

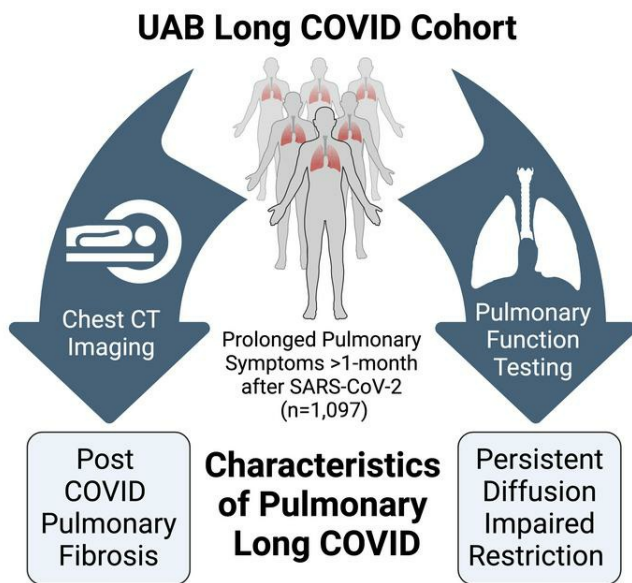
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Characteristics and Determinants of Pulmonary Long COVID

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39 **STRUCTURED ABSTRACT**

40 **BACKGROUND**

41 Persistent cough and dyspnea are prominent features of post-acute sequelae of SARS-
42 CoV-2 (also termed 'Long COVID'); however, physiologic measures and clinical features
43 associated with these pulmonary symptoms remain poorly defined. Using longitudinal
44 pulmonary function testing (PFTs) and CT imaging, this study aimed to identify the
45 characteristics and determinants of pulmonary Long COVID.

46 **METHODS**

47 This single-center retrospective study included 1,097 patients with clinically defined Long
48 COVID characterized by persistent pulmonary symptoms (dyspnea, cough, and chest
49 discomfort) lasting for ≥ 1 month after resolution of primary COVID infection.

50 **RESULTS**

51 After exclusion, a total of 929 patients with post-COVID pulmonary symptoms and PFTs
52 were stratified diffusion impairment and restriction as measured by percent predicted
53 diffusion capacity for carbon monoxide (DLCO) and total lung capacity (TLC). Longitudinal
54 evaluation revealed diffusion impairment (DLCO $\leq 80\%$) and pulmonary restriction (TLC
55 $\leq 80\%$) in 51% of the cohort overall (n=479). In multivariable modeling regression analysis
56 (adjusted odds ratio; aOR, 95% confidence interval [CI]), invasive mechanical ventilation
57 during primary infection conferred the greatest increased odds of developing pulmonary
58 Long COVID with diffusion impairment and restriction (aOR=9.89 [3.62-26.9]). Finally, a
59 sub-analysis of CT imaging identified radiographic evidence of fibrosis in this patient
60 population.

61 **CONCLUSIONS**

62 Longitudinal PFTs revealed persistent diffusion impaired restriction as a key feature of
63 pulmonary Long COVID. These results emphasize the importance of incorporating PFTs
64 into routine clinical practice for evaluation of Long COVID patients with prolonged
65 pulmonary symptoms. Subsequent clinical trials should leverage combined symptomatic
66 and quantitative PFT measurements for more targeted enrollment of pulmonary Long
67 COVID patients.

68

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70 This work was supported by the National Institute of Allergy and Infectious Diseases
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74 Birmingham.

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81 INTRODUCTION

82 A major consequence of the COVID-19 pandemic has been the complex and
83 frequently debilitating post-acute sequelae of SARS-CoV-2 infection (PASC, also termed
84 'Long COVID'), estimated to occur in 10% of patients after primary infection (1-2). To date,
85 over 150 distinct Long COVID symptoms involving every major organ system have been
86 reported (3). Recent efforts to develop a consensus definition for Long COVID using
87 symptom clustering have highlighted broad disease sub-types associated with chronic
88 fatigue, post-exertional malaise, brain fog, and loss of smell or taste (4). These efforts
89 represent an important first step for Long COVID research; however, characterizing
90 discreet endotypes with widely available quantitative physiologic measurements is
91 essential for standardizing Long COVID diagnosis and management.

92 Prolonged pulmonary symptoms, notably dyspnea and cough, are among the most
93 commonly reported manifestations of Long COVID (hereon referred to as 'pulmonary Long
94 COVID') (4-6). Although pulmonary complaints are frequently reported, the underlying
95 cause(s) and clinical trajectory of patients suffering these symptoms remains unclear. Prior
96 studies have suggested diffusion impairment that resolves within 1-year of hospitalization
97 is a common feature of post-acute COVID-19 (7-10). Other post-acute COVID follow-up
98 studies have reported radiologic evidence of lung pathology characterized by ground glass
99 opacities and fibrotic changes (11-18). While these results have provided valuable insight
100 into post-COVID lung pathology, these studies are limited by the cohort size and inherently
101 biased towards post-acute COVID patients, rather than Long COVID populations
102 experiencing persistent pulmonary complaints.

103 To address this knowledge gap, we leveraged a large demographically diverse cohort
104 exclusively comprised of Long COVID patients experiencing pulmonary symptoms for ≥ 1
105 month after resolution of SARS-CoV-2 infection. Using longitudinal pulmonary function
106 testing (PFT) and computerized tomography (CT) imaging, we identify specific disease
107 features and risk factors linked to the development of pulmonary Long COVID. These
108 presentations capture the population of patients with persistent clinical symptoms and
109 reflect the natural history of pulmonary Long COVID. Lastly, we provide evidence for a
110 previously undescribed endotype of Long COVID defined by persistent diffusion
111 impairment and pulmonary restriction.

112 **METHODS**

113 **Sex as a Biological Variable**

114 The retrospective design of this study had no exclusion criteria based on patient biological sex.
115 After exclusion (Figure 1), our cohort consisted of 66% female (n=609) and 34% male (n=302)
116 patients, reflecting previously reported biases towards development of Long COVID symptoms in
117 female patients (1-3). To evaluate biological sex as a risk factor for developing Pulmonary Long
118 COVID, patient biological sex was used as a variable in univariable and multivariable outcome
119 modeling (Table 1) and subsequent model sensitivity testing (Supplemental Tables 5-7, 10).

120 **Study Design and Population**

121 This single-center, retrospective cohort study was performed among adult patients (≥ 18
122 years) with a positive COVID-19 PCR and/or rapid antigen test during the study window
123 (03/2020-08/2023), followed by self- or physician referral to the University of Alabama at
124 Birmingham (UAB) Post-COVID Pulmonary Clinic for chief complaint of unresolved
125 respiratory symptoms categorized as dyspnea, cough, or chest discomfort (note: the
126 presence of extra-pulmonary symptoms was not an exclusion criteria; however, only a
127 single pulmonary chief complaint was recorded). Pulmonary Long COVID was defined as
128 pulmonary symptoms persisting for ≥ 1 month that had developed ≥ 28 days after resolution
129 of primary SARS-CoV-2 infection. PFTs were performed on all patients (if able to physically
130 complete the exam) referred for in-person clinic visit. Chest CT imaging orders were made
131 at the discretion of the attending physician. Baseline (1st visit) PFTs and CT scans were
132 defined by the first date of the measurement within a window of 14-days prior to and 6-
133 months after the patient's 1st Long COVID clinic visit date. Follow-up measurements
134 (termed 2nd and 3rd visit) were restricted to the study window and had to occur after the

135 first encounter measurement. The cohort was stratified by percent predicted diffusion
136 capacity for carbon monoxide (DLCO; normal=DLCO >80%, impaired=DLCO ≤80%) and
137 percent predicted total lung capacity (TLC) in accord with the American Thoracic Society
138 consensus definition for restrictive lung disease. Lung restriction sub-groupings were (1)
139 no restriction TLC >80%, (2) mild restriction TLC 71-80%, (3) moderate restriction TLC 51-
140 70%, (4) severe restriction TLC ≤50% (19-20). All pulmonary function studies were
141 conducted utilizing the same equipment (Vyntus™ system from Vyaire Medical
142 Incorporated). For further information on cohort stratification by primary SARS-CoV-2
143 infection severity, see Supplemental Table 9.

144

145 **Patient Variables Extracted from Electronic Medical Record and** 146 **Radiographic Images**

147 Clinical variables were extracted for all patients in the cohort including: advanced age
148 (≥65 years), biological sex, elevated BMI (≥30), smoking history (never, former, or current
149 smoker), pre-COVID vaccination status, ICU admission, COVID-19 severity (assessed
150 using the WHO score system representing maximum oxygen therapy support required),
151 and therapeutics (dexamethasone, remdesivir, days on oxygen a specific oxygen support
152 device) during primary infection, SARS-CoV-2 variant, and months from primary infection
153 to first Long COVID clinic visit (21). Pre-COVID comorbidities (renal, pulmonary, heart
154 failure or hypertension, diabetes, obstructive sleep apnea, and immunosuppression) were
155 determined by physician review of medical records. CT imaging was assessed by two
156 blinded cardiothoracic radiologists for the presence or absence of 6 pulmonary imaging
157 findings: lung consolidation, ground-glass opacities, reticulations, other fibrotic-like

158 changes (i.e. architectural distortion, traction bronchiectasis and honeycombing; termed
159 'other fibrosis'), bronchiectasis, and emphysema (see Supplemental Table 3 for two-
160 reader similarity evaluation and Supplemental Table 11 for analysis of PFT and CT
161 imaging in a sub-cohort of patients with 3-consecutive follow-up visits). An overall severity
162 score was determined using a previously defined image scoring system quantifying
163 abnormalities in all 5 lung lobes with scores ranging from 0 (no involvement) to 25 (multi-
164 lobe involvement) (22). Detailed information on variables extracted can be found in the
165 supplemental materials (Supplemental Table 1).

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167 **Statistical Analysis**

168 Cohort statistics were reported with mean \pm standard deviation or median [Q1-Q3] in Table
169 1. Alluvial diagrams were used to assess relative DLCO and TLC improvement or decline
170 in patients with 3-consecutive follow-ups visits (Figure 2C). Logistic regression models
171 (unadjusted variable and multi-variable adjusted) were used to discover risk factors for
172 developing diffusion impairment ($DLCO \leq 80\%$) with severe or moderate restriction
173 ($TLC \leq 70\%$) at 1st Long COVID clinic visit (Table 2; see Supplemental Table 1 for details
174 on model variables and Supplemental Table 5-7 and Supplemental Table 10 for model
175 sensitivity testing). All modeling results are reported as either unadjusted (OR) or adjusted
176 odds ratios (aOR) with bootstrapped (n=1000 iterations) 95% confidence intervals (CI).
177 All statistical analyses were performed using R (version 4.2, R Foundation).

178

179 **Study Approval**

180 The study was approved by the IRB of the University of Alabama at Birmingham (IRBs no.
181 300006291, 300006205).

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184 **Data Availability**

185 Select de-identified data from the University of Alabama at Birmingham (UAB) 2020–2022
186 pulmonary Long COVID cohort can be made available upon request with IRB approval
187 and signing of institutional data use agreements.

188 **RESULTS**

189 **Study Population**

190 A total of 1,097 patients with prolonged pulmonary symptoms after primary
191 SARSCoV-2 infection were identified based upon their evaluation in post-acute COVID
192 clinic. After exclusion, 929 patients with prolonged pulmonary symptoms (dyspnea, cough,
193 or chest discomfort) lasting ≥ 1 month after resolution of primary SARS-CoV-2 infection
194 and a subsequent PFT were included in this study (Figure 1, Table 1). To evaluate the role
195 of pulmonary abnormalities in DLCO and evidence of pro-fibrotic processes, we stratified
196 patients by diffusion impairment and severity of pulmonary restriction as measured by first
197 post-acute PFT. Median time from primary SARS-CoV-2 infection to 1st Long COVID clinic
198 visit was 125 days for diffusion impaired patients and 148 days for patients with normal
199 diffusion capacity (Table 1). Patient age (mean, \pm SD) for the diffusion impaired group was
200 56 ± 13 years compared to 48 ± 14 years in the normal diffusion group (Table 1). For both
201 groups, the majority of primary SARS-CoV-2 infections occurred during the alpha-variant
202 wave (range: 62-63%), followed by 21-23% and 15-16% occurring in the delta and omicron

203 waves, respectively (Supplemental Table 2). Differences in primary pulmonary symptom
204 reported at 1st Long COVID clinic visit were unremarkable between patients with and
205 without diffusion impairment (range; dyspnea: 76-79%, cough: 17-19%, chest discomfort:
206 4%).

207 We sought to determine how acute disease severity contributed to PFT findings for
208 patients with pulmonary Long COVID. Broadly, requiring higher intensity respiratory
209 support was associated with diffusion impairment and restriction. Acute disease severity
210 was stratified by peak WHO ordinal score. Of the 73 patients who required invasive
211 mechanical ventilation (IMV), only 3 were in the normal diffusion capacity group (Table 1).
212 Increased frequency and duration of oxygen support was observed among diffusion
213 impaired patients with the severe restriction group (IMV: 32%, HFNC: 22%) exceeding
214 that of the moderate (IMV: 9%, HFNC: 16%), mild (IMV: 6%, HFNC: 14%), and no
215 restriction groups (IMV: 3%, HFNC: 5%; Table 1). A similar trend of increased time of
216 oxygen therapy (median [Q1-Q3]) during primary infection was also observed in diffusion
217 impaired patients (IMV: 18 [8-35] days; HFNC: 5 [3-8] days, and nasal cannula: 7 [4-11]
218 days; Supplemental Table 2). Differences in vaccination, pre-existing pulmonary disease
219 or obstructive sleep apnea, and smoking history prior to primary SARS-CoV-2 infection
220 were minimal between diffusion impaired and normal groups (Table 1). Patients with
221 diffusion impairment had a greater proportion of pre-existing diabetes (21%) and heart
222 failure or hypertension (52%) compared to the normal diffusion group with 14% and 33%,
223 respectively (Table 1). Cumulative lung involvement (25 points total, 5 points per lobe;
224 median [Q1-Q3]) was higher in the diffusion impaired group (9 [1-17]) compared to the
225 normal group (0 [0-2]). The degree of lung involvement on CT imaging for diffusion
226 impaired patients correlated with increasing severity of lung restriction (none: 3 [1-7], mild:

227 3 [0-9], moderate: 7 [1-13], severe: 17 [9-21]; Table 1). Further characteristics of the cohort
228 are presented in Table 1 and Supplemental Table 2.

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234 **Longitudinal Evaluation of Pulmonary Function Testing**

235 To assess physiological differences between patients with pulmonary Long COVID,
236 we evaluated longitudinal PFTs over three total Long COVID visits. After 1st visit
237 stratification, patients without diffusion impairment had, on average, normal lung capacity
238 during the visit 2 visits (TLC 1st: 82±15%, 2nd: 79±13%) with mild decline on 3rd visit
239 (72±15%) compared to patients with diffusion impairment on respective follow-up visits
240 (TLC 1st: 65±18%, 2nd: 65±15%, 3rd: 64±15%) (Figure 2A, Supplemental Table 4). Diffusion
241 impaired patients with severe or moderate restriction experienced little to no improvement
242 in TLC at 2nd (severe: 51±14%, moderate: 66±11%) or 3rd visit (severe: 55±14%,
243 moderate: 65±12%) (Figure 2A, Supplemental Table 4). Overall, patients with normal
244 diffusion capacity at 1st visit maintained normal or above normal DLCO at the follow-up
245 visits (DLCO 1st: 95±12%, 2nd: 93±16%, 3rd: 90±15%), regardless of the level of 1st visit
246 restriction (Figure 2B, Supplemental Table 4). In contrast, patients with diffusion
247 impairment at 1st visit remained, on average, diffusion impaired at all follow-up visits
248 (DLCO 1st: 59±16%, 2nd: 66±19%, 3rd: 65±19%), with a clear association between

249 worsening TLC and DLCO (Figure 2B, Supplemental Table 4). Additional PFT
250 measurements are provided in Supplemental Table 4.

251 Alluvial diagrams were used to assess improvement or decline in diffusion impairment
252 and restriction for patients with 3-consecutive PFTs at the UAB pulmonary Long COVID
253 clinic (N=100, Figure 2C). Overall, we observed that the majority of patients with diffusion
254 impairment and severe or moderate restriction at 1st visit had persistent restriction and
255 diffusion impairment at 2nd and 3rd follow-up visits (Figure 2C). Improvement from diffusion
256 impairment at any level of restriction was rare, with only 5 patients regaining normal TLC
257 and DLCO by their 3rd visit. Over half of the normal diffusion capacity patients (n=11) had
258 some level of lung restriction at 1st visit (n=1 mild, n=9 moderate, n=1 severe) as well as
259 their 3rd visit (n=11 restricted). Notably, 7 of the 9 patients with normal TLC and DLCO at
260 1st visit had some level of restriction and/or diffusion impairment by the 3rd visit (Figure
261 2C). This observation among patients with normal lung function appears to represent an
262 ongoing and progressive pulmonary process resulting in restriction and/or diffusion
263 impairment. Overall, restriction or diffusion impaired restriction were the predominant
264 phenotypes observed by the 3rd follow-up visit, thereby indicating an earlier stage of
265 disease followed by progression among the normal diffusion capacity patients (Figure 2C).

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Risk Factors for Developing Pulmonary Long COVID with Severe Pulmonary Restriction

Logistic regression models were used to identify risk factors for developing Long COVID with combined diffusion impairment (DLCO \leq 80%) and severe or moderate restriction (TLC \leq 70%). Unadjusted univariable modeling revealed advanced age \geq 65 years (OR=1.63 [1.23-2.23]), male sex (OR=1.88 [1.43-2.48]), renal disease (OR=2.48 [1.47-4.15]), diabetes (OR=1.82 [1.30-2.51]), heart failure or hypertension (OR=2.54 [1.98-3.32]), smoking history (OR=1.39 [1.03-1.86]), ICU admission (OR=6.48 [4.45-10.0]), and use of nasal cannula (OR=4.21 [2.90-6.07]), high-flow nasal cannula (OR=6.10 [3.92-9.82]), and invasive mechanical ventilation (OR=16.0 [8.87-34.4]) as independent risk factors for developing pulmonary Long COVID with severe or moderate restriction (Table 2). After adjusting for all variables, we observed that invasive mechanical ventilation conferred the greatest increased odds of developing pulmonary Long COVID with diffusion impairment and severe or moderate restriction (aOR=9.89 [3.62-26.9]), followed by nasal cannula (aOR=3.97 [2.60-6.30]) and high-flow nasal cannula (aOR=3.64 [1.58-7.71]) use

292 during primary SARS-CoV-2 infection, heart failure or hypertension (aOR=2.09 [1.47-
293 2.98]) and male sex (aOR=1.44 [1.03-1.99]; Table 2; reference group: un-hospitalized
294 primary infection patients). In a sub-analysis using only hospitalized patients (WHO score
295 4-7), the association of invasive mechanical ventilation with diffusion impairment and
296 severe or moderate restriction was comparable with whole cohort results (aOR=9.56
297 [3.22-32.6] vs. reference group of hospitalized room-air patients; Supplemental Table 5).
298 To evaluate the effect of patients with pre-existing pulmonary comorbidities, further
299 sensitivity testing was performed (Supplemental Tables 6-7). Overall, the results show that
300 invasive mechanical ventilation still conferred the greatest risk for development of
301 pulmonary Long COVID with diffusion impairment and severe or moderate restriction
302 (Supplemental Table 6, cohort sans patients with pulmonary comorbidities vs. reference
303 group of non-hospitalized patients aOR=13.1 [4.41-48.1]; Supplemental Table 7 cohort
304 sans patients with pulmonary comorbidities vs. reference group of hospitalized room-air
305 patients aOR=15.2 [4.72-68.1]).

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Assessment of CT Imaging and Pathology

CT imaging was performed on a total of 308 patients (33%; n=246 diffusion impaired sub-group, n=62 diffusion normal sub-group; Table 1). CT pathology and increased lung involvement were predominantly found in diffusion impaired patients with severe or moderate restriction. CT scoring of images taken within 6-months of the 1st Long COVID visit identified ground glass opacities (85%), reticulations (82%), bronchiectasis (69%), and fibrotic changes (65%) as the defining pathologies in the majority of diffusion impaired severe restriction patients (Figure 3A, Supplemental Table 2). A similar pathologic profile was found in diffusion impaired patients with moderate restriction (Figure 3B). Univariable and multivariable logistic regression modeling was performed to determine if CT pathologies were associated with increased odds of developing pulmonary Long COVID with severe or moderate restriction (Supplemental Table 8). The significant unadjusted odds ratios for developing severe restriction were associated with ground glass opacities (OR=4.11 [2.50-6.96]), reticulations (OR=5.49 [3.24-9.35]), fibrotic changes (OR=5.27 [3.10-9.60]), bronchiectasis (OR=5.27 [3.10-9.60]), and consolidation (OR=2.35 [1.02-9.06]); however, only reticulations (aOR=2.12 [1.01-4.34]) maintained a significance in multivariable modeling (Supplemental Table 8).

340 **DISCUSSION**

341 Our current understanding of persistent pulmonary defects from SARS-CoV-2
342 infection are primarily derived from prospective follow-up studies assessing patient
343 outcomes after hospitalization with acute COVID-19. Gradual recovery of impaired
344 diffusion capacity ($DLCO \leq 80\%$) and radiographic evidence of fibrotic pulmonary tissue are
345 among the most commonly reported observations (7-10, 23-27). Although these studies
346 offer key insights into the trajectory of acute COVID recovery, their prospective study
347 design and inclusion of patients without post-COVID symptoms limit the applicability of
348 these findings to Long COVID patients with persistent dyspnea, cough, and chest
349 discomfort. To address this knowledge gap, we leveraged a large, demographically
350 diverse cohort comprised exclusively of Long COVID patients with persistent pulmonary
351 symptoms. For this cohort, we aligned robust medical record data requiring no imputation,
352 quantitative CT imaging, and longitudinal pulmonary function testing (PFT) to identify the
353 characteristics and determinants of pulmonary Long COVID. Our study establishes a clear
354 association between burden of acute COVID disease and the development of persistent
355 lung restriction with diffusion impairment. Collectively, these results represent a previously
356 undescribed pathology for Long COVID that can be readily measured with PFTs and
357 provides opportunity to better study the post-viral interplay of pulmonary symptoms with
358 alterations in lung physiology.

359 Demographic risk factors (aOR [95% CI]) associated with the development of
360 pulmonary Long COVID with diffusion impairment and severe or moderate restriction
361 included male sex (OR=1.63 [1.23-2.23]; aOR=1.22 [0.81-1.89]) and pre-existing heart
362 failure and hypertension (OR=2.54 [1.98-3.32]; aOR=2.09 [1.47-2.98]; Table 2). These

363 findings differ from a recent meta-analysis of multi-organ Long COVID symptoms that
364 noted an elevated risk in females (aOR=1.56) and individuals over 40 years of age
365 (aOR=1.21) (28). Our findings emphasize differences between the assessments obtained
366 from broad symptom observations and physiological readouts in pinpointing at-risk
367 populations. In Long COVID patients complaining of prolonged pulmonary symptoms,
368 prior studies have suggested that dyspnea is a major feature and that symptoms can
369 persist for months after initial infection (9, 29). Our study affirmed this observation with
370 78% (n=725) of the UAB pulmonary Long COVID cohort identifying dyspnea as the
371 primary symptom, followed by 18% (n=167) with cough and 4% (n=37) with chest
372 discomfort (Table 1). Notably, the complaint of dyspnea remained consistent (>70%)
373 across all degrees of diffusion impairment, restriction, and levels of lung involvement seen
374 on CT imaging (Table 1, Supplemental Table 2). This suggests symptoms alone do not
375 provide sufficient granularity to identify distinct endotypes of pulmonary Long COVID,
376 thereby highlighting the importance of incorporating routine PFTs in the diagnostic
377 evaluation of this patient population.

378 Our study demonstrates that the severity of hypoxia during primary SARS-CoV-2
379 infection is a critical factor in the development of pulmonary Long COVID with persistent
380 diffusion impairment and restriction (Table 2). Notably, the post-hospitalization PFT
381 impairments in pulmonary Long COVID contrast with previously described post ARDS
382 findings in non-COVID patients, where subjects predominately present with isolated
383 diffusion impairment which improves to normal levels over a 6 month-1 year period and
384 limited lung restriction at any time-point (30-33). In addition to marked differences in lung
385 physiology, the presence of reticulations, bronchiectasis, ground glass opacities, and
386 fibrotic changes in pulmonary Long COVID CT images are distinct from ARDS which has

387 been predominantly described by the presence of ground glass opacities and reticulations
388 (32). Cumulatively, our physiologic and radiographic evidence suggest that pulmonary
389 Long COVID is a pro-fibrotic disease process that is distinct from ARDS; however, future
390 studies are warranted and needed to further elucidate the differences.

391 The biologic mechanisms underlying these symptomatic, physiologic, and
392 radiographic changes are poorly understood, but there is increasing evidence that pro-
393 fibrotic interstitial lung changes are occurring in dyspneic patients as early as 1 month
394 post-COVID infection (18, 34-36). From a molecular perspective, several independent
395 lines of evidence have shown that altered immune function, dysregulation of systemic
396 neutrophilic signatures, and persistent inflammation and presence of viral antigens are
397 associated with Long COVID (37-40). While few studies have been conducted in the Long
398 COVID lung, a prior spatial transcriptomic lung autopsy study from COVID-19 acute lung
399 injury demonstrates a distinct fibro-proliferative phenotype relative to influenza infection
400 (41). If true, pulmonary fibrosis therapeutics like Nintedanib and Pirfenidone, which have
401 been sparingly used in post-COVID associated fibrosis, may be uniquely suited for the
402 subset of pulmonary Long COVID patients with diffusion impaired restriction (42-43, 46).
403 This report provides evidence for a distinct endotype of pulmonary Long COVID and
404 emphasizes the need to stratify patients with PFTs for targeted therapeutic and clinical
405 management.

406 This study has limitations. Due to the retrospective nature of the cohort, PFTs were
407 not taken before or during primary SARS-CoV-2 infection, and therefore could not be
408 compared to measurements taken at the first Long COVID clinic visit. While this large,
409 demographically diverse cohort offers a unique opportunity to characterize pulmonary
410 presentations of Long COVID, patients presented to the Long COVID clinic at different

411 time intervals after primary COVID infection, and follow-ups were limited to attended visits.
412 Similarly, inherent bias towards more severe disease is present in patients who had CT
413 imaging performed. Lastly, this study is limited by a lack of quality-of-life measurements
414 such as the 6-minute walk test performed during clinic visits. Despite these limitations, the
415 combination of an objective physiologic metric in longitudinal PFTs and a previously
416 established Long COVID symptomatic signature provide an important foundation for future
417 Long COVID studies.

418 Although dyspnea is present in a majority of pulmonary Long COVID patients,
419 reported symptoms were not representative of the degree of diffusion impairment and
420 restriction across the cohort (44). The additional granularity provided with PFTs highlights
421 the utility of a broadly available clinical test to identify pulmonary endotypes associated
422 with persistent physiologic impairment. These insights underscore the need for medical
423 providers to incorporate PFT measurements as a routine step for evaluating Long COVID
424 patients with pulmonary complaints. Informed stratification of patients experiencing
425 pulmonary Long COVID is critical as this population is likely to require high utilization of
426 health care services and would likely benefit from early therapeutic interventions (45).

427 **ACKNOWLEDGEMENTS**

428 **AUTHOR CONTRIBUTIONS**

429 Michael John Patton (MJP), Nathaniel Erdmann (NE), Donald Benson (DB), Scott
430 Grumbley (SG), Emily B. Levitan (EBL), Amit Gaggar (AG), Sarah W. Robison (SWR),
431 Raval Dhaval (RD), Kinner Patel (KP), Morgan L. Locy (MLL), Peter Morris (PM), and
432 Matthew Might (MM) co-conceived the project, prepared the main text, and oversaw the
433 UAB cohort creation. MJP processed and analyzed EMR data to create all tables and
434 figures in the main text and supplement of this manuscript. DB analyzed and scored CT
435 images. SG analyzed and scored a subset of CT images. We thank Dr. Jeanne Marrasso,
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438 at Birmingham (UAB IRBs: 300006291, 300006205). NE, MM, RD, and AG, obtained
439 funding and supervised the overall study. All co-authors reviewed and approved the final
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441

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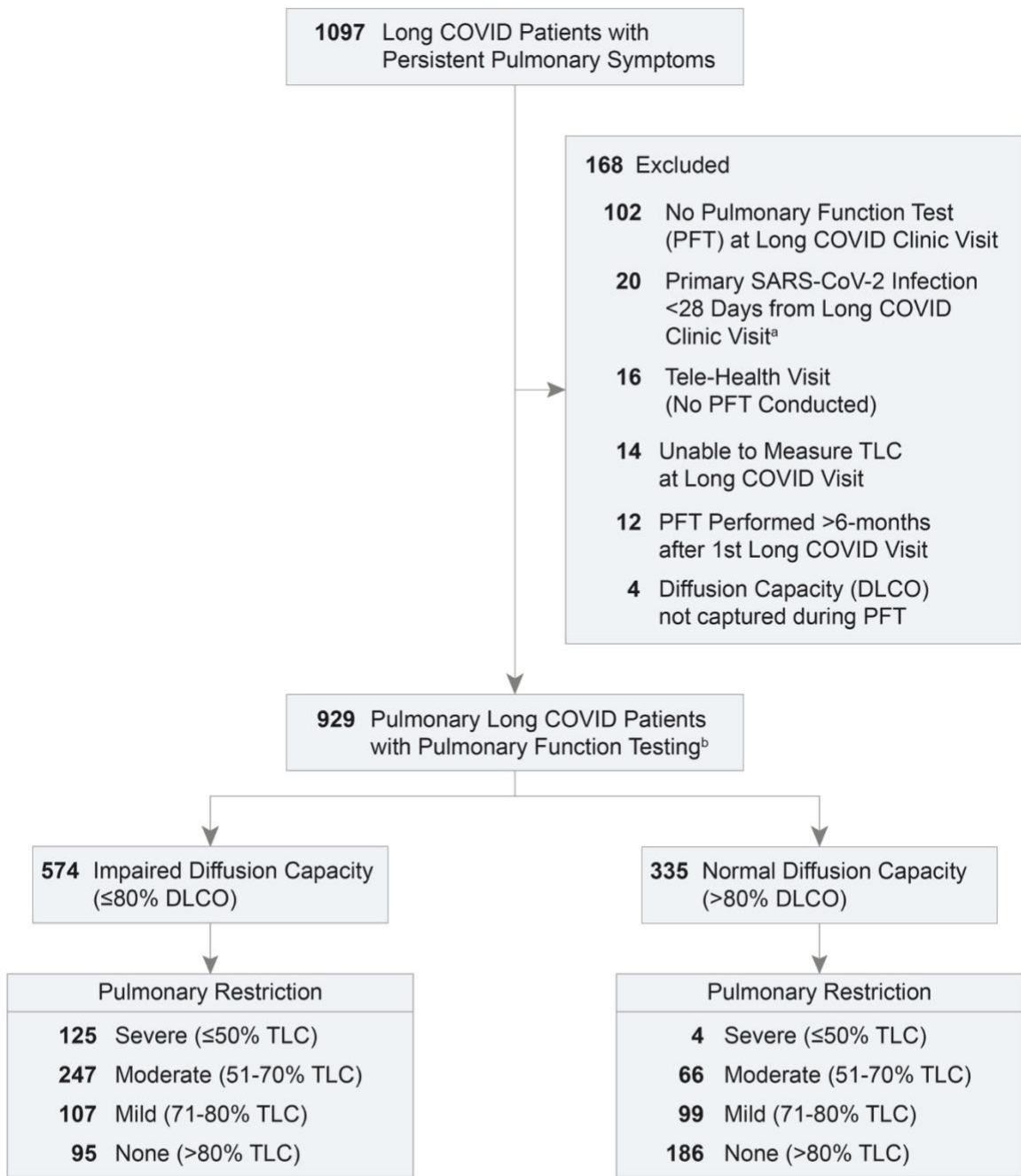
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627 **Figure 1: Accrual of Long COVID Patients with Persistent Pulmonary Symptoms in**
 628 **the UAB Health System**
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^aPrimary SARS-CoV-2 infection was defined as a positive result from a rapid antigen and/or polymerase chain reaction (PCR) test between 03/01/2020 - 08/01/2023

^bPercent predicted diffusion capacity for carbon monoxide (DLCO) and total lung capacity (TLC) was assessed at the 1st pulmonary Long COVID clinic visit

Table 1: Characteristics of Pulmonary Long COVID Patients Stratified by 1st Visit Diffusion Capacity and Restriction in the UAB Cohort

	Diffusion Impaired ($\leq 80\%$ DLCO)					Diffusion Normal ($> 80\%$ DLCO)				
	Restriction:	Severe	Moderate	Mild	None	Restriction:	Severe	Moderate	Mild	None
	TLC:	$\leq 50\%$	51-70%	71-80%	$> 80\%$	TLC:	$\leq 50\%$	51-70%	71-80%	$> 80\%$
	N=574	n=125	n=247	n=107	n=95	N=355	n=4	n=66	n=99	n=186
Age ¹	56 \pm 13	58 \pm 10	56 \pm 13	56 \pm 15	54 \pm 15	48 \pm 14	41 \pm 7	50 \pm 15	50 \pm 13	47 \pm 14
Sex										
Female	368 (64)	59 (47)	153 (62)	78 (73)	78 (82)	241 (68)	2 (50)	39 (59)	62 (63)	138 (74)
Male	206 (36)	66 (53)	94 (38)	29 (27)	17 (18)	114 (32)	2 (50)	27 (41)	37 (37)	48 (26)
Race										
White	340 (59)	65 (52)	131 (53)	70 (65)	74 (78)	250 (70)	0 (0)	30 (45)	71 (72)	149 (80)
African American	190 (33)	47 (38)	101 (41)	25 (23)	17 (18)	71 (20)	3 (75)	27 (41)	23 (23)	18 (10)
Asian	13 (2)	4 (3)	4 (2)	4 (4)	1 (1)	8 (2)	0 (0)	3 (5)	2 (2)	3 (2)
Hispanic American	9 (2)	3 (2)	3 (1)	3 (3)	0 (0)	5 (1)	0 (0)	1 (2)	0 (0)	4 (2)
Indian	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Multiple	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Refused	10 (2)	5 (4)	1 (0)	2 (2)	2 (2)	13 (4)	1 (25)	4 (6)	3 (3)	5 (3)
Not Reported	10 (2)	1 (1)	5 (2)	3 (3)	1 (1)	6 (2)	0 (0)	1 (2)	0 (0)	5 (3)
Body-mass Index ¹	33 \pm 9	35 \pm 10	34 \pm 8	32 \pm 7	30 \pm 8	33 \pm 9	46 \pm 14	36 \pm 9	35 \pm 9	32 \pm 8
Pre-COVID Comorbidities										
Pulmonary Disease	139 (24)	25 (20)	61 (25)	27 (25)	26 (27)	72 (20)	2 (50)	14 (21)	20 (20)	36 (19)
Renal Disease	56 (10)	10 (8)	30 (12)	13 (12)	3 (3)	10 (3)	0 (0)	3 (5)	5 (5)	2 (1)
Diabetes	119 (21)	32 (26)	55 (22)	24 (22)	8 (8)	49 (14)	2 (50)	17 (26)	15 (15)	15 (8)
Heart Failure/Hypertension	297 (52)	71 (57)	146 (59)	49 (46)	31 (33)	118 (33)	3 (75)	32 (48)	35 (35)	48 (26)
Obstructive Sleep Apnea	116 (20)	26 (21)	48 (19)	30 (28)	12 (13)	82 (23)	2 (50)	21 (32)	25 (25)	34 (18)
Smoking History										
Never smoker	377 (66)	82 (66)	157 (64)	71 (66)	67 (71)	260 (73)	3 (75)	49 (74)	71 (72)	137 (74)
Former smoker	170 (30)	40 (32)	81 (33)	31 (29)	18 (19)	79 (22)	1 (25)	13 (20)	24 (24)	41 (22)
Current smoker	27 (5)	3 (2)	9 (4)	5 (5)	10 (11)	16 (5)	0 (0)	4 (6)	4 (4)	8 (4)
Vaccination Status	104 (18)	22 (18)	51 (21)	18 (17)	13 (14)	80 (23)	1 (25)	13 (20)	21 (21)	45 (24)

Table 1: Characteristics of Pulmonary Long COVID Patients Stratified by 1st Visit Diffusion Capacity and Restriction in the UAB Cohort

	Diffusion Impaired (≤80% DLCO)					Diffusion Normal (>80% DLCO)				
	Restriction: Severe	Moderate	Mild	None		Restriction: Severe	Moderate	Mild	None	
TLC:	≤50%	51-70%	71-80%	>80%		≤50%	51-70%	71-80%	>80%	
	N=574	n=125	n=247	n=107	n=95	N=355	n=4	n=66	n=99	n=186
Primary COVID Infection										
COVID Severity										
(3) No Admission	217 (38)	20 (16)	96 (39)	46 (43)	55 (58)	260 (73)	3 (75)	43 (65)	77 (78)	137 (74)
(4) Room Air	60 (10)	8 (6)	21 (9)	16 (15)	15 (16)	45 (13)	0 (0)	10 (15)	11 (11)	24 (13)
(5) Nasal Cannula	139 (24)	29 (23)	69 (28)	24 (22)	17 (18)	32 (9)	0 (0)	8 (12)	5 (5)	19 (10)
(6) High-Flow Cannula	88 (15)	28 (22)	40 (16)	15 (14)	5 (5)	15 (4)	1 (25)	3 (5)	5 (5)	6 (3)
(7) Ventilation	70 (12)	40 (32)	21 (9)	6 (6)	3 (3)	3 (1)	0 (0)	2 (3)	1 (1)	0 (0)
ICU Admission	143 (25)	66 (53)	56 (23)	15 (14)	6 (6)	18 (5)	1 (25)	6 (9)	4 (4)	7 (4)
Long COVID Visit										
Primary Symptom										
Dyspnea	454 (79)	111 (89)	196 (79)	78 (73)	69 (73)	271 (76)	3 (75)	52 (79)	74 (75)	142 (76)
Cough	98 (17)	12 (10)	42 (17)	22 (21)	22 (23)	69 (19)	1 (25)	12 (18)	20 (20)	36 (19)
Chest Discomfort	22 (4)	2 (2)	9 (4)	7 (7)	4 (4)	15 (4)	0 (0)	2 (3)	5 (5)	8 (4)
Primary Infection to Long COVID Visit (days) ²	125 [72-222]	115 [77-170]	123 [67-221]	120 [71-242]	161 [81-256]	148 [80-295]	148 [117-216]	150 [89-403]	182 [81-320]	135 [78-255]
TLC (%) ¹	65±18	41±7	61±6	75±3	92±11	82±15	49±1	64±5	75±3	93±12
DLCO (%) ¹	59±16	45±17	61±12	65±14	68±12	95±12	89±6	92±10	92±8	98±14
CT at 1 st	246 (43)	91 (73)	113 (46)	28 (26)	14 (15)	62 (17)	1 (25)	20 (30)	19 (19)	22 (12)
Long COVID Clinic Visit										
CT Lung Involvement (0-25 Score) ²	9 [1-17]	17 [9-21]	7 [1-13]	3 [0-9]	3 [1-7]	0 [0-2]	1 [1-1]	0 [0-2]	0 [0-2]	0 [0-2]
Time from Long COVID Visit to CT Scan (days) ²	30 [7-82]	30 [7-70]	28 [7-93]	26 [10-66]	36 [9-94]	21 [7-83]	39 [39-39]	13 [7-55]	24 [10-64]	24 [2-95]

Statistics are reported as n, (%) unless otherwise specified by ¹Mean±SD or ²Median [Q1-Q3]

N=total patients per diffusion capacity stratification group, n=total patients per restriction stratification group

Lung Involvement was assessed with a 0-5 scale (0=no involvement, 1=1-5%, 2=5-25%, 3=25-50%, 4=50-75%, 5≥75%)

Abbreviations: TLC, percent predicted total lung capacity; DLCO, diffusion limitation of carbon monoxide; CT, computerized tomography; WHO, World Health Organization; COVID, coronavirus disease; UAB, University of Alabama at Birmingham

Figure 2: Diffusion impaired restriction is a key feature of persistent pulmonary Long COVID

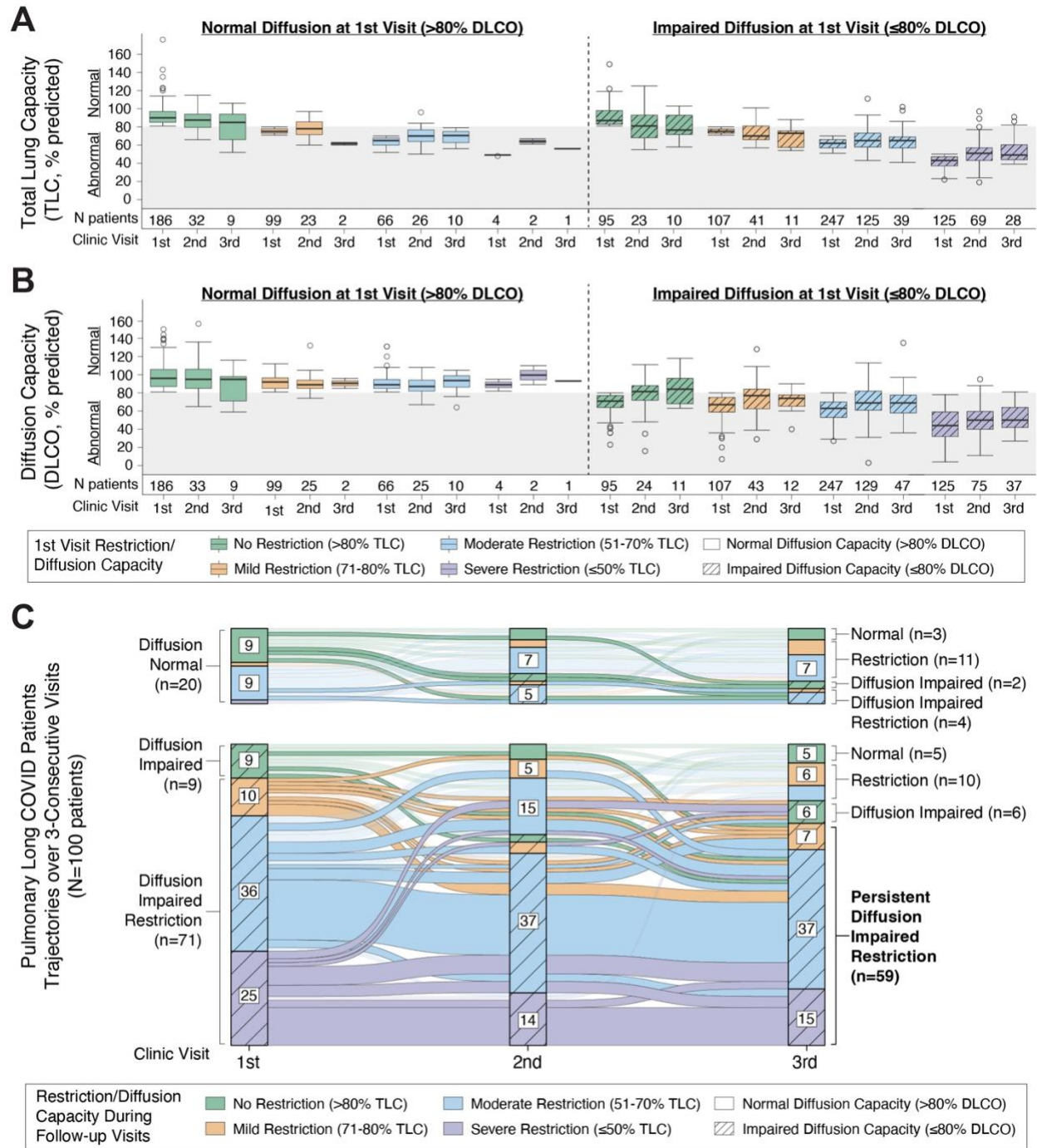


Figure 2 Legend: (A-B) Results of percent predicted total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) are shown for 3 clinic visits with stratification by restriction severity (color) measured during the 1st visit PFT and presence or absence of diffusion impairment (hashed lines). Boxplots represent the median black center line; 25th and 75th percentile box boundaries) for each PFT measured, with number of patients (N) reported below each group. Normal TLC and DLCO are denoted by the grey color on the plot at 80%. (C) Alluvial diagram displays patient PFT trajectories over 3-consecutive visits (N=100 total) with relative improvement or decline as measured by TLC (color) and DLCO (hashed lines). Labelling of alluvial diagram axes groups with <5 patients was omitted for visual clarity.

Table 2: Risk Factors for Pulmonary Long COVID with Diffusion Impaired Restriction

	Patients Total N	Diffusion Impaired Restriction ² N (% of Total)	Diffusion Impaired Restriction Unadjusted OR [95% CI] ¹	Diffusion Impaired Restriction Adjusted OR [95% CI] ¹
Advanced Age				
<65 years	743	280 (38)	—	—
≥65 years	186	92 (49)	1.63 [1.23-2.23]	1.22 [0.81-1.89]
Sex				
Female	609	212 (35)	—	—
Male	320	160 (50)	1.88 [1.43-2.48]	1.44 [1.03-1.99]
Elevated BMI				
<30	376	138 (37)	—	—
≥30	553	234 (42)	1.28 [0.97-1.66]	1.26 [0.91-1.77]
Pulmonary Disease				
No	718	286 (40)	—	—
Yes	211	86 (41)	1.04 [0.76-1.41]	0.95 [0.66-1.35]
Renal Disease				
No	863	332 (38)	—	—
Yes	66	40 (61)	2.48 [1.47-4.15]	1.03 [0.57-1.98]
Diabetes				
No	761	285 (37)	—	—
Yes	168	87 (52)	1.82 [1.30-2.51]	1.20 [0.79-1.78]
Heart Failure or Hypertension				
No	514	155 (30)	—	—
Yes	415	217 (52)	2.54 [1.98-3.32]	2.09 [1.47-2.98]
Obstructive Sleep Apnea				
No	731	298 (41)	—	—
Yes	198	74 (37)	0.88 [0.63-1.17]	0.51 [0.32-0.72]
Smoking History				
Never smoker	637	239 (38)	—	—
Current or Former Smoker	292	133 (46)	1.39 [1.03-1.86]	1.25 [0.89-1.74]
Vaccination Status				
No	745	299 (40)	—	—
Yes	184	73 (40)	0.99 [0.72-1.39]	1.34 [0.88-1.98]
Months from Primary Infection to Long COVID Clinic Visit				
1-3 Months	306	132 (43)	—	—
3-6 Months	292	139 (48)	1.19 [0.88-1.64]	0.96 [0.67-1.40]
6-12 Months	197	59 (30)	0.56 [0.38-0.81]	0.70 [0.44-1.10]
>12 Months	134	42 (31)	0.61 [0.40-0.89]	0.64 [0.37-1.09]
ICU Admission				
No	768	250 (33)	—	—
Yes	161	122 (76)	6.48 [4.45-10.0]	1.64 [0.76-3.73]
COVID Severity (WHO Score)				
(3) No Admission	477	116 (24)	—	—
(4) Room Air	105	29 (28)	1.20 [0.71-1.93]	1.02 [0.57-1.73]
(5) Nasal Cannula	171	98 (57)	4.21 [2.90-6.07]	3.97 [2.60-6.30]
(6) High-Flow Cannula	103	68 (66)	6.10 [3.92-9.82]	3.64 [1.58-7.71]
(7) Ventilation	73	61 (84)	16.0 [8.87-34.4]	9.89 [3.62-26.9]

¹Unadjusted odds ratio (OR) and adjusted odds ratio (aOR), 95% confidence interval (n=1000 bootstraps)²Diffusion impaired restriction is defined by a DLCO ≤80% and a TLC ≤70% measured by PFT at the 1st Long COVID clinic visit

Figure 3: CT Image Findings in Pulmonary Long COVID with Diffusion Impaired Restriction

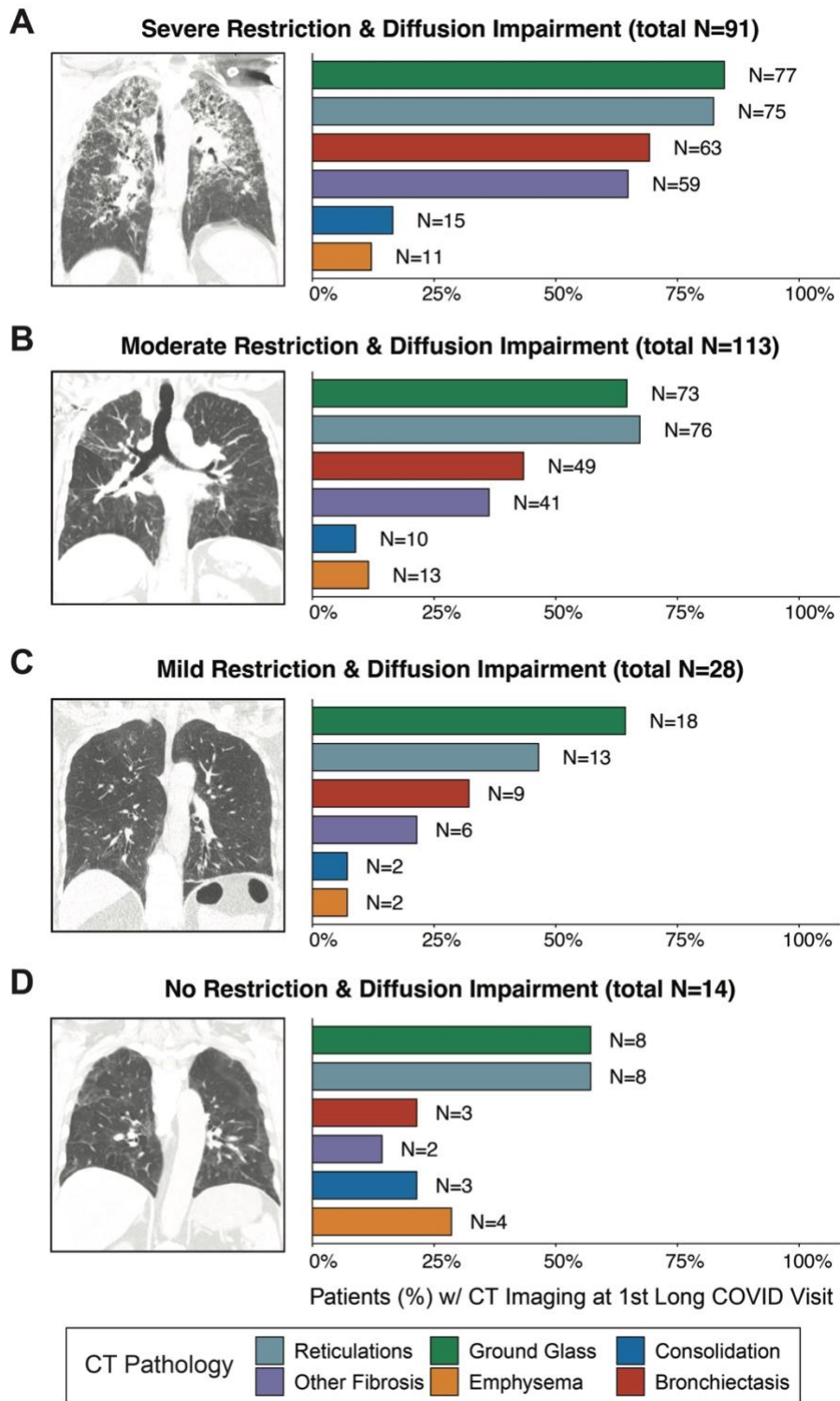


Figure 3 Legend: (A-D) Representative CT images of pulmonary Long COVID patients with diffusion impairment ($DLCO \leq 80\%$) with severe ($TLC \leq 50\%$), moderate ($TLC 51-70\%$), mild ($TLC 71-80\%$), and no restriction ($TLC > 80\%$) assessed at the 1st Long COVID clinic visit. Corresponding bar charts of CT pathology (% , N=patients) are displayed for each group. (Note: architectural distortion, traction bronchiectasis, and honeycombing are termed 'Other Fibrosis').