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Correlation of hematological parameters and cycle threshold in ambulatory patients with SARS-CoV-2 infection

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Abstract

Introduction: Former studies have shown that hematologic parameters are affected by the SARS-CoV-2 infection which has caused a global health problem. Therefore, this research aims to identify the most frequent symptoms and comorbidities in SARS-CoV-2 infected outpatients; besides, to analyze hematological parameters and their correlation with cycle threshold (Ct) values.

Methods: We analyzed a total of sixty outpatients with SARS-CoV-2 infection. They were divided according to sex. Afterward, a questionnaire was carried out to find out their symptoms and comorbidities. Additionally, blood biometry data were correlated with the Ct value, respectively.

Results: Sixty patients were analyzed; the mean age was 43 years. All patients were from Nayarit, Mexico. The frequency index showed that the main symptoms were headache and anosmia, and the comorbidities were obesity and smoking. The analysis of blood biometry showed a clear increase in red blood cells (RBC) related parameters in women. In both sexes an increase in the number of white blood cells (WBC) was observed. Also, all the hematological alterations correlated with the grade of infection.

Conclusion: Headache and anosmia are the most common symptoms according to the frequency index, the main comorbidities were obesity and smoking. Also, there is a Ct value correlation with hematological parameters (WBC, mean corpuscular volume, mean corpuscular hemoglobin, hemoglobin); they can be used as a prognostic marker of infection.

KEYWORDS

ambulatory patients, correlation, cycle threshold values, hematologic parameters, SARS-CoV-2

Daniel Alberto Girón-Pérez and Alma Betsaida Benitez-Trinidad contributed equally to this work.

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes the COVID-19 disease, currently classified as a pandemic, which until February 2021 has caused more than 100 million people infected and more than two million deaths worldwide.[1] Official data indicate that until April 21, 2021, 2 315 811 people in Mexico have been infected and 213 597 people have died from the disease. In the state of Nayarit, Mexico more than 11 622 infections and 1771 deaths due to this disease have been reported up to March 2021, which represents a lethality of 15%.[1]

In this COVID-19 pandemic, three kinds of infected patients have been identified: 1) asymptomatic individuals, who normally do not use diagnostic services, 2) individuals with mild or moderate signs and symptoms, who do use diagnostic services, but most symptoms disappear within approximately 10 days and 3) individuals with severe symptoms who use diagnostic services and require hospitalization services and intensive care medicine strategies.[2]

Symptoms presented during SARS-CoV-2 infection are variable and may be similar to other types of infectious diseases; however, the most common symptoms are fever, dry cough and fatigue, as well as loss of smell and/or taste, diarrhea, rash and headache or in more severe cases: difficulty breathing, chest pressure, and inability to speak or move.[3]

Currently, to diagnose COVID-19 the laboratory test considered the "gold standard" is the quantitative real time-polymerase chain reaction (qRT-PCR). Through this test, SARS-CoV-2 genes are amplified and depending on the cycle threshold (Ct) viral load can be inferred in each individual, which could be related to different signs and symptoms of each patient as well as hematological alterations.[4-7]

The hematological alterations can be determined through hematic biometry since it allows us to analyze the blood alterations which sometimes can serve as indicators of some infectious diseases; therefore, it is indispensable to know the variations in the parameters of the cells of the blood.[4-8]

The dynamic of SARS-CoV-2 infection is associated to the viral load and is determined as the Ct value, which is inversely proportional to this load.[9] Likewise, a higher viral load (thus a low Ct value) is related to the severity of the disease and to an increased risk of death.[10] In this sense, some laboratory parameters modifications such as increase in neutrophils counts, as well as, the lactate dehydrogenase and C-reactive protein levels, are suggested predictors of the COVID-19 outcome.[11] However, in outpatients, other hematological alterations that also can be used as a biomarkers need to be evaluated.

This study aimed to identify the most frequent symptomatology and comorbidities in ambulatory patients infected with SARS-CoV-2 as well as to analyze hematological parameters and correlate them with the Ct value during SARS-CoV-2 infection.

2 | MATERIALS AND METHODS

2.1 | Patients

All study participants signed the informed consent before samples, and clinical data were collected. This study was carried out under the guidelines stated in the Declaration of Helsinki and was approved by the local bioethics commission "Comisión Estatal de Bioética del Estado de Nayarit" (registry number CEBN/03/20).

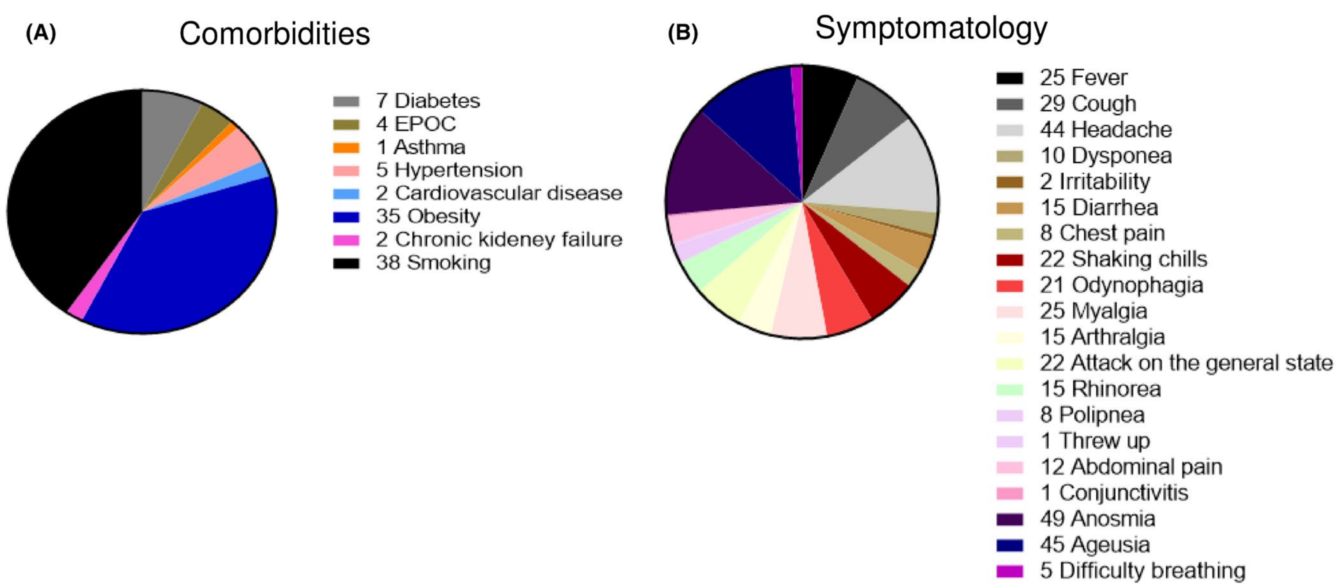

FIGURE 1 Frequency index of comorbidities and symptomatology of SARS-CoV-2-infected ambulatory patients. A, Comorbidities of ambulatory patients infected by SARS-CoV-2. B, Symptomatology of SARS-CoV-2-infected ambulatory patients regardless of sex, n = 60. Abbreviations: chronic obstructive pulmonary disease (EPOC) [Colour figure can be viewed at wileyonlinelibrary.com]

For swab sample collection, subjects were queried to avoid eating food, drink water, and brushing their teeth at least 4 hours before collection and were invited to willingly donate a blood sample (10 mL) by venipuncture.

The blood sample taken (2 mL), which was placed in tubes with anticoagulant (7.2 mg EDTA; Becton Dickinson, Diagnostic System) later on, and the hematic biometry was carried out on it in an automated equipment model XN-550 (Sysmex); besides, the differential count of WBC was carried out through clear field microscopy, using a “Wright stain” and there were taken values according to the Mexican population and an adjustment to the hematic biometry of ± 0.2 for hemoglobin and $+0.5$ for hematocrit due to the altitude of Tepic Nayarit, Mexico.[12]

2.2 | Determination of SARS-CoV-2 in patients

Molecular diagnosis of SARS-CoV-2 was performed on the same day that the blood biometry was performed. The molecular protocol was validated by the Mexican Ministry of Health (SSA-México). In brief, each patient was swabbed with a nasal and oropharyngeal sample, which was subjected to RNA extraction by QIAmp Viral RNA mini kit (Qiagen, Cat No/ID: 1020953). The RT-PCR was performed using the StarQ One-Step RT-qPCR kit (Qiagen, Cat No./ID: 210210).

The SARS-CoV-2 detection was performed using primers, probes and PCR conditions according to the Berlin protocol and validated by InDRE (Instituto de Diagnóstico y Referencia Epidemiológica).[13] All samples were analyzed in the ABI Prism 7500 Sequence Detector System (Applied Biosystems).

Before taking the sample, each patient was given a questionnaire to find out the symptoms of each patient and whether they presented any risk factors or comorbidities that could increase infection severity. All study participants signed the informed consent according to a protocol approved by the local bioethics commission (registry number CEBN/03/20).

2.3 | Data analysis

The demographic data were obtained through a survey which was carried out by laboratory personnel, then a comparative study was made between the reference values of blood biometry versus the blood values of the patients. Pearson's correlation analysis (r) with a confidence interval of 95% was also performed. As well as, an analysis between Ct and hematic biometry values was made. The statistical analysis was performed using a Student's t test for single comparisons. A P-value less than .05 was considered statistically significant. The graphs and correlation tests were graphed in Graph prism 8.4.

3 | RESULTS

Sixty ambulatory patients (30 men and 30 women) with an age range between 19 and 68 years and an average age of 43 years were analyzed. All the patients were from Tepic, Nayarit, Mexico. Subsequently, they were surveyed about comorbidities and symptoms. It was found that the most frequent comorbidities in these patients were obesity and smoking (Figure 1A); they also manifested several symptoms among which were headache, anosmia, ageusia, and general malaise (Figure 1B).

For the analysis of hematological parameters, the patients were divided according to sex and are displayed in Table 1.

It was found that the women infected with the SARS-CoV-2 virus increased their values of hematocrit; 18 women presented values superior to 0.472 (Figure 2A). Furthermore, 16 women were found to have increased the number of red blood cells (RBC; $>5.4 \times 10^{12}$/L; Figure 2B) this increase is also reflected in an increase in the mean corpuscular volume (>91 fL) of 17 women, (Figure 2C); in this way, 16 women presented higher values of mean corpuscular hemoglobin (>32 pg; Figure 2D). In men, no alterations were observed in the values for RBC parameters.

The analysis of the white blood cells (WBC) revealed that both men and women increased the number of these cells ($>10 \times 10^9$/L; Figure 2E); the different WBC strains analysis showed that only the total number of lymphocytes increased (>45%) in both sexes infected by SARS-CoV-2 (Figure 2F); these findings were independent of age in the analyzed ambulatory patients.

When analyzing the correlation between blood biometry and Ct (Figure 3), an inverse trend was observed between Ct values and RBC values. The highest Pearson correlation was detected between the Ct value and hematologic parameters: hematocrit, RBC, and mean corpuscular volume and mean corpuscular hemoglobin (Pearson's $r = .85$, $r = .80$, $r = .89$ and $r = .75$, $P = <.001$, respectively; Figure 3A-D); analysis of the WBC cells in both men and women showed similar behavior.

The Pearson correlation values of WBC (Pearson's $r = .75$ and $r = .80$, $P = <.001$) and lymphocytes (Pearson's $r = .89$ and $r = .93$, $P = <.001$) indicate a trend that the lower the Ct value, a higher WBC cells (Figure 4A-B).

4 | DISCUSSION

Comorbidities such as obesity and smoking are risk factors that may exacerbate SARS-CoV-2 infection. Obesity is regulated by adipose tissue hypertrophy, which releases TNF-α, IL-1, IL-6, TGF-β, leptins, CXCL5, and vascular endothelial growth factor (VEGF); besides, overweight increases the expression of angiotensin-converting enzyme (ACE) and ACE2 receptors, which are the key receptors for SARS-CoV-2-mediated infection that in turn causes a cytokine storm, which results in multiorgan failure in patients with severe COVID-19 disease.[14,15]

Smoking is another important risk factor for developing severe COVID-19 disease as it has been postulated that smoking increases the expression of ACE2 receptors as well as smoking affects the respiratory capacity by inducing apoptosis of pneumocytes and endothelial cells.[16,17] On the other hand, the blood biometry is the set of parameters that determine the number of blood cells such as RBC, WBC, platelets and also allows us to know the size and amount of hemoglobin

TABLE 1 Blood biometrics of male and female ambulatory patients infected with SARS-CoV-2

Parameters	Mean ± SD men	Reference parameter men	Mean ± SD women	Reference parameter women
Hemoglobin, (g/L)	145-185 (30)	145-185	125-165 (30)	125-165
Hematocrit (fraction)	>0.521 (1)	0.422-0.522	>0.472 (18)	0.372-0.472
	0.452-0.522(27)		0.372-0.472 (12)	
	<0.452 (2)		<0.372 (0)	
RBC, (10^{12}/L)	>6.3 (1)	4.5-6.3	>5.4 (16)	4.2-5.4
	4.5-6.3 (25)		4.2-5.4 (14)	
	<4.5 (4)		<4.2 (0)	
Mean corpuscular volume, (fL)	>91 (13)	76-91	>91 (17)	76-91
	76-91 (17)		76-91 (13)	
	<76 (0)		<76 (0)	
Mean corpuscular hemoglobin, (pg)	>32 (8)	27-32	>32 (16)	27-32
	27-32 (19)		27-32 (14)	
	<27 (3)		<27 (1)	
Mean corpuscular hemoglobin concentration, (g/L)	320-360 (30)	320-360	320-360 (30)	320-360
WBC, (10^9/L)	>10 (20)	4-10	>10 (19)	4-10
	4-10 (10)		4-10000 (11)	
	<4 (0)		<4000 (0)	
Neutrophils, (%)	40-75 (30)	40-75	40-75 (30)	40-75
Eosinophils, (%)	0-4 (30)	0-4	0-4 (30)	0-4
Basophils, (%)	0 (30)	0-1	0 (30)	0-1
Lymphocytes, (%)	>45 (27)	20-45	>45 (29)	20-45
	20-45 (3)		20-45 (1)	
	<20 (0)		<20 (0)	
Monocytes, (%)	0-10 (30)	0-10	0-10 (30)	0-10
Bands, (%)	0-1 (30)	0-1	0-1(30)	0-1
Platelet, (10^9/L)	150-400 (30)	150-400	150-400 (30)	150-400
Atypical lymphocytes, (%)	0-1 (30)	0-1	0-1 (30)	0-1
Neutrophils, (10^9/L)	1.8-8 (30)	1.8-8	1.8-8 (30)	1.8-8
Eosinophils, (10^9/L)	0-0.45 (30)	0-0.45	0-0.45 (30)	0-0.450
Basophils, (10^9/L)	0-0.1 (30)	0-0.1	0-0.1 (30)	0-0.1
lymphocytes, (10^9/L)	>5.2 (29)	1.2-5.2	>5.2(28)	1.2-5.2
	1.2-5.2 (1)		1.2-5.2 (2)	
	<1.2 (0)		<1.2 (0)	
Monocytes, (10^9/L)	0-0.8 (30)	0-0.8	0-0.8(30)	0-0.8
Bands, (10^9/L)	0-1 (30)	0-1	0-1 (30)	0-1

Note: This study is a frequency index of hematological parameters. The values in parentheses represent the numbers of subjects that are between at different ranges.

Abbreviations: %, percentage; fL, femtoliter; g/L, grams/Liter; L, liter; pg, picograms; RBC, red blood cells; WBC, white blood cells.

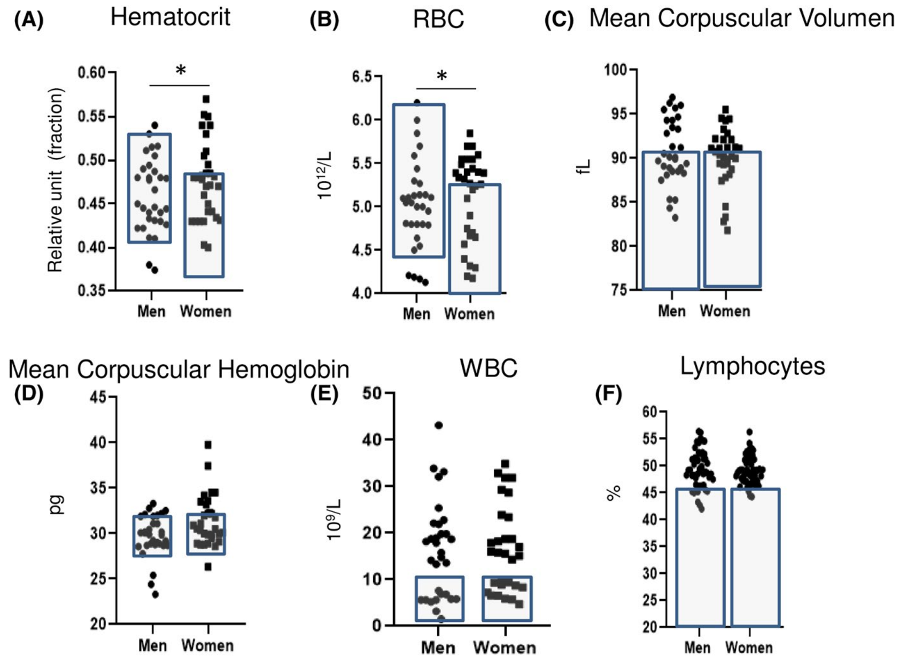

FIGURE 2 Blood biometry parameters of peripheral blood in SARS-CoV-2-infected men and women. A, Hematocrit (fraction), B, RBC (10^{12}/L), C, mean corpuscular volume (fL). D, Mean corpuscular hemoglobin (pg) E, WBC (10^9/L) F, Lymphocytes (%). n = 60, men (30) and women (30). The gray box represents patients who are in normal parameters of blood biometry. The statically analysis were performed using a student's *t* test, *P* values <.05 were considered significant. Single star (*) denotes $0.01 < P < .05$. Abbreviations: grams/deciliter (g/dL), picograms (pg), femtoliter (fL), liter (L). standard deviation (SD) [Colour figure can be viewed at wileyonlinelibrary.com]

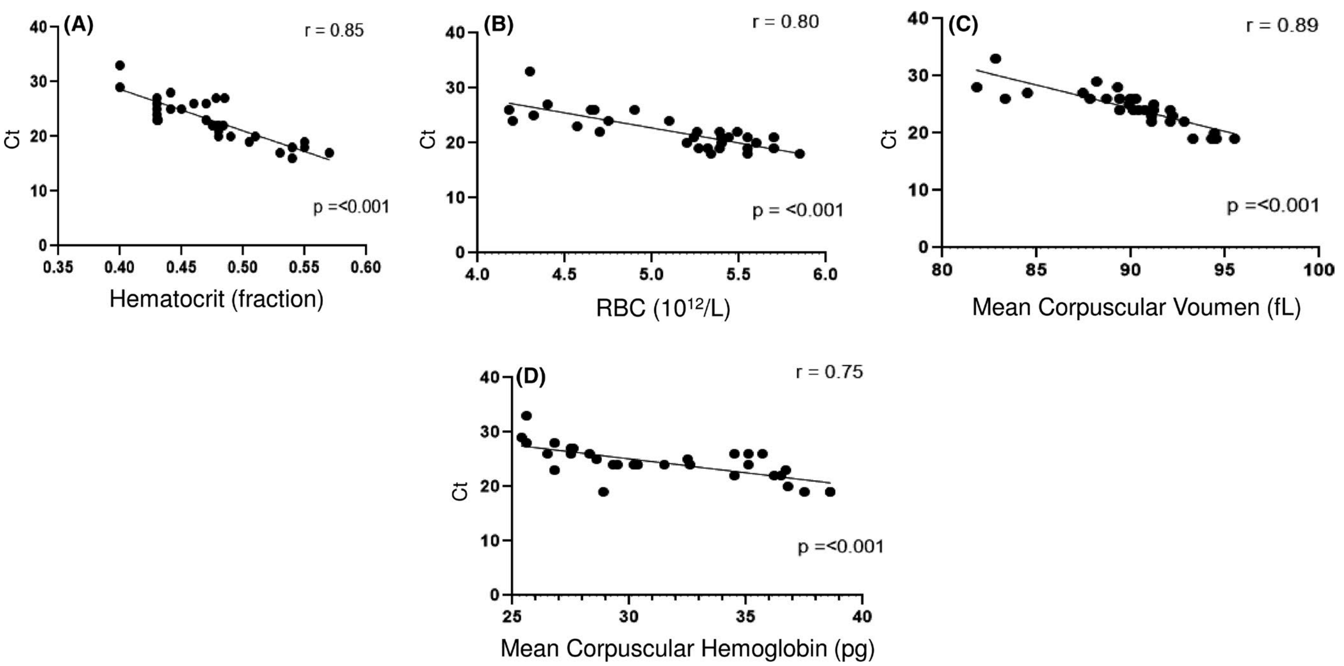

FIGURE 3 Correlation analysis of the parameters of the RBC of blood biometry in women against the Cycle threshold (Ct) value in ambulatory patients infected by SARS-CoV-2. A, Hematocrit (fraction) versus Ct value. B, RBC (10^{12}/L) versus Ct value. C, Mean corpuscular volume (fL) versus Ct value. D, Mean corpuscular hemoglobin (pg) versus Ct value. Pearson's correlation (95% confidence level) and is reported as "*r*" and the probability value as "*P*". n = 30. Abbreviations: cycle threshold (Ct), grams/deciliter (g/dL) picograms (pg), femtoliter (fL), liter (L), standard deviation (SD)

contained in RBC, as well as its relationship to blood volume, so it is an indispensable set of determinations for timely clinical diagnosis.[18,19]

The results obtained in the present investigation showed that SARS-CoV-2 infection causes an increase in RBC, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin in women compared to men; this suggests a sexual bias with respect to SARS-CoV-2 infection. This sex difference could be related to the sex hormones, since estradiol helps the immune system and allows the elimination of certain viruses (flu, HIV) and may regulate the level of cytokines (IL-6, IL-2, and IL-8) related to SARS-CoV-2 infection.[20,21]

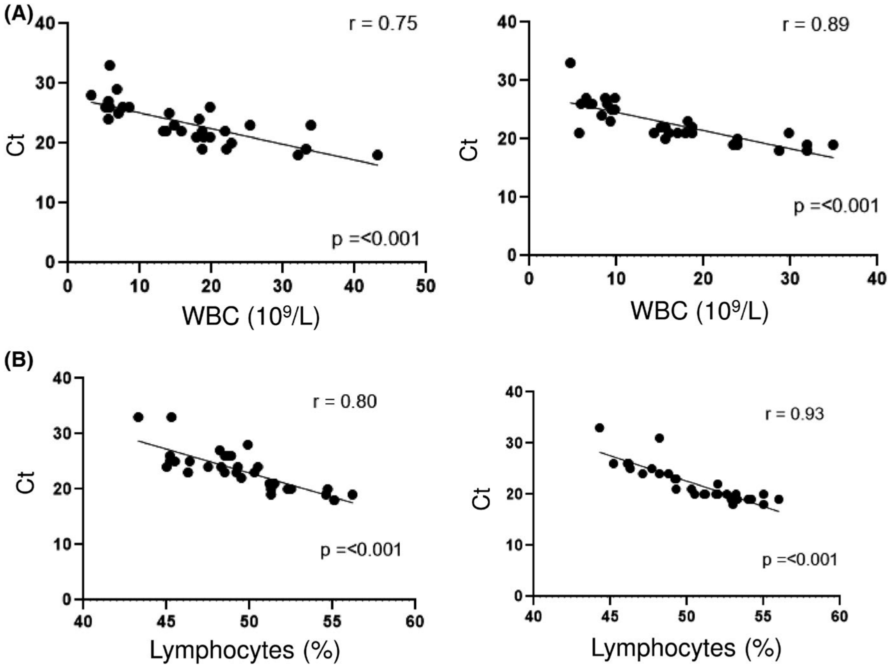

FIGURE 4 Correlation analysis of WBC values parameters of blood biometry in men and women against cycle threshold (Ct) value in SARS-CoV-2-infected ambulatory patients. A, WBC in men and women (10^9/L) versus Ct value. B, Lymphocytes of men and women (%) vs Ct value. Pearson's correlation (95% confidence level) and is reported as "*r*" and the probability value as "*P*". n = 30, n = 60, men (30) and women (30). Abbreviations: cycle threshold (Ct), picograms (pg), femtoliter (fL), percentage (%), liter (L), standard deviation (SD)

Additionally, it has been described that hormones such as testosterone (male hormone) can regulate the expression of the angiotensin-converting enzyme 2 (ACE2) receptor and in turn negatively regulates the immune response which causes an increase in the severity of the disease. [22]

The increase in RBC may be a signal sent by the organism to carry more oxygen to the body, a similar scenario occurs with hematocrit since other works show that estradiol causes an increase in hematopoiesis.[23] The RBC are critical for oxygen transport, since the decrease in patients with COVID-19, and can cause permanent damage to different organs; however, it is not fully known if the SARS-CoV-2 infection affects gas transport, metabolism, and circulation in these cells.[24,25]

The data obtained in this research suggest that the increase in RBC values in women is related to the presence of estradiol and is intended to increase oxygen transport to prevent hypoxia in SARS-CoV-2-infected patients.

The WBC are important to control viral infections; in severely infected COVID-19 patients, it has been shown that there are leukopenia and lymphopenia, due to high rate of apoptosis in these cells, due to increased expression in T, B, and NK cells of FAS and FAS-L markers. In addition, $CD4^+$ and $CD8^+$ cells have an "exhausted" phenotype due to the abundant expression of PD-1 and TIM-3, leading to a deregulation of the inflammatory cytokines.[26,27]

On the other hand, in patients with mild symptoms (fever, cough, and dyspnea) or who do not require hospitalization, it has been shown that their WBC increase above normal values.[2] Therefore, this can be considered as a biomarker that can predict recovery from the disease.

Results obtained show an increase in WBC and lymphocytes above normal values in both men and women, suggesting that the immune system increases its cell strains to control viral infection and the possible increase in cytokines (IL-10) or proteins (C-reactive protein or procalcitonin) in ambulatory patients.[28] Therefore, data suggest that increased WBC in nonsevere patients may be used as a marker of patient recovery regardless of gender and/or age.[29]

The correlation analysis between the RBC and lymphocytes values with the Ct value (it can indicate the viral load) suggests that there is a trend where for a lower value of Ct there is a greater number of cells in the RBC values; similar is the case in the WBC cells. Therefore, the viral load has a determining role in the behavior of these parameters and can affect the symptoms or the dynamics of infection.

The SARS-CoV-2 infection kinetic with respect to the lymphocytes indicates that it is possible that when there is a high viral load, $CD4^+$ or $CD8^+$ lymphocytes increase to release different cytokines such as IFN-γ or IL-10 to decrease inflammation or interfere with viral replication.[30] In turn, this would corroborate with the increase in red blood cells (RBC) in women, this increment is a compensatory mechanism to increase lung oxygen transport, since with lower Ct values (high viral load), this parameter increase (Figure 3B).[31] Therefore, knowing the values of blood biometry gives us a guide about possible scenarios during viral infection.

The dynamics of SARS-CoV-2 infection is linked to Ct value; a low Ct value is associated with a high risk of severe infection, while a high Ct value is associated with a mild infection.[32-34] Hematological parameters may be colinked to the Ct value, since for patients with severe infections, the values of total WBC, as well as parameters of the RBC series (mean corpuscular volume, mean corpuscular hemoglobin, hemoglobin), were decreased; on the other hand, in patients with mild or asymptomatic infections, these parameters increase.[35,36] In this work, it was observed that these values increased since the patients presented mild infections. We speculate that hematological parameters were related with post-COVID-19 symptoms (Fatigue).[37]

In our research, we found a similar phenomenon where the lower the Ct value, the lower the WBC and RBC and associated values. These associations are interesting because they may be a value that can be related to disease progression.

In conclusion, headache and anosmia are the most common symptoms according to the frequency index; while, obesity and smoking were the mainly reported comorbidities. There is also a correlation where hematological parameters (WBC, mean corpuscular volume, mean corpuscular hemoglobin) change according to the Ct value, so they can be used as a prognostic marker of infection.

5 | STUDY LIMITATIONS

Some limitations should be noted. First, all subjects were outpatients with mild symptoms. Second, most of patients were from Tepic Nayarit (Mexico). Therefore, it is necessary to evaluate patients with severe disease and from other geographical regions.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception, material preparation, data collection, and design.

ETHICAL APPROVAL

All study participants signed the informed consent before sample and clinical data collection, according to a protocol approved by the local bioethics commission (registry number CEBN/03/20).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Girón-Pérez M.I, upon reasonable request.

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