J Bras Pneumol. 2022;48(2):e20210204
https://dx.doi.org/10.36416/1806-3756/e20210204

Expiratory CT scanning in COVID-19 patients: can we add useful data?

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Submitted: 2 June 2021.
Accepted: 29 November 2021.

Study carried out at Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To evaluate small airway disease in COVID-19 patients using the prevalence of air trapping (AT) and correlating it with clinical outcomes. The relationship between CT-based opacities in small blood vessels and ventilation in patients with SARS-CoV-2 pneumonia was also assessed. **Methods:** We retrospectively included 53 patients with positive RT-PCR results for SARS-CoV-2 between March and April of 2020. All subjects underwent HRCT scanning, including inspiratory and expiratory acquisitions. Subjects were divided into two groups based on visual identification of AT. Small blood vessel volumes were estimated by means of cross-sectional areas < 5 mm^2 (BV5) derived from automated segmentation algorithms. Mixed-effect models were obtained to represent the BV5 as a function of CT-based lobar opacities and lobar ventilation. **Results:** Of the 53 participants, AT was identified in 23 (43.4%). The presence of AT was associated with increased SpO_2 at admission (OR = 1.25; 95% CI, 1.07-1.45; p = 0.004) and reduced D-dimer levels (OR = 0.99; 95% CI, 0.99-0.99; p = 0.039). Patients with AT were less likely to be hospitalized (OR = 0.27; 95% CI, 0.08-0.89; p = 0.032). There was a significant but weak inverse correlation between BV5 and CT-based lobar opacities (R^2 = 0.19; p = 0.03), as well as a nonsignificant and weak direct correlation between BV5 and lobar ventilation (R^2 = 0.08; p = 0.54). **Conclusions:** AT is a common finding in patients with COVID-19 that undergo expiratory CT scanning. The presence of AT may correlate with higher SpO_2 at admission, lower D-dimer levels, and fewer hospitalizations when compared with absence of AT. Also, the volume of small pulmonary vessels may negatively correlate with CT opacities but not with lobar ventilation.

Keywords: SARS-CoV-2; COVID-19; Tomography, X-ray.

INTRODUCTION

The SARS-CoV-2 pneumonia course is characterized by severe hypoxemia with preserved lung compliance.[1,2] The underlying causes of COVID-19-related acute respiratory failure are vascular injury and vasoconstriction, with microvascular injury causing the pulmonary exudate leak, which is characteristic of SARS-CoV-2 pneumonia.[1,2] The presence of inflammatory exudates in the airways leading to airway remodeling and destruction of alveolar walls has been described as the pathophysiology of other pulmonary diseases such as COPD and asthma. This damage to the small airways leads to airflow obstruction and air trapping (AT), which are markers of COVID-19 severity and prognosis.[3,4] AT has also been reported in pulmonary hypertension due to an increase in the caliber of arteries in areas of increased attenuation (hyperemia) when compared with smaller vessels in areas of low attenuation (oligemia).[5] A group of authors reported that the presence of AT was significantly more common in patients with COVID-19 admitted to the ICU or who died.[6] Thus, it is reasonable to question whether COVID-19 could result in small airway damage and AT and whether microvascular thrombosis may contribute to bronchiolar constriction or small airway disease.[7]

Chest CT has played a significant role in the COVID-19 evaluation, and abnormal CT findings have been reported in up to 90% of hospitalized patients.[8,9] The predominance of ground-glass opacities (GGO) is one of the most common patterns of SARS-CoV-2 pneumonia.[8,9] Although imaging cannot diagnose SARS-CoV-2, it can assess the severity and extension of lower respiratory tract involvement, as well as provide alternative diagnoses and concomitant pathologies, such as pulmonary embolism.[10,11] However, the role of expiratory CT acquisitions in COVID-19 remains unclear, and most imaging centers include only inspiratory phases to avoid patient exposure to additional radiation doses.[12] Thus, the prevalence of AT in COVID-19 patients might be underestimated. Some follow-up studies of SARS-CoV-2 pneumonia have demonstrated that AT may also be identified months after the infection.[13]

Quantitative CT imaging has been used to predict clinical outcomes of several pulmonary diseases, and the percentage of AT has been used as one of the

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Financial support: None.

quantitative CT tools in the evaluation of asthma, COPD, and interstitial lung diseases.[14-17] Regarding COVID-19, few articles have evaluated quantitative CT findings as markers of disease progression and prognosis. Increasing percentages of consolidation and GGO on chest CT have been found to estimate the risk of clinical deterioration or death in patients with COVID-19 pneumonia.[18] Also, a quantitative decrease in well-aerated lung volume has been reported to predict adverse outcomes in COVID-19.[19] Thus, the purpose of the present study was to evaluate small airway disease in COVID-19 patients by using the prevalence of AT and correlating it with clinical outcomes. The relationship between small blood vessels with CT opacities and ventilation in SARS-CoV-2 pneumonia patients was also assessed.

METHODS

The local institutional review board approved this cross-sectional retrospective study, and written consent was waived. We retrospectively included patients with positive SARS-CoV-2 RT-PCR results from throat swabs or lower respiratory tract samples between March 21, 2020 and April 20, 2020, in three hospitals. Patients should have undergone chest CT in the same period of a positive RT-PCR test.

Volumetric HRCT scans were obtained from all subjects, including acquisitions at full inspiration and the end of a normal expiration. The expiratory CT acquisition phase was already part of our institutional CT protocol to assess pulmonary infections before the COVID-19 pandemic. All CT scans were performed with a peak tube voltage of 120 kVp and a fixed tube current of 200 mAs for inspiratory CT and of 50 mAs for expiratory CT at a gantry rotation time of 0.5 s. The reconstructed slice thickness was 1.25 mm using a 64-slice CT scanner (LightSpeed VCT; GE Healthcare, Chicago, IL, USA).

Inspiratory and expiratory HRCT imaging datasets were analyzed using a digital database system (CARESTREAM Vue PACS, version 12.2.1.2; Carestream Health, Rochester, NY, USA), and the two radiologists (with 5 and 9 years of experience) who performed the analysis were blinded to clinical and laboratory results of the patients. The use of intravenous contrast media was requested at the discretion of the attending physician or radiologist. HRCT findings were described using the international standard nomenclature defined by the Fleischner Society glossary[20] and the British Society of Thoracic imaging classification of COVID-19 pneumonia (classic, probable, indeterminate, or non-COVID-19).[21] A semiquantitative score was used in order to estimate the parenchymal involvement with GGO and consolidation at inspiratory acquisitions by using the following lesion extension ranges: 0-24%; 25-49%; 50-74%; and 75-100%. Patients were divided into two groups based on the presence of AT, which was defined as parenchymal areas with less than the normal increase in attenuation and lack of volume reduction on end-expiration CT scans.[20] Regional AT was considered present when at least three secondary lobules were involved, as previously described.[22]

Data on airways and small vessels were also post-processed using functional respiratory imaging analysis, a technique to assess airway morphology that has been extensively validated in humans.[23-25] Three-dimensional reconstructions of the lung and pulmonary vasculature were created using a software program (FLUIDDA, Kontich, Belgium) approved by the US Food and Drug Administration. Using an automated blood vessel segmentation algorithm previously described,[26,27] we calculated the volume of blood contained in vessels in three ranges of cross-sectional areas: < 5 mm^3 (BV5); 5-10 mm^3 (BV5-BV10), and > 10 mm^3 (BV10). Three-dimensional visual representations of the blood vessels were created, and they were colored according to their size (Figures 1 and 2). From the data derived from gated inspiratory and expiratory CT scans, ventilation maps were created by assuming that regional changes in lung volume would relate to regional ventilation, as previously described.[28] Mixed-effect models were also obtained to represent the predicted percentage of BV5 as a function of volume of CT-based opacities within a lobe and lobar ventilation.

Demographic, clinical, and laboratory variables were collected from the electronic medical records of the institutions. Such parameters were based on previous investigations that found correlations between such variables and the severity of respiratory failure in patients with COVID-19.[29,30]

Data were presented as absolute and relative frequencies, as well as means and standard deviations or medians and interquartile ranges. The Shapiro-Wilk test was used to assess the normality of data distribution. We evaluated associations between variables with chi-squared tests. For comparing continuous variables, the Mann-Whitney test was used. The Student's t-test was used for continuous variables for two-group comparisons. All tests were two-tailed with a level of significance set at $p < 0.05$. Statistical analyses were performed using Stata statistical software package, version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

In total, 53 patients were included, and AT was identified in 23 patients (43.4%). There were no significant differences between the patients with AT (AT group) and those without AT (non-AT group) regarding their baseline characteristics (Table 1). Both groups presented similar prevalences of comorbidities that cause AT, such as asthma and COPD. In accordance with the imaging classification of COVID-19 pneumonia,[21] the non-COVID-19 pattern was identified in 6 and 6 patients in the AT and non-AT groups, respectively (Table 1). Although most patients in both groups presented with the classic/probable COVID-19 pattern on CT (Figure 1), no significant differences were found in the prevalence of classic/probable or indeterminate

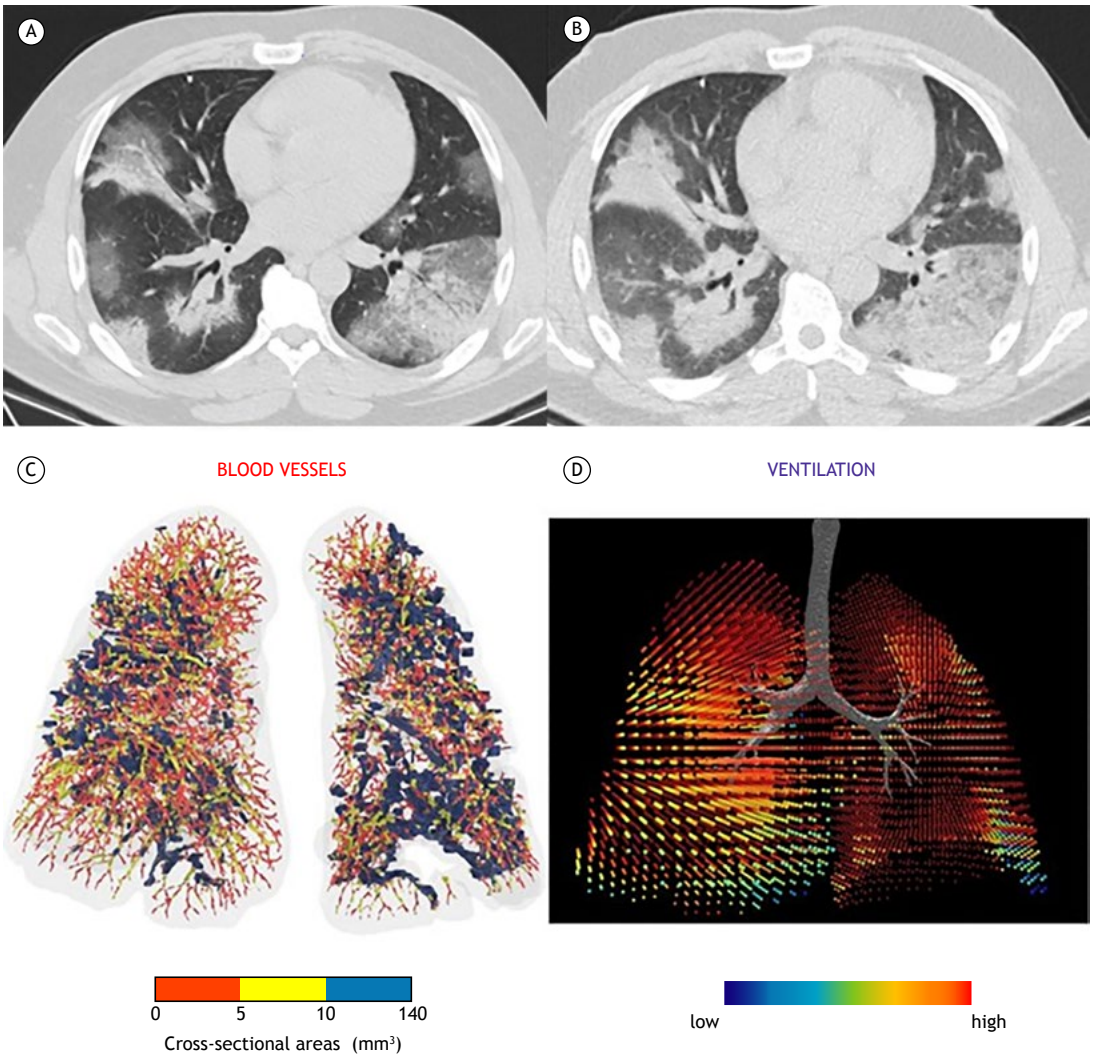

Figure 1. Typical appearance of COVID-19 (classic pattern)—50-74% parenchymal involvement. HRCT axial images obtained during inspiratory (in A) and expiratory (in B) acquisitions with no evidence of air trapping. In C, three-dimensional visual representation of blood vessels colored according to their size (red, yellow, and blue corresponding to small, mid-sized, and large vessels, respectively). Cross-sectional areas < 5 mm^3 are sparse throughout the lung, indicating severe diffuse vasoconstriction even in areas without consolidation. In the ventilation map (in D), most areas of the lung are colored red, representing a normal expansion of lobar volumes between inspiration and expiration, even in areas where there is severe vasoconstriction of small blood vessels.

COVID-19 patterns on CT between the groups (p = 0.196). Most patients included in our study presented with < 50% of lung involvement on their CT scans. Although the prevalences of lung involvement ≥ 50% were different between the groups, they were not statistically significant (p = 0.622).

Table 2 summarizes the comparison of outcomes between the groups. There were significant differences between the groups in SpO_2 at admission and D-dimer levels, as well as the need for hospitalization. In the initial evaluation, the non-AT group presented lower SpO_2 (p = 0.012) and higher D-dimer levels (p = 0.001) that did the AT group. A greater proportion of patients in the non-AT group required hospitalization when compared with those in the AT group (73.3% vs. 43.5%; p = 0.028).

The logistic regression univariate analysis compared the outcomes between the groups. The presence of AT was associated with a 25% increase in SpO_2 at admission (OR = 1.25; 95% CI, 1.07-1.45; p = 0.004) and lower D-dimer levels (OR = 0.99; 95% CI, 0.99-0.99; p = 0.039). Also, patients with AT were less likely to be hospitalized (OR = 0.27; 95% CI, 0.08-0.89; p = 0.032).

There was a significant but weak inverse correlation between BV5 and CT-based opacities (R^2 = 0.19; p = 0.03; Figure 3). Also, there was a nonsignificant and weak direct correlation between BV5 and lobar ventilation (R^2 = 0.08; p = 0.54; Figure 4).

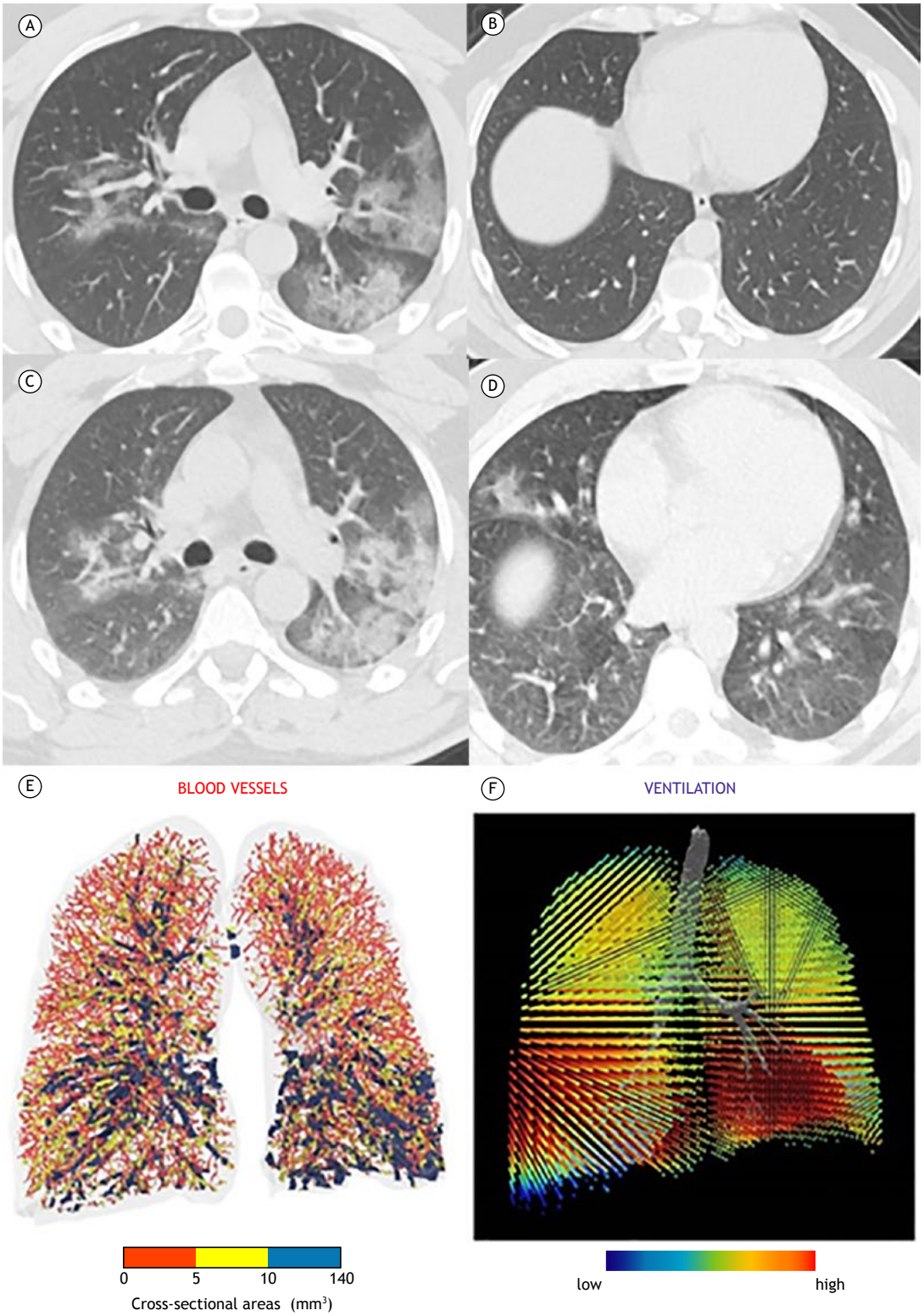

Figure 2. Typical appearance of COVID-19—25-49% parenchymal involvement. HRCT axial images obtained during inspiratory (in A and B) and expiratory (in C and D) acquisitions showing air trapping. In E, three-dimensional visual representation of blood vessels colored according to their size (red, yellow, and blue corresponding to small, mid-sized, and large vessels, respectively). Cross-sectional areas < 5 mm^3 are sparse throughout the lung, indicating severe diffuse vasoconstriction even in areas without consolidation. In the ventilation map (in F), most areas of the lung are colored red, representing a normal expansion of lobar volumes between inspiration and expiration, even in areas where there is severe vasoconstriction of small blood vessels.

Table 1. Characteristics of the patients at baseline (N = 53).[a]

Variable	Group		p
	Non-AT (n = 30)	AT (n = 23)	
Female	14 (46.7)	11 (47.8)	1.000
Age, years	55 ± 17	48 ± 15	0.091
Time to CT, days	4 [0-8]	4 [1-8]	0.483
Comorbidity			
Asthma	2 (6.7)	3 (13.0)	0.642
COPD	4 (13.3)	0 (0.0)	0.124
Diabetes mellitus	1 (3.3)	4 (17.4)	0.154
Hypertension	6 (20.0)	5 (21.7)	1.000
CT			
Imaging classification[21]			0.196
Non-COVID-19	6 (20.0)	6 (26.1)	
Classic/probable	21 (70.0)	11 (47.8)	
Indeterminate	3 (10.0)	6 (26.1)	
Grade, %			0.622
0-24	8 (33.3)	7 (41.2)	
25-49	8 (33.3)	7 (41.2)	
50-74	7 (29.2)	2 (11.8)	
75-100	1 (4.2)	1 (5.9)	
Symptoms			
Fever	18 (60.0)	14 (60.9)	1.000

AT: air trapping. [a]Values expressed as n (%), mean ± SD, or median [IQR].

Table 2. Comparison of outcomes between the groups (N = 53).[a]

Variable	Group		p
	Non-AT (n = 30)	AT (n = 23)	
SpO_2, %	92 ± 4	96 ± 2	0.012
D-dimer, ng/mL	959 [522-1,792]	367 [237-586]	0.001
Lymphopenia	13 (43.3)	8 (34.8)	0.581
Hospitalization	22 (73.3)	10 (43.5)	0.028
Length of hospital stay, days	9 [7-18]	8 [3-12]	0.172
Invasive mechanical ventilation	4 (15.4)	1 (4.3)	0.114
ICU admission	6 (25.0)	3 (13.6)	0.464

AT: air trapping. [a]Values expressed as n (%), mean ± SD, or median [IQR].

DISCUSSION

In the present study, we found that AT was a common finding among patients that underwent CT scanning with additional expiratory acquisitions. There was a significant difference between patients with and without AT in SpO_2 at admission, D-dimer levels, and hospitalization that was confirmed in the univariate regression analysis.

Previous studies have reported prevalences of AT up to 64% among subjects with normal pulmonary function.[31] Such a prevalence is comparable to the one found in our study (43.4%). Likewise, only 17% of the included patients had comorbidities that could lead to AT, such as asthma and COPD.

Loss of peripheral pulmonary vessels has been reported to correlate with worse clinical outcomes in asthma, COPD, and pulmonary hypertension.[32-35] On CT, peripheral vascular pruning can be represented as lower volumes of BV5. Our study found that the proportion of BV5 within a lung lobe was inversely correlated with the volume of CT-based lobar opacities but not with lobar ventilation. Hence, severely constricted areas were still well ventilated. This finding corroborates the hypothesis of hypoxia with preserved lung compliance. It also supports Lins et al.,[26] who suggested that COVID-19 is an infectious mimic of idiopathic pulmonary hypertension, since both diseases may present microvascular coagulopathy and increased muscularization of pulmonary arteries.

Serum D-dimer is a marker of microvascular injury. In patients with COVID-19, higher D-dimer levels are related to worse outcomes, respiratory failure, and pulmonary embolism.[29,30,36] This could be related to higher activation of blood coagulation secondary to a systemic inflammatory response syndrome or

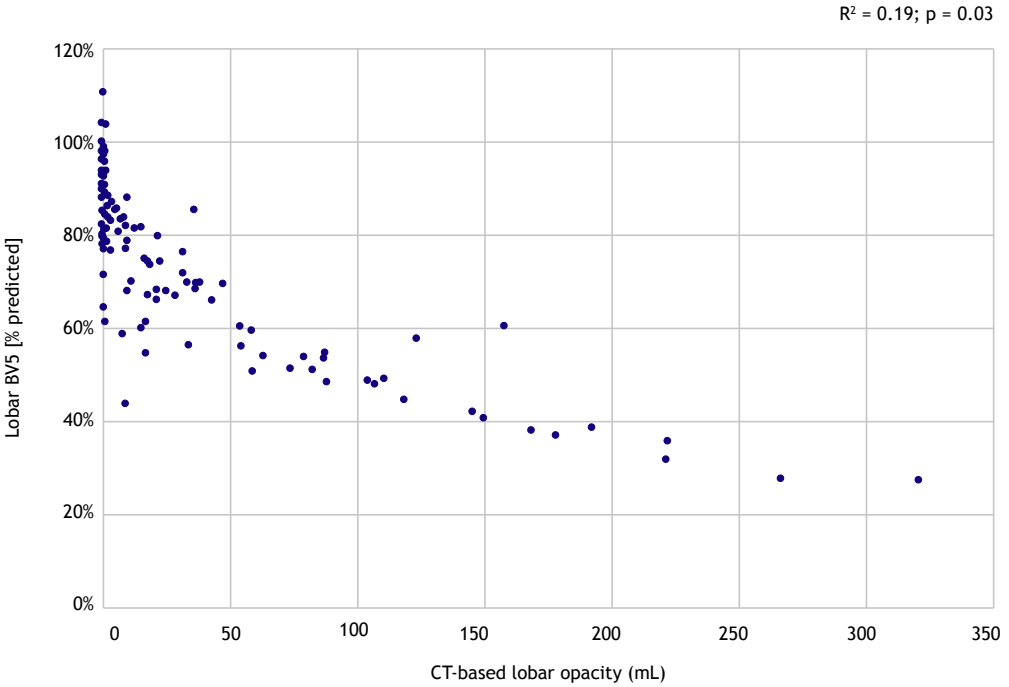

Figure 3. Mixed-effect model of blood volume in vessels with cross-sectional areas < 5 mm² (BV5) as a function of CT-based lobar opacity assessed per lobe.

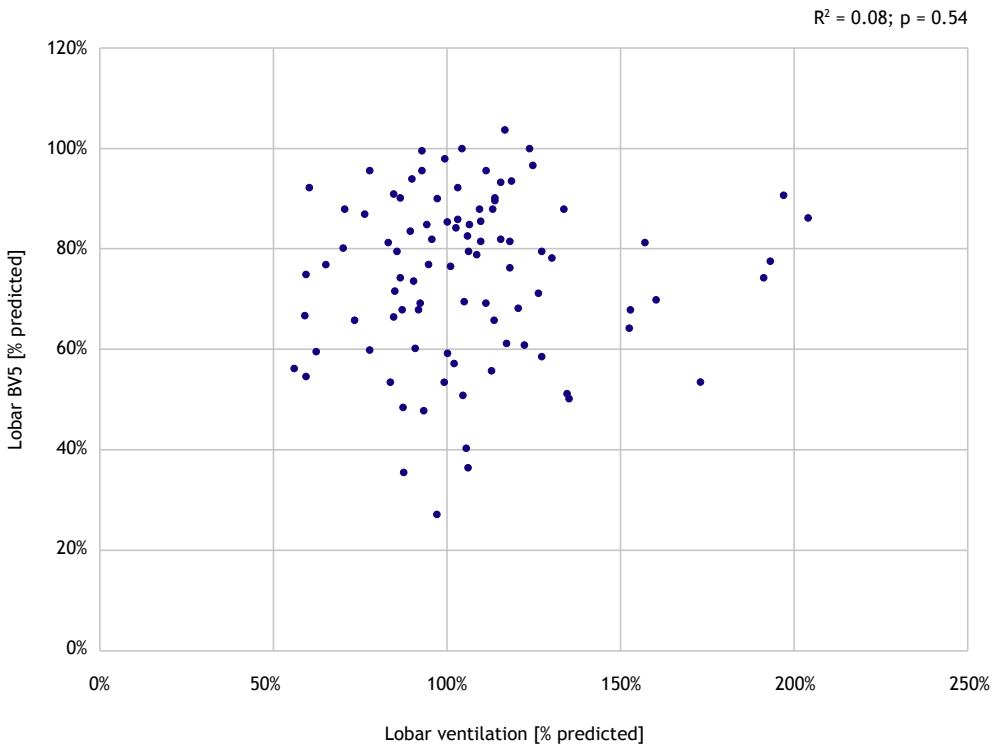

Figure 4. Mixed-effect model of blood volume in vessels with cross-sectional areas < 5 mm² (BV5) as a function of lobar ventilation assessed per lobe.

a direct consequence of the SARS-CoV-2 infection. Our data suggest that patients with AT have lower vascular damage and better outcomes. This could be related to the fact that patients with AT on chest CT have "more" airway disease than small vessel disease. Thus, we hypothesized that there might be two phenotypes of SARS-CoV-2 pneumonia. First, the small-vessel phenotype, characterized by severe

vasoconstriction and microvascular coagulopathy, which results in hypoxemia with preserved lung compliance. Second, the small-airway phenotype, characterized by small airway damage, represented on imaging by the presence of AT. These findings have to be further confirmed by larger studies, and it is still soon to make any recommendations on whether expiratory acquisitions should be included in CT scanning of all patients with COVID-19 pneumonia.

In a previous study of patients clinically diagnosed with COVID-19,[6] AT was more prevalent in those who had been admitted to the ICU or died. However, that study had several limitations that should be acknowledged, which might explain the difference between their results and ours. First, 34.4% of their sample had a negative SARS-CoV-2 RT-PCR test, which weakens the association between AT and worse outcomes because non-COVID-19 cases could have been included. In our study, all patients should have a positive SARS-CoV-2 RT-PCR result. Second, they included a small sample size of patients with poor outcomes.

Our study has some limitations. First, we acknowledge the preliminary nature of our findings, including the lack of a severe COVID-19 comparison group. Secondly, we could only include a small sample size, mainly due to concerns about the patients' exposure to additional radiation with no clear clinical benefits. These preliminary results might encourage further investigations with larger sample sizes to be carried out in the future.

In summary, we found that AT is a common finding in patients with COVID-19 who undergo expiratory CT acquisitions. The presence of AT may correlate with increased SpO_2 at admission, reduced serum D-dimer levels, and a decreased likelihood of hospitalization. Also, the volume of small pulmonary vessels may negatively correlate with CT opacities but not with lobar ventilation, suggesting that severely constricted areas are still well ventilated in COVID-19 patients.

AUTHOR CONTRIBUTIONS

BH: guarantor. RDC and BH: study design. RDC, NV, GW, TM, SPLA, MZ, JDB, BRL, EM, and BH: manuscript drafting. RDC, JDB, and BRL: data acquisition. RDC, NV, TM, SPLA, MZ, EM, BH GW, and BH: data interpretation. RDC, NV, GW, TM, SPLA, MZ, JDB, BRL, EM, and BH: critical review and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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