (version 4.2.1; Posit, MA, Boston for USA).

Among the 853 patients studied, a significant portion were male, and the majority fell within the age range of 18 to 65 years. The prevalence of SARS-CoV-2 infection was 33.8%, with males comprising more than half of the positive cases. In an analysis of COVID-19 positive patients, significant increases in CRP and ferritin levels were observed, exceeding the reference values in 90 (33.7%) and 183 (63.5%) cases, respectively. Furthermore, the frequency of hematological alterations was higher compared to patients without the infection. Leukopenia, lymphocytopenia, neutropenia, and thrombocytopenia were more prevalent among COVID-19 patients, indicating a significant impact of the disease on the hematological health of these individuals (**Table 1**). Approximately 89 (10.4%) of the included patients had an MLR less than the RV. Among the 89 patients, 74 (13.1%) tested negative for COVID-19 and 15 (5.2%) tested positive for COVID-19 (P = 0.0004) (Table 1).

Results

TABLE 1 – Biochemical and hematological markers in patients who tested positive and negative for COVID-19.

	Positive, n(%)	Negative, n(%)	Total, n(%)	P-value*
Total	288 (33.8)	565 (66.2)	853 (100)	
Sex female	132 (45.8)	272 (48.1)	404 (47.4)	0.52
Age, years				0.11
<18	10 (3.47)	18 (3.2)	28(3.3)	
18–65	254 (88.2)	520 (92.0)	774(90.7)	
>65	24 (8.3)	27 (4.8)	51(6)	
CPR >8.5 mg/L	90 (33.7)	132 (23.3)	222 (26.0)	0.01
D-dimer ≤600 ng/mL	228 (79.16)	451 (79.8)	679 (79.6)	0.82
Ferritin abnormal[a]	183 (63.5)	273 (48.3)	456 (53.5)	0.000
Leucocyte count, /µL				0.000
3,500–11,000	255 (88.0)	528 (93.0)	783 (91.8)	
>11,000	5 (1.7)	30 (5.3)	35 (4.1)	
<3,500	28 (9.7)	7 (1.2)	40 (4.1)	
Lymphocyte count, /µL				0.000
800–4,000	237 (82.2)	540 (95.6)	777 (91.1)	
>4,000	4 (1.4)	11 (1.9)	15 (1.8)	

TABLE 1 – Biochemical and hematological markers in patients who tested positive and negative for COVID-19. (CONT.).

	Positive, n(%)	Negative, n(%)	Total, n(%)	P-value*
<800	47 (16.3)	14 (2.5)	61 (7.1)	
MLR‡				0.000
<0.125	15 (5.2)	74 (13.1)	89 (10.4)	
0.125–2.5	273 (94.8)	491 (86.9)	764 (89.6)	
Monocyte count, /µL				0.38
100–1000	284 (98.6)	559 (98.9)	843 (98.8)	
>1000	3 (1.04)	6 (1.0)	9 (1.1)	
<100	1 (0.35)	0	1 (0.1)	
Neutrophil count, /µL				0.000
1,500–7,000	262 (90.1)	510 (86.7)	772 (90.5)	
>7,000	6 (2.1)	49 (89.1)	55 (6.4)	
<1,500	20 (76.9)	6 (1.0)	26 (3.1)	
NLR				0.02
1.75–1.875	10 (3.5)	39 (6.9)	49 (5.7)	
>1.875	158 (54.9)	262 (46.4)	420 (49.2)	
<1.75	120 (41.6)	264 (46.7)	384 (45.1)	
Platelet count, /µL				0.000
150,000–450,000	258 (89.6)	544 (96.3)	802 (94.0)	
>450,000	1(0.35)	4 (0.7)	5 (0.6)	
<150,000	27 (9.4)	17 (3.0)	44 (5.2)	
PLR				0.000
100.0–187.5	160 (55.5)	304 (53.8)	464 (54.4)	
>187.5	78 (27.1)	72 (12.7)	150 (17.6)	
<100	50 (17.4)	189 (33.4)	239 (28)	

CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.
*qui-square and‡ Fisher test. ǂNo patient presented with MLR >2.5.

The average Ct values for the N and ORF1AB genes were 26.7±3.9 and 25.9±4.8, respectively. A Ct value below the average value for the N and ORF1AB genes, which suggests a higher viral load, was observed in 152 (17.8%) and 157 (18.4%) samples, respectively. When comparing the Ct values between the group with abnormal results for inflammatory markers and the group with normal results, it was found that patients with an MLR below the RV had a lower viral load (a higher average Ct value) for both genes ($P < 0.05$) (**Table 2**).

TABLE 2 – Comparative analysis of the Ct values according to the hematological and biochemical parameters (n = 288).

	CT_N	P-value	CT_ORF1AB	P-value*
CPR		0.53		0.37
Normal	25.2±7.4		24.3±7.7	
Abnormal	25.7±6.3		25.1±6.6	
D-Dimer		0.23		0.26
Normal	25.6±7.0		24.9±7.3	
Abnormal	24.3±7.5		23.6±7.7	
Ferritin		0.69		0.79
Normal	25.2±7.2		24.5±7.5	
Abnormal	25.5±6.9		24.7±7.2	
Leucocytes		0.12		0.18
Normal	25.4±7.0		24.6±7.4	
Below	23.9±7.6		23.2±7.9	
Above	30.9±3.0		29.8±3.4	
Lymphocytes		0.78		0.91
Normal	25.4±7.3		24.6±7.6	
Below	24.9±6.3		24.2±6.6	
Above	27.1±4.3		25.6±4.7	
MLR		0.001		0.003
Normal	25.1±7.1		24.3±7.4	
Below	30.0±4.2		29.4±5.2	
Above	-		-	
Monocytes		0.62		0.67
Normal	25.3±7.1		24.5±7.4	
Below	30.1		26.7±4.1	
Above	28.015±3.8		30.1	
Neutrophils		0.09		0.08
Normal	25.4±7.2		24.6±7.5	
Below	23.5±6.2		22.2±6.3	
Above	30.7±3.7		29.8±4.4	
NLR		0.61		0.73
Normal	25.1±6.9		24.3±7.2	
Below	25.8±7.1		25.0±7.5	
Above	24.2±9.0		24.0±9.4	

TABLE 2 – Comparative analysis of the Ct values according to the hematological and biochemical parameters (n = 288). (CONT.).

	CT_N	P-value	CT_ORF1AB	P-value*
Platelets		0.35		0.40
Normal	25.5±7.0		23.7±7.3	
Below	24.0±7.8		23.3±8.2	
Above	31.6		29.8	
PLR		0.42		0.55
Normal	25.5±7.1		24.8±7.5	
Below	24.5±6.7		23.8±7.0	
Above	26.1±7.6		25.2±7.9	

CPR, C-Reactive Protein; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. * ANOVA.

Discussion

RT-qPCR using respiratory samples is recommended by the WHO for diagnosing COVID-19 (12). Its semiquantitative measure, expressed by the Ct, indicates that a high Ct value represents a low viral load (13). Studies have explored the correlation of Ct values with disease severity and outcomes (14, 15). Ct is a potential prognostic marker (8) and is associated with clinical findings and laboratory parameters (16). However, the relationship between Ct values and the hematological and biochemical markers remains controversial. In our study, there was a significant change in the inflammatory marker levels in the patients with COVID-19, which is like the findings of other studies (17, 18) and it was found that the MLR was affected by the Ct value.

Studies have used the Ct value as an indirect measure of viral load (19, 20). A study in the U.S. determined that 676/4,428 (15.3%) of the samples that tested positive for COVID-19 had Ct values below the average value, suggesting a high viral load (21). In our study, Ct values below the average for N and ORF1AB genes were observed in 152 (17.8%) and 157 (18.4%) of the samples, respectively. However, although using Ct values obtained in molecular reactions as indirect measures of SARS-CoV-2 viral loads is simple, it may have errors, such the cell or the sampled mucosal surface mass not being considered (22).

The elevated levels of CRP and ferritin observed in a significant proportion of COVID-19 patients align with existing literature that identifies these markers as indicators of the excessive inflammatory response associated with viral infection (23). Both ferritin and CRP, as acute-phase proteins, are widely described as predictors of systemic inflammation and are linked to disease severity and prognosis in conditions such as viral pneumonia (23, 24). This excessive inflammatory pattern, evidenced by the higher prevalence of leukopenia, lymphocytopenia, and thrombocytopenia among COVID-19-positive patients, highlights a distinctive feature of the clinical profile of COVID-19, setting it apart from other respiratory infections (23). Thus, the use of these biomarkers may be valuable not only for diagnosis but also for risk stratification and clinical management of COVID-19 patients.

In the present study, we did not find a significant difference in the D-dimer levels between the COVID-19-positive and COVID-19-negative patients. This finding may be directly related to the fact that the patients included in this study were not hospitalized and did not demonstrate severe symptoms. An increase in this marker level has been associated with increased morbidity

and mortality (24, 25).

The NLR, MLR, and PLR are reportedly significantly higher among patients with COVID-19 than among normal individuals, especially in very severe cases. Thus, they are important prognostic markers for COVID-19 (26, 27). In our study, more COVID-19-positive patients had higher NLR and PLR values than COVID-19-negative patients. However, the MLR was within the normal range for many COVID-19-positive patients and below the RV for a significantly large number of COVID-19-negative patients.

In our study, a lower MLR was associated with a higher Ct value, indicating that in situations of lower viral load (higher Ct value), the immune response may be less intense (28, 29), which attenuates lymphocytopenia and decreases the MLR.

This was a retrospective study using secondary data from an outpatient clinic that lacked clinical data for a better evaluation of the studied population. Therefore, clinical outcomes could not be determined. Furthermore, the Ct value was assumed to be a direct measure of viral load because there are no standardized kits on the market for converting the Ct value to a normalized quantitative measure. Future studies evaluating the immune response according to viral load may demonstrate the correlation between the "cytokine storm" and lymphocytopenia, which consequently leads to an early increase in MLR. Thus, this ratio may be a prognostic marker in COVID-19.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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