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Association between degree of pulmonary impairment due to ground-glass opacification and clinical and laboratory findings in patients with COVID-19 at hospital admission: a cross-sectional study

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***Abstract*—** *Objective: To investigate the clinical and laboratory parameters correlated with increased pulmonary involvement of ground-glass opacity in patients with coronavirus disease 2019 (COVID-19) at the time of hospital admission.*

Methods: This is a cross-sectional study with a total of 74 patients with COVID-19 and ground-glass opacification (GGO) visualized on chest computed tomography. Physical examinations, laboratory tests and computed tomography of the chest were performed during the first 2 days of hospitalization. Patients were divided into two groups: GGO≤50% (n = 43) and GGO> 50% (n = 31). All parameters were evaluated for comparison and association between groups.

Results: Patients with higher GGO were more commonly male (p = 0.035), with lower saturation (p = 0.038), with more dyspnea (p = 0.020), with a positive correlation with all these parameters (p <0.05). Lactic dehydrogenase (LDH) (p <0.001), ferritin (p = 0.001), C-reactive protein (CRP) (p <0.001), white blood cell count (p = 0.006), neutrophil count (p = 0.003), percentage of neutrophils (p = 0.025) were higher in the GGO group> 50% and the percentage of lymphocytes was lower (p = 0.014). All laboratory parameters increased in the GGO group> 50% showed correlation (p <0.05).

Conclusion: The factors associated with the more diffuse presentation of ground-glass opacification were: male gender, less saturation, dyspnea, greater DHL, greater ferritin, greater PCR, greater WBC count, greater count and percentage of neutrophils and lower percentage of lymphocytes.

I. INTRODUCTION

Chest tomography (CT) has proved to be important for determining the medical conduct of patients admitted to the health service with the disease caused by the SARS-CoV-2 virus (COVID-19), assisting to make decisions about hospitalization of patients in wards or in intensive care units, as well as to choose the most appropriate therapeutic intervention[1]. Ground-glass opacity (GGO), an increase in the attenuation coefficient of parenchyma, with preservation of bronchovascular markings, is the most common CT finding of patients with COVID-19. This type of lesion has a pooled prevalence between 64.6% (95% CI: 57.6-71.4)[2] and 83.31% (95% CI: 69.43-93.35)[3], varying according to the meta-analysis.

GGO can be present in any phase of COVID-19[4,5], but it is more common in the pre-symptomatic and initial symptomatic phase with isolated presentation. The progression of the disease can entail an increase in the number and size of GGO and an association with other radiological findings[4]. GGO may be related to a worse outcome when there is pulmonary impairment greater than 40%[6] or when it is associated with other radiographic findings of diffuse pulmonary impairment at the time of hospital admission[7]. Therefore, the CT quantification of pneumonia lesions in the first days of hospitalization makes it possible to predict the progression to severe disease[8].

An aspect that draws attention in studies of GGO prevalence consists of the different clinical and laboratory manifestations in similar contexts[2,3,9]. Therefore, the aim of this paper is to investigate the clinical and laboratory parameters correlated with increased pulmonary involvement of ground-glass opacity in patients with COVID-19 in the time of hospital admission.

II. MATERIAL AND METHODS

Study design, setting and population

This is a cross-sectional, descriptive and analytical, single-center study, with data analysis of the first two days of admission of all patients admitted between June 2, 2020 and August 18, 2020 at the State Field Hospital, located in the city of Teresina, capital of the state of Piauí, Brazil, who tested positive for SARS-CoV-2 in a reverse transcriptase polymerase chain reaction (RT-PCR) test of a nasopharyngeal swab sample, with clinical staging classified as moderate or high severity, and who underwent high-resolution computed tomography (CT) of the chest, showing ground-glass opacity (GGO) images. Participants whose CT reports did not reveal the degree of pulmonary impairment were excluded.

Data collection

HCEV has been planned since its establishment to be a health institution for research purposes. Therefore, the data collection instruments used were specific for this work, where the hospital team was previously trained. Patient demographic, clinical, laboratory and CT data were recorded. Double entry was made in the database to avoid typing errors, and all data were reviewed by a team of experienced medical. The symptoms and illnesses collected were self-reported and vital signs were checked by the staff nurses. Laboratory and CT scans were under the responsibility of a single experienced company in the market, and all information was passed on in full. It is underlined that all information was collected within 48 hours of patient admission.

Statistical analysis

For quantitative variables, the D'Agostino-Pearson normality test was performed. The results were expressed as mean and standard error of mean. In the case of normal distribution, the values were compared with the Student's t-test. When not normal, the values were compared with the Mann-Whitney U test. For qualitative variables, data were presented in absolute frequency and percentages, and then compared using the Pearson's Chi-square test or the Fisher's exact test. The percentages of the contingency tables were calculated in the columns. In inferential analysis, the dependent variable was defined as the presence of ground-glass pulmonary involvement. Associations with quantitative variables were expressed using the point-biserial correlation coefficient (r) and those with nominal qualitative variables were expressed using the Phi coefficient (φ). No imputation was made for missing data. Comparisons and associations with p-value less than 0.05 were considered statistically significant. The study data were processed in Statistical Package for the Social Sciences (IBM®) software, version 27.0.

Ethical aspects

This study was conducted in accordance with the Helsinki Declaration. The study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Piauí (Approval Number: 4.083.222). All research participants agreed to participate and signed the Free and Informed Consent Form.

III. RESULTS

Age, severity of the disease at the time of admission and time from the first day of symptom to hospitalization did not differ between the group with

ground-glass opacity greater than 50% (GGO>50%) and the group with equal ground-glass opacity or less than 50% (GGO≤50%). Greater pulmonary impairment was found in male participants (77.42%; p=0.035), with a weak positive correlation (r=0.245; p=0.035). The most frequent comorbidities in the studied sample were obesity, systemic arterial hypertension and diabetes, but there was no difference between the groups, nor any correlation, as well as the number of all reported comorbidities.The body mass index, the values of heart rate, respiratory rate and mean arterial pressure were not different between the degrees of pulmonary impairment, but the saturation was lower (94.57%; p=0.038) in the GGO group>50 % and with a weak negative correlation (r=-0.254; p=0.038) (Table 1). With regard to symptoms, only the frequency of dyspnea was significantly higher (93.55%; p=0.020) in the group with the highest GGO, and a weak association was found (φ=0.270; p=0.020) (Table 2).

Table1 – Relationship between clinical characteristics and degree of opacification in ground glass

Parameter	Comparison between groups					Association	
	≤50% GGO (n=43)		>50% GGO (n=31)		*p value*	r or φ	*p value*
	Mean or frequency	95% IC	Mean or frequency	95% IC			
Age – years	61.60 ±2.64	56.26 – 66.93	61.80 ± 3.17	55.32 – 68.28	0.891[m]	0.006	0.961
Male	23 (53.49%)	-	24(77.42%)	-	**0.035[q]**	0.245	**0.035**
Severe illness	31 (72.09%)	-	23 (74.19%)	-	0.593[q]	0.063	0.593
Days of symptoms until hospitalization	10.31 ± 1.08	8.11 – 12.50	9.96± 0.75	8.41 – 11.51	0.527[m]	-0.031	0.810
BMI – m²/Kg	30.53 ± 1.41	27.67 – 33.39	30.23 ± 1.22	27.43 – 32.74	0.572[m]	-0.019	0.880
Obesity	14 (38.90%)	-	13 (41.50%)	-	0.629[q]	0.060	0.629
SAH	25 (58.14%)	-	16 (51.61%)	-	0.577[q]	-0.065	0.577
Diabetes	15 (34.88%)	-	14 (45.16%)	-	0.372[q]	0.104	0.372
Smoking	7 (53.85%)	-	8 (57.14%)	-	0.863[q]	0.033	0.863
Number of comorbidities	1.58 ± 0.17	1.24 – 1.93	1.84 ± 0.28	1.26 – 2.42	0.689[m]	0.097	0.413
Heart Rate - bpm	86.33 ± 2.42	81.44 – 91.23	87.69 ± 2.76	82.00 – 93.38	0.720[t]	0.044	0.720
Respiratory frequency – RI/min	20.21 ± 0.41	19.38 – 21.05	19.54 ± 0.36	18.81 – 20.28	0.244[t]	-0.157	0.244
Mean blood pressure - mmHg	98.39 ± 3.43	91.46 – 105.30	99.48 ± 2.04	95.30 – 103.70	0.848[m]	0.030	0.806
Oxygen saturation – %	95.72 ± 0.34	95.03 – 96.40	94.57 ± 0.43	93.69 – 95.46	**0.038[t]**	-0.254	**0.038**

The comparison data were presented with mean ± standard error of mean or with absolute frequency (percentage) and the correlation data were presented using the point-biserial correlation coefficient (r) or the Phi coefficient (φ), as appropriate. Legend: SAH: systemic arterial hypertension; BMI: body mass index; t: Student's t test; m: Mann-Whitney U test; q: Pearson's chi-square test.

Table 2 – Relationship between symptoms and degree of opacification in ground glass

Parameter	Comparison between groups					Association	
	≤50% GGO (n=43)		>50% GGO (n=31)		*p value*	r or φ	*p value*
	Mean or frequency	95% IC	Mean or frequency	95% IC			
Fever	29 (67.44%)	-	24 (77.42%)	-	0.348	0.109	0.348
Cough	33 (76.74%)	-	26 (83.87%)	-	0.452[q]	0.087	0.452
Fatigue	9 (20.93%)	-	4 (12.90%)	-	0.371[q]	-0.104	0.371
Dyspnea	31 (72.09%)	-	29 (93.55%)	-	**0.020[q]**	0.270	**0.020**
Myalgia	29 (67.44%)	-	16 (51.61%)	-	0.169[q]	-0.160	0.169
Anorexia	5 (13.16%)	-	3 (9.68%)	-	0.130[q]	-0.176	0.130
Sore throat	13 (30.23%)	-	4 (12.90%)	-	0.080[q]	-0.203	0.080
Headache	16 (37.21%)	-	9 (29.03%)	-	0.523[q]	-0.075	0.523
Chest pain	12 (27.91%)	-	4 (12.90%)	-	0.139[q]	-0.173	0.139
Anosmia	7 (16.28%)	-	7 (22.58%)	-	0.451[q]	0.088	0.451
Ageusia	8 (18.60%)	-	5 (16.13%)	-	0.831[q]	-0.025	0.831
Diarrhea	15 (34.88%)	-	7 (22.58%)	-	0.290[q]	-0.124	0.290
Nausea / vomiting	5 (11.63%)	-	3 (9.68%)	-	1.000 [f]	-0.026	0.827
Number of symptoms	5.05 ± 0.38	4.28 – 5.81	4.55 ± 0.36	3.82 – 5.28	0.301[m]	-0.108	0.359

The comparison data were presented with mean ± standard error of mean or with absolute frequency (percentage) and the correlation data were presented using the point-biserial correlation coefficient (r) or the Phi coefficient (φ), as appropriate. Legend: t: Student's t test; m: Mann-Whitney U test; q: Pearson's chi-square test.

As for laboratory parameters (Table 3), (lactic dehydrogenase) (LDH) (p<0.001), ferritin (p=0.001), CRP (p<0.001), white blood cell count (p=0.006) and neutrophil count (p=0.003) were significantly higher in the group with GGO>50%, with a moderate positive correlation for all variables (r=0.435; r=0.390; r=0.405; r= 0.302; r=0.302; all with p<0.05; respectively). The percentage of neutrophils was higher in the GGO group>50% (p=0.025), and there was a weak positive correlation (r=0.268; p=0.024), while the percentage of lymphocytes showed a significantly lower percentage of lymphocytes (p=0.014) and weak negative correlation (r=-0.294; p=0.013). When stratifying the results of AST, ALT, ferritin and hemoglobin by gender, as recommended by the laboratory responsible for the analysis of blood samples, a moderate positive correlation (r=0.319; p=0.031) was found between ferritin and GGO values in male patients, with significantly higher levels in the group with greater pulmonary impairment (p= 0.032). No difference was found for these variables among female patients.

Table3 – Relationship between laboratory characteristics and degree of opacification in ground glass

Parameter	Comparison between groups					Association	
	≤50% GGO (n=43)		>50% GGO (n=31)		*p value*	r or φ	*p value*
	Mean or frequency	95% IC	Mean or frequency	95% IC			
Capillary glycemia – mg/dL	185.30 ± 20.01	141.20 – 229.3	249.50 ± 43.97	145.50 – 353.50	0.154[t]	0.331	0.154

ALT – IU/L	55.55 ± 9.27	36.81 – 74.29	67,61 ± 12.58	41.80 – 93.42	0.215[m]	0.097	0.433
ALT in women – IU/L	55.83 ± 16.42	21.18 – 90.48	45.20 ± 9.44	19.00 – 71.40	0.587[m]	-0.072	0.743
ALT in men – IU/L	55.32 ± 10.55	33.38 – 77.25	72.48 ± 15.06	41.24 – 103.70	0.296[m]	0.140	0.360
AST – IU/L	52.73 ± 5.38	41.83 – 63.62	71.86 ± 18.71	33.47 – 110.20	0.462[m]	0.138	0.261
AST in women – IU/L	57.28 ± 9.00	38.28 – 76.27	56.80 ± 6.02	40.09 – 73.51	0.587[m]	-0.006	0.979
AST in men – IU/L	49.00 ± 6.54	35.40 – 62.60	75.13 ± 22.78	27.89 – 122.40	0.394[m]	0.163	0.286
Creatinine – mg/dL	0.90 ± 0.07	0.76 – 1.04	0.91 ± 0.08	0.74 – 1.08	0.796[m]	0.008	0.949
Urea – mg/dL	46.24 ± 3.05	40.08 – 52.40	54.62 ± 5.79	42.76 – 66.48	0.186[m]	0.165	0.170
LDH – UI/L	339.30 ± 19.19	300.50 – 378.00	442.10 ± 30.49	379.60 – 504.50	**<0.001**[m]	0.340	**0.004**
Lactate – mg/dL	4.30 ± 0.28	3.74 – 4.86	4.53 ± 0.25	4.01 – 5.05	0.234[m]	0.076	0.568
Ferritin – ng/dL	935.60 ± 104.50	724.60 – 1147.00	1697.00 ± 221.40	1243.00 – 2151.00	**0.001[m]**	0.385	**0.001**
Ferritin in women – ng/dL	618.20 ± 86.74	436.00 – 800.40	910.70 ± 322.00	16.56 – 1805.00	0.581[t]	0.261	0.219
Ferritin in men – ng/dL	1198.00 ± 158.60	868.90 – 1527.00	1868.00 ± 248.40	1353.00 – 2383.00	**0.032[m]**	0.324	**0.028**
CRP – mg/L	5.92 ± 0.44	5.04 – 6.80	7.96 ± 0.39	7,17 – 8.76	**<0.001[m]**	0.367	**0.001**
Sodium – mmol/L	137.90 ± 0.71	136.4 – 139.3	137.50 ± 0.85	135.80 – 139.20	0.741[m]	-0.039	0.750
Potassium – mmol/L	4.67 ± 0.12	4.44 – 4.91	4.84 ± 0.13	4.57 – 5.11	0.343[t]	0.114	0.343
Red Blood Cells – 10^3 cells/ mm^3	4.77 ± 0.08	4.60 – 4.94	4.76 ± 0.10	4.55 – 4.97	0.788[m]	-0.011	0.931
Hemoglobin – g/dL	13.97 ± 0.25	13.47 – 14.47	13.83 ± 0.25	13.33 – 14.34	0.838[m]	-0.045	0.712
Hemoglobin in women – g/dL	13.6 ± 0.19	13.19 – 14.00	12.73 ± 1.24	11.43 – 14.03	0.095[m]	-0.370	0.063
Hemoglobin in men – g/dL	14.31 ± 0.44	13.40 – 15.22	14.12 ± 1.21	13.6 – 14.64	0.946[m]	-0.057	0.709
Hematocrit - %	42.08 ± 0.73	40.62 – 43.55	41.57 ± 0.78	39.97 – 43.17	0.815[m]	-0.057	0.639
White Blood cells – cells /mm^3	8548.00 ± 467.80	7604.00 – 9493.00	10784.00 ± 652.80	9447.00 – 12121.00	**0.006[t]**	0.326	**0.006**

Neutrophiles – cells / mm³	6753.00 ± 419.40	5906.00 – 7600.00	8896.00 ± 561.70	7745.00 – 10047.00	**0.003^{t}**	0.352	**0.003**
Neutrophiles – %	77.83 ± 1.33	75.15 – 80.52	8896.00 ± 561.70	7745.00 - 10047	**0.025^{m}**	0.280	**0.018**
Eosinophiles – cells / mm³	42.81 ± 8.48	25.69 – 59.93	44.17 ± 10.28	23.12 – 65.23	0.914^{m}	0.072	0.651
Eosinophiles – %	0.57 ± 0.11	0.35 – 0.79	0.45 ± 0.09	0.25 – 0.64	0.627^{m}	-0.097	0.422
Basophiles – cells/ mm³	18.67 ± 5.53	7.49 – 29.84	12.28 ± 7.50	-3.09 – 27.64	0.182^{m}	-0.023	0.886
Basophiles – %	0.24 ± 0.07	0.10 – 0.37	0.10 ± 0.06	-0.01 – 0.22	0.152^{m}	-0.171	0.154
Lymphocytes – cells / mm³	1035.00 ± 80.94	871.80 – 1199.00	946.30 ± 94.37	753.00 – 1140.00	0.374^{m}	-0.085	0.479
Lymphocytes – %	13.31 ± 1.13	11.03 – 15.59	9.51 ± 0.91	7.65 – 11.39	**0.014^{m}**	-0.281	**0.018**
Monocytes – cells / mm³	509.1 ± 45.13	418.00 – 600.30	536.00 ± 47.07	439.60 – 632.40	0.559^{m}	0.048	0.689
Monocytes – %	6.17 ± 0.49	5.17 – 7.16	5.03 ± 0.37	4.27 – 5.80	0.153^{m}	-0.199	0.096
Platelets – cells / mm³	227824 ± 12415	202752 - 252896	245379 ± 16397	211791 - 278967	0.388^{t}	0.104	0.388

The comparison data were presented with mean ± standard error of mean and the correlation data were presented using the point-biserial correlation coefficient (r) or the Phi coefficient (φ), as appropriate.Legend: ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactic dehydrogenase; CRP: C-reactive protein; PT: prothrombin time;t: Student's t test; m: Mann-Whitney U test; q: Pearson's chi-square test.

ALT and AST in women, as well as LDH, lactate, ferritin, CRP, percentage of neutrophils and prothrombin time (PT) in male and female patients were above the laboratory reference values in groups with GGO>50% and ≤50%. Urea and neutrophil count were higher only in the group with greater pulmonary impairment. The count and percentage of eosinophils and the percentage of lymphocytes were significantly lower than expected in both groups.

IV. DISCUSSION

In this study, the clinical parameters that were correlated with a higher degree of GGO were: male gender, presence of dyspnea and lower oxygen saturation. With regard to laboratory parameters, there was a positive correlation between GGO and increased LDH, ferritin and CRP values, WBC count, neutrophil count and percentage, as well as negative correlation with leukocyte percentage. It is underlined that these factors are directly or indirectly linked to the body's immune reaction against SARS-CoV-2[10]. The correlation between the higher GGO and the male gender can be justified, at least in part, because men seem a little more susceptible to the infection, i.e., have a greater chance of developing a more serious and more lethal form of the disease. These aspects related to gender may be related to genetic, hormonal and other biological factors[11]. As for the other clinical and laboratory correlations, the pathophysiology of SARS-CoV-2 infection can help explain them, as detailed below: after SARS-CoV-2 enters the host cells of the respiratory system and accelerates viral replication, the integrity of the epithelial-endothelial barrier is undermined. This virus accentuates the inflammatory response and stimulates the migration of monocytes and neutrophils. The result of this reaction is interstitial mononuclear inflammatory infiltrates and edema[12]. Concomitantly, pulmonary edema increases, there is formation of hyaline membrane, rupture of the endothelial barrier and dysfunctional alveolar-capillary oxygen transmission, changes that cause the clinical

manifestation of acute respiratory distress syndrome (ARDS). These changes are visualized through CT in GGO, decreased saturation, dyspnea and possible changes in inflammation markers and leukocytes[12,13].

Another study conducted with similar characteristics and clinical condition, which evaluated the correlation between laboratory parameters and pneumonia severity on initial CT, showed a strong correlation between diffuse pulmonary impairment and increased LDH and CRP, with the predominant radiographic finding being GGO[14]. CRP, produced by the liver in response to inflammatory mediators, is a non-specific marker of the acute phase of inflammatory diseases. CRP levels are significantly higher during the early periods of severe cases of COVID-19 and may reflect the development of the disease[10]. LDH is a glucose metabolism enzyme responsible for the conversion of pyruvate into lactate and its secretion is triggered by cell membrane necrosis, resulting from viral infection or lung lesion[10].

Like CRP, ferritin can be used as a non-specific marker of the acute phase of inflammatory conditions, and it is also used as a marker of therapeutic response. Furthermore, there are indications that this factor may actively contribute to the cytokine storm, which is typical of COVID-19. Ferritin is higher the greater the gravity of COVID-19[15]. Regarding the relationship with the cells of the immune system, in the study by Sun et al. (2020), in a study conducted with patients with laboratory-confirmed COVID-19, who underwent chest CT without contrast at the time of hospital admission and laboratory tests 1 day before or after of the imaging exam, found positive correlations in relation to the ratio between GGO and the total radiographic lesion in critically ill patients with the percentage of neutrophils, and negative with the count and percentage of lymphocytes, but found no correlation with WBC[16]. Similarly, Li et al. (2020), in a study with patients who underwent a series of chest CT and laboratory exams on the same day, tested and found these same correlations; however, with chest CT severity scores[17]. Although high WBC count is associated with an underlying infection, this parameter is not reliable as a biomarker for COVID-19, since the use of glucocorticoids and concomitant infections may influence its outcome[10][10].

The main limitation of this study was the possible selection bias. A study that includes patients with a condition classified as mild could contribute to improving the quality of the results. Moreover, the cross-sectional and temporal cut does not allow establishing a relationship between cause or consequence of a higher GGO; however, it is possible to raise hypotheses and search for justifications in the scientific literature to explain the factors associated with it. Nevertheless, this is a pioneering study in the state, which was conducted at the first field hospital that started operating with services for people from all regions of the state capital and also from cities in the metropolitan area.

V. CONCLUSION

The factors associated with the more diffuse presentation of ground-glass opacity are those involved in the pathophysiology of pulmonary involvement caused by COVID-19: male gender, lower saturation, dyspnea, higher LDH, higher ferritin, higher CPR, higher WBC count, higher neutrophil count, higher percentage of neutrophils and lower percentage of lymphocytes. Therefore, the identification of these factors at the time of hospital admission can help in predicting pulmonary impairment.

VI. CONFLICTS OF INTEREST STATEMENT AND FUNDING

The authors declared no conflict of interest. This research was funded by the authors themselves.

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