# Morphological changes in leukocytes of acute SARS-CoV-2 infection patients, Amazon, Brazil

## Alterações morfológicas em leucócitos de pacientes com infecção aguda por SARS-CoV-2, Amazônia, Brasil

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**RESUMO**

**Introdução:** A pandemia pelo novo coronavírus (SARS-CoV-2) trouxe muitas incertezas sobre quais parâmetros laboratoriais seriam mais adequados durante a evolução da COVID 19. **Objetivos:** Correlacionar os resultados do hemograma (HGM), da relação neutrófilos/linfócitos (R N/L), da proteína C reativa (PCR) e dos achados morfológicos de indivíduos diagnosticados com infecção por SARS-CoV-2 através de Reação em Cadeia da Polimerase em Tempo Real (RT-PCR) em um laboratório particular de Belém, Pará, no período de março a setembro de 2020. **Materiais e Métodos:** Estudo retrospectivo com 30 indivíduos, de ambos os sexos, qualquer idade e queixa clínica, de origem domiciliar ou hospitalar que realizaram HGM, PCR e RT-PCR para COVID 19 até o 8º dia de infecção. As alterações morfológicas foram analisadas após a seleção das lâminas desses pacientes. **Resultados:** Amostra composta por 15 homens e 15 mulheres, com idades entre 7 e 92 anos. Desses, 12/30 indivíduos estavam em domicílio e 18/30 internados. As principais queixas foram febre, mal-estar geral, diarreia e desconforto respiratório. O estudo estatístico mostrou a existência de relação de dependência direta entre os aumentos da R N/L, PCR e necessidade de internação (p=0,0005). A análise morfológica mostrou neutrófilos hipossegmentados com granulações tóxicas, monócitos vacuolizados e linfócitos reativos com citoplasma basofílico. **Conclusão:** Nossos resultados associam os níveis intermediários e elevados da R N/L com o aumento de PCR e a gravidade da doença, porém, sem relação com os achados morfológicos em neutrófilos, linfócitos e monócitos que foram comuns a todos os pacientes diagnosticados até o 8º dia de infecção.

**Palavras-Chave**: Infecções por coronavírus, COVID 19, SARS-CoV-2, Monócitos, Linfócitos, Neutrófilos, Patologia clínica.

**ABSTRACT**

**Introduction:** The pandemic for the new coronavirus (SARS-CoV-2) brought many uncertainties about which laboratory parameters would be most suitable during the evolution of COVID 19. **Objectives:** Correlate the results of the blood count (BC), the neutrophil/lymphocyte ratio (N/LR), the C-reactive protein (CRP) and morphological findings of individuals diagnosed with SARS-CoV-2 infection through Polymerase Chain Reaction in Real Time (RT-PCR) in a private laboratory in Belém, Pará, from March to September 2020. **Materials and Methods:** Retrospective study with 30 individuals, of both sexes, any age and clinical complaint, of home or hospital origin who underwent BC, CRP and RT-PCR for COVID 19 until the 8th day of infection. Morphological changes were analyzed after selecting the slides for these patients. **Results:** Sample composed of 15 men and 15 women, aged between 7 and 92 years. Of these 12/30 individuals were at home and 18/30 were hospitalized. The main complaints were fever, malaise, diarrhea and respiratory distress. The statistical study showed a direct dependency relationship between increases in N/LR, CRP and the need for hospitalization (p = 0.0005). Morphological analysis showed hyposegmented neutrophils with toxic granulations, vacuolated monocytes, and reactive lymphocytes with basophilic cytoplasm. **Conclusion:** Our results associate intermediate and elevated levels of N/LR with increased CRP and disease severity, however, unrelated to the morphological findings in neutrophils, lymphocytes and monocytes that were common to all patients diagnosed up to the 8th day of infection.

**Keywords:** Coronavirus infections, SARS Vírus, COVID 19, Monocytes, Lymphocytes, Neutrophils, Clinical pathology.

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## INTRODUCTION

The pandemic caused by the new coronavirus (SARS-CoV-2), associated with Severe Acute Respiratory Syndrome – SARS has made the global healthcare system face significant uncertainties regarding how the virus would be manifested outside of China; what would be the main clinical manifestations of the host facing the disease caused by this coronavirus (COVID-19); what would be the most acceptable laboratory parameters in the investigation of suspected cases of COVID 19, during the initial and advanced phases of the disease; furthermore, what would be the best therapeutic strategy to adopt[1,2,3,4].

It has been a year since the beginning of the new coronavirus pandemic, and there are still many unanswered questions. However, it has already been possible to define some clinical and laboratory parameters that must be followed to diagnose and monitor COVID 19 patients. But this has only been possible due to the great effort exerted by the scientific community to transform the initial results published during the pandemic to produce more consistent results based on studies performed on scientific evidence.

Various laboratory parameters have already been tested since January 2020, although few have indeed shown importance in evaluating the development of COVID-19[2,3,5,6,7]. For instance: the best way of diagnosing the presence of the SARS-CoV-2 virus is through the Real-Time Polymerase Chain Reaction technique (RT-PCR)[8]; the ratio of absolute neutrophil-lymphocyte count (N/L R) seems to be closely related to the seriousness of COVID 19 in certain kinds of patients[3,9,10,11,12,13]; the increase of c-reactive protein (CRP) displays a clinical value associated with the infectious condition[3,11,14]. Thereby, the clinical status of the individual worsens the D-Dimer and creatine kinase (CK) increases[3,4,14].

The first reports were very important but somewhat unmatched regarding the morphological findings observed in blood counts of COVID-19 patients. We found reports in the literature on leftward statistical biases due to myocytes and even conditions related to leukoerythroblastic reactions[15].

Thus, the purpose of this study has been to correlate the general blood count results, neutrophils/lymphocytes relationship, c-reactive protein, and the morphological findings on leukocytes, observed on a slide, in individuals who have sought a private laboratory in Belém, Pará State, and who were diagnosed with SARS-CoV-2 by RT-PCR.

## MATERIALS AND METHODS

### *Casuistic*

The study is retrospective, quantitative, and statistically based on gender, age, main clinical complaint, healthcare location (home or hospital), blood count (HGM) data, from the blood-count-microscope-slide cabinet in patients investigated for the SARS-CoV-2 virus, C - reactive protein (CRP), D-dimer, Ferritin and Lactic Dehydrogenesis (LDH) in 30 individuals diagnosed up to the 8$^{th}$ day of the SARS-CoV-2 virus infection by Real-Time Polymerase Chain Reaction (RT-PCR).

All the data on gender, age, main clinical complaints, healthcare location (home or hospital), and laboratory exams were obtained through a query in the laboratory Soft-LAB® computer software system at a private clinical analysis lab Belém, Pará State from March to September 2020.

The data regarding the morphological changes were obtained after selecting slides from patients who were positive for SARS-CoV-2 in the referred laboratory's microscope slide cabinet. Afterward, the analysis was performed by experienced professionals, applying the double-blind method through a common-light microscope with an attached camera on the immersed lens.

### *Inclusion criteria*

It was established that patients would be included in the study who were tested as positive for the SARS-CoV-2 virus by testing RT-PCR from nasal and oropharyngeal secretion, individuals from both genders, and any age. Even if there were complete blood counts, available slides in the laboratory, results from C-reactive protein, information on healthcare location (home or hospital), and the main clinical complaint reported from March to September 2020 (Figure 1).

### *Ethical criteria*

It is a retrospective pandemic-type study for only collecting numerical data on lab exams, type of healthcare (home or hospital), main clinical complaint on the healthcare, age, research subject gender, who are only identified by their record number, and their respective clinical analysis result.

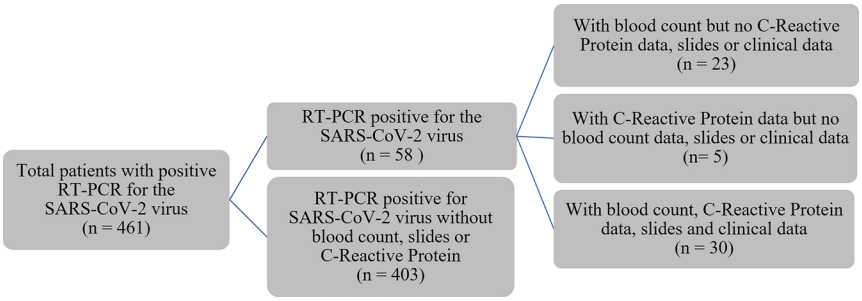


**Figure 1.** Representative flowchart of inclusion and exclusion criteria for the patients RT-PCR positive for the SARS coronavirus virus-2.

The researchers are committed to maintaining secrecy on the collected data by signing a Non-Disclosure, Secrecy, and Data-Protection Agreement at the institution responsible for data. The situation as defined in CNS (National Health Council) Resolution # 466/2012.

### *Statistic analysis*

All the data were tabulated and submitted to descriptive statistical methods for defining the average, standard deviation, mean, and minimum and maximum values, as well as non-parametric tests as ANOVA for two criteria, the Fisher's Exact test, independent G Test, and the Chi-Squared test for independent samples by running the Bioestat 5.0 software. The p-value ≤ 0.05 is considered as being statistically significant.

## RESULTS

Data analysis was performed on 30 individuals who tested positive for the SARS-CoV-2 infection diagnosed with symptoms up to the 8$^{th}$ day (Table 1).

**Table 1.** Quantitative analysis of the age, sex, the relationship between the absolute values of neutrophils and lymphocytes, C-reactive protein concentrations, symptoms of individuals diagnosed with SARS-CoV2 by the RT-PCR exam e disease severity, March to September 2020.

| Index | Type of service | | Total |
|---|---|---|---|
| | Home | Hospital | |
| **Age (**years old**)** | | | |
| 7 - 14 | 3 | 0 | **3** |
| 29 -38 | 1 | 2 | **3** |
| 41 - 68 | 6 | 15 | **21** |
| 74 - 92 | 2 | 1 | **3** |
| **Sex** | | | |
| Men | 6 | 9 | **15** |
| Women | 6 | 9 | **15** |
| **Relationship between the absolute values of neutrophils and lymphocytes** | | | |
| Low risk (0,54 e 2,21) | 9 | 8 | **17** |
| Intermediate risk (2,21 e 4,82) | 3 | 4 | **7** |
| High risk (4,82 e 88,09) | 0 | 6 | **6** |
| **C-reactive protein concentrations (mgL)** | | | |
| 0,2 – 4,0 | 8 | 10 | **18** |
| 7,6 – 213,1 | 4 | 8 | **12** |
| **Symptoms** | | | |
| Fever, general malaise and headache | 10 | 7 | **17** |
| Diarrhea | 2 | 0 | **2** |
| Fever, general malaise and respiratory discomfort | 0 | 11 | **11** |
| **Disease severity** | | | |
| Light | 10 | 11 | **21** |
| moderate | 2 | 4 | **6** |
| Severe | 0 | 3 | **3** |
| **Total** | **12** | **18** | **30** |

It involved 15 men and 15 women, their ages ranged from 7 to 92 years old, and the mean age was 50 years old. 12/30 (40%) of these subjects were submitted to blood collection and nasal and oropharyngeal secretion at home. These subjects presented fever, general malaise, and diarrhea as their main clinical complaints; while the others 18/30 (60%) individuals were also submitted to the same collections, but in hospital settings, and they presented fever, general malaise, and eventual respiratory discomfort as their main clinical complaints.

The blood count results from the subjects from this research are in (Table 1) which revealed that only 4/30 (13.3%) individuals, among those hospitalized, displayed anemic conditions, and 3/30 (10%) had a low platelet count. Regarding the number of leukocytes, only 6/30 (20%) of the individuals displayed leukocytosis and only 4/30 (13.3%) leukopenia.

Following that, we sought to verify the dependent relationship between neutrophils and lymphocytes (N/L R) and the C – reactive protein (CRP) where we observed that 16/30 (53.3%) analyzed individuals displayed normal N/L R and normal CRP; 6/30 (20%) demonstrated normal N/L R and increased CRP and 8/30 (26.7%) individuals who showed increased N/L R and CRP. The Fisher's Exact test and the G test were applied for these results displaying direct dependency between the increased N/L R and CRP values (p=0.0005).

Considering the high-risk levels for developing severe forms of COVID-19 attributed to N/L R (low risk – from 0.54 to 2.21; intermediate risk – from 2.21 to 4.82; high risk – from 4.82 to 88.09) (Liu et al., 2020), in our study 06/30 individuals were observed to display a high risk of serious evolution of the disease-related to increased CRP, whereas all those were hospitalized; 07/30 individuals who showed intermediate risks of serious development of the disease 06/07 among these there was a proven increase of CRP, whereas 04/06 of these patients were hospitalized; and 17/30 individuals displayed a low risk of evolving severe forms of COVID-19, among these 08/17 are hospitalized, and only 02/17 individuals showed increased CRP. There was no level of dependency displayed between the increased N/L R and CRP based on the patient's hospitalized or home care condition after applying the Fisher's Exact test (p=0.1414).

Based on these results, we sought to verify the dependency between the increased CRP and the number of monocytes and eosinophils. However, that analysis was not possible due to the high standard deviation displayed in these analytes' distribution.

The blood count and scatter plots of the leukocytes were acquired in the BC6000 hematology analyzer from the *Mindray*® Company; after individually verifying each plot, the respective equipment did not generate any morphological flags in the scatter plots from the cellular populations regarding differential leukocytes (Figure 2A). Furthermore, COVID-19 investigation samples were prepared, stained, and the blood smears were stored during this study.

After getting the positive RT-CRP results for SARS-CoV-2, a morphological analysis was performed on leukocytes from these individuals on slides, where the following morphological alterations were observed on all the slides: hyposegmented neutrophils similar to rod-shaped (Figure 2D) or with only two lobulations (regular sizes or not) reminding us of Pelger-Huet

**Table 2.** Quantitative analysis of the blood count parameters and C-reactive protein concentrations of individuals diagnosed with SARS-CoV2 by the RT-PCR exam, examined at a private laboratory in Belém, Pará State, March to September 2020.

| **Erythrogram, Platelet count, & Leukogram** | **Red Blood Cells (X10⁶/mm³)** | **Hemoglobin (g/dL)** | **Hematocrit (%)** | **Leukocytes (/mm³ )** | **Platelets (/mm³ )** | **PCR (mg/L )** | **#** |
|---|---|---|---|---|---|---|---|
| X ± S.D. | 4.51±0.766 | 13.3±2.12 | 41.2±6.68 | 8,050±4,861 | 241,200±73.44 | 40.1±56.2 | |
| Mean | 4.05 | 13.4 | 41.6 | 6,000 | 245.00 | 9.4 | 30 |
| Min-Max | 2.68 – 6.04 | 8.2 – 17.0 | 25.7 – 53.0 | 3,420 – 21,680 | 177,000 – 383,000 | 1.4 – 213.1 | |
| **Leukocyte Differential** | **Neutrophils (/mm³ )** | **Lymphocytes (/mm³)** | **N/L Relationship** | **Monocytes (/mm³)** | **Eosinophils (/mm³)** | **Basophils (/mm³)** | |
| X ± S.D. | 5,650±5,244 | 1,738±1,008 | 6.34±8.56 | 439±187 | 167±239 | 9±19 | |
| Mean | 3,500 | 1,520 | 2.13 | 1,042 | 1,114 | 0 | 30 |
| Min-Max | 1,376 – 20,378 | 526 – 4,284 | 0.85 – 30.96 | 120 – 1,042 | 0 – 1,114 | 0 - 80 | |
| | | | **TOTAL** | | | | 30 |

Legend: # – total number of samples; X ± S.D. – average (X) pretty near the standard deviation (SD); Min-Max – minimum and maximum values obtained; (CRP) C - reactive protein; N/L Relationship – the relationship between the absolute values of neutrophils and lymphocytes. Relationship – the relationship between the absolute values of neutrophils and lymphocytes.

type cellular alterations, as well as toxic granulations (Figure 2E); vacuum-sealed monocytes, and cytoplasmic projections suggesting cellular activation (Figures 2B, 2H, and 2I), regardless of the presence of absolute or relative monocytosis; and reactive lymphocytes with increased cytoplasm and intensely basophilic (Figures 2C, 2D, 2E, and 2F) and sometimes even displaying a plasmacytoid appearance (Figure 2G), even when the individual presented absolute lymphopenia.

Following that, we sought to verify some dependence relationship between N/L R and CTP and dosages of D-dimer, Ferritin, and LDH. However, since not all the research subjects performed these exams, where only 22/30 individuals had taken dosages of Dimer D; 10/30 individuals dosages of ferritin, and only 12/30 individuals dosages of LDH, it was not possible to perform the eventual statistical correlation based on these parameters.

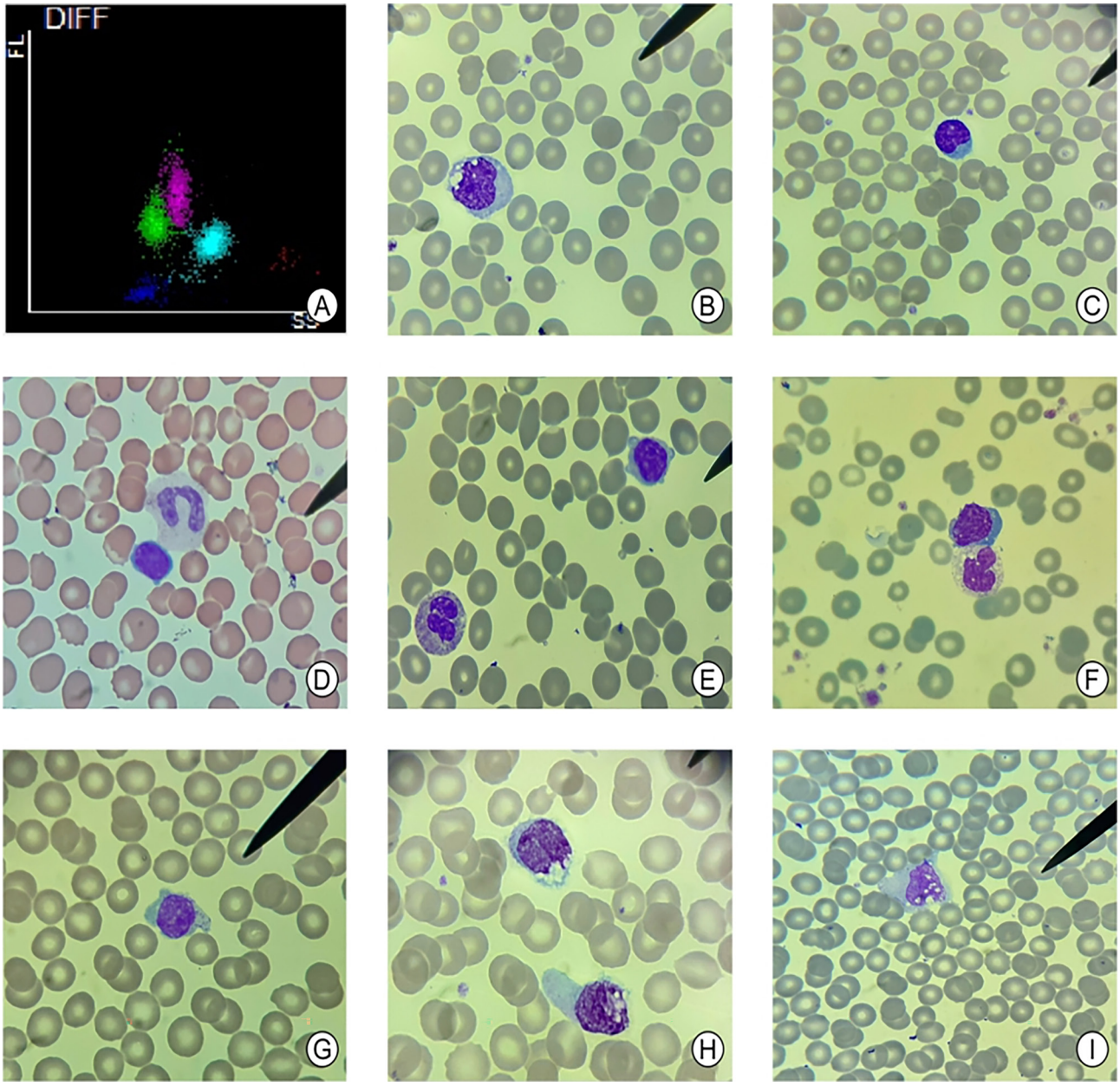


**Figure 2.** 2A. Scatter plot of the cellular populations from differential leukocytes produced by the BC6000 hematology analyzer from the *Mindray*® Company. 2D and 2E. hyposegmented neutrophils similar to rods and with only two lobulations similar to Pelger-Huet type cellular alterations and toxic granulations. 2B, 2H, and 2I. Vacuolated monocytes and cytoplasmic projections were suggesting cellular activation. 2C, 2D, 2E, and 2F. Reactive lymphocytes with increased cytoplasm and intensely basophilic. 2G. Reactive lymphocyte displaying a plasmacytoid appearance.

## DISCUSSION

In this study, we have observed the increase of the neutrophils/lymphocytes relationship (N/L R), retrospectively, for intermediate and high levels, and c-reactive proteins (CRP) are directly related to the greatest risk of evolving the most severe forms of COVID-19, patients who need to be hospitalized and suffer from respiratory symptoms who are RT-CRP positive for SARS-CoV-2 diagnosed up to the 8th day of infection, regardless the age of the individual. These data are corroborated by the studies of Liu et al. [11], Mo P et al. [13], Qin C et al. [12] and Lippi and Plebani[14], who associated patients who have displayed an increase in N/L R in severe cases of COVID-19, who have the greatest need for hospitalization and risk of death.

Thevarajan et al. [7], Zini, Bellesi, Ramundo and d'Onofrio[16], and Frater, Zini, d'Onofrio, and Rogers[17] in their studies suggested that monocytes frequently decreased in the period from 7 to 9 days in the peripheral blood of a patient who has COVID-19, possibly due to the efflux of these blood cells to the pulmonary site. In our study, we also did not observe a change in the number of monocytes, or even eosinophils, in patients up to the 8th day of infection. However, even within the normality limits, the monocytes displayed morphological changes suggestive of cellular activation, such as vacuolation and cytoplasmic projections in all the analyzed patients.

Weinberg, Behdad, and Ji[18,] in a study on morphological changes in the leukocytes of patients with COVID-19, observed medium and large-sized atypical lymphocytes, loose chromatin, and basophilic cytoplasm or plasmacytoid appearance occurred in 93.3% (14/15) of the analyzed smears. Similar data were also observed in our results.

Zini, Bellesi, Ramundo, and d'Onofrio[16] in their studies also displayed the same alterations as already reported in lymphocytes and even added morphological observations in neutrophils ranging from dark cytoplasmic granulations (similar to toxic granulations) to dimorphic nuclear alterations associated with hypolobulations reminding us of the pseudo-Pelger alterations, as well as neutrophils shaped like rods. The neutrophil alterations were also similar to those observed in our study.

Frater, Zini, d'Onofrio, and Rogers[17] observed neutrophils with hyposegmented nuclei and enlarged granulations, as well as immature forms of granulocytes (myelocytes and metamyelocytes) and neutrophils with pre-apoptotic chromatin, similar to what was reported by Zini, Bellesi, Ramundo, and d'Onofrio[16] on neutrophils and lymphocytes. Mitra et al. [15] observed a leukoerythroblastic reaction in a COVID-19 patient. Although all those findings on the apoptotic aspect of cells, in the immature forms of neutrophil myelocytes and metamyelocytes, as well as erythroblasts, they were not observed in our study even when the N/L R was high, a fact that may suggest that these eventual and related findings occur in more severe cases of the disease[16].

Since Liu et al. [19] related to eosinophils suggests that the counting of these cells play a potential predator role in COVID-19, as to reduce eosinophils that could be related to an acute pulmonary lesion caused by SARS-CoV-2, while the continual improvement in the eosinophil quantitative in the posterior phase could be associated with the progress of the clinical condition. We have not observed any significant variation in the counting of the eosinophils in our results related to the total of the evaluated individuals.

Regarding the presence of reduced red blood cells, hemoglobin, and hematocrit; platelet count; and/or leukocytosis or leukopenia in the blood counts of the subjects being studied, we observed that these changes were only eventual, and they occurred mainly in individuals who were already hospitalized and consequently displayed intermediate or high levels in their N/L R and without that it has been possible to define any relationship among these indicators. It was also impossible to observe any association among the morphological alterations described here in leukocytes regarding the total of leukocytes, red blood cells, hemoglobin, hematocrit, and platelets. Nonetheless, just like other authors[3,8,10,14,17,20,21], we also understand that the number of leukocytes and platelets is vital in evaluating the clinical evolution of the patient.

We also attempted to evaluate any dependency relationship between the N/L R, the CRP, and the dosages of Dimer D, Ferritin, and LDH. However, as not all subjects in this research study performed these exams, it was impossible to carry out a statistical survey for this purpose. Despite this, just as other authors[2,5,6,9,22], we also understand that there may be an association among eventual alterations in these results and worsened clinical evolution of the patient.

## CONCLUSION

In this study, we could observe an association between the intermediate and high levels of the neutrophil/lymphocyte relationship to the increase of C-reactive protein and the seriousness of the disease. However, the morphological findings on the observed neutrophils, lymphocytes, and monocytes were common in all patients yet not maintain the correlation to these indicators in individuals diagnosed with the SARS-CoV-2 infection through RT-CRP up to the 8$^{th}$ day of symptoms. Regarding the overall blood count results, total leukocytes, red blood cells, hemoglobin, hematocrit, and platelets, it was not possible to establish any association with the intermediate or high levels in N/L R or even in the morphological alterations in leukocytes, herein described in the acute phase of COVID-19.

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**Contribution:** In the acquisition and analysis of research data **(APSP)**
**Contribution:** In the design of the work; acquisition, analysis, and interpretation of research data; and in writing with intellectual contribution. **(VICP)**
**Contribution:** In the acquisition and analysis of research data **(RISF)**
**Contribution:** In the design of the work; acquisition, analysis, and interpretation of research data; and in writing with intellectual contribution. **(RSG)**
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