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CORRELATION OF FERRITIN AND D-DIMER WITH TOMOGRAPHIC LUNG INJURIES IN COVID-19

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ABSTRACT

A retrospective study of 114 medical records from a cohort in the Amazon, northern Brazil, of individuals with COVID-19 during up to 14 days of infection, under outpatient control, was carried out through the analysis of inflammatory biomarkers (D-Dimer and Ferritin) and lung CT scans. This study was conducted in the same laboratory between January and April 2021. All participants were over 18 years old, of both sexes and residents in the state of Pará. Females were the majority (57%) and with ages between 46-60 years (40.4%). CT scans showed bilateral involvement (88.6%), around 10 to 25% of the lung fields (41.2%), containing lesions with thickening of the interlobular septa prevailing (29.8%). There was a predominance of the normality pattern of inflammatory biomarkers such as Ferritin (66.7%) and D-Dimer (74.6%). There was no relation between altered Ferritin and D-Dimer with a greater extent of involvement in lung CT images, ranging from 10-75%. The same clinical and laboratory behavior already recorded on several continents was observed, showing that the virus-host relationship is mediated by the immune response, and other parameters yet to be discovered that will define the clinical evolution of COVID-19, between mild, moderate and severe. Biomarker and tomographic parameters are of great importance in the joint analysis, supporting the decisions taken regarding keeping these patients out of hospital.

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INTRODUCTION

The first signs of COVID-19 emerged in late 2019, in Wuhan, China. First, there was an epidemic of pneumonia, which killed several people, requiring the adoption of social isolation at that location (COWLING; LEUNG, 2020). Initial investigations pointed out that it was a virus of the Coronaviridae family, related to bats consumed in markets, and possible transmitters of the virus to humans (TIAN *et al.*, 2020). It was SARS-CoV-2, a betacoronavirus composed of a single-stranded RNA, that causes COVID-19 (CASTRO-DE-ARAUJO *et al.*, 2020). The virus has proteins on its surface that help its entry into host cells that are related to pathogenesis, and it mutates more frequently than deoxyribonucleic acid (DNA) viruses (TIAN *et al.*, 2020).

It is responsible for clinical forms that range from asymptomatic, mild and even fatal, in which, in addition to pulmonary involvement, other manifestations are increasingly identified. This virus is easily transmissible through respiratory droplets, and thus it reached thousands of people in the world, assuming a pandemic character due to its high global propagation capacity and thousands of death cases, making the World Health Organization (WHO) declare its status of pandemic in March 2020 (ANDERSON, 2020). In the lungs, the virus reaches the alveoli, multiplying and causing cell disruption, triggering the immune system, with a cascade of cytokines promoting an intense inflammatory process (KIM; GANDHI, 2020). Due to the exacerbated inflammatory process, macrophages are activated with greater iron uptake, increasing the hepatic synthesis of ferritin, a protein considered as a marker of organ failure in COVID-19 (RAMOS; OTA, 2020). Another important exam is the D-Dimer,

whose increase is related to the degree of severity of the clinical picture of the disease, with possible thromboembolism, one of the expected complications (RAMOS; OTA, 2020). Therefore, in addition to the respiratory condition, there are several symptoms that vary from individual to individual with the need to expand the investigation of patients with COVID-19, performing various laboratory and radiological tests, both for diagnosis and for the follow-up of patients with mild forms treated in outpatient clinics, and moderate and severe cases treated at the hospital level. The correlation of pulmonary tomographic images and the aforementioned tests, all performed in a single service will be the objective of this retrospective study, in a cohort of 114 non-hospitalized individuals in northern Brazil, observed between January and April 2021.

MATERIALS AND METHODS

We retrospectively evaluated 114 electronic medical records from a cohort with a symptomatic clinical picture diagnosed within 14 days as acute COVID-19, treated at the Amaral Costa Laboratorial and Diagnostic service. Patients were 18 years old or older, of both genders, coming from Belem-PA, who underwent pulmonary tomography, Ferritin and D-Dimer blood exams, in addition to other tests. All patients were under outpatient care. There was no personal contact or commitment to clinical follow-up, and all ethical parameters for research involving human beings in Brazil were complied with. Inflammatory tests were performed in accordance with the manufacturers' guidelines and the parameters for evaluation of pulmonary tomography followed the protocols of the Brazilian College of Radiology (PROKOP *et al.*, 2020).

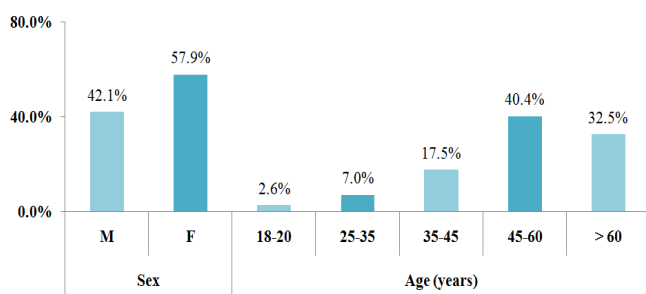
RESULTS

The cohort consisted of 114 individuals who performed the following exams, among others, chest CT scan, Ferritin and/or D-Dimer, and had the following demographics: male (43%), female (57%), ages ranging from 18-25, 26-35, 36-45, 46-60 and >60, with no significant difference in the proportion between the sexes, however, it was statistically significant in patients aged between 46 and 60 years (Figure 1; Table 1).

Table 1. Distribution of patients with COVID-19 according to sex and age group, Amazon cohort, northern Brazil, 2021

Variables	Frequency	% (N = 114)	p-value
Sex			0,0918
Female	66	57,9%	
Male	48	42,1%	
Age (years)			< 0.0001*
18 a 25	3	2,6%	
26 a 35	8	7,0%	
36 a 45	20	17,5%	
46 a 60*	46	40,4%	
> 60	37	32,5%	

*G-adherence test. Source: authors.



Source: authors.

Figure 1. Distribution of patients with COVID-19 according to sex and age group, Amazon cohort, northern Brazil, 2021

Table 2. Distribution of patients with COVID-19 according to the pattern, extent and laterality of pulmonary involvement observed on CT scan, Amazon cohort, northern Brazil, 2021

Variables	Frequency	% (N = 114)	p-value
Pattern of involvement			< 0.0001*
Typical*	103	90,4%	
Undetermined	8	7,0%	
Not informed	3	2,6%	
Impairment			< 0.0001*
< 10%	33	28,9%	
10 a 25%*	47	41,2%	
26 a 50%	20	17,5%	
51 a 70%	11	9,6%	
Not informed	3	2,6%	
Laterality			< 0.0001*
Bilateral*	101	88,6%	
Unilateral - Left	8	7,0%	
Unilateral - Right	5	4,4%	

*G-adherence test.

Source: authors.

Pulmonary CT scans showed predominantly bilateral involvement (88.6%), with typical aspects of involvement (90.4%), affecting 10 to 25% of the lung fields in (41.2%) of the cases (Table 2). There was statistically significant proportion among the highlighted variables. Injuries with thickening of the interlobular septa prevailed (29.8%) (Table 3). As for laboratory tests Ferritin and D-Dimer, normal values were observed in the vast majority: Ferritin results were normal in 76 exams (66.7%) and only 30 (26.3%) were altered, and 5 (4.4%) did not perform it; in the same way, the D-Dimer results were normal in 85 tests (74.6%) and only 10 (8.8%) were altered, and 19 (16.7%) did not take this test (Table 4). Between altered Ferritin and D-Dimer exams there was no concomitance, and between these high inflammatory markers and pulmonary tomographic images, the extent of involvement ranged from 10-75%.

Table 3. Distribution of patients with COVID-19 according to types of lesions observed on pulmonary CT scans, Amazon cohort, northern Brazil, 2021

Variables	Frequency	% (N = 114)
Interlobular septa thickening	34	29,8%
Nodules	17	14,9%
Ground-glass opacity	16	14,0%
Atheromatous calcifications in the aorta and coronary arteries	9	7,9%
Atelectasis	2	1,8%
Hepatic steatosis	2	1,8%
Lymph node enlargement	2	1,8%
Others	15	13,2%

Source: authors.

Table 4. Distribution of patients with COVID-19 according to Ferritin and D-dimer results and other laboratory tests, Amazon cohort, northern Brazil, 2021

Variables	Frequency	% (N = 114)	p-value
Ferritin			0.0004*
Below normal range	3	2,6%	
Within normal range*	76	66,7%	
Above normal range	30	26,3%	
Not collected	5	4,4%	
D-dimer			< 0.0001*
Within normal range*	85	74,6%	
Above normal range	10	8,8%	
Not collected	19	16,7%	

*G-adherence test.

Source: authors.

DISCUSSION

The temporal advance of the COVID-19 pandemic brought knowledge that demonstrated that the disease had a systemic involvement, starting in the airways and with an important

inflammatory component and vascular involvement, through various mechanisms (LANA *et al.*, 2020). Worldwide studies have shown that patients with high levels of LDH, C-reactive protein, ferritin, IL-6 and D-Dimer had a higher risk of hospital admission and severe outcome (WHO, 2020). Thus, it has been established that these biomarkers and the patterns of involvement and extension observed in pulmonary CT scans can be predictors of severity (SBMT, 2020). However, there is no specific value of these exams capable of separately diagnosing the severity of the involvement by COVID-19 (XAVIER *et al.*, 2020). The simultaneous ordering of these tests is not recommended for all patients, however, in Brazil they are now requested for the majority, regardless of their clinical condition. The patients observed in our cohort followed an epidemiological pattern compatible with most other services: without gender variation, aged from 18 to over 60 years, in which the most symptomatic prevailed (VARGAS; CORTÉS, 2020). As for laboratory and tomographic results, those with exams within normal parameters predominated, both for ferritin (66.7%) and for D-Dimer (74.6%). As for pulmonary tomographic imaging, it was more common, an involvement of up to 25% (41, 2%), bilateral (88.6%) with thickening of the interlobular septa (29.8%), as observed in most cases of patients with COVID-19 under outpatient follow-up. Those with elevated Ferritin (26.3%), D-Dimer (8.8%) and more pulmonary lesions (29.8%) were not correlated with each other, probably reflecting another cause of their elevation, and with pulmonary impairment without reflex in the biomarkers results. Only one patient had extensive impairment with 75% with age of 60 years, which reflects several studies showing this parameter correlation with the age (GUO *et al.*, 2020; LIMA, 2020).

CONCLUSION

In this cohort of outpatients from the Amazon, northern Brazil, it was possible to observe the same behavior recorded in different continents, showing that the virus-host relationship is mediated by the immune response, and other parameters yet to be discovered. Thus, these information divide the clinical evolution of the COVID-19, between mild, moderate and severe forms, and it was also observed that the parameters of the biomarkers currently used are of great importance for decisions regarding the management of COVID-19 patients.

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