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Article

Association of serum lipoproteins and inflammatory parameters derived from the blood test with renal function in COVID-19 outpatients

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Changes in lipoprotein metabolism are among the main causes of hemodynamic impairment in renal function. COVID-19 is an multisystemic inflammatory disease, aggravating this situation. This cross-sectional study investigated the relationship of serum lipoprotein profile with inflammatory parameters and renal function in 95 COVID-19 outpatients in comparison with 173 with flu-like symptoms. Serum samples were collected for the determination of total cholesterol and fractions, apolipoproteins (Apo A-I and Apo B), urea (sUr) and creatinine (sCr). The glomerular filtration rate (eGFR) was calculated. Neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios were calculated as inflammatory parameters derived from the blood tests. COVID-19 patients presented lower high-density lipoprotein cholesterol (HDL-c) (47.90 ± 1.543 vs. 51.40 ± 0.992) and higher PLR (190.9 ± 9.410 vs. 137.6 ± 5.534) and NLR (3.40 ± 0.22 vs. 2.80 ± 0.15). Both NLR and PLR correlated with each other ($r = 0.639$). Furthermore, the Apo B/Apo A-I ratio was correlated with PLR ($r = 0.5818$) and eGFR ($r = -0.2630$). COVID-19 patients classified as at high risk of developing acute myocardial infarction based on the Apo B/Apo A-I ratio had higher values for sUr/sCr. Thus, serum apolipoproteins, PLR, and NLR could be related to renal dysfunction in COVID-19.

Keywords: SARS-CoV-2. Apolipoproteins. Glomerular filtration rate.

INTRODUCTION

Renal and cardiovascular diseases are a worldwide concern due to high morbidity and mortality rates (Hill *et al*., 2016). In COVID-19, they were among the main risk factors for the development of severe forms and death (Azevedo *et al*., 2020). The inflammatory reaction triggered by the viral infection itself can drop the levels of cholesterol associated with high-density lipoprotein (HDL-c). Despite the lack of a clear mechanism, it is common for people with systemic inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, meningitis, and obesity to also have changes in lipoprotein metabolism (Feingold, Grunfeld, 2022). The researchers explain that some viruses interact with the host's lipid metabolism to promote replication and avoid the immune response, which can occur in COVID-19 due to changes in the lipoprotein profile (Sviridov, Bukrinsky, 2014).

The mechanism of infection by SARS-CoV-2 reveals that it binds to the angiotensin converting enzyme 2

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(ACE2) receptors through its S protein (Spike), affecting several organs concomitantly, such as the vascular endothelium, kidneys, and especially the lungs. After infection, complications involving the cardiovascular and renal systems are proposed to occur through two main mechanisms: the virus induces cytotoxicity in cells that express ACE2 receptors and/or thrombo-inflammation, leading to multiple organ dysfunction (Lopes-Pacheco *et al*., 2021).

The severe form of COVID-19 is mainly associated with the intrinsic characteristics of each individual, such as age (70 years or older) and comorbidities (diabetes *mellitus*, hypertension, obesity, and coronary heart disease) (Lopes-Pacheco *et al*., 2021). Changes in lipid metabolism, such as dyslipidemia, have long been established as risk factors for cardiovascular disease. In addition to the laboratory analysis of serum lipids such as cholesterol and triglycerides, the analysis of the protein components of lipoproteins, apolipoproteins, mainly A-I and B (Apo A-I and B), has shown good prediction for cardiovascular events and for organic impairments, such as a reduction in the glomerular filtration rate (GFR) (Aguilar-Ramirez *et al*., 2021; Henry *et al*., 2021).

The inflammatory response in severe COVID-19 is characterized by a cytokine storm and a hematological profile with numerical and morphological changes, indicating neutrophilia, lymphopenia, and thrombocytopenia (Coradi, Vieira, 2021). Endothelial activation with vascular adhesion molecules and neutrophilia caused by COVID-19 can initiate the process of inflammatory cell migration to the subendothelial compartment, which can intensify to the point of causing endothelial wall damage, favoring platelet activation and thrombus formation (Nagashima *et al*., 2020). Thus, the risk of dysfunction in multiple organs, such as the kidneys, liver and heart, tends to increase in those individuals affected by COVID-19 that have a previous proatherogenic lipid profile (Tang *et al*., 2021).

The severity of COVID-19 is associated with an inflammatory cytokine storm and a prothrombotic state. White blood cells and platelets play a prominent role, as is evident from the hemogram analysis of COVID-19 patients, where neutrophilia, lymphopenia, and thrombocytopenia have been reported. Moreover, the accumulating evidence shows that neutrophil/lymphocyte (NLR) and platelet/lymphocytes (PLR) are useful hemogram-derived ratios in diagnosing COVID-19 (López-Escobar *et al*., 2021; Yang *et al*., 2020). Furthermore, dyslipidemia aggravates the inflammatory state by generating free radicals, which activate pro-inflammatory genes and recruit leukocytes, especially neutrophils. The activated genes and neutrophils release inflammatory mediators, leading to increased platelet adhesion, which results in an inflamed and pro-thrombotic microenvironment (Padró, Vilahur, Badimon, 2018).

Kidneys are highly vascularized organs whose functions are dependent on cardiovascular health in terms of arteriole caliber, perfusion pressure, vasodilation, and vasoconstriction, events such as atherosclerosis, thrombosis, embolism, and endothelial dysfunction reduce glomerular irrigation and, as a result, filtration capacity (Guan, VanBeusecum, Inscho, 2015). In COVID-19, it is suggested that, in addition to the infection causing direct damage to podocytes and tubular cells, resulting in tubular necrosis with an inflammatory infiltrate, the increased action of angiotensin II on AT1 receptors causes hyperinflammation with cytokine storm and lymphopenia, leading to a state of hypercoagulation and hemostasis (Głowacka *et al*., 2021; Piñeiro *et al*., 2021). Thus, the kidneys play a major role in the prognosis of COVID-19 because to their inherent characteristics, with acute kidney injury being related with prolonged hospital stays and mortality in hospitalized patients (Głowacka *et al*., 2021).

Early assessment of acute kidney injury (AKI) is a key point in the prognosis of these patients since the kidneys are essential for the maintenance of homeostasis (Legrand *et al*., 2021). Therefore, the present study aimed to investigate the relationship of serum lipoprotein profile with inflammatory parameters and renal function in COVID-19 outpatients.

METHODS

Study, location, sample, duration

This is a descriptive, analytical, and cross-sectional study that analyzed laboratory parameters of lipid profile,

renal function, and hematology in 268 outpatients treated with suspected COVID-19 in a Sentinel Unit in the city of Fortaleza from February to June 2021, during the second wave of COVID-19 cases in Brazil. The work was approved by the Ethics in Research Committee of the Federal University of Ceará (CEP/UFC) under the number 40615320.90000.5054.

The inclusion criteria for this study were those in the age group between 18 and 60 who have mild flu-like symptoms. Exclusion criteria were patients with a history of cardiovascular diseases and a previous laboratory diagnosis of dyslipidemia according to the update of the Brazilian guideline on dyslipidemia and atherosclerosis prevention (2017), which considers the laboratory classification of dyslipidemia to be: isolated hypercholesterolemia (LDL-c ≥ 160 mg/dL); isolated hypertriglyceridemia (TG ≥ 150 mg/dL or ≥ 175 mg/dL, if the sample is obtained without fasting); mixed hyperlipidemia (LDL-c ≥ 160 mg/dL and TG ≥ 150 mg/dL or ≥ 175 mg/dL, if the sample is obtained without fasting) and low HDL-c (men < 40 mg/dL and women < 50 mg/dL) dL) (Faludi *et al.,* 2017).

Participants were divided according to the RT-qPCR (Reverse Transcriptase Quantitative Polymerase Chain Reaction) test result for SARS-CoV-2 when they were categorized as COVID-19 positive or negative (those with other respiratory syndromes).

Laboratory parameters

Lipid profile

Serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) were measured by the enzymatic method (Bioclin®), in addition to apolipoproteins A-I and B (Apo A-I and Apo B) by turbidimetry (Randox®) on a BS-120 Mindray spectrophotometer. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula, considering that patients with dyslipidemia were excluded and those with triglycerides ≥ 400 mg/dL, the main limitation of the formula, were not part of the sample. Non-HDL cholesterol (non-HDL-c) was calculated by subtracting HDL-c from TC. Regarding the interpretation parameter, Apo B/Apo A-I ratio was adopted (Faludi *et al*., 2017; Friedewald *et al*., 1972).

Kidney function

Serum levels of urea (sUr) and creatinine (sCr) were measured using the kinetic method (Bioclin®) in a BM-200 Mindray automatic equipment, in addition to calculating the urea/creatinine (sUr/sCr) ratio. The Cockcroft-Gault formula was also used to measure the estimated glomerular filtration rate (eGFR), calibrated by age, sex, and body surface area (Cockcroft, Gault, 1976).

Hematological parameters of inflammation

The markers proposed by Yang *et al.* (2020) were obtained from the absolute values of leukocyte and platelet populations present on the blood tests and the ratios of neutrophils/lymphocytes (NLR) and platelets/lymphocytes (PLR).

Statistical analysis

Statistical analyses were performed using the GraphPad Prism® version 6 software, where the Shapiro-Wilk test was applied to verify the distribution of the continuous variables regarding normality. Means were compared by unpaired Student's T test (2 groups) and analysis of variance (ANOVA) (> 2 groups) with the Turkey post-test, expressed as mean ± standard error of mean (SEM). Pearson's correlation was applied in order to verify a linear relationship between the variables. The frequencies between the groups of categorical variables were compared by chi-square (X^2). A significance level of $p < 0.05$ was adopted.

RESULTS

A total of 268 patients were included, among which 95 (35.45%) tested positive for the SARS-CoV-2 virus by the RT-qPCR test. The population sociodemographic and anthropometric data studied show a predominance of females with a mean age between 38 and 39 years and a having mean body mass index (BMI) of 27 kg/m^2 (Table I).

TABLE I – Sociodemographic and anthropometric data of the studied population

Data		COVID-19 Positive (N = 95)	COVID-19 Negative (N = 173)	*p*
Sex - n (%)	Male	29 (30.53%)	71 (41.04%)	#**0.011**
	Female	66 (69.47%)	102 (58.96%)	
Age – $\bar{x}$ ± SEM		39.52 ± 1.37	38.26 ± 1.12	*0.492
BMI – $\bar{x}$ ± SEM		27.56 ± 0.56	27.81 ± 0,43	*0.735

Chi-square test; * Unpaired t test (mean ± standard error of mean); BMI – body mass index; Significance of $p < 0.05$.

Comparing the laboratory parameters between patients, COVID-19 patients had reduced levels of HDL-c and, consequently, decreased TC. Regarding renal function parameters, there was no difference. In addition, the complete blood test revealed upregulation of inflammatory markers in these individuals, especially the PLR, which increased by 40% (Table II). The comparison regarding the NLR and PLR relationships between the two groups is shown in Figure 1.

TABLE II – Comparison of lipid profile, renal function, and inflammation parameters among COVID-19 positive and negative patients

Parameters	COVID-19 Positive ($\bar{x}$ ± SEM)	COVID-19 Negative ($\bar{x}$ ± SEM)	*p*
Lipid profile			
TC (mg/dL)	189.4 ± 4.88	202.4 ± 3.92	**0.027**
HDL-c (mg/dL)	47.9 ± 1.54	51.4 ± 0.99	**0.040**
LDL-c (mg/dL)	108.5 ± 4.44	118.9 ± 3.53	0.074
Non-HDL-c (mg/dL)	140.6 ± 4.79	151.0 ± 3.81	0.096
TG (mg/dL)	173.1 ± 14.65	165.4 ± 8.34	0.729
Apo B/Apo A-I	0.57 ± 0.019	0.57 ± 0.013	0.893
Kidney function			
Creatinine (mg/dL)	0.86 ± 0.094	0.78 ± 0.013	0.248
Urea (mg/dL)	24.6 ± 0.97	25.4 ± 0.63	0.477
Urea/Creatinine	31.6 ± 0.83	33.2 ± 0.81	0.209
eGFR (mL/min/m^2)	121.4 ± 2.70	117.6 ± 3.38	0.398
Inflammation (derived from the blood tests)			
NLR	3.40 ± 0.22	2.80 ± 0.15	**0.025**
PLR	190.9 ± 9.41	137.6 ± 5.53	**< 0.001**

TC – total cholesterol; TG – triglycerides; HDL-c – HDL cholesterol; LDL-c – LDL cholesterol; Non-HDL-c – non-HDL cholesterol; Apo B/Apo A-I – apolipoprotein B/apolipoprotein A-I; eGFR – estimated glomerular filtration rate; NLR – neutrophils/lymphocytes ratio; PLR – platelet/lymphocyte ratio; Unpaired t test (mean ± standard error of mean); Significance of $p < 0.05$.

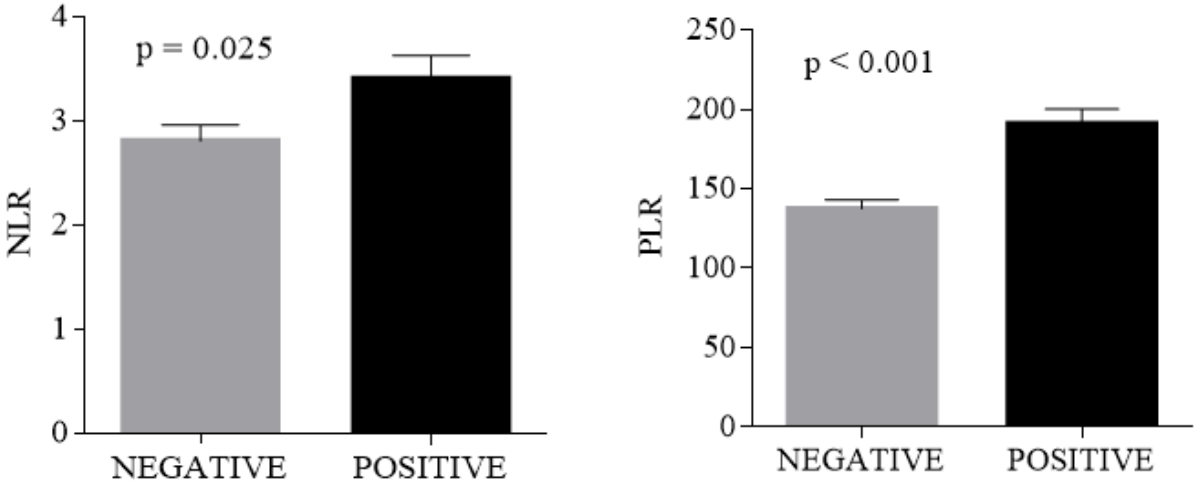

FIGURE 1 – Comparison regarding NLR and PLR among COVID-19 positive and negative patients.

NLR – neutrophils/lymphocytes ratio; PLR – platelet/lymphocyte ratio; Unpaired t test (mean ± standard error of mean); Significance of $p < 0.05$.

Furthermore, we analyzed whether these hematological markers would be helpful if investigated collectively in clinical evaluation. The NLR and PLR ratios have a strong positive correlation among individuals with COVID-19 (Figure 2).

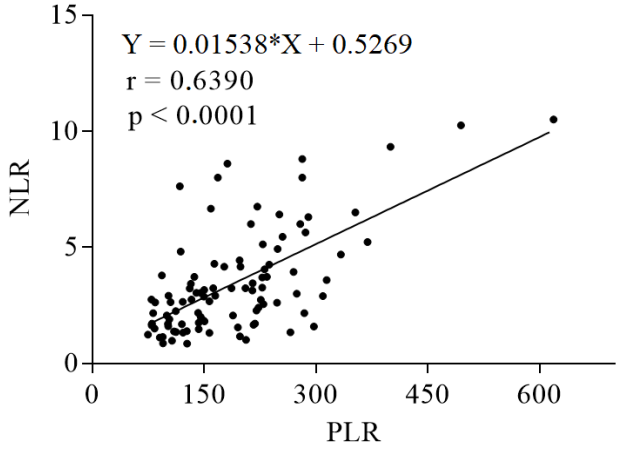

FIGURE 2 – Correlation between PLR and NLR ratios in COVID-19 outpatients. NLR – neutrophils/lymphocytes ratio; PLR – platelet/lymphocyte ratio; Pearson's correlation; Significance of $p < 0.05$.

The Apo B/Apo A-I ratio, which reflects the balance of pro- and anti-atherogenic lipoproteins, showed no difference between patients with and without COVID-19 (Figure 3). We further investigated whether the Apo B/Apo A-I ratio correlated with hematologic markers of inflammation and kidney function in individuals with COVID-19. Forward, a moderate positive correlation (r = 0.5818) was found with PLR and a negative correlation (-0.2630) with eGFR values (Figure 4).

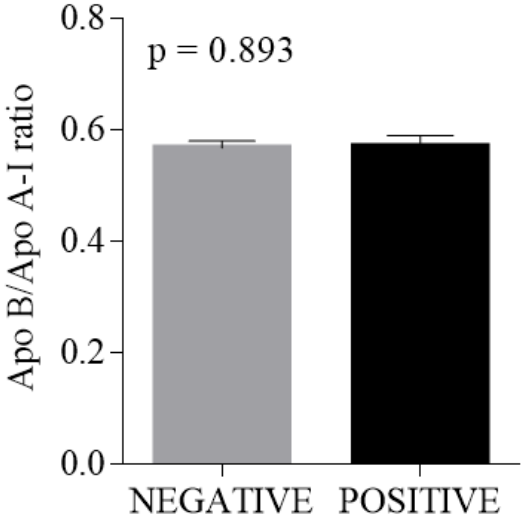

FIGURE 3 – Apo B/Apo A-I comparison among COVID-19 positive and negative patients. Apo B/Apo A-I – apolipoprotein B/apolipoprotein A-I; Unpaired t-test (mean ± standard error of mean); Significance of $p < 0.05$.

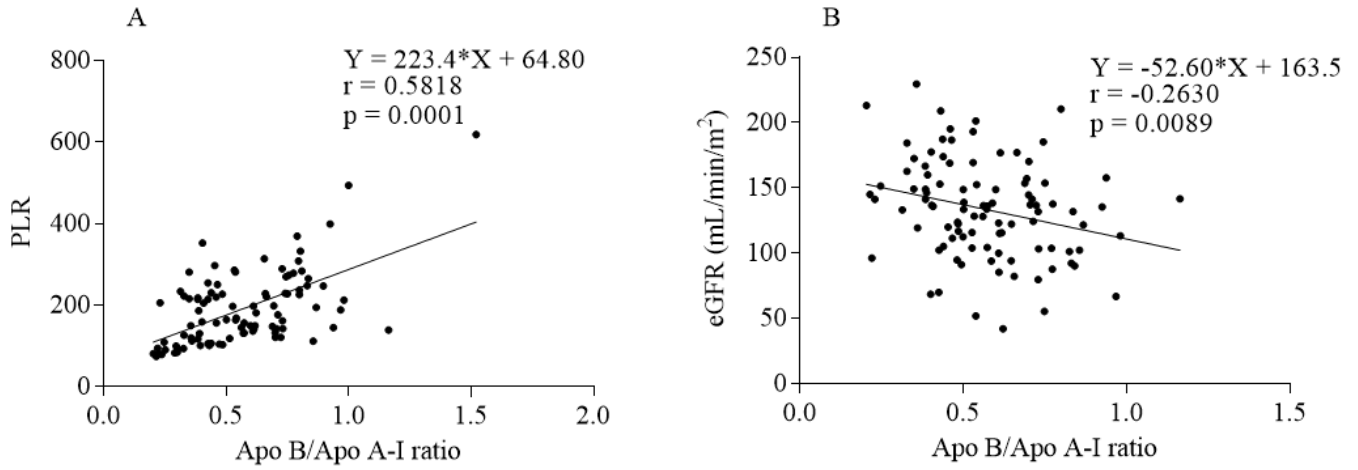

FIGURE 4 – Correlation between Apo B/Apo A-I ratio with PLR and eGFR in COVID-19 outpatients. Figure 5A - Correlation between PLR and Apo B/Apo A-I; Figure 5B - Correlation between eGRF and Apo B/Apo A-I; Apo B/Apo A-I – apolipoprotein B/apolipoprotein A-I; PLR – platelet/lymphocyte ratio; eGFR – estimated glomerular filtration rate; Pearson's correlation; Significance of $p < 0.05$;

To verify the impact on eGFR, individuals with COVID-19 were stratified into three groups according to the level of acute myocardial infarction (AMI) risk proposed by Lima *et al*. (2007) based on Apo B/Apo A-I ratio values for each sex (Figure 5). The risk of the individuals was classified as "low", "moderate" and "high" and the values of the urea/creatinine ratio (sUr/sCr) between the groups were compared. A difference was observed between the mean values of the sUr/sCr ratio between individuals with "low" and "high" risk, where the higher the risk, the higher the sUr/sCr ratio (Figure 5).

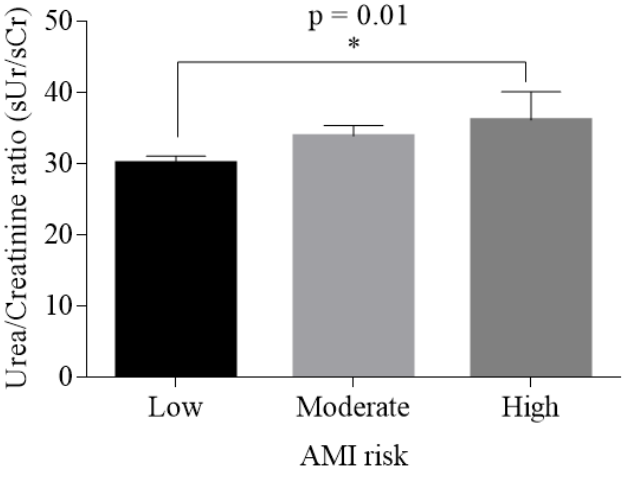

FIGURE 5 – Distinction in Urea/Creatinine ratio based on acute myocardial infarction risk.

Acute Myocardial Infarction (AMI) risk classification based on Apo B/Apo A-I ratio values for each sex (Male: low 0.40 - 0.69; moderate 0.70 - 0.89; high 0.90 - 1.10; Female: low 0.30 - 0.59; moderate 0.60 - 0.79; high 0.80 - 1.00), according to Lima *et al*. (2007); ANOVA (mean ± standard error of mean) with Tukey's post-test; Significance of $p < 0.05$.

DISCUSSION

The present study has indicated a predominance of females aged between 38 and 39 years and overweight. Also, COVID-19 outpatients had lower HDL-c, a greater inflammatory state, and association between

apolipoproteins and a decreased estimated glomerular filtration rate. The epidemiological data of COVID-19 in the State of Ceará corroborates the results of this study, where it was found that females are more frequent (54.9%) in confirmed cases, while males are more frequent in cases of hospitalization (55.5%) and deaths (54.8%) (Ceará, 2023). In relation to Latin America, this difference is more evident, where 60 % of victims were male and over 70 years of age. The mortality rate per 10,000 inhabitants is 50.69 for males and 31.59 for females (OPAS, 2021).

Patients included in the present study met the criteria for being overweight (mean BMI of 27 kg/m^2). Studies show that overweight individuals are prone to systemic inflammation, endothelial dysfunction, and atherosclerosis. These patients are at high risk of hospitalization, admission to the intensive care unit, and the need for invasive mechanical ventilation if compared to patients with a normal BMI who contract COVID-19 (Yang *et al*., 2021). Furthermore, one of the main metabolic alterations observed in overweight individuals is the decrease in the amount and functionality of HDL-c, mainly due to the reduction in the production of Apo A-I (Stadler, Marsche, 2020).

The current study found that COVID-19 outpatients had lower mean TC and HDL-c levels, as well as higher inflammatory markers. These findings support previous research on COVID-19 cardiovascular complications, indicating that the pathophysiological mechanisms that lead to cardiovascular events include an exacerbated inflammatory response with inflammatory infiltrate, endothelial damage, and disseminated coagulation (Iba, Connors, Levy, 2020). Furthermore, the state of each individual at the moment of infection with the SARS-CoV-2 virus is linked to the outcome, because the virus's entry into cells produces direct damage and activation of the NLRP3 inflammasome (Potere *et al*., 2022).

Overweight, low HDL-c, and inflammation are all favorable circumstances for atherosclerosis pathogenesis and plaque instability (Sousa, Ribeiro, 2019). In COVID-19, endothelial activation brought on by the SARS-CoV-2 virus increases the expression of vascular adhesion molecules, which facilitates the entry of neutrophils and monocytes into the subendothelial compartment and increases the production of pro-inflammatory cytokines like interleukin 1β (IL-1β), IL-6, and IL-18, making macrophages hyperactive (Shi *et al*., 2022). However, the development of atherosclerosis is a very slow process, that takes years or decades to become evident. It is important to emphasize that the association between low HDL-c and the immune biomarkers evaluated in the present study could only be limited to patients showing advanced plaques or under secondary prevention at very high cardiovascular risk.

The gravity of COVID-19 has been extensively screened using laboratory markers. The use of markers such as troponin, d-dimer, C-reactive protein (CRP), procalcitonin, and IL-6 were investigated, but these measures either require specialized attention or have significant related costs (Zeng *et al*., 2020). The NLR and PLR ratios derived from the blood tests, on the other hand, have been described as predictors of the severe form of COVID-19, providing a rapid and low-cost alternative for diagnostic and prognostic evaluation (Yang *et al*., 2020). In the present study, NLR and PLR were correlated and elevated in COVID-19 outpatients, demonstrating their power to predict inflammatory diseases, as well as being considered important in the diagnosis and prognosis of cancer, rheumatoid arthritis, chronic obstructive pulmonary disease, and vaso-oclusive crises (Guven, Kilic, 2020; Kang *et al*., 2021; Li, Xie, 2021; Perrotta *et al*., 2020).

In regard to microvascular health, the Apo B/Apo A-I ratio indicates the balance of pro-atherogenic compared to anti-atherogenic lipoproteins (Lima *et al*., 2007; Sniderman *et al*., 2011). Although the Apo B/Apo A-I ratio did not differ between the groups, it was positively correlated with PLR and negatively correlated with eGFR in COVID-19 outpatients. These data show that the microvasculature's health and the risk of vaso-occlusive events, as measured by Apo B/Apo A-I and PLR ratios, may have a direct impact on eGFR (Asha *et al*., 2014; Ye *et al*., 2020).

The kidneys are highly vascularized and metabolically active organs that play an important role in the cardiovascular system through the renin-angiotensin-aldosterone system (RAAS). Studies associate the actions of angiotensin II with the pathogenesis of atherosclerosis,

which involves vasoconstriction, oxidative stress, and a pro-thrombotic state (Silva *et al*., 2020). In COVID-19, the direct binding of the virus to ACE2 receptors leads to its internalization and, consequently, impacts the enzyme's action in converting angiotensin II into angiotensin 1-7, thus, the decrease in renal function in these patients can be caused by the increased actions of angiotensin II (Gonçalves *et al*., 2023).

Lipoprotein metabolism disorders are linked to impaired renal function, albeit the reasons are unknown. Population studies have associated elevated levels of Apo B/Apo A-I with arterial calcification and contrast-induced acute kidney injury (Kim *et al*., 2017; Tao *et al*., 2021). In the present study, COVID-19 outpatients were classified according to the risk of acute myocardial infarction (AMI) based on the Apo B/Apo A-I ratio, when the values of the sUr/sCr ratio were compared, a difference was observed between individuals with low and high risk of AMI. A Chinese population-based study found a strong association of elevated Apo B levels and stages of chronic kidney disease (Zhao *et al*., 2020).

As a result, despite the difficulties encountered in carrying out this work due to public health conditions, such as a reduced number of patients and the impossibility of controlling one's dietary status. Important discoveries have been achieved regarding the knowledge of COVID-19, as well as the applicability of quickly and at low costs analyzing values derived from blood tests. Furthermore, the population was chosen in a public health reference unit, allowing for the observation of heterogeneity in the characteristics of the participants in this study. This work strongly encourages investigation of the pathophysiological mechanisms that link lipoprotein metabolism and renal function.

CONCLUSIONS

In conclusion, COVID-19 outpatients presented lower HDL-c and a thrombo-inflammation profile that can be monitored via hematological parameters quickly and without much cost. The Apo B/Apo A-I ratio was positively correlated with the risk of thrombus established by the PLR and negatively with the eGFR. NLR and PLR in association with the lipid profile have shown promising results for application in the hospital admission and clinical follow-up of these patients.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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