Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Quantitative Chest CT Assessment of Small Airways Disease in Post-Acute SARS-CoV-2 Infection

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Conflicts of interest are listed at the end of this article.

See also the editorial by Elicker in this issue.

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Background: The long-term effects of SARS-CoV-2 infection on pulmonary structure and function remain incompletely characterized.

Purpose: To test whether SARS-CoV-2 infection leads to small airways disease in patients with persistent symptoms.

Materials and Methods: In this single-center study at a university teaching hospital, adults with confirmed COVID-19 who remained symptomatic more than 30 days following diagnosis were prospectively enrolled from June to December 2020 and compared with healthy participants (controls) prospectively enrolled from March to August 2018. Participants with post-acute sequelae of COVID-19 (PASC) were classified as ambulatory, hospitalized, or having required the intensive care unit (ICU) based on the highest level of care received during acute infection. Symptoms, pulmonary function tests, and chest CT images were collected. Quantitative CT analysis was performed using supervised machine learning to measure regional ground-glass opacity (GGO) and using inspiratory and expiratory image-matching to measure regional air trapping. Univariable analyses and multivariable linear regression were used to compare groups.

Results: Overall, 100 participants with PASC (median age, 48 years; 66 women) were evaluated and compared with 106 matched healthy controls; 67% (67 of 100) of the participants with PASC were classified as ambulatory, 17% (17 of 100) were hospitalized, and 16% (16 of 100) required the ICU. In the hospitalized and ICU groups, the mean percentage of total lung classified as GGO was 13.2% and 28.7%, respectively, and was higher than that in the ambulatory group (3.7%, $P < .001$ for both comparisons). The mean percentage of total lung affected by air trapping was 25.4%, 34.6%, and 27.3% in the ambulatory, hospitalized, and ICU groups, respectively, and 7.2% in healthy controls ($P < .001$). Air trapping correlated with the residual volume–to–total lung capacity ratio ($\rho = 0.6$, $P < .001$).

Conclusion: In survivors of COVID-19, small airways disease occurred independently of initial infection severity. The long-term consequences are unknown.

Online supplemental material is available for this article.

SARS-CoV-2, the virus that causes COVID-19, primarily infects the respiratory tract and causes a wide range of disease severity, including respiratory failure due to acute respiratory distress syndrome (1). Survivors of severe COVID-19 have pulmonary function abnormalities that persist for weeks to months after resolution of the acute illness (2,3). Additionally, lung parenchymal abnormalities are frequently observed on lung images following severe infection. These findings are consistent with literature on the long-term respiratory sequelae of acute respiratory distress syndrome (4,5) and observations from previous severe coronavirus outbreaks (6,7).

Early reports indicate that more than 50% of adult survivors of SARS-CoV-2 infection experience post-acute sequelae of COVID-19 (PASC), or "long COVID" (8,9). Respiratory symptoms, including cough and dyspnea, are reported by nearly 30% of patients with PASC, including those who experienced mild infection not requiring hospitalization (10,11). The long-term effects of SARS-CoV-2 infection in these patients are poorly understood, but the potential impact on our health care systems is enormous given the millions of infections worldwide, most of which led to mild disease. We hypothesized that SARS-CoV-2 infection leads to small airways disease, as has been observed in other severe respiratory viral infections (12,13). Thus, our aim was to test whether SARS-CoV-2 infection leads to small airways disease in patients with persistent symptoms.

Abbreviations

DLCO = diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, fSAD = functional small airways disease, FVC = forced vital capacity, GGO = ground-glass opacity, ICU = intensive care unit, PASC = post-acute sequelae of COVID-19, RV = residual volume, TLC = total lung capacity

Summary

In survivors of COVID-19, quantitative analysis of expiratory chest CT images demonstrated that small airways disease with the presence of air trapping is a long-lasting sequela of SARS-CoV-2 infection.

Key Results

- In a prospective study of 100 survivors of COVID-19 with persistent symptoms and 106 healthy controls, air trapping was detected on expiratory chest CT images.
- The percentage of lung affected by air trapping was similar across COVID-19 severity groups (ambulatory, 25.4%; hospitalized, 34.6%; requiring intensive care, 27.3%; $P = .10$) and persisted in eight of nine participants imaged more than 200 days after diagnosis.
- Air trapping correlated with measurements of lung volumes but not spirometry.

Materials and Methods

Study Design

We prospectively enrolled adults 18 years and older with confirmed SARS-CoV-2 infection who remained symptomatic for more than 30 days following diagnosis and were referred to the post-acute COVID-19 clinic at a university teaching hospital from June to December 2020. On the basis of prior literature for detection of air trapping using quantitative CT analysis (14), we prespecified an enrollment target of 100 ($\alpha = .05$, power = 0.95). Participants were enrolled consecutively and classified as ambulatory, hospitalized but did not require the intensive care unit (ICU) (hereafter, hospitalized), and required the ICU based on the highest level of care received during acute COVID-19. Confirmed COVID-19 was defined as a positive rapid antigen or reverse transcriptase–polymerase chain reaction test from a nasopharyngeal or oropharyngeal swab or a positive SARS-CoV-2 antibody test, and the period of acute infection with SARS-CoV-2 was defined as 21 days following diagnosis (8). As a control group, asymptomatic healthy adults aged 20–80 years ($n = 106$) were prospectively enrolled from March to August 2018 as part of a separate protocol and matched to participants with PASC based on age, sex, and race and ethnicity. Healthy participants (controls) had no prior history of cardiopulmonary disease and were nonsmokers, defined as less than one pack of cigarettes in their lifetime. All study protocols were approved by the institutional review board and were Health Insurance Portability and Protection Act–compliant. Participants provided written informed consent prior to inclusion.

Given disparities in COVID-19 outcomes, race and ethnicity were extracted from electronic medical records along with clinical and laboratory data. During the clinic visit, participants were asked to retrospectively recount their symptoms and detail whether these symptoms persisted using a structured questionnaire (Appendix E1 [online]). Breathlessness was quantified using the modified Medical Research Council dyspnea scale (15,16). Pulmonary function testing and chest CT were performed on the clinic visit day. A single set of measurements from each participant was included, obtained at their initial clinic visit.

Chest CT Acquisition

For all healthy control participants and 87 participants with PASC, chest CT scans were obtained with a Somatom Force (Siemens) scanner; for the remaining four participants with PASC who were imaged, a Definition AS+ (Siemens) scanner was used. All scans were acquired using tube current modulation. Standardized noncontrast chest CT imaging was performed by obtaining an inspiratory scan at total lung capacity (TLC) and an expiratory scan at residual volume (RV) as previously described (17,18). Images were generated using iterative reconstruction with ADMIRE 5 (Somatom Force) or SAFIRE 5 (Definition AS+) at 1 × 0.5 mm (section thickness × interval). Images were assessed for breath-hold quality, and the morphology of tracheal contour was used to ensure inspiration and expiration. Only scans within acceptable limits were included in the analysis.

Image Analysis

Images were analyzed qualitatively by a thoracic radiologist blinded to group (P.N., with 12 years of experience) and quantitatively as previously described (17,19–24). Briefly, Adapted Multiple Feature Method–based texture analysis quantifies ground-glass opacity (GGO) as a percentage of total lung volume at TLC by using gray-scale patterns within images. The disease probability measure, calculated using Lung Print software (VIDA Diagnostics), quantifies the voxel-to-voxel difference in Hounsfield units between matched inspiratory and expiratory images to estimate the probability of air trapping such that the probability is inversely proportional to the relative differences in Hounsfield units (24). Air trapping quantified by the disease probability measure indicates functional small airways disease (fSAD) (14,24,25). Quality control measures for quantitative analysis are included in Appendix E2 (online).

Statistical Analysis

No imputation was made for missing data. Continuous variables are reported using medians and IQRs or means with standard error measurements. Categorical variables are reported as counts and percentages. Prespecified comparisons across the ambulatory, hospitalized, and ICU groups and between the ambulatory group and healthy controls were performed. Univariable comparisons were made using the χ^2 test, one-way analysis of variance, or Kruskal-Wallis test. Post hoc comparisons between groups were performed using the Dunn test. For the χ^2 test, Bonferroni correction was applied for multiple comparisons. Multivariable linear regression was used to adjust for age, sex, and body mass index and the least square means were calculated; correction for multiple comparisons was performed using the Tukey test. Spearman correlation coefficients (ρ) were used to assess the strength of association between pairs of predefined variables. Differences were considered statistically significant when $P < .05$ based on a two-sided test. Statistical analyses were performed using GraphPad Prism (version 9.2) or R (version 4.0.2, *http://www.r-project.org*).

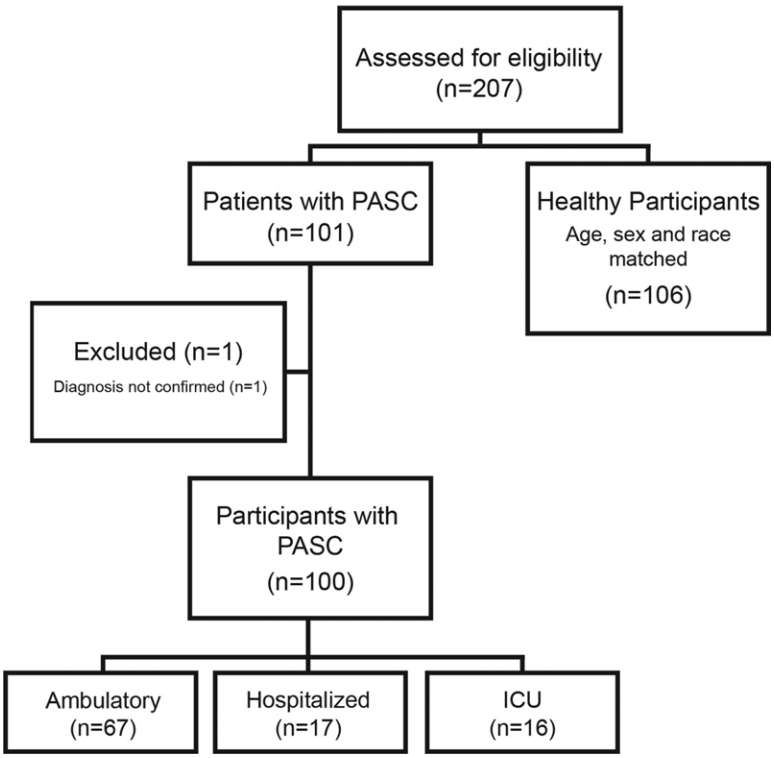

Figure 1: Flowchart of study participants. ICU = intensive care unit, PASC = post-acute sequelae of COVID-19.

Results

Demographic and Baseline Clinical Characteristics of the Participants

A total of 100 participants with PASC and 106 healthy participants were included in the final analysis (Fig 1). One participant with PASC was excluded as SARS-CoV-2 infection could not be confirmed. The demographic and baseline clinical characteristics of the participants are shown in Table 1. Sixty-seven percent (67 of 100) of participants with PASC were treated in the ambulatory setting during the acute COVID-19 period, 17% (17 of 100) were hospitalized, and 16% (16 of 100) required the ICU. The median age of participants with PASC was 48 years, and 66 of 100 (66%) were women. Compared with the ambulatory group, participants with PASC who were hospitalized or who required the ICU were older (median age, 44 vs 64 and 60 years; $P < .001$ and $P = .002$, respectively). Of the 100 participants with PASC, 5% (five of 100) were Black, 10% (10 of 100) were Hispanic or Latino, and 85% (85 of 100) were White. At least one comorbidity was present in 76% (76 of 100) of participants with PASC; obesity (59 of 100) and hypertension (27 of 100) were the most common. Asthma (26 of 100 participants) was the most common coexisting pulmonary disorder, followed by chronic obstructive pulmonary disease (six of 100 participants) and interstitial lung disease (four of 100 participants). The majority of participants with PASC were never smokers (75 of 100). Current or former smoking was more common in the hospitalized group (53%, nine of 17) compared with the ambulatory group (15%, 10 of 67; $P = .002$). The median time from COVID-19 diagnosis to the clinic visit was 74.5 days.

Clinical Characteristics of Acute COVID-19 and PASC

The most common symptoms during acute COVID-19 infection were fatigue (84%, 82 of 98 participants), dyspnea (83%, 82 of 99 participants), and cough (71%, 70 of 98 participants) (Fig E1, Table E1 [online]). None of the participants in the ambulatory group required supplemental oxygen, while 10 of the 17 participants in the hospitalized group (59%) and all 16 participants in the ICU group required supplemental oxygen. Additional details of the clinical characteristics of acute COVID-19 are provided in Tables E1 and E2 (online). Similar to acute infection, the most commonly reported persistent symptoms at presentation in the post–COVID-19 clinic were dyspnea (73%, 73 of 100 participants), fatigue (56%, 56 of 100 participants), and cough (34%, 34 of 100 participants) (Fig E1, Table E3 [online]). Additional clinical data obtained at the clinic visit are provided in Table E3 (online).

Outcomes

The median score on the modified Medical Research Council dyspnea scale for participants with PASC was 2 and was higher in participants in the hospitalized group compared with the ambulatory group (modified Medical Research Council dyspnea scale: 3 vs 1, respectively; $P = .02$) (Fig E1, Table E4 [online]). The median percent predicted prebronchodilator forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in participants with PASC were 95% and 93%, respectively (Fig 2, Table E4 [online]). Compared with the ambulatory group, the hospitalized and ICU groups had a lower FVC (103% vs 86% and 66%; $P = .003$ and $P < .001$, respectively) and FEV_1 (99% vs 87% and 72%; $P = .02$ and $P < .001$, respectively). We found no evidence of differences in the FVC (103% vs 100%, $P = .78$) and FEV_1 (93% vs 98%, $P = .55$) of participants in the ambulatory group compared with healthy controls. The median prebronchodilator percent of FVC exhaled in the first second (FEV_1/FVC) was 80%, and we found no evidence of differences across groups (ambulatory, 79%; hospitalized, 79%; ICU, 83%; $P = .09$). No response to a bronchodilator was observed in any of the PASC groups. In participants with PASC, the median percent predicted TLC was 96% and the median percent predicted RV was 82%. Compared with the ambulatory group, the hospitalized and ICU groups had a lower TLC (102% vs 87% and 55%; $P = .009$ and $P < .001$, respectively). Participants who required the ICU also had a lower RV than those in the ambulatory group (53% vs 91%, respectively; $P = .007$). Compared with healthy controls, the ambulatory group had a higher TLC (95% vs 102%, $P = .01$) but the RV was similar (89% vs 91%, $P = .51$). The median percent predicted diffusing capacity of the lung for carbon monoxide (D_{LCO}) was 96% in participants with PASC. Participants in the hospitalized and ICU groups had a lower D_{LCO} compared with those in the ambulatory group (103% vs 72% and 54%; $P < .001$ for both comparisons). The D_{LCO} was higher in the ambulatory group compared with healthy controls (103% vs

Table 1: Demographic and Baseline Clinical Characteristics of the Participants

Characteristic	Control Group (n = 106)	PASC Group (n = 100)	Ambulatory Group (n = 67)	Hospitalized Group (n = 17)	ICU Group (n = 16)	P Value*	P Value†
Median age (y)‡	48 (31–57)	48 (36–61)	44 (29–53)	64 (53–72)	60 (45–68)	<.001	.002
Sex							
M	46 (43)	34 (34)	19 (28)	6 (35)	9 (56)		
F	60 (57)	66 (66)	48 (72)	11 (65)	7 (44)		
Race and ethnicity							
Black, non-Hispanic	3 (3)	5 (5)	3 (5)	1 (6)	1 (6)		
Hispanic or Latino	6 (6)	10 (10)	5 (8)	2 (12)	3 (19)		
White, non-Hispanic	97 (92)	85 (85)	59 (88)	14 (82)	12 (75)		
Median BMI (kg/m^2)‡	25 (22.7–28.1)	32 (26.6–38.1)	31 (23.7–36.6)	36 (30.1–48.2)	33 (26.7–38.0)	.02	
Comorbidity							
Asthma		26 (26)	18 (27)	4 (24)	4 (25)		
Cancer		9 (9)	5 (8)	3 (18)	1 (6)		
Chronic kidney disease		4 (4)	0 (0)	1 (6)	3 (19)		.008
Chronic obstructive pulmonary disease		6 (6)	1 (2)	1 (6)	4 (25)		.006
Coronary artery disease		8 (8)	4 (6)	2 (12)	2 (13)		
Diabetes type I		2 (2)	1 (2)	1 (6)	0 (0)		
Diabetes type II		12 (12)	3 (5)	3 (18)	6 (38)		.002
Heart failure		1 (1)	0 (0)	1 (6)	0 (0)		
Hypertension		27 (27)	10 (15)	8 (47)	9 (56)	.02	.003
Immunocompromise or HIV		8 (8)	3 (5)	3 (18)	2 (13)		
Interstitial lung disease§		4 (4)	2 (3)	2 (12)	0 (0)		
Obesity		59 (59)	36 (54)	13 (77)	10 (63)		
Thromboembolic disease		3 (3)	0 (0)	2 (12)	1 (6)		
Tobacco use						.002	
Never	106 (100)	75 (75)	57 (85)	8 (47)	10 (63)		
Former		23 (23)	8 (12)	9 (53)	6 (38)		
Current		2 (2)	2 (3%)	0 (0)	0 (0)		
Median pack-year‡‖		8 (4.8–25.5)	12 (5.0–27.5)	5.5 (3.1–20.5)	10 (2.5–40.0)		
Median time to follow-up (d)‡#		74.5 (45.8–118.0)	68 (42.0–126.0)	109 (70.5–204.0)	59.5 (50.3–97.8)		

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. Percentages may not total 100 because of rounding. For continuous variables, P values were calculated using the Dunn test for post hoc comparisons between groups. For categorical variables, P values were calculated using the χ^2 test with Bonferroni correction. BMI = body mass index, ICU = intensive care unit, PASC = post-acute sequelae of COVID-19.

* Ambulatory group versus hospitalized group.

† Ambulatory group versus ICU group.

‡ Data are medians, with IQRs in parentheses.

§ Included sarcoidosis, nonspecific interstitial pneumonitis, bleomycin-induced interstitial lung disease, and hypersensitivity pneumonia.

‖ Only calculated for former and current smokers. One pack-year is defined as smoking one package of cigarettes per day on average for 1 year.

Time from laboratory-confirmed diagnosis to the post–COVID-19 clinic visit.

88%, respectively; $P < .001$). Differences in spirometry, lung volumes, and DLCO remained significant after adjusting for age, sex, and body mass index (Fig E2 [online]).

Qualitative analysis of chest CT images identified air trapping as the most common imaging abnormality (58%, 50 of 86 participants) (Table 2, Fig E3 [online]). GGO, which is frequently observed during acute COVID-19 and often in an organizing pneumonia pattern (26,27), was identified in 51% (46 of 91) of participants with PASC. GGO has been reported to persist for months following infection in survivors of severe disease (2) and was more common in the ICU group (94%, 15 of 16) compared with the ambulatory group (36%, 21 of 59; $P < .001$). Of the participants with air trapping, 52% (26 of 50) also had GGO. To assess GGO and air trapping more fully, quantitative analysis of chest CT images was performed (Fig 3). In the hospitalized and ICU groups, the mean percentage of total lung classified as GGO was 13.2% and 28.7%, respectively, and was higher than that of the ambulatory group (3.7%, $P < .001$ for both comparisons). Although the amount of GGO observed in the ambulatory group was

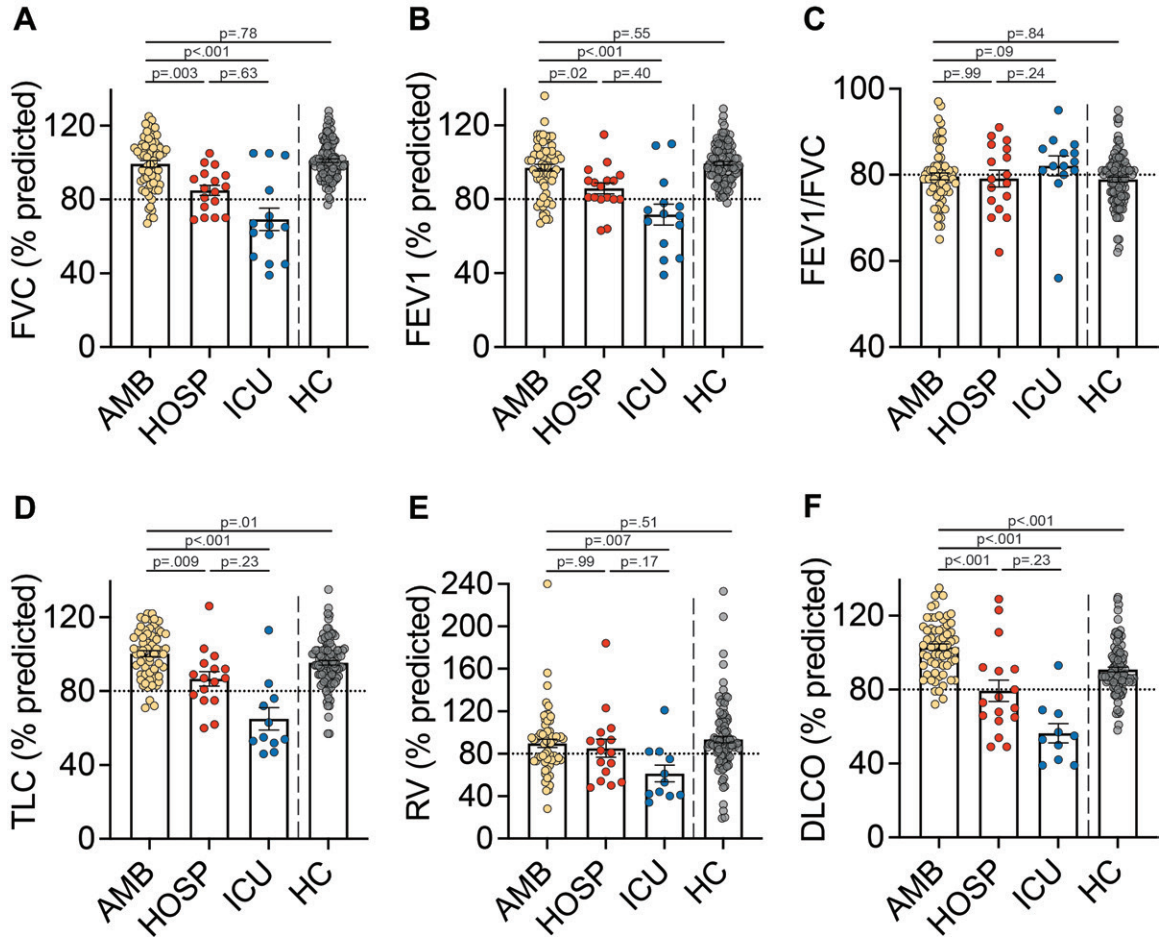

Figure 2: Bar graphs show results of pulmonary function testing in post-acute COVID-19 according to participant group. **(A)** Percent predicted forced vital capacity (FVC). **(B)** Percent predicted forced expiratory volume in 1 second (FEV1). **(C)** Percent of FVC exhaled in the first second (FEV1/FVC). **(D)** Percent predicted total lung capacity (TLC). **(E)** Percent predicted residual volume (RV). **(F)** Percent predicted diffusing capacity of the lung for carbon monoxide (DLCO). Data are displayed as means with standard error measurements. Horizontal dashed lines indicate the lower limit of normal. *P* values were calculated using the Dunn test for post hoc comparisons between groups. AMB = ambulatory, HC = healthy controls, HOSP = hospitalized, ICU = intensive care unit.

low, it was higher than in the healthy controls (0.06%, $P < .001$). GGO as a percentage of total lung correlated with the percent predicted TLC ($\rho = -0.6$, $P < .001$) and DLCO ($\rho = -0.47$, $P < .001$). Disease probability measure analysis revealed that the mean percentage of total lung affected by air trapping was 25.4%, 34.6%, and 27.3% in the ambulatory, hospitalized, and ICU groups, respectively, and we found no evidence of differences in the amount of air trapping across PASC groups ($P = .10$). The percentage of lung affected by air trapping was higher in participants in the ambulatory group (25.4%) compared with that of healthy controls (7.2%, $P < .001$). These differences remained significant after adjusting for age, sex, and body mass index (Fig E4 [online]). We found no evidence of differences in the percentage of lung affected by air trapping when participants with PASC were stratified by history of asthma (no asthma vs asthma: 28% vs 26%, $P = .46$) (Fig E4 [online]).

Air trapping can also be detected using lung volume measurements, specifically the RV/TLC ratio. Therefore, we assessed the RV/TLC ratio using both plethysmography and quantitative CT. Quantitative CT measurements of RV and TLC were obtained during the same effort from which air trapping was measured. The RV/TLC ratio calculated using plethysmography was higher in the hospitalized group than in the ambulatory group (37% vs 28%, $P = .006$) and trended toward higher in the ICU group (35%, $P = .06$) (Fig 3). A similar pattern was observed for the RV/TLC ratio when measured using quantitative CT (ambulatory group [56%] vs hospitalized group [65%] vs ICU group [66%], $P = .06$) (Fig E5 [online]). The RV/TLC ratio calculated using plethysmography correlated with the presence of air trapping measured per the disease probability measure ($\rho = 0.6$, $P < .001$), as did the ratio calculated using quantitative CT ($\rho = 0.84$, $P < .001$). Finally, we assessed whether there was a relationship between the severity of pulmonary function or CT abnormalities in participants with PASC and the time since acute infection. We found no evidence of significant correlations between GGO ($\rho = 0.05$, $P = .62$) (Fig E6 [online]) or air trapping and days from diagnosis to CT scan ($\rho = -0.06$, $P = .60$). We also found no evidence of differences in the amount of air trapping observed in participants imaged less than 60 days from diagnosis compared with those imaged more than 60 days from diagnosis (26% vs 28%,

Table 2: Chest CT Findings

Finding	PASC Group	Ambulatory Group*	Hospitalized Group*	ICU Group	*P* Value†	*P* Value‡
Air trapping§	50/86 (58)	32/56 (57)	11/15 (73)	7/15 (47)		
Without GGO	24/50 (48)	20/32 (63)	4/11 (36)	0/7 (0)		
With GGO	26/50 (52)	12/32 (38)	7/11 (64)	7/7 (100)		
GGO	46/91 (51)	21/59 (36)	10/16 (63)	15/16 (94)		<.001
Pulmonary nodule	32/91 (35)	19/59 (32)	9/16 (56)	4/16 (25)		
Nodule type						
Solid	22/32 (69)	13/19 (68)	7/9 (78)	2/4 (50)		
Ground glass	6/32 (19)	5/19 (26)	0/9 (0)	1/4 (25)		
Mixed	4/32 (13)	1/19 (5)	2/9 (22)	1/4 (25)		
Traction bronchiectasis	23/91 (25)	5/59 (8)	7/16 (44)	11/16 (69)	.005	<.001
Architectural distortion, honeycombing, or scar	22/91 (24)	2/59 (3)	7/16 (44)	13/16 (81)	<.001	<.001
Bronchial wall thickening	7/91 (8)	4/59 (7)	2/16 (13)	1/16 (6)		
Lymphadenopathy	3/91 (3)	0/59 (0)	0/16 (0)	3/16 (19)		
Emphysema	3/91 (3)	0/59 (0)	1/16 (6)	2/16 (13)		
Consolidation	2/91 (2)	0/59 (0)	0/16 (0)	2/16 (13)		
Pleural effusion	0/91 (0)	0/59 (0)	0/16 (0)	0/16 (0)		

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. Percentages may not total 100 because of rounding. *P* values were calculated using the χ^2 test with Bonferroni correction. GGO = ground-glass opacity, ICU = intensive care unit, PASC = post-acute sequelae of COVID-19.

* Imaging data were not available for eight participants in the ambulatory group and one participant in the hospitalized group.

† Ambulatory group versus hospitalized group.

‡ Ambulatory group versus ICU group.

§ Expiratory images were not available for three participants in the ambulatory group, one participant in the hospitalized group, and one participant in the ICU group.

P = .73). Notably, air trapping persisted in eight of nine participants imaged more than 200 days from the initial infection.

Discussion

Respiratory symptoms are common among survivors of COVID-19, even in patients who do not require hospitalization (10,11). Therefore, we set out to identify whether SARS-CoV-2 infection leads to small airways disease using quantitative chest CT analysis. In this prospective cross-sectional case series, we established that the mean percentage of lung affected by air trapping was 25.4% for individuals with mild COVID-19 not requiring hospital admission who remained symptomatic more than 30 days following diagnosis; similar proportions were observed in the lungs of individuals who required hospitalization (34.6%) or the intensive care unit (27.3%).

In contrast to most published studies, 67% of participants with PASC in our cohort did not require hospitalization during acute infection and were classified as ambulatory (9). Spirometry and lung volumes in ambulatory participants were not different compared with healthy controls, but the percentage of lung affected by GGO was higher (3.7% vs 0.06%, $P < .001$), suggesting ongoing lung inflammation, edema, or fibrosis. Strikingly, the mean percentage of lung affected by air trapping in ambulatory participants was 25.4%, which was significantly higher than that in healthy controls (7.2%, $P < .001$) and similar to the mean amount of air trapping observed in participants who were hospitalized (34.6%) or in the ICU (27.3%) during acute COVID-19. We did not observe airflow obstruction with spirometry in any group, suggesting that air trapping in our cohort is due to involvement of small rather than large airways. Small airways, defined as noncartilaginous airways with an internal diameter less than 2 mm, contribute little to total airway resistance and, thus, small airways disease is typically not detected with spirometry until a large percentage (>75%) of all small airways are obstructed (28–30). Small airways are not readily identified with lung imaging, but several studies have established the presence of air trapping on chest CT scans as a marker of fSAD (14,24,25). Taken together, our findings suggest that SARS-CoV-2 infection itself leads to fSAD and air trapping, while restrictive lung disease and impairment in gas exchange result from lung injury and adult respiratory distress syndrome.

Airway involvement is not typically observed on chest CT scans during acute SARS-CoV-2 infection (26,31). However, the angiotensin-converting enzyme 2, or ACE2, receptor, which facilitates SARS-CoV-2 infection, is expressed throughout the airway tract, including in the small airways (32,33). Thus, the fSAD observed in individuals with PASC could result from direct infection of the small airways, even in those with mild acute infection. Alternatively, the immune response induced by SARS-CoV-2 could lead to fSAD in individuals with PASC, which might represent postinfectious constrictive bronchiolitis as has been described following other severe viral infections (12,13). In contrast to airway involvement, GGO in an organizing pneumonia pattern is commonly observed on chest CT scans during acute SARS-CoV-2 infection (26,27). Organizing pneumonia is characterized histopathologically by buds of

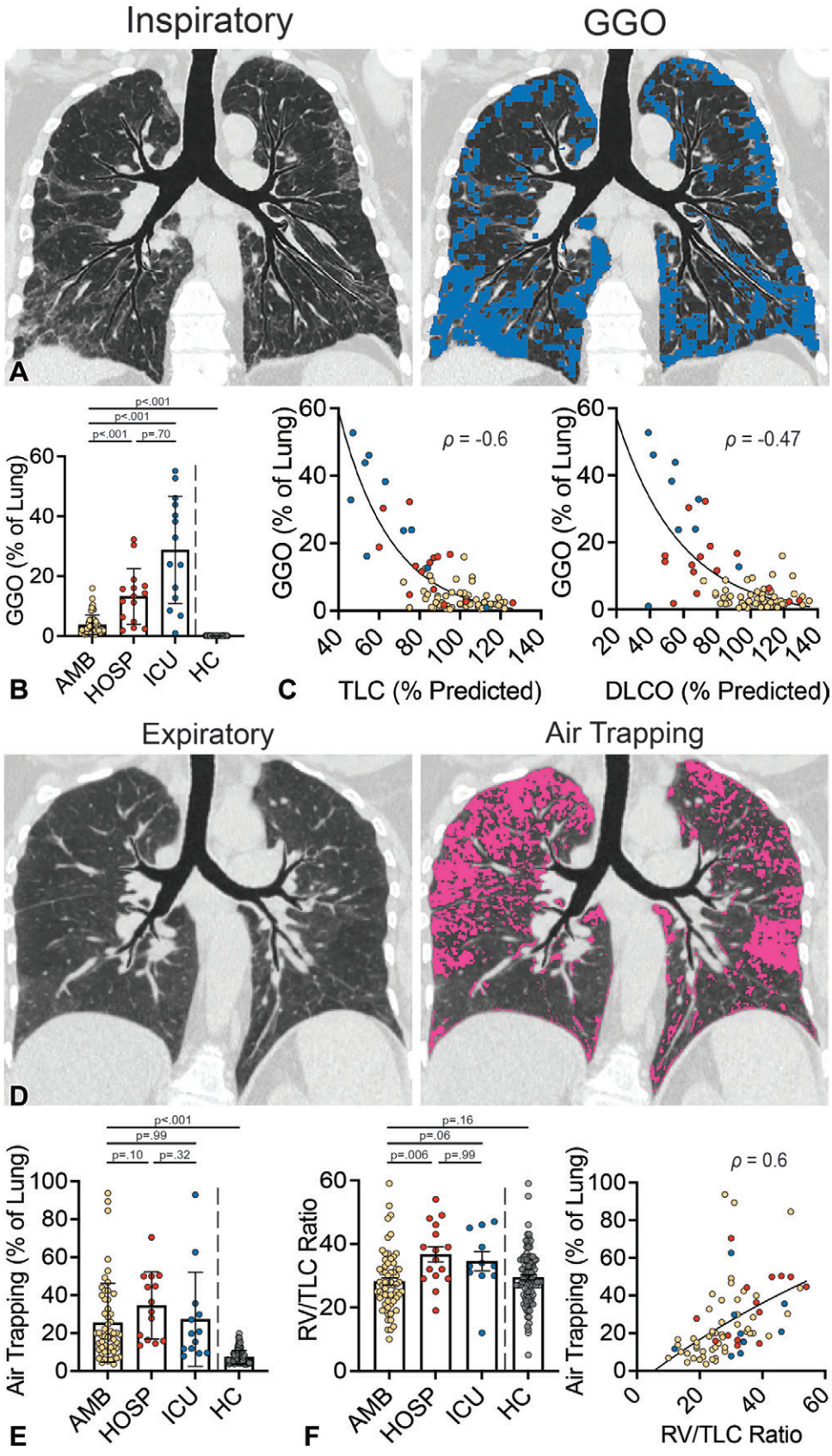

Figure 3: Quantitative chest CT and correlation with pulmonary function. **(A)** Chest CT images in a 60-year-old man with post-acute sequelae of COVID-19 (hospitalized group). Representative coronal image from inspiratory noncontrast chest CT (left) obtained at total lung capacity (TLC). The corresponding texture analysis map (right) highlights ground-glass opacity (GGO) in blue. **(B)** Bar graphs show quantification of GGO measured with texture analysis. **(C)** Bar graphs show correlation of GGO with percent predicted TLC (left) and diffusing capacity of the lung for carbon monoxide (DLCO; right). **(D)** Chest CT images in a 61-year-old woman with PASC (ambulatory group). Representative coronal image from expiratory noncontrast chest CT obtained at residual volume (RV) (left). The corresponding disease probability measure map (right) highlights air trapping in pink. **(E)** Bar graph shows quantification of air trapping measured per the disease probability measure. **(F)** Bar graphs show RV/TLC ratio measured with plethysmography (left) and correlation of air trapping with the RV/TLC ratio (right). Images in **A** and **D** were prepared using topographic multiplanar reformat rendering, which serves to display the airways and associated parenchyma on the same plane (17,27). Data in **B, E**, and **F** are displayed as means with standard error measurements. Yellow circles on graphs indicate ambulatory group (AMB); red circles, hospitalized group (HOSP); and blue circles, intensive care unit (ICU) group. *P* values in **B, E,** and **F** were calculated using the Dunn test for post hoc comparisons between groups. The Spearman correlation was used to calculate ρ values in **C** and **F**. HC = healthy controls.

inflammatory tissue within the small airways, potentially contributing to fSAD (34,35). Of the 50 participants with PASC in whom air trapping was identified, approximately half (26 of 50) also had GGO. Of note, we did not observe a relationship between air trapping and time from diagnosis to CT. The median time from diagnosis to chest CT was approximately 75 days. The persistence of respiratory abnormalities in this time frame raises concern for permanent airway remodeling and fibrosis following SARS-CoV-2 infection. Small airways disease also occurs as a result of chronic inflammatory disorders such as connective tissue disease and inflammatory bowel disease, immunodeficiency, and following exposure to certain noxious stimuli (28). In many of these disorders, irreversible and sometimes progressive lung impairment is observed.

Our study had limitations. First, this is a single-center study that enrolled participants infected early during the COVID-19 pandemic. Therefore, the generalizability of our findings may be limited as treatment during acute illness was highly variable and more recent variants, including Delta and Omicron, are not represented. Second, although participants with PASC had more GGO and air trapping than our matched healthy controls, we did not have baseline images from participants with PASC. However, it is important to note that most of the participants with PASC in our study had no history of lung disease. Third, we evaluated a relatively small number of participants, all of whom were symptomatic; therefore, we cannot comment on the prevalence of pulmonary function testing and imaging abnormalities among all survivors of COVID-19. Larger studies will be needed to determine whether the presence of fSAD correlates to respiratory symptoms.

In conclusion, patients with post-acute sequelae of COVID-19 (PASC) have a high prevalence of long-lasting air trapping at imaging, regardless of the initial severity of infection. Air trapping is often missed with spirometry but can be detected using inspiratory and expiratory CT and plethysmography. Studies aimed at determining the natural history of functional small airways disease (fSAD) in patients with PASC and the biologic mechanisms that underlie these findings are urgently needed to identify therapeutic and preventative interventions. Longitudinal assessment will be required to determine whether fSAD in patients with PASC improves over time or whether it leads to persistent or progressive lung disease.

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