Longitudinal recovery trajectories and ventilatory modalities in COVID-19 acute respiratory distress syndrome survivors

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Longitudinal pulmonary recovery trajectories vary by ventilatory support modalities in COVID-19 ARDS survivors. Delayed intubation implies the worst outcomes. NIMV patients show slower lung recovery and more radiological abnormalities compared to HFNC. https://bit.ly/3NHfl75

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Abstract

Background The impact of different ventilatory support modalities and timing of intubation on longitudinal lung recovery trajectories in patients with severe coronavirus disease 2019 (COVID-19) is unknown.

Methods This was a multicentre, prospective observational study conducted in 52 Spanish intensive care units (ICUs) involving critically ill COVID-19 patients admitted between 25 February 2020 and 8 February 2021. 1854 COVID-19 patients were followed after hospital discharge at 3, 6 and 12 months with diffusing capacity of the lung for carbon monoxide (D_{LCO}) measurements and chest imaging. Patients were classified regarding the ventilatory support received during the ICU stay: noninvasive mechanical ventilation (NIMV), high-flow nasal cannula (HFNC) and invasive mechanical ventilation (IMV), divided

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into early IMV (intubation within 24 h) and late IMV (intubation after 24 h). The primary objective was to evaluate the impact of the different respiratory support modalities during the ICU stay and the time of intubation on D_{LCO} measurements and their recovery trajectories over a 1-year follow-up. Secondary outcomes included other pulmonary function parameters and chest imaging findings.

Results A total of 360 (19.4%) and 290 (15.6%) patients received HFNC and NIMV, respectively. 1204 (64.9%) patients underwent IMV; 966 received early IMV and 238 received late IMV. The latter exhibited a significantly worse percentage predicted D_{LCO} during the 1-year follow-up with adjusted differences of 6.9 (95% CI 3.9–10; p<0.001), 4.2 (95% CI 1.1–7.2; p=0.007) and 4.9 (95% CI 1.7–8.2; p=0.003) at 3, 6 and 12 months compared with early IMV. NIMV patients exhibited greater lung damage at follow-up than those under HFNC with an adjusted difference of percentage predicted D_{LCO} of 5.2 (95% CI 1.7–8.7; p=0.003) at 6 months and greater presence of radiological abnormalities during follow-up. Matched and sensitivity analysis showed results consistent with those reported.

Conclusions Delay in intubation implies the worst outcomes; however, patients with NIMV exhibited a slower lung recovery in terms of D_{LCO} measurements and more radiological abnormalities compared with HFNC patients. These results should be used to optimise follow-up protocols for COVID-19 acute respiratory distress syndrome (ARDS) survivors.

Introduction

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected, efforts have focused on generating large clinical cohorts of patients to gain the most knowledge possible to better understand coronavirus disease 2019 (COVID-19) [1]. This effort has been particularly important in the field of pulmonary sequelae after suffering acute respiratory distress syndrome (ARDS) [2–7]. In this line, the most characteristic short- and long-term medical complication in surviving ARDS patients, whether related to COVID-19 or not, is impairment of diffusing capacity of the lung for carbon monoxide (D_{LCO}) [8–10]. Other respiratory parameters, such as forced vital capacity (FVC) and total lung capacity, exhibit normal values from the initial early assessment [8–10].

A population with a predisposition to this pulmonary alteration during follow-up are patients who previously required any advanced respiratory support [5], especially invasive mechanical ventilation (IMV) [6]. Notably, the timing of intubation is one of the most significant predictors of pulmonary sequelae in these patients [11–13]. Apart from studies on intubated patients, there is a lack of research assessing the differential impacts of other noninvasive respiratory support modalities, such as noninvasive mechanical ventilation (NIMV) and high-flow nasal cannula (HFNC), on pulmonary sequelae.

The COVID-19 pandemic provided us with the opportunity to create unique cohorts of critically ill patients with very large sample sizes in a short amount of time, as had never been seen before. Owing to the debate over the management of acute respiratory failure during the initial year of the pandemic, considerable variability emerged in the selection of ventilatory support strategies for patients with ARDS. Some authors recommended the use of noninvasive ventilation modes, such as NIMV or HFNC [14], while others advocated for early intubation and initiation of IMV to protect the lungs from the excessive central respiratory drive observed in these patients [15]. Current evidence indicates that patients treated with NIMV experienced higher hospital mortality compared to those who used HFNC [16–18]. Along the same lines, patients who were intubated and connected to IMV later exhibited increased mortality compared to those who received early intubation [11, 13]. The underlying principle in both scenarios is consistent: both NIMV and delayed intubation excessively damage the lungs, perpetuate inflammation and thus adversely affect the prognosis in these patients [16–18]. Nonetheless, the literature remains sparse on extending these findings to the long-term respiratory consequences experienced by survivors.

Given the aforementioned, our objective was to identify the possible impact of the different respiratory support modalities (noninvasive and invasive), as well as the timing of intubation, on pulmonary sequelae and their recovery trajectories (D_{LCO}) as well as radiological affectation in patients who survived ARDS due to COVID-19. Therefore, we operate under the hypothesis that survivors who predominantly received NIMV during their ICU stay or who underwent delayed intubation, similarly to how they have been associated with poorer outcomes in the acute phase, would exhibit more long-term respiratory sequelae. For this purpose, we analysed a large prospective and multicentric cohort of critically ill patients in Spain who survived COVID-19, and performed a long-term follow-up with D_{LCO} measurements and chest imaging (computed tomography (CT) or radiography).

Methods

Study design

This article is based on the CIBERESUCICOVID study (ClinicalTrials.gov: NCT04457505), which was an observational, pragmatic, multicentre, prospective study in critically ill COVID-19 patients admitted to intensive care units (ICUs) of Spanish hospitals [1]. The primary objective was to identify risk factors and prognostic indicators for critical illness in COVID-19 patients. This study included a 1-year follow-up of the maximum number of COVID-19 patients admitted to each participating hospital during the pandemic. The follow-up during the first year was established as a secondary objective, with a protocol dictating visits at 3, 6, and 12 months post-hospital discharge, regardless of symptom presence. These visits comprised clinical evaluation, airway function tests and chest imaging as indicated [1].

We reported results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Study population

The data for the current analyses correspond to critical COVID-19 patients admitted to 52 Spanish ICUs from 25 February 2020 to 28 February 2021. All included patients met the World Health Organization definition for critical COVID-19 [19] and had a positive nasopharyngeal swab PCR test for SARS-CoV-2. The follow-up period extended through July 2022. Patients who did not survive hospitalisation and patients missing a lung function test at their follow-up visit after discharge were excluded from the analyses.

Measures

Baseline and in-hospital variables

Sociodemographic, anthropometric, comorbidity and lifestyle data were collected at hospital admission. Detailed information collected at hospital and ICU admission, including vital signs, respiratory support devices, pharmacological treatments, laboratory findings and mechanical ventilation settings, was recorded.

Follow-up visit after hospital discharge

Pulmonary function parameters and chest structural abnormalities were evaluated at 3, 6 or 12 months after hospital discharge. These parameters were objectively assessed at a follow-up visit by means of a lung function test (D_{LCO}, forced expiratory volume in 1 s (FEV_1) and FVC) and a thoracic CT scan or a chest radiograph (persistent infiltrates and fibrotic lesions). Chest CT images were interpreted as part of routine clinical practice by thoracic radiologists at each hospital, following the Fleischner Society glossary [20, 21]. The radiologists were blinded to the clinical data. Persistent pulmonary infiltrates and fibrotic lesions were defined as follows. 1) Persistent pulmonary infiltrates: infiltrate ("opacity") refers to any focal or diffuse nonspecific area of increased attenuation. The term is a general descriptor that does not indicate the nature of the condition causing the opacity. Radiologists refer to infiltrates as persistent if they were present on previous imaging studies from the acute phase. 2) Fibrotic lesions: fibrotic lesions were defined according to the Fleischner Society glossary of thoracic imaging terms, including reticulation, architectural distortion, traction bronchiectasis and honeycombing [20].

Primary and secondary outcomes

The main outcome was to assess the impact of the different respiratory support modalities used during the ICU stay and the time of intubation on pulmonary sequelae (D_{LCO}) and recovery trajectories during the 12-month follow-up. Secondary outcomes were other pulmonary functional parameters (FEV_1 and FVC) and chest imaging findings (persistent infiltrates and fibrotic lesions).

Study groups

Patients were grouped according to the type of ventilatory support (invasive (IMV) or noninvasive (NIMV or HFNC)) used during the ICU stay. Patients who received NIMV at any time in the ICU were included in the NIMV group (primary ventilatory support modality). Patients included in the HFNC group only received HFNC (*i.e.* no other type of respiratory support). Intubated patients were classified as either early or late IMV. Early IMV was defined as initiation of invasive ventilatory support within the first 24 h and late IMV was defined as support initiated >24 h after ICU admission, in accordance with previous reports [11, 13]. Finally, we compared NIMV to HFNC and early IMV to late IMV.

Ethics and data protection

The CIBERESUCICOVID study received approval from the Internal Review Board of the Hospital Clinic of Barcelona, Barcelona, Spain (Comité Ètic d'Investigació Clínica; registry number HCB/2020/0370). The participating hospitals obtained ethics approval from their ethics boards. Participants or their relatives provided informed consent when possible or, when unfeasible, an informed consent waiver was authorised

by the ethics board. Data were pseudonymised and stored in a REDCap database hosted in the Centro de Investigación Biomédica en Red (CIBER) premises in Madrid, Spain. The study followed the tenets of the Declaration of Helsinki and complied with national and international laws on data protection.

Statistical analyses

Descriptive statistics were used to summarise the characteristics of the study population. Absolute and relative frequencies were used for qualitative data. Mean±standard deviation and median (interquartile range (IQR)) were estimated for quantitative variables with normal and nonnormal distributions, respectively. The Shapiro–Wilk test was used to analyse data with a normal distribution.

To assess the population representativeness of the sample, we compared the clinical data obtained during hospitalisation in patients with and without follow-up using the t-test (or Wilcoxon signed-rank test for variables with a nonnormal distribution) for continuous variables. The Chi-squared test (or Fisher's exact test when the expected frequencies were <5 in some cells) was used for qualitative variables. We compared the clinical data between the noninvasive groups (NIMV *versus* HFNC) and the IMV groups (early *versus* late IMV).

The primary outcome measure, *i.e.* change in lung function (D_{LCO}), was evaluated using a linear mixed effect model including time, study groups and time×group interaction as fixed effects, and patients and hospital category as random effects. In Spain, hospital category is classified according to the number of available beds (Group 1: <200 beds; Group 2: 200–500 beds; Group 3: 501–1000 beds; Group 4: >1000 beds). Unadjusted and adjusted models were created with age, sex, chronic lung disease, body mass index (BMI), smoking status, antibiotics and corticoids as confounding factors. Some variables were excluded from inclusion as adjustment variables, such as obesity due to collinearity with BMI, and Acute Physiology and Chronic Health Evaluation (APACHE) II score and blood test measures due to excessive missing data. Differences in D_{LCO} values between the study groups at each time-point were assessed for an interaction between study group and visit. The main comparatives assessed in the model were NIMV *versus* HFNC and early *versus* late IMV. To evaluate changes in D_{LCO} values over time for each group, a multivariate generalised additive mixed model (GAMM) with a penalised cubic regression spline was fitted, including confounding factors, time, study groups and time×group interaction as fixed effects, and patients and hospital category as a random effect. The GAMM included a simple factor smooth interaction (time×ventilatory groups) using thin plate regression splines. Furthermore, matched analysis for the primary outcome was performed using nearest-neighbour matching with a propensity score calliper distance of 0.1 to select matched patients between groups. Two matching processes were performed to enable comparability between the noninvasive respiratory support groups (NIMV *versus* HFNC) and IMV groups (early *versus* delayed IMV). A standardised mean difference between groups <0.1 was defined as an optimal quality match. The matching process included age, sex, chronic pulmonary disease, BMI, smoking status, respiratory rate at ICU admission, antibiotics and corticosteroids. The differences between groups were assessed using unadjusted linear mixed effect models. Finally, a sensitivity analysis for the primary outcome was performed assuming a MNAR (missing not at random) mechanism (see supplementary methods).

Secondary outcomes were evaluated with unadjusted and adjusted models using a linear mixed effect model for continuous variables (FEV_1 and FVC) and logistic regression models for categorical variables (persistent infiltrates and fibrotic lesions) with available data at each visit. The models included time, study groups and time×group interaction as fixed effects, and patients and hospital category as random effects. Unadjusted and adjusted models were performed. Imputation processes were not applied to secondary outcomes.

R version 4.0.1 (www.r-project.org) was used to perform all statistical analyses.

Results

Baseline characteristics of the cohort

Of the initial 4269 critically ill COVID-19 patients who were discharged from participating hospitals, 1854 underwent D_{LCO} measurements at a follow-up visit and were included in the present study (supplementary figure S1). There were no clinically relevant differences between patients with and without follow-up (supplementary table S1). Sociodemographic, clinical characteristics and ICU data of included patients are presented in supplementary table S1.

Clinical data during hospital stay according to the different ventilatory support modalities

Patients were classified based on the different ventilatory support modalities required during their ICU stay. With respect to the noninvasive groups, 360 (19.4%) and 290 (15.6%) received HFNC and NIMV,

respectively. A total of 1204 (64.9%) required IMV, and were classified into early IMV (n=966) and late IMV (N=238) groups according to the day intubation started (first 24 h of ICU stay or later). In the late IMV group, 94 (39.5%) had received HFNC, 135 (56.7%) had received NIMV and nine (3.8%) had received conventional oxygen as the initial respiratory support mode. The median (IQR) time from ICU admission to intubation in the late IMV group was 3 (2–4) days.

Patients who received NIMV exhibited significant differences in BMI, smoking status, metabolic disorders, pharmacological treatment, APACHE II score and respiratory rate compared with patients receiving HFNC at ICU admission. There were also differences in pharmacological treatment received between these groups. Furthermore, the NIMV group had a longer ICU stay with a median (IQR) of 7 (4–10) days compared with 6 (4–8) days in the HFNC group (table 1).

With regard to the IMV groups, similar sociodemographic and clinical data at ICU admission were observed, although early IMV was associated with a slightly higher APACHE II score compared with the late IMV group. Differences in pharmacological treatment were also observed between the groups. At the start of IMV, there were no relevant differences in ventilatory parameters between the groups. As expected, the late IMV group exhibited a significantly longer ICU stay with a median (IQR) of 24 (15–41) days compared with 21 (13–36) days in the early IMV group (table 1). Furthermore, no significant differences were observed in the use of pronation with 738 (76.6%) patients in the early IMV group and 190 (80.1%) patients in the late IMV group.

Overview and trajectories of pulmonary sequelae after hospital discharge according to ventilatory support

Pulmonary function parameters were evaluated at 3, 6 or 12 months after hospital discharge with a median (IQR) follow-up of 2.9 (2.2–3.3), 5.8 (4.9–6.8) and 11.3 (9.6–12.3) months, respectively. Globally, patients exhibited a mean±SD percentage predicted D_{LCO} of 70.2±18.6%, 73.4±18.5% and 75.6±17.9% at the 3-, 6- and 12-month follow-ups, respectively. As expected, D_{LCO} tended to improve over time in all groups, with the late IMV group exhibiting significantly worse D_{LCO} at the 1-year follow-up (figure 1a). Modelling of D_{LCO} over continuous time revealed a nonlinear evolution and different trajectories according to the study groups (figure 1b).

Noninvasive respiratory support modalities groups (NIMV versus HFNC)

Patients who received HFNC exhibited faster percentage predicted D_{LCO} recovery, with significantly better values at 6 months, than those who received NIMV, with an adjusted mean difference of 5.2 (95% CI 1.7–8.7; p=0.003). These differences were reduced at 1 year of follow-up. There were no significant differences between the groups with respect to other respiratory measurements during follow-up (FEV_1 and FVC). With respect to the radiological findings, the NIMV group exhibited a greater risk of developing fibrotic lesions during the follow-up period and persistent pulmonary infiltrates at the 3- and 6-month follow-ups (table 2).

To reinforce the results of the comparison between the NIMV and HFNC groups, a matched analysis based on propensity score matching was performed. There were no clinically relevant differences between the NIMV and HFNC groups in the matched population (n=177 per group) (supplementary figure S2a and supplementary table S3). The results for percentage predicted D_{LCO} were similar to the adjusted model in the unmatched population, with a mean difference of 4.6 (95% CI 0.2–9; p=0.039) at the 6-month follow-up. With respect to chest imaging findings, there was a greater presence of persistent pulmonary infiltrates at the 3- and 12-month follow-ups in the NIMV group. Moreover, fibrotic lesions were more frequent at 3, 6 and 12 months in the NIMV compared to the HFNC group (supplementary table S4 and supplementary figure S3a). Finally, the sensitivity analysis for the comparison of D_{LCO} between the study groups showed results consistent with those presented previously (supplementary table S5 and supplementary figure S4).

Invasive respiratory support modalities (early versus late IMV)

Patients who required IMV exhibited a mean±SD percentage predicted D_{LCO} of 68.7±18.6%, 72.1±18.5% and 74.7±18.1% at the 3-, 6- and 12-month follow-ups, respectively. After adjusting for potential confounding factors, the late IMV group exhibited worse D_{LCO} values during the follow-up period. Furthermore, delayed IMV was associated with a greater presence of fibrotic lesions at 3 months with an adjusted OR of 1.83 (95% CI 1.18–2.83; p=0.007) and a lower presence of persistent pulmonary infiltrates at the 6-month follow-up (table 2).

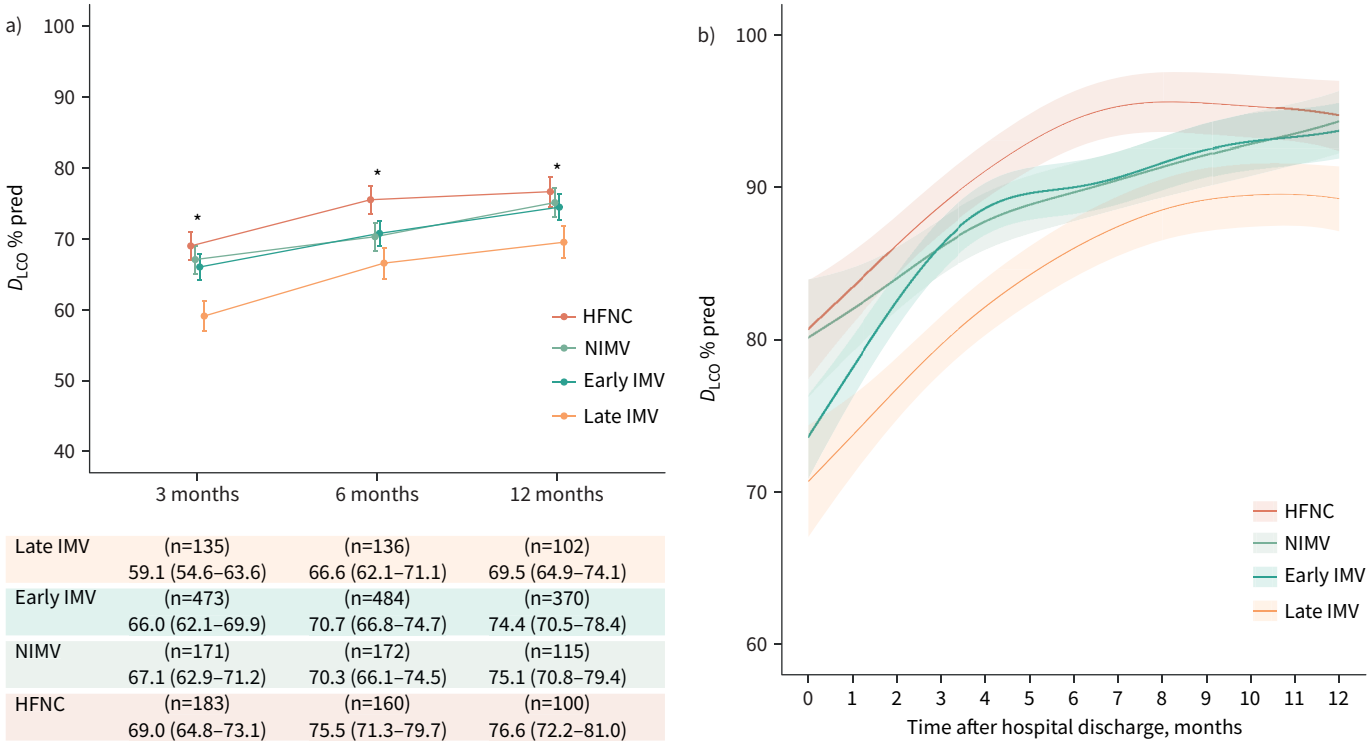
To reinforce the comparison between the late and early IMV groups for the primary outcome, a matching process was performed to balance confounding factors between these two groups (supplementary figure S2b).

TABLE 1 Sociodemographic and clinical characteristics of patients according to respiratory support mode

	Noninvasive respiratory support			Invasive respiratory support			Patients, n
	HFNC (n=360)	NIMV (n=290)	p-value	Early IMV (n=966)	Late IMV (n=238)	p-value	
Sociodemographic data							
Female	100 (27.8)	88 (30.3)	1.000	268 (27.7)	68 (28.6)	1.000	
Age, years	58.0 (49.0–66.0)	60.0 (50.0–67.0)	0.144	61.0 (53.0–68.0)	61.0 (53.0–66.0)	0.243	1854
Body mass index, kg·m^{-2}	27.8 (25.7–31.2)	29.8 (26.9–34.6)	<0.001	29.4 (26.3–32.8)	28.5 (26.4–31.5)	0.102	1759
Smoking history			0.001			0.012	1794
Ex-smoker	105 (29.7)	129 (45.4)		314 (33.9)	102 (44.2)		
Nonsmoker	231 (65.3)	146 (51.4)		559 (60.4)	122 (52.8)		
Current smoker	18 (5.08)	9 (3.17)		52 (5.62)	7 (3.03)		
Comorbidities							
Obesity	96 (26.7)	138 (47.6)	<0.001	407 (42.1)	90 (37.8)	0.255	1854
Hypertension	136 (37.8)	127 (43.8)	0.282	448 (46.4)	106 (44.5)	0.794	1854
Diabetes mellitus	51 (14.2)	54 (18.6)	0.307	200 (20.7)	47 (19.7)	0.829	1854
Chronic heart disease	30 (8.36)	32 (11.0)	0.983	90 (9.32)	22 (9.24)	1.000	1853
Chronic renal disease	17 (4.72)	17 (5.86)	0.956	35 (3.62)	12 (5.04)	0.897	1854
Chronic pulmonary disease	26 (7.22)	34 (11.7)	0.312	86 (8.90)	17 (7.14)	0.551	1854
Metabolic disorders	70 (19.4)	86 (29.7)	0.009	270 (28.0)	71 (29.8)	0.748	1854
On ICU admission							
Symptoms to hospital admission, days	7.00 (5.00–10.0)	7.00 (6.00–10.0)	0.228	7.00 (5.00–10.0)	7.00 (5.00–9.00)	0.957	1845
Hospitalisation duration before ICU entrance, days	2.00 (0.00–4.00)	1.00 (0.00–3.25)	0.775	1.00 (0.00–3.00)	1.00 (0.00–3.00)	0.775	1845
APACHE II score	9.00 (6.00–11.0)	11.0 (8.00–13.0)	0.003	11.0 (9.00–15.0)	10.0 (7.00–13.0)	<0.001	1128
SOFA score	3.00 (3.00–4.00)	4.00 (3.00–4.00)	0.969	6.00 (4.00–8.00)	4.00 (3.00–4.00)	<0.001	994
pH	7.45 (7.42–7.47)	7.46 (7.43–7.48)	0.192	7.40 (7.33–7.45)	7.45 (7.43–7.48)	<0.001	1540
P_{aO_2}, mmHg	74.0 (63.6–91.0)	71.2 (58.0–89.0)	0.084	80.0 (63.5–107)	71.2 (59.0–84.8)	<0.001	1494
P_{aCO_2}, mmHg	35.0 (32.0–39.0)	36.0 (31.0–39.0)	0.587	40.0 (34.5–48.0)	34.8 (32.0–37.9)	<0.001	1472
P_{aO_2}/F_{IO_2} ratio	122 (94.5–169)	132 (90.5–210)	0.738	117 (83.0–167)	108 (84.0–176)	0.675	1212
Respiratory rate, breaths·min^{-1}	25.0 (20.0–30.0)	27.0 (24.0–32.0)	<0.001	25.0 (22.0–32.0)	27.0 (24.0–32.0)	0.019	1717
Haemoglobin, g·dL^{-1}	13.4 (12.5–14.4)	13.5 (12.6–14.5)	0.490	13.2 (12.1–14.4)	13.6 (12.7–14.6)	0.005	1595
White blood count, ×10^9 L^{-1}	7.81 (5.85–10.4)	8.01 (5.32–10.6)	0.689	9.09 (6.41–12.0)	8.24 (6.00–10.5)	0.034	1202
Creatinine, mg·dL^{-1}	0.76 (0.64–0.88)	0.75 (0.63–0.90)	0.621	0.82 (0.67–1.02)	0.84 (0.69–0.99)	0.876	1788
D-dimer, mg·L^{-1}	652 (349–1200)	400 (268–882)	<0.001	834 (431–1750)	544 (286–943)	<0.001	1382
CRP, mg·dL^{-1}	125 (77.8–188)	135 (74.0–206)	0.992	158 (83.5–254)	132 (70.1–235)	0.084	1323
Pharmacological treatment							
Corticosteroids	301 (83.8)	276 (95.2)	<0.001	815 (84.5)	217 (91.6)	0.014	1850
Antibiotics	294 (81.9)	197 (68.2)	<0.001	949 (98.2)	232 (97.5)	0.431	1852
Hydroxychloroquine	141 (39.2)	81 (27.9)	0.005	523 (54.1)	66 (27.7)	<0.001	1854
Remdesivir	52 (14.4)	47 (16.2)	0.911	86 (8.90)	36 (15.1)	0.013	1854
Tocilizumab	132 (36.7)	190 (65.5)	<0.001	438 (45.3)	128 (53.8)	0.024	1854
Convalescent plasma	28 (7.78)	10 (3.45)	0.060	33 (3.42)	7 (2.95)	1.000	1851
Complications							
Bacterial pneumonia	6 (1.67)	7 (2.41)	0.697	366 (38.0)	84 (35.3)	0.590	1851
Pulmonary embolism	39 (11.0)	22 (7.61)	0.382	119 (12.4)	21 (8.90)	0.382	1837
Acute renal failure	32 (8.89)	21 (7.27)	0.545	276 (28.6)	45 (18.9)	0.004	1853
Outcomes							
ICU stay, days	6.00 (4.00–8.00)	7.00 (4.00–10.0)	0.003	21.0 (13.0–36.0)	24.0 (15.0–41.0)	0.003	1854
Hospital stay, days	15.0 (12.0–21.0)	16.0 (12.0–23.0)	0.225	35.0 (24.0–54.0)	38.0 (24.0–55.8)	0.192	1846

Data are presented as n (%) or median (interquartile range), unless otherwise stated. HFNC: high-flow nasal cannula; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; F_{IO_2}: inspiratory oxygen fraction; CRP: C-reactive protein.

There were no clinically relevant differences in sociodemographic and clinical characteristics between the early IMV and late IMV groups in the matched population (n=202 per group) (supplementary table S3). Analysis of the matched population confirmed the results obtained in the unmatched population (supplementary table S4 and supplementary figure S3b). Furthermore, the sensitivity analysis for the comparison of D_{LCO} between the study groups showed results consistent with those presented previously (supplementary table S5 and supplementary figure S4).



Late IMV	(n=135)	(n=136)	(n=102)
	59.1 (54.6–63.6)	66.6 (62.1–71.1)	69.5 (64.9–74.1)
Early IMV	(n=473)	(n=484)	(n=370)
	66.0 (62.1–69.9)	70.7 (66.8–74.7)	74.4 (70.5–78.4)
NIMV	(n=171)	(n=172)	(n=115)
	67.1 (62.9–71.2)	70.3 (66.1–74.5)	75.1 (70.8–79.4)
HFNC	(n=183)	(n=160)	(n=100)
	69.0 (64.8–73.1)	75.5 (71.3–79.7)	76.6 (72.2–81.0)

FIGURE 1 Longitudinal trajectories of diffusing capacity of the lung for carbon monoxide (D_{LCO}) according to the ventilation groups. a) D_{LCO} evolution was fit using linear mixed models including confounding factors (age, sex, body mass index, smoking status, chronic pulmonary disease, antibiotics and corticoids). Estimated marginal mean±SD values of outcomes over time are presented in the graph. *: statistically significant differences ($p<0.05$) in at least one of the main comparatives (noninvasive mechanical ventilation (NIMV) *versus* high-flow nasal cannula (HFNC) or early *versus* late invasive mechanical ventilation (IMV)). The table displays the available sample size and estimated marginal mean (with 95% confidence intervals) at each time-point. b) Changes in D_{LCO} over continuous time. A multivariate generalised additive mixed model (GAMM) was fitted, including confounding factors, time, study groups and time–group interaction as fixed effects, and patient and hospital category as a random effect. The GAMM included a simple factor smooth interaction (time×ventilatory groups) using thin plate regression splines.

Discussion

Different longitudinal pulmonary recovery trajectories based on the type of respiratory support used and the timing of intubation in a large prospective multicentric cohort of COVID-19 ARDS survivors are described here for the first time. The first important message is that patients with delayed intubation exhibited the worst D_{LCO} outcomes of all groups, showing lower values at both short- and long-term follow-up. The second and more novel finding is that patients who received NIMV exhibited slower recovery in terms of D_{LCO} measurements and greater radiological abnormalities than patients who were treated with HFNC. Despite the descriptive nature of the study and the presence of potential confounding factors, this clinical information could prove valuable for future research and for optimising the follow-up care of these patients.

Timing of intubation and recovery of lung function

The need for IMV has a major impact on both mortality and pulmonary sequelae in patients with ARDS [22, 23]. This impact is even stronger if we consider the timing of intubation [13, 24]. Regardless of the time-point considered for delay, it is associated with a high risk of in-hospital, ICU and 90-day mortality [13, 24, 25]. Furthermore, our group has previously described the association of delayed intubation not only with mortality but also with pulmonary sequelae [11]. However, that study only included 205 patients and did not explore the impact on lung recovery sequelae of other noninvasive ventilatory support modalities over the long term. Our present work presents an important overview of how important intubation timing is in the recovery trajectories, as we were able to compare this timing with the trajectories of the other noninvasive support modalities.

One might assume that this is due to greater severity among patients in the delayed intubation group. However, in both our cohort and previous studies, no differences in severity were observed. In all studies,

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TABLE 2 Structural and functional pulmonary sequelae according to type of respiratory support mode

	Noninvasive respiratory support						Invasive respiratory support					
	Descriptive		Differences				Descriptive		Differences			
	NIMV	HFNC	Unadjusted model		Adjusted[#] model		Late IMV	Early IMV	Unadjusted model		Adjusted[#] model	
Pulmonary function	**Mean±SD**	**Mean±SD**	**Mean difference (95% CI)**	**p-value**	**Mean difference (95% CI)**	**p-value**	**Mean±SD**	**Mean±SD**	**Mean difference (95% CI)**	**p-value**	**Mean difference (95% CI)**	**p-value**
D_{LCO} % pred	(n=290)	(n=360)					(n=966)	(n=238)				
3 months	72.2±17.3	73.2±19.3	1.2 (−2.3–4.7)	0.491	1.9 (−1.5–5.4)	0.275	63.9±19.3	70.1±18.2	6.6 (3.5–9.6)	<0.001	6.9 (3.9–10)	<0.001
6 months	73.6±18.4	78.3±17.7	4.8 (1.3–8.4)	0.007	5.2 (1.7–8.7)	0.003	68.7±17.0	73.0±18.9	4.6 (1.5–7.6)	0.003	4.2 (1.1–7.2)	0.007
12 months	78.4±16.6	77.0±18.2	0.7 (−3.3–4.7)	0.722	1.5 (−2.4–5.5)	0.446	70.8±16.4	75.8±18.4	5 (1.7–8.2)	0.002	4.9 (1.7–8.2)	0.003
FVC % pred	(n=289)	(n=358)					(n=955)	(n=238)				
3 months	84.8±15.3	87.3±17.1	1.8 (−1.3–4.8)	0.251	2.2 (−0.9–5.4)	0.162	80.9±17.2	84.5±16.7	2.8 (0–5.5)	0.046	2.3 (−0.5–5.1)	0.107
6 months	85.8±16.3	91.2±14.8	2.5 (−0.6–5.6)	0.107	2.5 (−0.7–5.7)	0.129	86.2±17.5	87.5±17.7	1.2 (−1.5–3.9)	0.368	0.6 (−2.1–3.4)	0.659
12 months	92.3±14.2	89.7±17.8	−1.3 (−4.7–2.1)	0.458	−1.8 (−5.3–1.8)	0.324	87.8±18.3	90.0±17.2	1.7 (−1.1–4.5)	0.243	1 (−1.9–4)	0.488
FEV_1 % pred	(n=288)	(n=356)					(n=957)	(n=237)				
3 months	89.4±17.1	89.2±17.3	−0.1 (−3.3–3)	0.927	0.2 (−3.1–3.5)	0.917	85.4±17.8	88.9±17.5	2.4 (−0.4–5.3)	0.094	1.9 (−1–4.8)	0.207
6 months	90.1±17.7	93.9±15.4	1.3 (−1.9–4.6)	0.419	1.3 (−2–4.7)	0.440	91.2±17.8	91.7±18.2	1 (−1.8–3.8)	0.496	0.3 (−2.5–3.2)	0.813
12 months	95.5±16.1	92.3±18.4	−3.2 (−6.8–0.4)	0.086	−3.7 (−7.4–0)	0.052	92.2±20.0	93.2±17.9	1.2 (−1.8–4.1)	0.435	0.5 (−2.5–3.6)	0.742
Radiological findings	**n (%)**	**n (%)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**n (%)**	**n (%)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Persistent pulmonary infiltrates	(n=167)	(n=323)					(n=178)	(n=882)				
3 months	54 (37.8)	67 (26.4)	1.8 (1.16–2.78)	0.008	1.56 (0.98–2.5)	0.062	43 (30.5)	263 (38.8)	0.73 (0.5–1.07)	0.108	0.73 (0.49–1.1)	0.132
6 months	28 (30.4)	29 (17.8)	2.13 (1.17–3.86)	0.012	2.6 (1.38,4.88)	0.003	28 (25.2)	179 (35.5)	0.62 (0.39–0.98)	0.042	0.53 (0.32–0.9)	0.017
12 months	15 (24.2)	13 (12.7)	2.39 (1.04–5.53)	0.040	3.33 (1.33–8.3)	0.009	24 (31.6)	127 (33.2)	0.93 (0.55–1.58)	0.788	0.82 (0.46–1.45)	0.495
Fibrotic lesions	(n=167)	(n=233)					(n=178)	(n=882)				
3 months	34 (23.8)	21 (8.27)	3.33 (1.84–6.02)	<0.001	3.26 (1.74–6.13)	<0.001	39 (27.7)	125 (18.5)	1.58 (1.04–2.41)	0.031	1.83 (1.18–2.83)	0.007
6 months	25 (27.2)	25 (15.3)	2.04 (1.08–3.86)	0.027	2.15 (1.1–4.2)	0.025	32 (28.8)	148 (29.4)	1.02 (0.65–1.61)	0.923	1.03 (0.63–1.69)	0.894
12 months	18 (29.0)	18 (17.6)	1.91 (0.9–4.03)	0.091	2.51 (1.12–5.66)	0.026	14 (18.4)	100 (26.1)	0.7 (0.38–1.28)	0.243	0.77 (0.41–1.46)	0.422

NIMV: noninvasive mechanical ventilation; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: adjusted for age, sex, body mass index, smoking status, chronic pulmonary disease, antibiotics and corticoids. The threshold p-value corrected for multiple comparisons was set to 0.016.

including ours, appropriate analyses were conducted with adjustments for severity-related variables. The most plausible pathophysiological explanation for this finding is that exposure to vigorous spontaneous respiratory effort during the noninvasive respiratory support previous to the intubation can exacerbate the underlying lung damage, inducing what has come to be called "patient self-inflicted lung injury" (p-SILI) [26–28].

Noninvasive respiratory support and recovery of lung function

Another novel finding is the deleterious impact of NIMV on D_{LCO} and its slower recovery compared with the other noninvasive respiratory modality (HFNC). NIMV was widely associated with higher rates of failure and mortality compared to HFNC in the management of acute respiratory failure [17, 18, 29–31]. Unfortunately, the use of helmet NIMV is not widely adopted in Spain, limiting our ability to observe its potential beneficial effects in the management of these patients [32, 33]. The same pathophysiological pathway that explains the worse acute outcomes in this group (and in the late IMV group) may explain the long-term consequences [26, 34] and is based on spontaneous ventilation and uncontrolled lung volume. Patients treated with NIMV are also exposed to an uncontrolled lung volume due to the high inspiratory efforts and positive inspiratory pressure associated with high transpulmonary pressures, leading to excess stress and increased pulmonary inflammation, contributing to the worsening of pre-existing p-SILI [35, 36]. This is a possible theory, as unfortunately we do not have direct measurements of respiratory effort. No differences in severity were observed in this group either, and the analyses were appropriately adjusted for confounding factors related to severity. Patients treated with HFNC are not under any high positive inspiratory pressure, which would mimic a "more protective mode of ventilation". For this reason, we hypothesise that patients who received NIMV in our study exhibited more severe lung damage and, consequently, more radiological abnormalities (persistent pulmonary infiltrates and fibrotic lesions), leading to a slower D_{LCO} recovery. Although we do not have data on symptoms and quality of life, a reduced D_{LCO}, whether related to COVID-19 or not, is associated with poorer clinical outcomes [37–39].

It is important to emphasise that at the onset of the pandemic there was considerable controversy regarding the optimal initial ventilation strategy, leading to significant variability in the choice of ventilatory support. With similar baseline patient characteristics, some centres opted for reservoir masks and early intubation, while others extended the use of HFNC or NIMV, resulting in delayed intubation. Furthermore, these decisions were highly dependent on the resources available at each hospital; some were equipped with NIMV, while others primarily used HFNC. This variability in ventilatory support was often independent of patient severity. Rather than being a limitation, this variability has provided us with a unique opportunity to analyse the consequences of different therapeutic decisions that might not have been possible otherwise.

Clinical implications

Gaining insight into the different lung recovery trajectories based on the respiratory support of COVID-19 ARDS survivors could have significant clinical implications.

First, even though most patients show a complete recovery, it is important to understand that a follow-up visit is necessary for all patients who receive any respiratory support. However, the follow-up protocol may vary slightly depending on the respiratory support received, as well as the assessment of other factors such as the severity of the acute phase and the presence of comorbidities. Given the significant impact of intubation on D_{LCO}, an early respiratory assessment is imperative for all intubated patients, especially if the intubation was delayed. For those in noninvasive treatment groups, the most notable difference in percentage predicted D_{LCO} occurs at 6 months (nearly 5% worse in NIMV group), with this disparity resolving by 12 months. Therefore, the initial respiratory evaluation for noninvasively treated patients, particularly those with HFNC, might be most beneficial at 6 months post-discharge. If these patients exhibit no respiratory involvement at this medium-term follow-up visit, and a comprehensive evaluation is performed, it may be unnecessary to continue respiratory follow-up appointments. Due to the substantial implications of this information and because it could be relevant not only in COVID-19, there is an urgent need to validate these results in non-COVID-19 ARDS.

Strengths and limitations

This study has some important strengths: 1) the availability of a large volume of information (well recorded, revised and validated) throughout the acute COVID-19 phase, 2) the large number of patients (1854) with follow-up and D_{LCO} information, and 3) the representativeness of our study population (multicentric study).

On the other hand, we must highlight some limitations. 1) An observational design was used. Despite our efforts to adjust and compare the estimates with various analytical perspectives, the observational nature of

the study may still be affected by uncontrolled biases in the included analyses. For example, we cannot rule out that the late IMV patients may have experienced a critical event, previous to IMV, not recorded in this study, which could have resulted in more severe illness. 2) We employed a pragmatic approach to follow-up with a standardised protocol as a secondary objective, adapting to the different pandemic scenarios in each participating hospital and producing uneven follow-up. However, in addition to the large number of patients, adequate statistical analyses were performed to control for this bias. 3) The large number of nonincluded patients was due to a lack of D_{LCO} measurements during the follow-up, although this was mitigated by the large study cohort and confirmed by the absence of clinically significant differences between included and nonincluded patients. 4) The study may suffer from statistical underpowering due to the absence of a specific sample size calculation for this substudy within the CIBERESUCICOVID project. 5) The chest images were not reviewed centrally; rather, each thoracic radiologist at their respective hospital interpreted the images for their patients. This approach introduces inherent variability in the readings. Additionally, performing a chest CT was not mandatory for follow-up. The decision to perform chest CT or radiography was primarily left to the clinician's discretion and was dependent on the hospital's available resources.

Conclusions

In conclusion, the different trajectories of lung recovery between different respiratory support modalities in COVID-19 ARDS survivors are described here for the first time. Patients who experienced a delay in intubation had the worst short- and long-term outcomes; however, patients with NIMV exhibited a slower lung recovery in terms of D_{LCO} measurements and more radiological abnormalities compared with patients with HFNC. This information should be used to improve the follow-up of COVID-19 ARDS survivors.

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