



## Reduced Diffusion Capacity in COVID-19 Survivors

To the Editor:

As of December 22, more than 71 million cases of confirmed coronavirus disease (COVID-19) have been reported worldwide (1). After the acute phase, millions of patients will require follow-up for potential respiratory sequelae, among others. This will put a strain on the pulmonary function test (PFT) laboratories. A small few descriptive reports, with a hundred patients or fewer, have been published showing a considerable prevalence of altered diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ) percentage in survivors (2–4). However, it is unknown which clinical variables might be associated with the alteration of diffusion capacity after COVID-19. This work aims to identify clinical variables during the acute phase associated with  $DL_{CO}$  values in COVID-19 survivors in the follow-up.

This is a retrospective study including consecutive patients aged 18–84 years with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection discharged from the Pneumology Department, at La Fe University and Polytechnic Hospital in Valencia (Spain), from March 23 to August 20. All patients ( $N = 239$ ) were referred to the follow-up clinic with an appointment for PFT, including forced spirometry and  $DL_{CO}$  by the single-breath method adjusted for hemoglobin. For the analysis, we classified patients as normal  $DL_{CO}$  ( $\geq 80\%$  predicted) or altered  $DL_{CO}$  ( $< 80\%$  predicted) according to the Global Lung Function Initiative (5). We estimated  $DL_{CO}$  after COVID-19 admission using multiple linear regression analysis including key points such as demographics, preexisting conditions, inflammation, vascular alterations, and severity (those requiring intensive care unit [ICU] admission) based on their potential clinical relevance. The logarithm was applied to the peaks to avoid extreme data when appropriate.

We recruited 239 patients; however, 24 declined to attend follow-up clinic or did not perform the PFT maneuvers correctly, preventing their interpretation. Finally, 215 patients were included for the analysis. The median (first, third quartile) time from discharge to PFT was 87 (62–109) days. The results for FVC (forced vital capacity) % predicted value (pred),  $FEV_1$  (forced expiratory volume in 1 s) % pred,  $FEV_1/FVC$ ,  $DL_{CO}$  % pred, and  $DL_{CO}$ /alveolar volume % pred are presented in Table 1. Only 10 (4.7%) and 19 (8.8%) patients had FVC and  $FEV_1$  pred  $< 80\%$ , respectively. Of the 215 patients, 162 (75.3%) had a normal  $DL_{CO}$  and 53 (24.7%) an altered  $DL_{CO}$ . Among the latter (53), 40

(75.5%) had a mild alteration (60 to  $< 80$   $DL_{CO}$ %), 13 (24.5%) moderate (40 to  $< 60$   $DL_{CO}$ %), and none severe ( $< 40$   $DL_{CO}$ %), respectively.

In Table 1, clinical variables are displayed in relation to altered  $DL_{CO}$ . Briefly, in our cohort the patients with altered  $DL_{CO}$  were mainly women and had more prevalence of smoking history, higher C-reactive protein and D-dimer concentration during admission, and more severe pneumonia. In the linear regression analysis, female sex, smoking history, and D-dimer levels were associated with lower  $DL_{CO}$  values (Table 2). Median  $DL_{CO}$  values for women (84 [74–93]), patients with smoking history (84 [74.5–96]), or those admitted to the ICU (78 [63–92.5]) were lower in comparison with men (91 [82–102]), never-smokers (88 [81–99]), and those with nonsevere pneumonia (88 [82–99]). In addition, from admission to pulmonary function tests appointment, pulmonary embolism was detected in 15 (7%) patients. ICU admission was more frequent in these patients (11/15 vs. 29/200;  $P < 0.001$ ). These patients showed worse  $DL_{CO}$  values compared with those without pulmonary embolism diagnosis (74 [59–94] vs. 88 [81–99];  $P = 0.025$ ). The Spearman correlations between the peak of C-reactive protein and D-dimer levels with  $DL_{CO}$  were  $-0.127$  ( $P = 0.062$ ) and  $-0.238$  ( $P < 0.001$ ), respectively.

In our study, we found lower prevalence of altered  $DL_{CO}$  (24.7%) compared with smaller studies such as Mo and colleagues (47.2%) and Shah and colleagues (52%) but more similar to that reported by Zhao and colleagues (16.4%, 9/55) in a cohort without severe cases (2, 4, 6). In the first one, PFT was performed before discharge, and in the last one, PFT was performed 3 months after discharge. Our data, together with these others, support the hypothesis that too early a functional assessment is likely to overestimate the chronic impact of disease on  $DL_{CO}$ .

We found sex differences in  $DL_{CO}$  that could be associated with sex-specific airway response to the disease as occurs in women with emphysema, who had thicker small airways (7, 8). In some studies, impaired  $DL_{CO}$  and persistence of symptoms was also more prevalent in women (4, 9), but these sex differences should be further explored and clarified. Chronic respiratory disease was not associated with worse  $DL_{CO}$  values. However, the patients were predominantly asthmatic and the prevalence of chronic obstructive pulmonary disease or interstitial lung diseases was low. On the other hand, smoking history was associated with poorer  $DL_{CO}$ , as expected. Finally, maximum D-dimer levels were also associated with lower diffusion capacity. Severe COVID-19 is associated with unspecific diffuse alveolar damage, characterized by edema, hemorrhage, and fibrin deposition (10). In addition, COVID-19 causes relevant vascular changes with characteristics of microangiopathy such as thrombosis, necrosis, or abnormal neoangiogenesis (10). This fact could be related to poorer  $DL_{CO}$  in survivors and should be prospectively evaluated in the long term.

Our study has several limitations. This is a single-center study with a limited number of cases, and further studies are needed to validate our findings. In addition, we lack previous functional data preventing its comparison. In any case, the model was adjusted for chronic respiratory disease and smoking history to overcome this limitation. Nonetheless, to the authors' knowledge, this is the largest follow-up study with PFT evaluation in COVID-19.

In the last international guidance on the management of COVID-19, 60% of experts were in favor of routine posthospital PFT within 30–60 days regardless of the disease severity (11). An accurate early identification of patients requiring follow-up PFT is complex and larger studies are needed.

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Supported by a Río Hortega grant from the Instituto de Salud Carlos III (CM19/00182) (R.M.). P.G.-J. is the recipient of a postresident research grant supported by the Health Research Institute La Fe (2019-053-1).

**Author Contributions:** Conceptualization and study design: R. Méndez and R. Menéndez. Patient enrollment and database management: R. Méndez, A.L., P.G.-J., L.F., L.B., K.Y., A.F., E.Z.-O., and S.R. Statistical analysis: R. Méndez. Drafting the manuscript: R. Méndez. Assistance in drafting the manuscript and critical review: R. Menéndez. Revision of the manuscript and approval of the final version: all authors. R. Méndez and R. Menéndez are the guarantors.

**Table 1.** Baseline characteristics and altered diffusing capacity of the lung for carbon monoxide

Variables	Total (N = 215)	Normal DL <sub>CO</sub> (N = 162)	Altered DL <sub>CO</sub> (N = 53)
Demographics			
Age, yr	55 (47, 66)	54 (46, 65)	59 (49, 68)
Male sex	130 (60.5)	106 (65.4)	24 (45.3)
Smoking			
Former or current	64 (29.8)	44 (27.2)	20 (37.7)
Coexisting conditions			
Hypertension	67 (31.2)	47 (29)	20 (37.7)
Diabetes	32 (14.9)	26 (16)	6 (11.3)
Dyslipidemia	57 (26.5)	41 (25.3)	16 (30.2)
Chronic heart disease	12 (5.6)	7 (4.3)	5 (9.4)
Chronic renal disease*	3 (1.4)	1 (0.6)	2 (3.8)
Chronic respiratory disease <sup>†</sup>	27 (12.6)	19 (11.7)	8 (15.1)
Radiological data			
Number of lobes with infiltrates	2 (1–4)	2 (1–4)	2 (1–4)
Analytical parameters			
Peak CRP, mg/L <sup>‡</sup>	89.5 (42.3–163.4)	80.1 (41–154.8)	110.3 (55.6–253.2)
Peak D-dimer, ng/ml <sup>‡</sup>	941 (485–1,706)	772.5 (437–1,530)	1,295 (577–6,982)
Respiratory support			
Need for supplemental oxygen	111 (51.6)	79 (48.8)	32 (60.4)
Severity			
ICU admission	40 (18.6)	19 (11.7)	21 (39.6)
PFT			
FVC, %	106 (96–116)	109 (99–116)	100 (90–110)
FEV <sub>1</sub> , %	103 (92–113)	105 (96–115)	96 (85–105)
FEV <sub>1</sub> /FVC	78.9 (75.3–83.5)	78.9 (75.5–83.5)	78.9 (74.3–83.6)
DL <sub>CO</sub> , %	88 (80–99)	93 (85–103)	70 (60–75)
DL <sub>CO</sub> /VA	102 (90–112)	105 (96–115)	86 (80–90)

*Definition of abbreviations:* CRP = C-reactive protein; DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; ICU = intensive care unit; PFT = pulmonary function test; VA = alveolar volume.

Data are summarized as n (%) or median (first, third quartile), as appropriate.

\*Stage ≥2.

<sup>†</sup>Four patients with chronic obstructive pulmonary disease, 16 with asthma, and 7 with other chronic respiratory diseases.

<sup>‡</sup>Maximum concentration during admission.

**Table 2.** Multiple linear regression analysis for DL<sub>CO</sub> percentage estimation after COVID-19 admission

Variables	Estimate*	SE	95% CI	P Value
Age	−0.07	0.1	−0.27 to 0.12	0.455
Male sex	7.64	2.49	2.73 to 12.55	0.002
Former or current smoking	−5.06	2.62	−10.22 to 0.11	0.055
Chronic respiratory disease	1.91	3.64	−5.26 to 9.08	0.599
Log peak CRP	0.131	2.85	−5.49 to 5.75	0.964
Log peak D-dimer	−7.20	2.80	−12.72 to −1.69	0.011
ICU admission	−6.26	4.09	−14.32 to 1.81	0.128

*Definition of abbreviations:* CI = confidence interval; COVID-19 = coronavirus disease; CRP = C-reactive protein; DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; ICU = intensive care unit; SE = standard error.

\*Estimated percentage point change in DL<sub>CO</sub>.

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

**Acknowledgment:** The authors thank Antonio J. Cañada (Data Science, Biostatistics & Bioinformatics, Health Research Institute La Fe) for his supervision in the statistical analysis. They also thank all patients and colleagues for their cooperation and assistance in this study. Always in our memory are those who are no longer among us because of this pandemic.

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## References

- 1 European Centre for Disease Prevention and Control. COVID-19 situation update worldwide. 2020 [accessed 2020 Dec 22]. Available from: <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>.
- 2 Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, *et al*. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020;55:2001217.
- 3 Frija-Masson J, Debray M-P, Gilbert M, Lescure F-X, Travert F, Borie R, *et al*. Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. *Eur Respir J* 2020;56:2001754.
- 4 Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, *et al*. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020;25:100463.
- 5 Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, *et al*. Global Lung Function Initiative TLCO working group; Global Lung Function Initiative (GLI) TLCO. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017;50:1700010.
- 6 Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, *et al*. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax* [online ahead of print] 3 Dec 2020; DOI: 10.1136/thoraxjnl-2020-216308.
- 7 Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, *et al*. National Emphysema Treatment Trial Research Group. Sex differences in severe pulmonary emphysema. *Am J Respir Crit Care Med* 2007;176:243–252.
- 8 Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* 2020;20:442–447.
- 9 Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax* [online ahead of print] 3 Dec 2020; DOI: 10.1136/thoraxjnl-2020-216377.
- 10 Jonigk D, Märkl B, Helms J. COVID-19: what the clinician should know about post-mortem findings. *Intensive Care Med* 2021;47:86–89.
- 11 Bai C, Chotirmall SH, Rello J, Alba GA, Ginns LC, Krishnan JA, *et al*. Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force (29 July 2020). *Eur Respir Rev* 2020;29:200287.

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## Association of Controller Use and Exacerbations for High-Deductible Plan Enrollees with and without Family Members with Asthma

To the Editor:

High out-of-pocket costs can be a barrier to asthma controller medication use for children and adults (1–6). Families in high-deductible health plans (HDHPs) face annual average deductibles of >\$3,000 (7) and must balance the healthcare needs and costs of multiple members. Exempting important services such as medications from the deductible and applying copayments may mitigate these barriers (8), although deductible costs for other services in HDHPs could strain family budgets and lead to underuse of medications and other health care for some family members in preference to others (9, 10). We evaluated whether the impact of HDHPs on asthma controller medication use and exacerbations is worse for families with multiple members with asthma.

## Methods

Using a cohort of enrollees aged 4–64 years with commercial coverage in a large national commercial and Medicare Advantage claims database between January 1, 2002, and December 31, 2014, we identified those with ≥12 months' enrollment in a traditional plan

with a low (<\$500) or no deductible (baseline) who either were switched by their employer to a plan with an individual deductible of ≥\$1,000 or remained in the traditional plan (controls) for another 12 months (follow-up) among employers who offered only one deductible level per benefit year (Figure 1). An index date separated the baseline and follow-up periods. We directly measured deductible levels when available and otherwise imputed this information using aggregated enrollee out-of-pocket spending within employers (11, 12). HDHPs required higher cost sharing for specialist, acute care, and emergency department visits than traditional plans; prescription drugs were usually subject to copayments, except for Health Savings Account-eligible HDHPs that subjected all nonpreventive care to the deductible. We included enrollees who met Health Effectiveness Data and Information Set criteria for persistent asthma before baseline (13). We identified enrollees who had another family member in the study population with persistent asthma sharing their insurance plan and selected one enrollee per family.

We measured 30-day controller medication fills by identifying all fills for inhaled corticosteroids (ICS), leukotriene inhibitors (LTI), and ICS–long-acting β-agonists (ICS-LABA) in pharmacy claims and used the days' supply recorded for each fill to calculate the number of 30-day fills per enrollee per medication type in each study period. In the follow-up period, we measured the percentage of enrollees whose controller fills were subject to the deductible and the mean copayment per fill for those paying copayments. We measured asthma exacerbations using rates of oral corticosteroid (OCS) bursts, defined as a dispensing of a 3–21 days' supply without a dispensing in the prior 30 days (14).

We used a coarsened exact matching approach that balanced employer propensity to switch to offering HDHPs and enrollee-level propensity to work for these employers (Table 1) (11, 12, 15–17). We applied match-generated weights in all analyses (12, 15, 17, 18).

Supported through a Patient-Centered Outcomes Research Institute Project Program Award (IHS-1602-34331). All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its Board of Governors, or its Methodology Committee.