Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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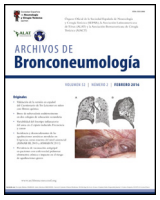

Original article

Key Factors Associated With Pulmonary Sequelae in the Follow-Up of Critically Ill COVID-19 Patients

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Abbreviations: ARDS, acute respiratory distress syndrome; CT, chest computed tomography; CLD, chronic lung disease; D_{LCO}, diffusing lung capacity for carbon monoxide; EGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; IMV, invasive mechanical ventilation; MAR, missing at random; MICE, multiple imputation by chained equations; LASSO, multiple imputation grouped adaptive least absolute shrinkage and selection operator; NIMV, noninvasive mechanical ventilation; PCR, polymerase chain reaction.

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ABSTRACT

Introduction: Critical COVID-19 survivors have a high risk of respiratory sequelae. Therefore, we aimed to identify key factors associated with altered lung function and CT scan abnormalities at a follow-up visit in a cohort of critical COVID-19 survivors.
Methods: Multicenter ambispective observational study in 52 Spanish intensive care units. Up to 1327 PCR-confirmed critical COVID-19 patients had sociodemographic, anthropometric, comorbidity and lifestyle characteristics collected at hospital admission; clinical and biological parameters throughout hospital stay; and, lung function and CT scan at a follow-up visit.
Results: The median [p_{25}–p_{75}] time from discharge to follow-up was 3.57 [2.77–4.92] months. Median age was 60 [53–67] years, 27.8% women. The mean (SD) percentage of predicted diffusing lung capacity for carbon monoxide (D_{LCO}) at follow-up was 72.02 (18.33)% predicted, with 66% of patients having D_{LCO} < 80% and 24% having D_{LCO} < 60%. CT scan showed persistent pulmonary infiltrates, fibrotic lesions, and emphysema in 33%, 25% and 6% of patients, respectively. Key variables associated with D_{LCO} < 60% were chronic lung disease (CLD) (OR: 1.86 (1.18–2.92)), duration of invasive mechanical ventilation (IMV) (OR: 1.56 (1.37–1.77)), age (OR [per-1-SD] (95%CI): 1.39 (1.18–1.63)), urea (OR: 1.16 (0.97–1.39)) and estimated glomerular filtration rate at ICU admission (OR: 0.88 (0.73–1.06)). Bacterial pneumonia (1.62 (1.11–2.35)) and duration of ventilation (NIMV (1.23 (1.06–1.42), IMV (1.21 (1.01–1.45)) and prone positioning (1.17 (0.98–1.39)) were associated with fibrotic lesions.
Conclusion: Age and CLD, reflecting patients' baseline vulnerability, and markers of COVID-19 severity, such as duration of IMV and renal failure, were key factors associated with impaired D_{LCO} and CT abnormalities.

Introduction

As of 21st December 2022, more than 650 million COVID-19 cases have been confirmed globally, and more than 6.6 million people have died.[1] The clinical spectrum of SARS-CoV-2 pneumonia ranges from mild to critically ill cases, with a proportion of 20–30% of hospitalized patients resulting in acute respiratory distress syndrome (ARDS).[2] This has generated a surge of patients who require respiratory support with invasive or noninvasive mechanical ventilation (IMV and NIMV), overburdening intensive care units (ICU) worldwide.[3,4]

Patients who survive critical COVID-19 have the highest prevalence (56–89%) of pulmonary involvement represented by an abnormal diffusing lung capacity for carbon monoxide (D_{LCO}) and chest computed tomography (CT) scan after hospital discharge.[5–8] With COVID-19 continuing to be a public health emergency and the enormous global disease burden of surviving patients, it is crucial to understand the key factors associated with pulmonary sequelae after critical COVID-19 hospital discharge and plan the follow-up accordingly.

Some predictors of pulmonary involvement after COVID-19 have been described in the literature, the most important being

the severity of the disease in the acute phase[7,9] and its respiratory management,[10] sex,[7,11,12] age,[12] and previous comorbidities.[11,12] These studies are descriptive cohorts of patients in which the primary objective was to assess pulmonary sequelae during the follow-up. In addition, only one of these studies[10] focused on critically ill survivors. In this regard, there is a lack of studies aiming to determine the key factors associated with respiratory sequelae after hospital discharge that have a representative sample of critically ill COVID-19 patients with the required characterization and follow-up.

Our main objective was to assess the key factors associated with an altered D_{LCO} at a follow-up visit after hospital discharge using data from a large ambispective and multicentric cohort of patients who needed ICU admission due to COVID-19. Additionally, we intended to evaluate key factors associated with abnormalities in chest CT and the involvement of other spirometry values.

Materials and methods

Study design

The current manuscript is based on data from the CIBERESUCICOVID study,[13] which is an observational, pragmatic, multicenter, ambispective study including critically ill COVID-19 patients admitted to the ICUs of 55 Spanish hospitals. CIBERESUCICOVID was registered in ClinicalTrials.gov with the identifier NCT04457505. The study collected retrospective data from patients admitted to participating ICUs before May 2020 and prospective data from then onward. CIBERESUCICOVID included a follow-up within the first year after hospital discharge of the maximum number of patients that the pandemic situation allowed in each participating hospital, without a specific protocol and regardless of whether the patients presented symptoms or not.

Study population

The data for the current analyses correspond to consecutive COVID-19 patients admitted to 52 Spanish ICUs from March 2020 to August 2021. All included patients had a confirmed COVID-19 diagnosis (positive nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2) and were admitted to the ICU. Patients not surviving the hospital stay or patients transferred to other hospitals during or after ICU admission were not considered eligible. Patients lacking a follow-up visit with lung function test after discharge was excluded from the analyses. Additionally, patients receiving palliative care or with severe mental disability precluding pulmonary function tests after discharge were also excluded. The study flow chart is shown in Fig. 1.

Additionally, an external cohort consisting of 200 critically ill COVID-19 patients participating in the Post-COVID study[5] held at the University Hospital Arnau de Vilanova and Santa Maria in Lleida, Spain, was used as a validation cohort.

Measures

Sociodemographic, anthropometric, comorbidity and lifestyle variables were collected using a large predetermined checklist at hospital admission (see Comorbidity checklist in the online supplement). Detailed information from the ICU stay included arterial blood gas test and complete blood test (at ICU admission and through ICU stay), including estimated glomerular filtration rate (EGFR) by means of the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation[14]; medical procedures before and during ICU stay, including ventilatory support; pharmacological treatment; and in-hospital complications such as ARDS, infections, thrombotic events or acute organ failure. Sequelae were objectively assessed at a follow-up visit by means of a thoracic CT scan (persistent infiltrates, emphysema and fibrotic lesions) and a lung function test (forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and D_{LCO}).

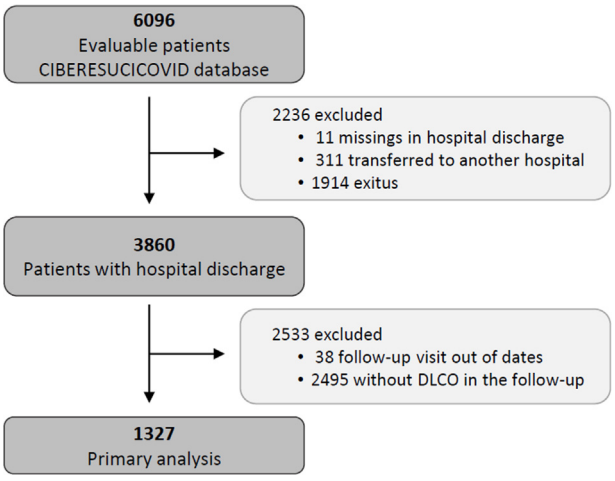

Fig. 1. Flowchart of the study.

Primary and secondary outcomes

The primary outcome of this study was D_{LCO} as measured at a follow-up visit. Secondary outcomes were also assessed at the same visit and included CT scan findings and other parameters of the lung function test (FEV_1 and FVC).

Ethics and data protection

The participating hospitals obtained ethical approval from the corresponding governing board. Study number: HCB/2020/0370; date of approval: 14/05/2020; original project title: "Factores de riesgo, pronóstico personalizados y seguimiento a un año de los enfermos ingresados en las unidades de Cuidados Intensivos Españolas infectados por el virus COVID19: CIBERESUCICOVID" (Risk factors, personalized prognosis and one-year follow-up of patients admitted to Spanish Intensive Care units infected with the COVID19 virus: CIBERESUCICOVID); governing board granting approval: Clinical Research Ethics Committee of Hospital Clínic de Barcelona. Participants or their relatives provided informed consent when possible or, when unfeasible, an informed consent waiver was authorized by the ethics board. Procedures were followed in accordance with the ethical standards of the Clinical Research Ethics Committee of Hospital Clínic de Barcelona and with the Helsinki Declaration of 1975 and its most recent amendments. Data were pseudonymized and stored in a REDCap database hosted in the Centro de Investigación Biomédica en Red (CIBER) premises in Madrid, Spain. The study complied with national and international law on data protection.

Similarly, the Post-COVID study, used as a validation cohort, was approved by the Clinical Research Ethics Committee of the University Hospital Arnau de Vilanova and Santa Maria (ref.: CEIC/2273; Title: "Factores de riesgo, pronósticos personalizados y seguimiento a un año de los enfermos ingresados en las unidades de Cuidados Intensivos Españolas infectados por el virus COVID19: ESTUDIO CIBERESUCICOVID" (Risk factors, personalized prognoses and one-year follow-up of patients admitted to Spanish Intensive Care units infected with the COVID19 virus: CIBERESUCICOVID STUDY); date: 02/06/2020); which was conducted in accordance with the ethi-

cal standards of the Clinical Research Ethics Committee of Hospital Arnau de Vilanova and Santa Maria and with the Helsinki Declaration of 1975 and its most recent amendments, and complied with national and international law on data protection.

Statistical analyses

Descriptive statistics were used to summarize the characteristics of the study population. Absolute and relative frequencies were used for qualitative data. The means (SD) or medians (25–75th percentile) were estimated for quantitative variables with normal and non-normal distributions, respectively. Normal distributions were assessed by the Shapiro–Wilk test.

Clinical data during the hospital stay were compared between surviving patients with and without follow-up using a *t* test (or Wilcoxon signed-rank test for variables with nonnormal distribution) for continuous variables and a chi-squared test (or Fisher exact test when the expected frequencies were less than 5 in some cells) for qualitative variables.

Hospital factors were compared to D_{LCO} severity (categorized as: D_{LCO} < 80%, 60% < D_{LCO} < 80% and D_{LCO} < 60%) using Mantel–Haenszel test of trend for categorical factors and Pearson test (or Spearman test in non-normal distribution) for continuous variables.

The missingness mechanism was assumed to be missing at random (MAR). In multivariable analyses, missing values were handled with multiple imputation by chained equations (MICE).[15] Primary and secondary outcomes were included in the imputation models but were not imputed. The MICE procedure created 10 complete datasets. A minimum threshold of absolute correlation of 0.15 was used to select predictors in the imputation models. The predictors included in final multivariable model for each outcomes were selected using multiple imputation grouped adaptive least absolute shrinkage and selection operator (LASSO).[16] The lambda value was set to the sparsest model within one standard error of the minimum 5-fold cross-validation error. Finally, final multivariable models were based on a logistic model (or linear model for continuous outcomes) for each outcome with variables selected (in LASSO regression) as predictors. The results across the multiply imputed datasets were combined using Rubin's rules.[17] Additionally, a sensitivity analysis was carried out by fitting the final multivariable models in the population of complete cases.

The individual association between the primary outcome and the selected important variables was represented by violin plots or bar charts for dichotomous outcomes, and representations of generalized additive models for continuous outcomes.

Odds ratios were estimated to assess the direction and magnitude of the associations between the selected factors and the primary outcome in an independent cohort. This was used as a validation of the main results.

R statistical software, version 4.0.1 (R Project for Statistical Computing), was used for all analyses.

Results

Baseline characteristics of the cohort

From a total of 3860 severe COVID-19 patients discharged from participating hospitals, 1327 had D_{LCO} measured in a follow-up visit after discharge and were included in the current analyses (Fig. 1). A comparison of patients with and without follow-up visits is shown in the online supplement (eTable 1), showing that both groups of patients were similar and had no striking or clinically relevant differences a part from the higher use of hydroxychloroquine among the included patients. The included patients had a median [p_{25}; p_{75}] age of 60 [53; 67] years, 27.8% were women, and 59.9% were never smokers. The most common comorbidities were hypertension (44.8%), obesity (35.8%) and diabetes mellitus (17.6%). The median hospital stay was 27 [17; 43] days. The median [p_{25}; p_{75}] time from hospital discharge to the first follow-up visit was 3.57 [2.77; 4.92] months (eFigure 1).

Primary outcome

The mean (SD) percentage of predicted diffusion capacity at the follow-up visit was 72.02 (18.33)% predicted. A total of 877 (66%) patients showed an impairment of diffusion capacity (D_{LCO} < 80%), and 318 (24%) had moderate to severe impairment (D_{LCO} < 60%).

A univariate analysis was performed to evaluate the dose–response association between hospital factors and D_{LCO} impairment using p for trend. Briefly, age, comorbidities (except obesity), duration of IMV, and most hospital complications increased according to the level of D_{LCO} impairment (Tables 1 and 2).

The multivariate model, which included the most relevant variables associated with D_{LCO}, was based on LASSO models. The most relevant variables associated with D_{LCO} < 80% in the multivariate analyses were age (OR[per 1 SD] (95% CI): 1.23 (1.07–1.41)), female sex (1.89 (1.42–2.51)), current smoking (2.19 (1.11–4.32)), duration of IMV (1.57 (1.30–1.89)), duration of NIMV (1.25 (1.05–1.49)), EGFR at ICU admission (0.75 (0.67–0.88)) and hospital infectious complications (1.27 (0.94–1.70)) (Fig. 2, Table 3, and eFig. 2). Regarding moderate/severe impairment diffusion capacity (D_{LCO} < 60%), the multivariate model included age (1.39 (1.18–1.63)), chronic lung disease (CLD) (1.86 (1.18–2.92)), duration of IMV (1.56 (1.37–1.77)), urea at ICU admission (1.16 (0.97–1.39)) and EGFR at ICU admission (0.88 (0.73–1.06)) (Fig. 3, Table 3, and eFig. 2). Furthermore, age and duration of IMV and EGFR at ICU admission showed a linear dose–response association with D_{LCO} in a multivariate linear regression model (eFigs. 2 and 3, and Table 3). Most of these results were validated using an external cohort, with the exception of female sex, which had a different prognostic value in each of the two cohorts (eTable 2). Similarly, the inclusion of time since hospital discharge as a confounder in sensitivity analyses of the associations between clinical parameters at hospitalization and lung diffusion capacity impairment, CT scan findings and spirometry parameters at the follow-up visit did not affect the magnitude of the associations (eTable 3).

Secondary outcomes

The CT scan exploration at the follow-up visit showed prevalent lung damage in the cohort. The prevalence of the assessed CT scan abnormalities was as follows: persistent pulmonary infiltrate (n: 322 (32.59%) patients), fibrotic lesions (244 (24.69%)), and emphysema (56 (5.66%)).

Table 4 shows, on the one hand, the key variables associated with CT findings at the follow-up visit. Briefly, the duration of ventilatory support (NIMV (1.23 (1.06–1.42)) and IMV (1.21 (1.01–1.45)), bacterial pneumonia (1.62 (1.11–2.35)) and the duration of prone positioning (1.17 (0.98–1.39)) were associated with fibrotic lesions. Acute respiratory distress syndrome (OR: 1.93 (1.33–2.79)), need for a prone position (OR: 1.98 (1.44–2.71)) and antiviral treatment (1.66 (1.14–2.40)), APACHE score (1.13 (0.95–1.33)), neutrophil (1.13 (0.98–1.30)) and platelet count at ICU admission (1.17 (1.02–1.35)), and the partial pressure of carbon dioxide (1.09 (0.94–1.26)) were associated with pulmonary infiltrates. Finally, emphysema was only determined by smoking status (former: 7.04 (3.56–13.92); current: 3.20 (0.67–15.11)). On the other hand, Table 4 shows the key variables associated with lung function parameters (FEV_1 and FVC) measured at the follow-up visit. In this regard, the combination of baseline chronic lung

Table 1
Univariate analyses and dose–response relations between sociodemographic data, comorbidities, and treatment at hospitalization and degree of D_{LCO} impairment at the follow-up.

Variables	Global $n = 1327$ Median [p_{25}; p_{75}] or n(%)	≥80% $n = 450$ Median [p_{25}; p_{75}] or n(%)	60% ≤ x < 80% $n = 559$ Median [p_{25}; p_{75}] or n(%)	<60% $n = 318$ Median [p_{25}; p_{75}] or n(%)	p for trend	N
Sociodemographic data						
Sex, *woman*	369 (27.8%)	100 (22.2%)	175 (31.3%)	94 (29.6%)	**0.013**	1327
Age, *years*	60.0 [53.0;67.0]	57.0 [48.0;64.0]	61.0 [53.0;67.0]	64.0 [58.0;70.0]	<**0.001**	1327
Smoking history					**0.004**	1282
Former	457 (35.6%)	114 (26.6%)	213 (39.4%)	130 (41.5%)		
Non smoker	768 (59.9%)	302 (70.6%)	304 (56.2%)	162 (51.8%)		
Current	57 (4.45%)	12 (2.80%)	24 (4.44%)	21 (6.71%)		
Comorbidities						
Body mass index					**0.004**	1246
Normal/overweight	744 (59.7%)	232 (55.5%)	310 (59.2%)	202 (66.4%)		
Obese Class I	338 (27.1%)	128 (30.6%)	134 (25.6%)	76 (25.0%)		
Obese Class II	164 (13.2%)	58 (13.9%)	80 (15.3%)	26 (8.55%)		
Obesity	475 (35.8%)	160 (35.6%)	215 (38.5%)	100 (31.4%)	0.333	1327
Hypertension	595 (44.8%)	162 (36.0%)	258 (46.2%)	175 (55.0%)	<**0.001**	1327
Diabetes mellitus (Type I/II)	233 (17.6%)	62 (13.8%)	101 (18.1%)	70 (22.0%)	**0.003**	1327
Chronic renal disease	58 (4.37%)	9 (2.00%)	22 (3.94%)	27 (8.49%)	<**0.001**	1327
Chronic lung disease	98 (7.39%)	20 (4.44%)	35 (6.26%)	43 (13.5%)	<**0.001**	1327
Rheumatic disease	67 (5.05%)	15 (3.33%)	31 (5.55%)	21 (6.60%)	**0.035**	1327
Hematology disorders	50 (3.77%)	13 (2.89%)	23 (4.11%)	14 (4.40%)	0.254	1327
Treatment						
Antivirals	1011 (76.2%)	357 (79.5%)	427 (76.4%)	227 (71.4%)	**0.010**	1326
Antibiotics	1244 (93.8%)	421 (93.8%)	520 (93.0%)	303 (95.3%)	0.459	1326
Corticosteroids	1104 (83.4%)	362 (80.6%)	474 (85.3%)	268 (84.3%)	0.134	1323
Anticoagulant	1288 (97.2%)	435 (96.9%)	539 (96.6%)	314 (98.7%)	0.161	1325
NIMV duration, days	0.00 [0.00;2.00]	0.00 [0.00;1.00]	0.00 [0.00;2.00]	0.00 [0.00;2.00]	<**0.001**	1315
IMV duration, days	8.00 [0.00;20.0]	5.00 [0.00;13.0]	9.00 [0.00;21.0]	14.0 [0.00;31.0]	<**0.001**	1318
Prone position	726 (54.9%)	224 (49.9%)	312 (56.1%)	190 (59.9%)	**0.005**	1322
Prone position duration, days	12.0 [0.00;48.0]	0.00 [0.00;43.0]	15.0 [0.00;50.0]	19.0 [0.00;59.8]	**0.001**	1293
Lung recruitment maneuvers	19 (1.43%)	6 (1.33%)	6 (1.07%)	7 (2.20%)	0.376	1327
Renal replacement therapy	60 (4.52%)	11 (2.44%)	25 (4.48%)	24 (7.55%)	**0.001**	1326
Ionotropic/Vasoconstrictor drugs	741 (56.2%)	211 (47.3%)	330 (59.2%)	200 (63.5%)	<**0.001**	1318
Neuromuscular-blocking drugs	731 (55.4%)	205 (45.9%)	324 (58.4%)	202 (63.7%)	<**0.001**	1319

Abbreviations: D_{LCO}, lung diffusing capacity; NIMV, non-invasive mechanic ventilation; IMV, invasive mechanic ventilation. Note: significant p-values are shown in bold. Univariate analysis was performed with available data.

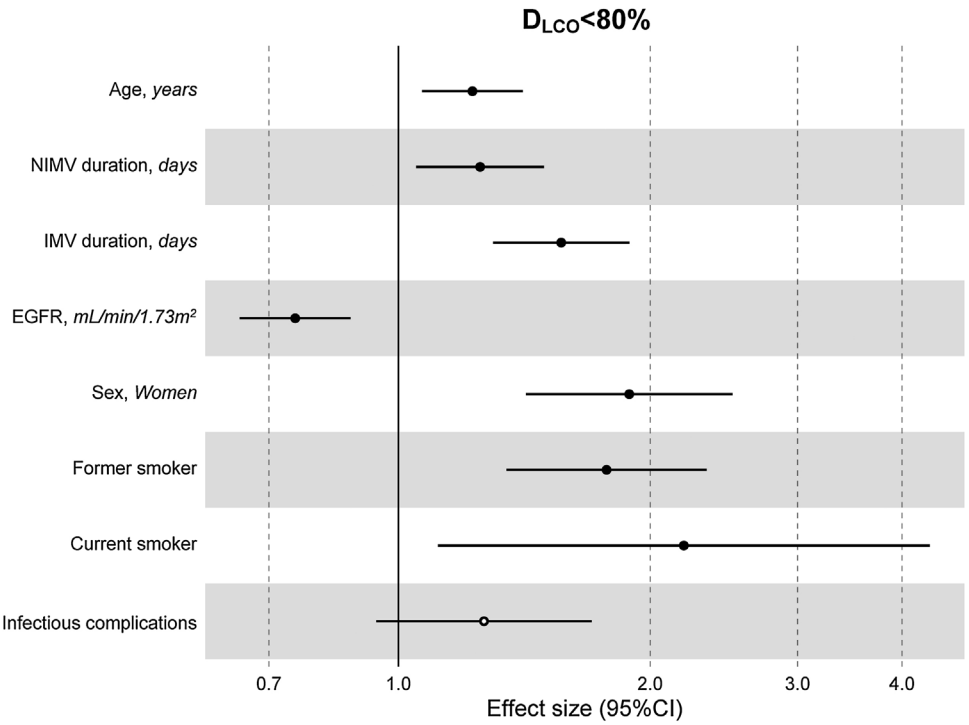

Fig. 2. Hospital factors related to diffusion capacity impairment (D_{LCO} < 80%) at the follow-up visit. Logistic LASSO regression. *Abbreviations*: D_{LCO}: lung diffusing capacity; NIMV, non-invasive mechanic ventilation; IMV, invasive mechanic ventilation; EGFR, Estimated Glomerular Filtration Rate; LASSO, least absolute shrinkage and selection operator.

Table 2
Univariate analyses and dose–response relations between hospital complications, laboratory data at ICU admission, arterial blood gas at ICU admission, worst arterial blood gas during ICU admission, and scores at hospitalization and degree of D_{LCO} impairment at the follow-up.

Variables	Global $n = 1327$ Median [p_{25}; p_{75}] or n(%)	≥ 80% $n = 450$ Median [p_{25}; p_{75}] or n(%)	60% ≤ x < 80% $n = 559$ Median [p_{25}; p_{75}] or n(%)	<60% $n = 318$ Median [p_{25}; p_{75}] or n(%)	p for trend	N
Hospital complications						
Bacterial pneumonia	339 (25.6%)	73 (16.2%)	141 (25.3%)	125 (39.3%)	<**0.001**	1325
ARDS	1001 (75.4%)	314 (69.8%)	431 (77.1%)	256 (80.5%)	<**0.001**	1327
Pulmonary embolism	171 (13.0%)	47 (10.6%)	85 (15.3%)	39 (12.3%)	0.340	1315
Bacteremia	324 (24.4%)	82 (18.2%)	139 (24.9%)	103 (32.5%)	<**0.001**	1326
Acute renal failure	266 (20.0%)	68 (15.1%)	111 (19.9%)	87 (27.4%)	<**0.001**	1327
Liver dysfunction	389 (29.3%)	141 (31.3%)	162 (29.0%)	86 (27.0%)	0.192	1327
Hyperglycemia	905 (68.2%)	274 (60.9%)	383 (68.5%)	248 (78.0%)	<**0.001**	1327
Infectious complications	602 (45.4%)	146 (32.4%)	267 (47.8%)	189 (59.4%)	<**0.001**	1326
Laboratory data at ICU admission						
Lymphocyte count, $\times 10^9$/L	0.70 [0.50;1.00]	0.70 [0.50;1.00]	0.73 [0.50;1.00]	0.68 [0.44;0.98]	0.106	1306
Neutrophil count, $\times 10^9$/L	7.24 [5.10;10.1]	7.23 [5.22;9.96]	7.17 [4.91;10.3]	7.31 [5.12;10.2]	0.939	1302
Platelet count, $\times 10^9$/L	237 [189;309]	238 [195;311]	237 [191;312]	231 [174;303]	0.090	1314
International Normalized Ratio	1.14 [1.07;1.24]	1.15 [1.06;1.24]	1.14 [1.07;1.25]	1.13 [1.07;1.23]	0.483	1173
D-dimer, mg/L	800 [429;1635]	748 [414;1359]	790 [404;1685]	941 [516;1964]	**0.016**	1170
C-reactive protein, mg/dL	137 [70.0;225]	134 [62.4;214]	136 [75.5;230]	148 [65.8;230]	0.207	1273
Bilirubin, mg/dL	0.60 [0.43;0.84]	0.60 [0.43;0.84]	0.60 [0.40;0.87]	0.60 [0.47;0.82]	0.615	1131
Urea, mg/dL	41.0 [29.4;54.0]	38.0 [28.0;49.0]	41.0 [29.0;53.5]	47.0 [32.3;63.0]	<**0.001**	1167
Blood urea nitrogen, mg/dL	19.1 [13.6;25.2]	17.7 [13.1;22.9]	19.1 [13.6;24.8]	21.9 [15.0;29.4]	<**0.001**	1164
EGFR, mL/min/1.73 m^2	98.4 [82.5;107]	102 [91.6;111]	97.9 [79.8;107]	94.0 [71.5;103]	<**0.001**	1316
Procalcitonine, ng/mL	0.18 [0.09;0.39]	0.16 [0.09;0.29]	0.20 [0.09;0.46]	0.18 [0.10;0.42]	**0.018**	920
Ferritin, log	3.09 [2.84;3.28]	3.11 [2.90;3.28]	3.09 [2.82;3.29]	3.04 [2.81;3.26]	0.064	767
Arterial blood gas at ICU admission						
Partial pressure of oxygen, daily, mmHg	76.0 [62.2;98.0]	75.9 [64.0;97.0]	75.2 [62.0;97.0]	78.0 [61.0;101]	0.953	1134
Partial pressure of carbon dioxide, daily, mmHg	37.6 [33.0;44.0]	37.0 [33.0;44.0]	37.9 [33.0;44.0]	38.0 [32.8;44.8]	0.963	1136
PaO_2 to FiO_2 ratio	115 [84.0;166]	110 [83.2;163]	117 [86.2;170]	119 [83.0;173]	0.229	1122
pH, daily	7.43 [7.37;7.46]	7.44 [7.38;7.47]	7.43 [7.37;7.47]	7.42 [7.36;7.45]	**0.006**	1191
Bicarbonate, daily, mmol/L	24.5 [22.1;27.0]	24.8 [22.9;27.0]	24.6 [22.2;27.0]	24.0 [21.3;26.8]	**0.005**	1130
Respiratory rate, rpm	25.0 [22.0;31.0]	26.0 [22.0;31.0]	25.0 [22.0;31.0]	25.0 [21.0;31.0]	0.272	1242
Worst arterial blood gas during ICU admission						
PaO_2 to FiO_2 ratio (min)	105 [76.6;143]	100 [75.1;136]	107 [77.7;146]	103 [75.0;146]	0.363	1216
Partial pressure of oxygen, mmHg (min)	64.0 [54.1;73.4]	64.0 [54.5;73.3]	64.0 [54.6;73.2]	64.0 [54.0;74.0]	0.839	1257
Partial pressure of carbon dioxide, mmHg (max)	45.3 [39.0;52.0]	45.0 [39.4;51.0]	45.7 [38.9;52.0]	46.0 [40.0;53.0]	0.494	1254
pH (min)	7.38 [7.33;7.43]	7.39 [7.34;7.43]	7.38 [7.33;7.43]	7.37 [7.32;7.42]	**0.002**	1284
Bicarbonate, mmol/L (min)	23.1 [21.0;25.3]	23.4 [21.4;25.3]	23.1 [21.0;25.2]	22.7 [20.4;25.2]	**0.004**	1254
Scores						
APACHE score	10.0 [8.00;13.0]	9.50 [7.00;12.0]	11.0 [8.00;14.0]	11.0 [9.00;15.0]	<**0.001**	855
SOFA score	4.00 [3.00;7.00]	4.00 [3.00;6.00]	4.00 [3.00;7.00]	5.00 [3.00;7.00]	**0.004**	972

Abbreviations: D_{LCO}, lung diffusing capacity; ARDS, acute respiratory distress syndrome; EGFR, Estimated Glomerular Filtration Rate. Note: significant p-values are shown in bold. Univariate analysis was performed with available data.

Table 3
Associations between clinical parameters at hospitalization and lung diffusion capacity impairment at the follow-up visit.

D_{LCO}	>80% (n = 450)	<80%(n = 450)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Predictors					
Age, years	56.0 (11.2)	60.8 (10.9)	1.53 (1.37–1.73, p < 0.001)	1.17 (1.02–1.35, p = 0.030)	1.23 (1.07–1.41, p = 0.004)
Sex, woman	100 (22.2%)	269 (30.7%)	1.55 (1.19–2.02, p = 0.001)	1.87 (1.40–2.50, p < 0.001)	1.89 (1.42–2.51, p < 0.001)
Smoking history					
Non smoker	302 (70.6%)	466 (54.6%)	–	–	–
Former	114 (26.6%)	343 (40.2%)	1.95 (1.51–2.53, p < 0.001)	1.81 (1.37–2.40, p < 0.001)	1.77 (1.35–2.34, p < 0.001)
Current	12 (2.8%)	45 (5.3%)	2.43 (1.31–4.88, p = 0.008)	2.27 (1.17–4.68, p = 0.020)	2.19 (1.11–4.32, p = 0.023)
NIMV duration, days	1.1 (3.2)	1.9 (4.9)	1.30 (1.11–1.55, p = 0.002)	1.32 (1.10–1.61, p = 0.004)	1.25 (1.05–1.49, p = 0.012)
IMV duration, days	8.4 (11.4)	15.8 (18.6)	1.79 (1.54–2.11, p < 0.001)	1.61 (1.33–1.97, p < 0.001)	1.57 (1.30–1.89, p < 0.001)
Infectious complication	146 (32.4%)	456 (52.1%)	2.26 (1.79–2.87, p < 0.001)	1.20 (0.88–1.63, p = 0.242)	1.27 (0.94–1.70, p = 0.120)
EGFR, mL/min/1.73 m²	98.9 (18.5)	89.7 (23.5)	0.62 (0.54–0.71, p < 0.001)	0.73 (0.62–0.86, p < 0.001)	0.75 (0.65–0.88, p < 0.001)
D_{LCO}	>60%(n = 1009)	<60%(n = 318)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Predictors					
Age, years	58.0 (11.2)	62.9 (10.4)	1.63 (1.41–1.88, p < 0.001)	1.36 (1.14–1.62, p = 0.001)	1.39 (1.18–1.63, p < 0.001)
Chronic lung disease	55 (5.5%)	43 (13.5%)	2.71 (1.77–4.12, p < 0.001)	2.02 (1.25–3.25, p = 0.004)	1.86 (1.18–2.92, p = 0.007)
IMV duration, days	11.0 (13.9)	20.5 (22.3)	1.66 (1.47–1.88, p < 0.001)	1.57 (1.38–1.79, p < 0.001)	1.56 (1.37–1.77, p < 0.001)
Urea at ICU admission, mg/dL	42.9 (22.6)	53.8 (31.9)	1.48 (1.30–1.69, p < 0.001)	1.18 (0.98–1.42, p = 0.087)	1.16 (0.97–1.39, p = 0.106)
EGFR, mL/min/1.73 m²	95.1 (20.8)	85.5 (25.2)	0.67 (0.59–0.75, p < 0.001)	0.89 (0.73–1.08, p = 0.223)	0.88 (0.73–1.06, p = 0.182)
D_{LCO} (Continuous)	Coefficient (univariable)		Coefficient (complete cases)		Coefficient (multiple imputation)
Predictors					
Age, years	−4.23 (−5.19 to −3.27, p < 0.001)		−2.49 (−3.54 to −1.43, p < 0.001)		−2.51 (−3.55 to −1.46, p < 0.001)
IMV duration, days	−4.85 (−5.81 to −3.89, p < 0.001)		−4.22 (−5.16 to −3.28, p < 0.001)		−4.13 (−5.06 to −3.19, p < 0.001)
EGFR, mL/min/1.73 m²	4.39 (3.43–5.36, p < 0.001)		2.64 (1.59–3.70, p < 0.001)		2.61 (1.56–3.67, p < 0.001)

Abbreviations: D_{LCO}, lung diffusing capacity; NIMV, non-invasive mechanic ventilation; IMV, invasive mechanic ventilation; EGFR, Estimated Glomerular Filtration Rate; ICU, intensive care unit. Note: odds ratios are presented for the 1-SD change of continuous variable. In descriptive data, mean (SD) or n(%) accordingly.

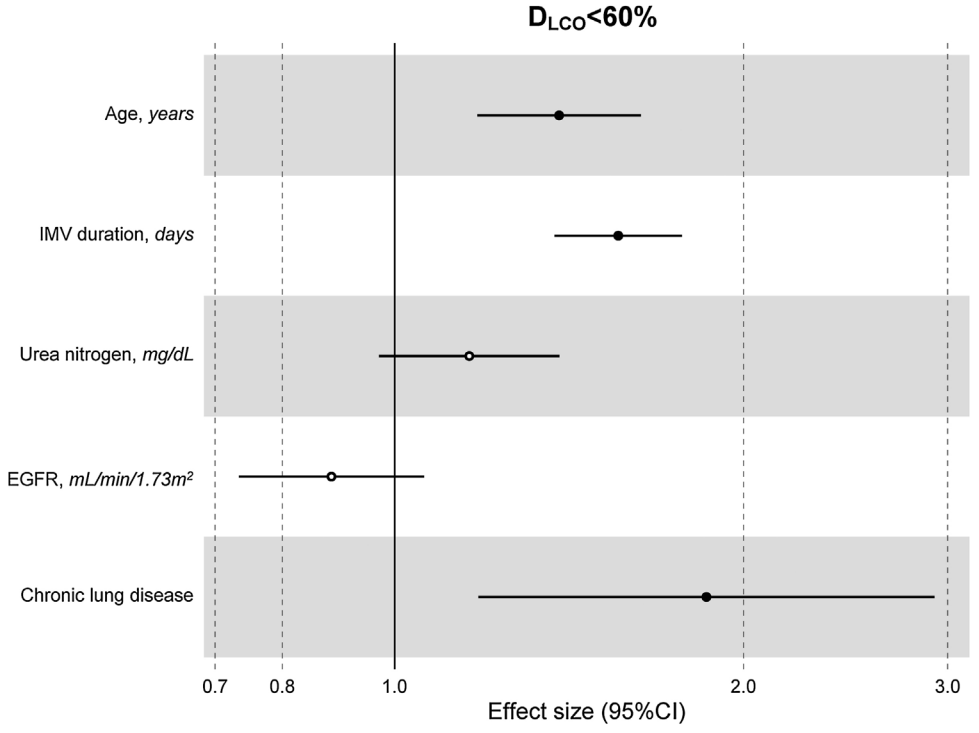

Fig. 3. Hospital factors related to diffusion capacity impairment (D_{LCO} < 60%) at the follow-up visit. Logistic LASSO regression. *Abbreviations*: D_{LCO}: lung diffusing capacity; IMV, invasive mechanic ventilation; EGFR, Estimated Glomerular Filtration Rate; LASSO, least absolute shrinkage and selection operator.

or renal disease, renal function at ICU admission and the duration of ventilatory procedures were the main determinants of FEV_1 and FVC.

Discussion

In this ambispective multicentric cohort of patients who needed an ICU admission due to COVID-19, the most important factors related to a moderate/severe impairment in D_{LCO} (<60%) after hospital discharge were: age, baseline CLD, duration of IMV, and renal function in terms of urea and EGFR at ICU admission. Similarly, renal function, duration of ventilatory procedures and baseline chronic renal disease were associated with other parameters of spirometry (FEV_1 and FVC). Finally, fibrotic lesions in the chest CT were also associated with the length of IMV and NIMV, prone positioning and bacterial complications. The identified factors

Table 4
Associations between clinical parameters at hospitalization and CT scan findings and spirometry parameters.

	CT findings (n = 988)				
	Persistent pulmonary infiltrate				
Predictors	No (n = 666)	Yes (n = 322)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Antiviral treatment	506 (76.0%)	275 (85.4%)	1.85 (1.30–2.67, p = 0.001)	1.43 (0.94–2.21, p = 0.099)	1.66 (1.14–2.40, p = 0.008)
Prone position	328 (49.6%)	227 (70.5%)	2.43 (1.83–3.23, p < 0.001)	1.72 (1.17–2.54, p = 0.006)	1.98 (1.44–2.71, p < 0.001)
ARDS complication	472 (70.9%)	276 (85.7%)	2.47 (1.74–3.55, p < 0.001)	1.35 (0.89–2.10, p = 0.165)	1.93 (1.33–2.79, p = 0.001)
Neutrophil count at ICU admission, $\times 10^9$/L	7.9 (4.9)	8.9 (4.5)	1.22 (1.07–1.39, p = 0.002)	1.17 (0.96–1.43, p = 0.118)	1.13 (0.98–1.30, p = 0.103)
Platelet count at ICU admission, $\times 10^9$/L	251.4 (106.7)	270.9 (103.3)	1.19 (1.05–1.36, p = 0.007)	1.18 (0.99–1.40, p = 0.057)	1.17 (1.02–1.35, p = 0.030)
APACHE score	11.1 (4.9)	12.3 (5.7)	1.26 (1.07–1.49, p = 0.006)	1.14 (0.96–1.37, p = 0.143)	1.13 (0.95–1.33, p = 0.161)
Partial pressure of carbon dioxide, mmHg (max)	46.6 (11.1)	49.8 (13.6)	1.29 (1.13–1.47, p < 0.001)	1.08 (0.88–1.32, p = 0.444)	1.09 (0.94–1.26, p = 0.258)
	Emphysema				
Predictors	No (n = 932)	Yes (n = 56)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Smoking history					
Non smoker	558 (61.9%)	10 (18.2%)	–	–	–
Former	313 (34.7%)	43 (78.2%)	7.67 (3.96–16.35, p < 0.001)	7.67 (3.96–16.35, p < 0.001)	7.04 (3.56–13.92, p < 0.001)
Current	31 (3.4%)	2 (3.6%)	3.60 (0.54–14.42, p = 0.108)	3.60 (0.54–14.42, p = 0.108)	3.20 (0.67–15.11, p = 0.141)
	Fibrotic lesions				
Predictors	No (n = 744)	Yes (n = 244)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
NIMV duration, days	1.6 (3.5)	2.7 (6.7)	1.24 (1.08–1.43, p = 0.002)	1.25 (1.08–1.46, p = 0.003)	1.23 (1.06–1.42, p = 0.006)
IMV duration, days	12.3 (15.7)	19.5 (19.8)	1.46 (1.28–1.67, p < 0.001)	1.18 (0.97–1.41, p = 0.087)	1.21 (1.01–1.45, p = 0.036)
Prone duration, hours	28.9 (44.5)	46.6 (62.0)	1.41 (1.21–1.64, p < 0.001)	1.18 (0.99–1.41, p = 0.068)	1.17 (0.98–1.39, p = 0.076)
Bacterial pneumonia	166 (22.3%)	97 (39.9%)	2.31 (1.69–3.15, p < 0.001)	1.71 (1.16–2.51, p = 0.006)	1.62 (1.11–2.35, p = 0.012)
	Spirometry (n = 1319)				
	FEV_1				
Predictors	>80 (n = 886)	<80 (n = 433)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Chronic renal disease	28 (2.8%)	30 (9.3%)	3.51 (2.06–6.00, p < 0.001)	2.69 (1.48–4.87, p = 0.001)	2.99 (1.71–5.24, p < 0.001)
Chronic lung disease	58 (5.9%)	40 (12.3%)	2.27 (1.47–3.45, p < 0.001)	1.83 (1.14–2.92, p = 0.011)	1.9 (1.22–2.97, p = 0.005)
IMV duration, days	12.0 (15.1)	17.4 (20.9)	1.33 (1.18–1.50, p < 0.001)	1.33 (1.18–1.51, p < 0.001)	1.3 (1.15–1.47, p < 0.001)
Urea at ICU admission, mg/dL	43.9 (23.9)	50.8 (30.0)	1.28 (1.13–1.45, p < 0.001)	1.13 (0.99–1.30, p = 0.076)	1.12 (0.98–1.28, p = 0.101)
	FVC				
Predictors	>80 (n = 991)	<80 (n = 324)	OR (univariable)	OR (complete cases)	OR (multiple imputation)
Chronic renal disease	22 (2.5%)	36 (8.3%)	3.56 (2.08–6.22, p < 0.001)	3.37 (1.94–5.96, p < 0.001)	3.47 (1.99–6.06, p < 0.001)
NIMV duration, days	1.4 (3.6)	2.3 (5.6)	1.23 (1.10–1.40, p = 0.001)	1.22 (1.08–1.39, p = 0.002)	1.20 (1.06–1.37, p = 0.004)
IMV duration, days	11.3 (14.3)	17.3 (20.4)	1.42 (1.26–1.59, p < 0.001)	1.41 (1.26–1.59, p < 0.001)	1.42 (1.26–1.60, p < 0.001)

Abbreviations: CT, chest thorax; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; NIMV, non-invasive mechanic ventilation; IMV, invasive mechanic ventilation; FEV_1, forced expiratory volume in 1 second; FVC, Forced vital capacity. Note: odds ratios are presented for the 1-SD change of continuous variable. In descriptive data, mean (SD) or n(%) accordingly.

showed similar associations with the outcome in an independent external cohort.

One of the most well-known prognostic factors regarding pulmonary sequelae after COVID-19 is age.[5,7] Tissue repair and remodeling responses to a lung injury such a severe COVID-19 infection may be altered by the aging process and cellular senescence.[18] These processes are associated with a decline in the immune system and promote inflammation,[19] in addition to generating more oxidative stress[18] and a deterioration in the repair capacity of damaged cells.[18] Therefore, it is plausible that these age-related limitations imply worse clinical outcomes with more lung damage in older subjects. In this line, patients with CLD, especially COPD, also show an ineffective repair response to lung damage (most commonly caused by toxic inhalants)[20] which could explain the worse outcomes in both, the acute phase[21–24] and in follow-up.[11,12,25] Moreover, patients with COPD also have a higher expression of ACE-2 receptors in the bronchial epithelium[26,27] and impairment of immune response.[28] Importantly, patients with CLD probably have worse baseline pulmonary function before COVID-19 infection.

Another key variable associated with decreased D_{LCO} is the length of IMV. Clearly, the respiratory management of these patients is crucial, and factors such as the timing of intubation[10] or indices such as ventilatory ratio[29] have important implications in terms of mortality and pulmonary sequelae. However, developing ARDS and the duration of IMV are directly related to a more severe disease that often involves more complications, such as ventilator-induced lung injury and ventilator-associated pneumonia, leading to more mechanical stress and lung damage.[30,31] In addition, and as our study highlights, survivors of more severe COVID-19 who developed ARDS and need to be intubated have already been associated with the presence of chest CT abnormalities (such as fibrotic lesions or persistent pulmonary infiltrates) or with the involvement of other respiratory parameters, such as FEV_1 and FVC, during follow-up.[32–34]

A similar phenomenon surrounds the link between renal and pulmonary involvement. Acute renal failure could be caused directly by SARS-CoV-2 or secondary to end-organ damage in severe COVID-19 patients with hemodynamic instability, inflammatory cytokines and consequences of ICU therapies.[35] In this

way, renal failure could also be seen as a marker of the severity of COVID-19, involving more global vascular damage with important prognostic values in the acute phase.[36] This global vascular damage could be related to the distinctive vascular features found in COVID-19 patients, with severe endothelial injury associated with widespread thrombosis and microangiopathy,[37] contributing to the deterioration of D_{LCO} after discharge.

Our results have relevant clinical consequences, as a substantial proportion of survivors of critical COVID-19 will face mid- to long-term respiratory or functional sequelae. The identification of key variables associated with a moderate/severe D_{LCO} impairment or chest CT abnormalities after hospital discharge allows a more personalized planning of the patients' follow-up, while also helping to estimate the health resources that should be allocated to its monitoring. We know from other respiratory diseases the importance of presenting a moderate/severe deterioration of D_{LCO} for patients, generating more symptoms, worse exercise performance and quality of life.[38] This work contributes to laying the foundations for planning the follow-up of critically ill COVID-19 patients and highlights the importance of the pulmonologists who will follow up with the patients having access to and accounting for the data collected during the critical stage of the illness. For all these reasons, and knowing the high proportion of patients (up to 30%) who continue to present abnormal D_{LCO} values one year after hospital discharge,[39] it should be mandatory to carry out a complete study in a first follow-up.

This study has some key strengths: (i) the availability of a huge amount of information at different time points of the COVID-19 course; (ii) the fact that all data were thoroughly revised and validated, in contrast to registry-based studies; (iii) the representativeness of our study population, including multiple sites and pandemic waves; and, (iv) the validation of our results in an independent cohort of critically ill COVID-19 patients, which, furthermore, included different pandemic waves thus making the current results timeless. In this regard, female sex, which was the only variable that was not validated, has been reported as a key factor determining full recovery one year after discharge in other large cohorts.[40] On the other hand, some limitations must be acknowledged: (i) the observational design; (ii) the pragmatic design, adapting to the different pandemic scenarios in each participating hospital and producing uneven follow-up; (iii) the lack of information on the period between hospital discharge and the follow-up visit, especially in terms of treatment, rehabilitation and other procedures; (iv) the high number of patients lacking a D_{LCO} measure in the follow-up and consequently not included in our analyses, although this was mitigated by the large study cohort and confirmed by the lack of clinically significant difference between included and non-included patients; and, (v) the short-term follow-up. In this regard, we have divided the cohort into mild D_{LCO} deterioration (<80%) and moderate/severe deterioration (<60%) to try to identify more significant lung damage that requires at least a first short-term follow-up.

Conclusions

In this cohort of critically ill COVID-19 patients, we identified key factors directly associated with worse D_{LCO} and chest CT abnormalities at a postdischarge follow-up visit. They include nonmodifiable factors such as age and CLD, reflecting a more vulnerable population with poor host response to viral infection and poor lung repair, and markers of a more severe disease, such as duration of IMV and renal function. Physicians should consider all of these variables to plan the follow-up of critically ill COVID-19 survivors.

Authors' contributions

Conceptualization (JG, JdB, IDB, FB), data curation (IDB, CG-P, AM-M), formal analysis (IDB), funding acquisition (AT, FB), investigation (all), methodology (IDB, JdB, JG, AT, FB), project administration (AT, FB), supervision (AT, FB), writing – original draft (JG, JdB, IDB), and writing – review & editing (all). All authors provided final approval of the version submitted for publication.

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Conflicts of interests

None declared.

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2022.12.017.

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