Neutrophil/lymphocyte ratio and C-reactive protein in patients with COVID-19: correlations in deceased and surviving patients

Relación neutrófilos/linfocitos y proteína C reactiva en pacientes con COVID-19: correlaciones en pacientes fallecidos y sobrevivientes

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Abstract

Introduction: COVID-19 is caused by SARS-CoV-2 associated with the activation of the inflammatory process. Various studies have determined the importance of the neutrophil/lymphocyte ratio (NLR) in different inflammatory processes. C-reactive protein (CRP) is involved in several infectious processes as a marker of inflammation. **Objective:** To determine the values of NLR and CRP in COVID-19 patients and controls and to determine these values in COVID-19 survivors and deceased patients. **Method:** This retrospective study was conducted in patients with suspected COVID-19 from various clinical institutions in Portoviejo, Manabí, Ecuador, from March to June 2021. A total of 41 SARS-CoV-2-positive COVID-19 patients were included and evaluated. Patients were classified into two groups according to their results (survivors: 22 and deceased: 19). **Result:** Overall, lymphocyte counts, NLR, and CRP values increased significantly during COVID-19. It was observed that during the disease, there were more positive correlations between the different inflammatory parameters studied than between the controls. The results show that surviving patients had increased lymphocyte counts and CRP content compared to deceased patients; however, the latter presented the highest NLR values and the lowest lymphocyte values, establishing a prognostic value of severe evolution. The number of significant correlations observed in surviving and deceased patients was similar. **Conclusion:** This study suggests the importance of leukocytes and CRP in COVID-19 and a possible predictive value for the severe evolution of NLR in the disease.

Keywords: COVID-19, neutrophil-to-lymphocyte ratio, C-reactive protein, disease progression, correlations.

Resumen

Introducción: La COVID-19 es causada por el SARS-CoV-2 asociado a la activación del proceso inflamatorio. Diversos estudios han determinado la importancia de la relación neutrófilos/linfocitos (NLR) en diferentes procesos inflamatorios. La proteína C reactiva (PCR) participa en varios procesos infecciosos como marcador de inflamación. **Objetivo:** Determinar los valores de NLR y CRP en pacientes y controles de COVID-19 y determinar estos valores en pacientes sobrevivientes y fallecidos de COVID-19. **Método:** Este estudio retrospectivo se realizó en pacientes con sospecha de COVID-19 de diversas instituciones clínicas de Portoviejo, Manabí, Ecuador, de marzo a junio de 2021. Se incluyeron y evaluaron un total de 41 pacientes COVID-19 positivos para SARS-CoV- 2. Los pacientes fueron clasificados en dos grupos según sus resultados (supervivientes: 22 y fallecidos: 19). **Resultado:** En general, durante la COVID-19, los recuentos de linfocitos, los valores de NLR y PCR aumentaron significativamente. Se observó que durante la enfermedad existían más correlaciones positivas entre los diferentes parámetros inflamatorios estudiados que entre los controles. Los resultados muestran que los pacientes supervivientes tenían mayores recuentos de linfocitos y contenido de PCR en comparación con los pacientes fallecidos; sin embargo, estos últimos presentaron los valores más altos de INL y los valores más bajos de linfocitos, estableciendo un valor pronóstico de evolución severa. El número de correlaciones significativas observadas en pacientes supervivientes y fallecidos fue similar. **Conclusión:** Este estudio sugiere la importancia de los leucocitos y la PCR en COVID-19 y un posible valor predictivo para la evolución grave del NLR en la enfermedad.

Palabras clave: COVID-19, relación neutrófilos/linfocitos, proteína C reactiva, progresión de la enfermedad, correlaciones.

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. This virus affects different organs and tissues by inducing exacerbated inflammation[1,2] due to the interaction of the virus with its enzymatic receptor ACE2 (angiotensin-converting enzyme 2), inducing a decrease in the activity and expression of this enzyme and a subsequent increase in angiotensin II (Ang II) and a severe systemic proinflammatory state known as "cytokine storm"[2–5].

Previous reports have identified Ang II as an inducer of proinflammatory cytokines, including C-reactive protein (CRP), so the increase in this indicator in SARS-CoV-2 infection has been associated with mortality, capable of causing damage during SARS-CoV-2 infection[2,6-8]. C-reactive protein has long been used to indicate acute phase inflammation[9]; However, in COVID-19, it is related to tissue damage and poor disease prognosis[10]. In this regard, elevated levels of CRP in the early phase of COVID-19 have been associated with lung damage and disease severity[11-13].

The relationship between the absolute neutrophil count and the absolute lymphocyte count (neutrophil/lymphocyte ratio: NLR) has become a crucial marker of systemic inflammation in recent years[14], and its elevation has been described in several chronic inflammatory processes as it reflects both the adaptive immune response (mediated by lymphocytes) and the innate immune response (mediated by neutrophils)[14,15].

Two recently published works suggest that an increase in NLR predicts severe disease due to COVID-19. Although these are post hoc analyses of retrospective studies carried out in the Chinese population, these studies use the NLR value with different cut-off points and at different times of the disease[16,17]. So far, we have not found any published work on NLR and COVID-19, nor have we even found NLR and CRP in Ecuador, which would provide important information on the pathophysiological implications of the disease.

The general population of Ecuador was subjected to the COVID-19 pandemic for several months, resulting in a large number of affected people and numerous deaths[18,19]. The application of many inflammatory markers has been limited in daily clinical practice due to their costs and technical difficulties in measurement. The role that determining NLR would play during COVID-19 and its relationship with another inflammation marker, such as CRP, has not been reported in this disease. All studies focused on analysing the pathogenesis of this disease will be beneficial for the preventive and therapeutic approaches of patients affected by the disease in the country.

Studying the association of these inflammatory parameters (NLR, CRP) can provide important information on the pathophysiological implications of COVID-19. Both parameters have been described as sensitive markers of the inflammatory response. However, it is worth noting that NLR measurement is a cheaper, more routine and easily measurable variable calculated by quantifying routinely analysed leukocytes. This research aims to determine NLR values and CRP levels in patients with COVID-19, comparing the results between infected individuals who survived and those who died.

Materials and methods

This retrospective study was conducted on patients with suspected COVID-19 from various clinical institutions in Portoviejo, Manabí, Ecuador, from March to June 2021. A total of N=41 COVID-19-positive patients were included and evaluated for SARS-CoV-2. A nasopharyngeal swab sample was taken from each patient to detect SARS-CoV-2 RNA by RT-PCR using the cobas® SARS-CoV-2 Qualitative assay from Roche Molecular Systems INC. The collected samples were taken using a standard technique in viral culture medium and sent to molecular biology laboratories for processing in hospitals authorised by the National Institute of Public Health Research (INSPI) of Ecuador, which met the requirements in time and form for the study. The patients were classified into two groups according to their results (survivor: 22 and deceased: 19).

Data such as age and sex, complete blood count with differential count (lymphocyte and neutrophil count) and C-reactive protein levels were collected from each patient's medical records. A venous blood sample with EDTA anticoagulant (3 ml) was taken to perform a Complete Hematology, which was processed by the electrical impedance method for the count and the SFT method for haemoglobin in a BC-2600 Auto Hematology Analyzer (Vitalab Distributor). Neutrophil/lymphocyte ratio (NLR) calculation was made by dividing the absolute neutrophil count by the absolute lymphocyte count. To determine C-reactive protein (CRP), blood without anticoagulant (5 ml) was taken from each patient to obtain serum. PCR was assessed using an Azmoon PARS CRP immunoturbidimetry kit on a HITACHI 7600-020 automated biochemical analyser.

The study was reviewed and approved by the Bioethics Committee of the Faculty of Health Sciences of the Technical University of Manabí under number CB-265-21, dated November 8, 2021, in compliance with the Ethical Standards and Principles.

Statistical analysis: was performed using the Jamovi project, version 2.3 (2022). Measurement data with normal distribution are represented as mean ± standard deviation. For continuous variables that were normally distributed, differences between the two groups were compared using Welch's t-test. Correlation analysis was calculated using the Pearson correlation test. A p-value < 0.05 was considered statistically significant.

This study included 41 patients infected with SARS-CoV-2, of which 36.6% were men[15] and 63.4%[26] were women. Table 1 depicts blood variables and C-reactive protein values of deceased patients with those who survived. Excluding age, significant differences were observed in all variables compared to deceased vs survivor patients, in which circulating neutrophils, lymphocytes, and CRP were significantly lower in deceased patients than survivors, while N/L ratio was significantly higher in deceased patients.

Table 2 displays a correlation matric analysis between age (X±SD: 54.58± 16.42) haematologic variables, NLR, and CRP in deceased patients. It was observed that there was a positive and statistically significant correlation between lymphocytes and age, NLR and age, and NLR and neutrophils. In contrast, a statistically significant negative correlation was observed between NLR and lymphocytes. The correlation coefficients (r) ranged from 0.493 to 0.544, indicating a moderate association between these variables.

Table 3 displays a correlation matric analysis between age (X±SD: 52.91±17.12), haematologic variables, NLR, and CRP in survivor patients. It was observed that there was a positive and statistically significant correlation between Neutrophils and age, lymphocytes and age, Neutrophils and lymphocytes, and CRP with Age, Neutrophils and Lymphocytes. The correlation coefficients (r) ranged from 0.521 to 0.797, indicating a moderate to strong association between these variables.

Table 1. Blood markers between surviving and deceased COVID-19 patients

	All patients			Deceased			Survivors			
Parameters	**X±SD**	**Min value**	**Max value**	**X±SD**	**Min value**	**Max value**	**X±SD**	**Min value**	**Max value**	***P values***
Age	53.68±16.61	16	86	54.58± 16.42	18	86	52.91± 17.12	16	84	***NS***
Neutrophils (K/μL)	12.16±5.78	3.11	23.65	9.35±5.32	3.11	23.65	14.58±5.10	3.51	19.34	***0.003***
Lymphocytes (K/μL)	4.40±3.24	0.22	11.0	1.49± 0.90	0.22	3.05	6.90± 2.26	1.84	11.02	***< .001***
NLR	6.44±11.95	1.12	75.23	11.29±16.43	1.21	75.23	2.25±1.13	1.13	6.68	***0.028***
CRP (mg/L)	51.73±29.86	12.0	96.0	30.02± 21.50	13.0	77.0	71.38±21.66	12.0	96.0	***< .001***

Welch t-test was used for all pairwise comparisons. **Abreviations:** CRP: C-reactive protein; NLR: Neutrophil / Lymphocyte ratio; COVID-19: N=41; Deceased: n = 19; Survivors: n = 22. Results are expressed as mean ± standard deviation (X±SD); Min: value minimum; Max: value maximum; NS: No statistically significant.

Table 2. Correlation analysis matrix between quantitative variables in deceased patients.

Variables	**AGE**		**Neutrophils (K/μL)**		**Lymphocytes (K/μL)**		**NLR**		**CRP (mg/L)**	
	r value	***p-value***	***r value***	***p-value***	***r value***	***p-value***	***r value***	***p-value***	***r value***	***p-value***
AGE	-	-								
Neutrophils (K/μL)	0.115	0.639	-	-						
Lymphocytes (K/μL)	**0.544***	**0.016**	-0.104	0.673	-	-				
NLR	**0.520***	**0.023**	**0.493***	**0.032**	**-0.538**	**0.017**	-	-		
CRP (mg/L)	0.382	0.106	0.086	0.725	-0.011	0.966	0.025	0.920	-	-

Pearson's correlations test. NLR: CRP: C-reactive protein; Neutrophil / Lymphocyte ratio; Deceased: n=19.

Table 3. Correlations analysis matrix between quantitative variables in survivor patients.

Variables	**AGE**		**Neutrophils (K/μL)**		**Lymphocytes (K/μL)**		**NLR**		**CRP (mg/L)**	
	r value	***p-value***	***r value***	***p-value***	***r value***	***p-value***	***r value***	***p-value***	***r value***	***p-value***
AGE	-	-								
Neutrophils (K/μL)	**0.521***	**0.013**	-	-						
Lymphocytes (K/μL)	**0.690*****	**<0.001**	**0.645***	**0.001**	-	-				
NLR	0.299	0.176	0.321	0.146	-0.400	0.065	-	-		
CRP (mg/L)	**0.715*****	**<0.001**	**0.593****	**0.004**	**0.797*****	**<0.001**	0.330	0.134	-	-

Pearson's correlations test. NLR: CRP: C-reactive protein; Neutrophil / Lymphocyte ratio; Survivors: n=22.

Discussion

The disease caused by SARS-CoV-2 infection (COVID-19) began spreading at the end of 2019 and became a pandemic in 2020. This virus is highly contagious and has threatened health and life worldwide since its onset[20]. Most infected individuals are asymptomatic or present mild symptoms and have early remission[21]. However, some patients develop severe symptoms that can lead to death. There are few studies on the characteristics of biometric parameters associated with disease severity and progression in patients who have died and those who have survived COVID-19.

The increase in CRP has been previously documented in this viral infection, representing a cytokine not only as a marker of inflammation but also as an effector, contributing to the damage caused by SARS-CoV-2[2]. Most patients show normal white blood cell counts or lymphopenia, which may be involved in the higher NLR values[22]. High NLR values have been associated with inflammatory processes[14,15,23]; SARS-CoV-2 infection represents a parameter for severe disease evolution[24-2].

In pathophysiological terms, lymphopenia represents a depletion of lymphocytes in response to excessive inflammation where the organism, to compensate for this situation, produces abundant proinflammatory cytokines, leading to a cytokine storm and severe disease evolution[27]. This association was evidenced in our findings, where deceased patients showed higher NLR values than survivors, possibly due to higher lymphocyte count values in surviving patients. The lower lymphocyte production in deceased patients is possibly related to disease severity. In this regard, the number of lymphocytes has been reported to be decreased in SARS-CoV-2 infection, associated with high viral load and increased organ damage, and thus the severe course of the disease[26].

Correlation analyses between the different parameters were significant between deceased and surviving patients. Regarding the number of correlations, there were significant differences related to the pathogenesis of the disease in survivor patients. In this regard, CRP values were positively correlated with neutrophil counts, lymphocyte counts, and age in survivor patients. The effector role of CRP in COVID-19 as an inflammation-inducing cytokine has been previously reported[2]. The correlation between CRP and the number of neutrophils and lymphocytes suggests a role of this cytokine in leukocyte increment. In this regard, CRP may induce hepatic production of IL-6[28,29], a leukocytosis-inducing cytokine.

IL6 is essential in the progression of COVID-19, perpetuating the cytokine storm in patients, thus promoting the differentiation and activation of immune cells residing in different tissues; an example occurs in alveolar macrophages, alveolar megakaryocytes and neutrophils, which, when exposed to high amounts of IL6, release extracellular quantities of neutrophils to the affected bloodstream or parenchyma. Neutrophils can behave as damage-associated molecular patterns (DAMPs), activating macrophages, platelets (PLT) and lymphocytes, and an elevated proinflammatory and pro-thrombotic profile. Consequently, leukocyte migration to sites of extensive tissue damage increases signalling and alteration in immune regulation, with a decrease in the lymphocyte population responsible for self-limiting inflammatory stimuli. On the other hand, IL6 stimulates the production of fibrinogen/fibrin due to endothelial injury, producing an increase in C-reactive protein (CRP). This mechanism could explain the high CRP levels in patients who managed to survive COVID-19[30].

However, although the poor prognosis of COVID-19 has been reported in patients with high levels of CRP and leukocytosis[31], in this study, the CRP behaviour was different; that is, it was high in survivors. Many of the discrepancies shown in various studies concerning the parameters evaluated may be due to the demographic characteristics and comorbidities of the population studied, sample size and type of study carried out.

In the case of deceased patients, age was correlated with leukocytosis at the expense of lymphocytes, which is probably related to the negative tension between NLR values and lymphocytes, which could represent a detrimental factor in the deceased group. Studies report similar results where CRP is positively correlated with NLR and NLR is negatively correlated with total leukocyte count in patients without defining the degree of severity[24].

The value of NLR as a predictor factor of COVID-19 evolution remains controversial[32]. Some studies have reported that the NLR value predicts the severe evolution of SARS-CoV-2 infected patients. It has also been reported[22-33] that NLR values of 5.5 or higher are highly predictive in COVID-19 diagnosis and progression (91.4%). However, other researchers disagree with those findings, as NLR values can be affected by various conditions such as other infections, corticosteroids, malignancies, alcohol consumption, bleeding, and other conditions, concluding that the routine use of NLR in the prognosis and progression of COVID-19 to severity requires further study[34,35]. Our study shows that the severe evolution of patients infected by SARS-CoV-2 (patients who died) was related to high NLR values.

The present study had several limitations, some of them being the number of samples analysed and selected, limiting the possibility that the results could be extrapolated to other populations. As it is retrospective, the data collected corresponds to clinical electronic history records, subject to biases inherent to data recording. The study was carried out at the beginning of the pandemic, when

the behaviour of the virus variants that affected the population at that time was still unknown, making it difficult to track and monitor each marker given the emergency condition with which these patients were admitted to the hospital. On the other hand, the vaccine application had not yet come into effect, which is why the clinical symptoms were much more serious. Although we found significant associations associated with the severity of the disease, more multicenter studies are needed with a larger number of participants, allowing our findings to be replicated in a large percentage of the national population.

Conclusions

In conclusion, patients who progressed to death had low leukocyte counting with lower CRP levels alongside higher NLR values compared with surviving patients. The number of correlations was similar in deceased and surviving patients. In deceased patients, CRP was positively correlated with leukocytes, neutrophils, and age. In surviving patients, CRP was positively correlated with lymphocytes and age and negatively correlated with NLR, while age was positively correlated with lymphocytes and negatively correlated with NLR. This study shows the importance of leukocytes and CRP in the pathophysiology of COVID-19 and a possible predictive value for the severe evolution of NLR in the disease.

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