ICU-Acquired Pneumonia is a Risk Factor of a Poor Health Post-Covid-19 Syndrome

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Research

Keywords: COVID-19, CT abnormalities, ICU, lung function, SARS-CoV-2, sequelae, Post-COVID.

Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-885672/v1>

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Abstract

Background. Some patients who had previously presented with COVID-19 have been reported to develop persistent COVID-19 symptoms. Whilst this information has been adequately recognised and extensively published with respect to non-critically ill patients, less is known about the prevalence and risk factors and characteristics of persistent COVID_19 . On other hand these patients have very often intensive care unit-acquired pneumonia (ICUAP). A second infectious hit after COVID increases the length of ICU stay and mechanical ventilation and could have an influence in the poor health post-Covid 19 syndrome in ICU discharged patients

Methods: This prospective, multicentre and observational study was done across 40 selected ICUs in Spain. Consecutive patients with COVID-19 requiring ICU admission were recruited and evaluated three months after hospital discharge.

Results: A total of 1,255 ICU patients were scheduled to be followed up at 3 months; however, the final cohort comprised 991 (78.9%) patients. A total of 315 patients developed ICUAP (97% of them had ventilated ICUAP) Patients requiring invasive mechanical ventilation had persistent, post-COVID-19 symptoms than those who did not require mechanical ventilation. Female sex, duration of ICU stay, and development of ICUAP were independent risk factors for persistent poor health post-COVID-19.

Conclusions: Persistent, post-COVID-19 symptoms occurred in more than two-thirds of patients. Female sex, duration of ICU stay and the onset of ICUAP comprised all independent risk factors for persistent poor health post-COVID-19. Prevention of ICUAP could have beneficial effects in poor health post-Covid 19

Introduction

Clinical presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranges from mild to severe[1]. Disease severity, including refractory acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS), may require admission to an intensive care unit (ICU)[2]. Patients often need invasive mechanical ventilation and can develop multiorgan failure[3]. Duration of ICU stay is long amongst survivors, and mortality can be high in patients with ARDS, reaching between 40–50%[4]. On the other hand ICU admitted patients, especially those requiring mechanical ventilation, have a high prevalence of other infections complications such as ICU acquired pneumonia (ICUAP) [5]that could have a role in the persistence of symptoms after discharge Additionally, although often sufficiently recovered for hospital discharge, patients with either mild or severe disease are at risk of developing a condition known as persistent poor health post-COVID-19, post-COVID syndrome or long COVID[6][7][8].

Currently, no consensus definition for the symptoms of poor health post-COVID-19 exist; however, the most common symptoms include fatigue, shortness of breath, weakness and asthenia[9]. Some publications have reported a high prevalence of persistent poor health post-COVID-19. Specifically, fatigue and dyspnoea were the most frequent symptoms, and their prevalence and intensity were not

correlated with initial disease severity [10]. With respect to information regarding persistent poor health post-COVID-19 in patients that have survived a stay in the ICU, little remains known[11][12][13]. Very importantly risk factors that are present in the acute period of the disease are not well known. As pointed out in a recent position manuscript the recognition of risk factors during the acute period is a research priority to understand the long-term sequelae of COVID-19[14].

In the present manuscript, we analysed the poor health post-COVID-19 in the initial cases of hospitalised patients with COVID-19 at 3-month follow-up since hospital discharge. We hypothesised that critically ill patients presented with a high, persistent post-COVID-19 symptoms and significant abnormalities in both lung function tests and radiology. Herein, we summarised poor health post-COVID-19, functional respiratory parameters and radiologic features of patients discharged from the ICU at the 3-month follow-up. The main objective of this study was to determine the risk factors of the acute period associated with poor health post-COVID-19 in ICU survivors at the 3-month follow-up since hospital discharge and identify risk factors associated with poor recovery. We also aimed to analyse lung function and radiologic abnormalities in critically ill patients after hospital discharge.

Material And Methods

Study design and population

We carried out a prospective, multicentre and observational study at 40 selected ICUs in Spain with critically ill patients initially admitted after 16 February 2020. We consecutively recruited patients with COVID-19 requiring ICU admission and performed a follow-up at three months since hospital discharge. This study is a pre-planned analysis of the ongoing multicentre study called CIBERESUCICOVID (ClinicalTrials.gov Identifier: NCT04457505). We then asked staff from each centre to prospectively obtain data for ICU-admitted patients aged 18 years or older with positive polymerase chain reactions (PCR) for SARS-CoV-2. Re-admitted patients and previously tracheostomised patients were not included. The study received approval by the institution's Internal Review Board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370). We obtained informed consent for most patients by using emergency consent mechanisms in accordance with ethics approval guidelines for the study. Further participating centres either received ethics approval from their institutions or had waived ethics approval. Finally, we de-identified all clinical data to allow for the waiver of informed consent.

Data collection

Recorded data included demographic characteristics, comorbidities, time course of illness, treatments administered, laboratory and microbiologic data, radiologic findings on chest x-rays, CT scans, ventilatory parameters in patients with invasive mechanical ventilation, complications during ICU stay, and outcomes. We determined disease severity and assessed organ failure using the Sequential Organ Failure Assessment (SOFA) score, calculating both within the first day of ICU admission[15]. Ventilatory management strategies were not standardised amongst centres and were left to the discretion of the attending clinician, based on National Ministry of Health recommendations, and supported by

international guidelines. We defined ICU-acquired pneumonia (ICUAP) as pneumonia developing in patients in the ICU for ≥ 48 hours. Basis of ICUAP diagnosis comprised new or progressive radiologic pulmonary infiltrates together with at least two of the subsequent characteristics: temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; leucocytosis $> 12,000/\text{mm}^3$ or leucopenia $< 4,000/\text{mm}^3$; or purulent respiratory secretion [5, 16]. We confirmed an ARDS diagnosis using the Berlin definition[17].

Procedures

Poor health post-COVID-19 was defined by the presence of any of the following symptoms: dyspnoea, weakness, asthenia, myalgia, cough, numbness, headache, anosmia and ageusia. We provided electronic case report forms using a secure website. For all patients, we recorded demographic characteristics, duration of ICU and hospital stays, the McCabe classification of comorbidities and likelihood of survival (likely to survive 5 years, 1–5 years [ultimately fatal], or < 1 year [rapidly fatal]), the SOFA score to predict hospital mortality, and outcome (ICU mortality). We calculated static compliance of the respiratory system as tidal volume/(end-inspiratory plateau pressure–total PEEP). Chest CT scans and CT pulmonary angiograms were obtained when clinically indicated and technically feasible. The Modified Medical Research Council (mMRC) dyspnoea scale grades the impact of dyspnoea on daily activities throughout the prior seven days and thereby quantifies the disability or physical limitations associated with dyspnoea [18]. Finally, to aid analysis, we clustered patients into groups according to clinical resolution.

Outcomes

The primary outcome of our study was to determine the risk factors and prevalence of poor health post-COVID-19 in critically ill patients per clinical presentation at three months of hospital discharge. The secondary outcome included determining associations between poor health post-COVID-19 symptoms and abnormalities in lung function tests, radiologic characteristics, and laboratory parameters.

Statistical analysis

The study sample size was not formally calculated but instead based on the nature of the study and pre-planned dates. We used SPSS (version 20) for data analysis. All p values were two-tailed. We considered differences as significant if p was less than 0.05. We reported categorical variables as numbers and frequencies (%), normally distributed continuous variables as means (standard deviation [SD]), and skewed continuous variables as medians ((interquartile range [IQR]). We performed both χ^2 tests or Fisher's exact test to compare qualitative variables and Student's t tests and ANOVAs or Mann-Whitney U and non-parametric Kruskal-Wallis tests to compare normally distributed or skewed continuous variables, whenever appropriate. We undertook univariate analyses of predictors of post-covid syndrome, using the χ^2 test and Student's t test. We entered all variables from the univariate analysis with p values below 0.1 or which were clinically relevant into regression analyses as potential predictor variables. We made two adjustments to determine which risk factors were associated with poor health post-COVID-19 and possible confounders: 1) we calculated adjusted estimates of the effect size and corresponding 95%

confidence intervals (CIs) using a multivariable logistic regression model (backward stepwise selection model) and 2) to account for centre effects, we performed a mixed-effects multivariable model for sensitivity analysis, as defined by a binomial probability distribution and a logit link function, and centres as a random effect.

Results

Definition of the population

We monitored patients after hospital discharge for a median of 77 [57–99] days. A total of 1,255 patients were scheduled to be followed up for three months. However, we could not perform a 3-month follow-up of 264 patients. The final cohort comprised 991 (78.9%) patients. A total of 731 (73.8%) patients developed persistent post-COVID-19 symptoms. A flow chart with the percentage of patients with persistent post-COVID-19 symptoms are displayed in Fig. 1. Patient characteristics are shown in Table 1.

Table 1

Patient characteristics of the population enrolled in the study based on persistent post-COVID-19 symptoms at 3-month follow-up.

Demographic item	n
Age*, mean (SD), years	58.2 (SD12.3)
Sex (Female), n (%)	405(32.3)
SOFA*, mean (SD)	4.6(SD 2.8)
CHF, n (%)	118(9.5)
Hypertension), n (%)	552(44.2)
COPD), n (%)	100(8.0)
Asthma), n (%)	79(6.3)
CKD), n (%)	69(5.5)
Cirrhosis), n (%)	15(1.2)
Mild liver failure), n (%)	27(2.2)
Neurologic), n (%)	66(1.8)
Dementia), n (%)	6(0.2)
Autoimmune), n (%)	71(5.7)
Gastrointestinal), n (%)	100(8.1)
Endocrine), n (%)	90(7.2)
Obesity (BMI > 30 kg/m ²), n (%)	483(38.7)
Diabetes Mellitus), n (%)	247(19.8)
Haematologic disease), n (%)	73(5.8)
Solid cancer), n (%)	37(3.0)
Transplant), n (%)	12(0.3)
HIV), n (%)	8(0.6)
Smoking), n (%)	49(3.9)

Abbreviations: SOFA: Sequential Organ Failure Assessment. CHF: congestive heart failure. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. BMI: Body mass index. HIV: Human immunodeficiency virus. NIVM: Non-invasive mechanical ventilation. iMV: Invasive mechanical ventilation. ICU: Intensive care unit. ECMO: Extracorporeal membrane oxygenation. CRRT: Continuous renal replacement therapy. NMB: Neuromuscular blockade. CPR: Cardiopulmonary resuscitation. ICUAP: Intensive care unit-acquired pneumonia. ARDS: Acute respiratory distress syndrome. *Mean and SD

Demographic item	n
Alcohol), n (%)	32(2.6)
Oxygen requirement), n (%)	1228(99.5)
NIV), n (%)	440(35.9)
iMV), n (%)	858(69.0)
Prone), n (%)	717(57.6)
Tracheostomy), n (%)	378(30.6)
ICU length of stay),,, mean (SD), days	20.1 (18.2)
ECMO), n (%)	24(1.9)
CRRT), n (%)	62(5.0)
Shock), n (%)	756(20.1)
NMB), n (%)	706(57.3)
Corticosteroids), n (%)	943(25.1)
CPR), n (%)	10(0.8)
ICUAP), n (%)	315(25.5)
ARDS), n (%)	955(77.3)
NTX), n (%)	58(4.7)
COP), n (%)	52(4.2)
PE), n (%)	108(8.7)
Delirium), n (%)	301(24.4)
Abbreviations: SOFA: Sequential Organ Failure Assessment. CHF: congestive heart failure. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. BMI: Body mass index. HIV: Human immunodeficiency virus. NIVM: Non-invasive mechanical ventilation. iMV: Invasive mechanical ventilation. ICU: Intensive care unit. ECMO: Extracorporeal membrane oxygenation. CRRT: Continuous renal replacement therapy. NMB: Neuromuscular blockade. CPR: Cardiopulmonary resuscitation. ICUAP: Intensive care unit-acquired pneumonia. ARDS: Acute respiratory distress syndrome. *Mean and SD	

General assessment and hospital burden

We performed the mMRC dyspnoea scale in 402 patients, of whom 59% were grade 1; 28.4%, grade 2; 10%, grade 3; and 2.2%, grade 4. Physical examination of patients revealed crackles in 8.2% (n = 82) and showed a trend of its presence in patients with persistent post-COVID-19 symptoms (9.9% vs 5.8%, p = 0.05). After discharge, 33 (3.2%) patients presented with infectious complications; 172 (15.1%) attended the emergency department; and 63 (5%) were readmitted to hospital. No significant differences were

observed in patients with or without persistent post-COVID-19 symptoms with respect to follow-up clinic visits (63.5% vs 59.6%, p 0.3). Patients with persistent post-COVID-19 symptoms required additional respiratory therapy after hospital discharge (Supplementary Table 1).

Clinical features and associations with functional (lung function tests), imaging and laboratory results at 3-month follow-up

We performed a radiologic work-up in 471 (47.5%) patients. A similar number of patients with or without persistent post-COVID-19 symptoms underwent either chest radiography (51.4% vs 48.1%, p 0.3) or chest CT scans (40.5% vs 45.9%, p = 0.1). Persistently abnormal chest x-rays were observed in 21.4% of patients. Patients with persistent post-COVID-19 symptoms more frequently had abnormal x-rays and chest CT scans showing diffuse interstitial lung patterns than those without such symptoms. Patients who required invasive mechanical ventilation more often presented interstitial lung disease patterns in chest CT scans. Further details are shown in Table 2.

Table 2

Chest imaging and lung function tests in patients with persistent post-COVID-19 symptoms and in those who underwent invasive mechanical ventilation at 3-month follow-up.

	Post-COVID			Invasive mechanical ventilation		
	Yes	No	p	Yes	No	P value
Chest x-ray, n (%)						
Abnormal	597(81.7)	182(70)	< 0.01	715(83.3)	294(76.2)	0.004
ILD	2(0.8)	5(0.7)	0.5	5(0.6)	2(0.5)	0.9
Persistent infiltrates	34(13.1)	130(17.8)	0.08	129(15)	46(11.9)	0.1
Fibrotic tract	12(4.6)	54(7.4)	0.1	50(5.8)	19(4.9)	0.5
Emphysema	0	3(0.4)	0.5	3(0.3)	0	0.5
CT scan, n (%)						
Abnormal	685(93.7)	238(91.5)	0.2	810(94.4)	364(94.3)	0.9
ILD	0	18(2.5)	0.006	6(1.6)	12(1.4)	0.8
Persistent infiltrates	43(16.5)	118(16.1)	0.9	131(15.3)	42(10.9)	0.04
Fibrotic	27(10.4)	88(12)	0.5	88(10.3)	35(9.1)	0.5
Emphysema	4(1.5)	23(3.1)	0.2	20(2.3)	7(1.8)	0.5
PE, n (%)	2(0.8)	11(1.5)	0.2	12(1.4)	1(0.3)	0.07
LFTs, n (%)						
FEV1	94.2(18.2)	87.5(18.1)	< 0.01	89.3(19.1)	88.1(17.1)	0.4
FEV1/FVC	91.4(16.3)	97.2(14.6)	< 0.01	96.1(14.9)	96.8(15.8)	0.5
DLCO (mL/min/mm Hg)	78.3(17.4)	67.1(17.7)	< 0.01	67.0(18.1)	74.1(17.4)	< 0.01
DLCO 80	205(78.8)	459(62.8)	< 0.01	626(73)	280(72.5)	0.4
Data are mean (SD) or number of patients (%). Abbreviations: SD: Standard deviation. CT: Computed tomography. ILD: Diffuse interstitial lung disease. PE: Pulmonary embolism. LFT: Lung function test. FEV1: Forced expiratory volume in the first second. FVC: Forced vital capacity. DLCO: Diffusing capacity for carbon monoxide.						

We performed lung function tests (LFT) in 535 (53.9%) patients and diffusing capacity of the lungs for carbon monoxide (DLCO) in 464 (46.8%). LFTs (57.1% vs 49%, $p = 0.03$) were performed more often in patients with persistent post-COVID-19 symptoms, whilst there were no significant differences in performing DLCO between patients with or without persistent post-COVID-19 symptoms (50.7% vs 55.3%, $p = 0.2$). A total of 665 (67.4%) patients underwent invasive mechanical ventilation. Patients with invasive mechanical ventilation had a higher percentage of persistent post-COVID-19 symptoms than those

without mechanical ventilation (70.2% vs 59.6%, $p = 0.003$). Table 3 shows invasive mechanical ventilator and oxygenation parameters obtained sequentially at days 1 and 3 after the initiation of invasive mechanical ventilation. Only pulmonary compliance calculated at the time of initiation of mechanical ventilation and the value of $\text{PaO}_2/\text{FiO}_2$ at day 3 were significantly worse in patients with persistent post-COVID-19 symptoms.

Table 3

Respiratory parameters in patients with invasive mechanical ventilation based on persistent post-COVID-19 symptoms at 3-month follow-up

		Post-COVID		
Variable	Time-point	No	Yes	P-value
PaO ₂ /FiO ₂ , mean (SD)	Intubation	130.5 (73.4)	131.6 (74.9)	0.8
	Day 3	192.0 (85.7)	180.0 (75.0)	0.1
	Change from intubation	66.3 (100.8)	49.0 (111.7)	0.1
PaCO ₂ , mean (SD), mmHg	Intubation	39.4 (9.5)	40.4 (10.6)	0.2
	Day 3	43.0 (9.4)	44.8 (9.8)	0.03
	Change from intubation	3.4 (11.5)	3.4 (12.2)	1.0
VT admission, mean (SD), mL	Intubation	7.1 (1.2)	6.9 (3.0)	0.5
	Day 3	7.2 (1.2)	7.1 (3.1)	0.7
	Change from intubation	0.2 (1.0)	0.3 (1.6)	0.6
PEEP, mean (SD), cmH ₂ O	Intubation	12.5 (2.5)	12.4 (2.5)	0.7
	Day 3	12.0 (2.7)	12.1 (2.7)	0.5
	Change from intubation	-0.6 (2.8)	-0.4 (2.9)	0.6
ΔP , mean (SD)	Intubation	10.8 (4.6)	11.8 (4.7)	0.1
	Day 3	10.7 (4.2)	11.8 (4.8)	0.2
	Change from intubation	-0.6 (3.0)	-0.1 (5.1)	0.7
Compliance, mean (SD)	Intubation	66.3 (86.4)	47.9 (35.9)	0.02
	Day 3	42.6 (79.0)	46.0 (29.0)	0.6
	Change from intubation	-26.1 (127.4)	0.2 (43.0)	0.1
VR, mean (SD)	Intubation	1.7 (0.5)	1.7 (0.5)	0.7
	Day 3	1.8 (0.5)	1.8 (0.5)	0.8
	Change from intubation	0.2 (0.5)	0.2 (0.6)	0.7
Data are mean (SD). Abbreviations: VT: Tidal volume. ΔP : Driving pressure PEEP: Positive end-expiratory pressure. VR: Ventilatory ratio. The delta measurements were computed as the difference in amplitude between day 3 of initiation of invasive mechanical ventilation and day 1 of initiation of invasive mechanical ventilation.				

Laboratory data at day 1 of ICU admission are detailed in Table 4. No significant differences were observed in most parameters; however, fibrinogen was significantly higher in patients with persistent

post-COVID-19 symptoms.

Table 4

Laboratory parameters in patients with invasive mechanical ventilation based on persistent post-COVID-19 symptoms at 3-month follow-up.

	Post-COVID		P value
	No	Yes	
	Value (SD)	Mean	
Haemoglobin, mean (SD), g/dL	14.7(11.3)	13.9(1.5)	0.3
WCC, mean (SD), x 10 ⁹ /L	7.3(2.2)	6.81(2.3)	0.06
Lymphocytes, mean (SD), x 10 ⁹ /L	2.2(0.9)	2.3(1.4)	0.6
Neutrophils, mean (SD), x 10 ⁹ /L	4.4(3.6)	3.7(1.9)	0.09
Monocytes, mean (SD), x 10 ⁹ /L	0.6(0.5)	0.5(0.2)	0.2
Haematocrit, mean (SD), x 10 ⁹ /L	41.4(5.2)	42.1(4.6)	0.1
Platelets, mean (SD), x 10 ⁹ /L	259.3(73.5)	247.4(88.7)	0.2
Prothrombin time, mean (SD), sec	11.9(6.8)	11.8(4.1)	0.9
INR, mean (SD), IU	1.3(0.6)	1.1(0.3)	0.5
D-dimer, mean (SD), ng/mL	410.2(445.1)	433.2(393.4)	0.6
Fibrinogen, mean (SD), ng/mL	271.2(249.7)	358.8(192.5)	< 0.01
CRP, mean (SD), mg/L	6.3(0.4)	6.9(0.6)	0.7
AST, mean (SD), IU/L	22.3(13.4)	23.1(20.2)	0.6
ALT, mean (SD), IU/L	24.8(22.4)	24.1(14.3)	0.6
GGT, mean (SD), IU/L	49.4(5.6)	35.4(5.7)	0.2
Urea, mean (SD), mg/dL	5.9(1.8)	5.8(1.2)	0.9
Creatinine (mg/dL	0.9(0.8)	0.8(0.4)	0.4
CK, mean (SD), IU/L	78.2(6.7)	88.8(9.9)	0.4
LDH, mean (SD), IU/L	250.4(104.2)	235.7(90.1)	0.1
Data are mean (SD). Abbreviations: L: Litres. Mg: milligrams. WCC: White blood cells. INR: international normalised ratio. Sec: seconds. IU: International Units. CRP: C-reactive protein. AST: Aspartate Transaminase. ALT: Alanine Aminotransferase. GGT: Gamma Glutamyl Transferase. CK: Creatine kinase. LDH: Lactate dehydrogenase (LDH)			

Risk factors for persistent post-COVID-19 symptoms

Table 5 shows risk factors associated with persistent post-COVID-19 symptoms. Many variables showed a significant association in the univariate analysis. A multivariable analysis found that three factors were associated with persistent post-COVID-19 symptoms: female sex, duration of ICU stay, and the onset of ICUAP. In terms of percent change, the odds of persistent post-COVID-19 symptoms in females are 94% higher than those in males; for a 1-unit increase in the duration of ICU stay, there is an expected 3% increase in the odds of no clinical resolution; and the odds of persistent post-COVID-19 symptoms for the onset of ICUAP are 73% higher than the odds for no onset of ICUAP. Among 315 patients who had ICUAP only 34 (11%) had not a pathogen detected and the majority of them were not ventilated. Length of mechanical ventilation was 26 days (15–37 days). The length of ICU stay was 33 days (22.46). Among the 282 patients with confirmed pathogen the mean period of days from ICU admission was 12 days (7–21 days). Among the 258 patients with confirmed pathogen ,220 were ventilated. 44 (20%) had early VAP and 176 (80%) had late VAP. Gram negatives represented most pathogens isolated were Gram negatives, but *S. aureus* was present in 46 (16%) cases. 40 patients had polymicrobial pneumonia. A sensitivity analysis introducing the centre variable as a random effect in the mixed-effects multivariable model yielded similar results.

Table 5

Univariate and multivariate analyses of risk factors associated with persistent post-COVID-19 symptoms at 3-month follow-up

	Univariate			Multivariable(n = 991)	
	Post-COVID			OR (95% CI)	p
	Yes	No	p		
Age, mean (SD), years	57.85(12.9)	58.74(11.5)	0.3		
Female sex, n (%)	66(25.4)	260(35.6)	< 0.01	1.94(1.28–2.94)	0.002
SOFA, mean (SD)	4.6(2.8)	(5.2(3.1)	0.01		
CHF, n (%)	28(10.8)	64(8.8)	0.3		
Hypertension, n (%)	115(44.2)	326(44.7)	0.9		
COPD, n (%)	18(6.9)	63(8.6)	0.4		
Asthma, n (%)	21(8.1)	44(6)	0.2		
CKD, n (%)	10(3.8)	43(5.9)	0.2		
Cirrhosis, n (%)	0	13(1.8)	0.02		
Mild liver failure, n (%)	5(1.9)	14(1.9)	0.9		
Neurological, n (%)	9(3.5)	39(5.3)	0.3		
Dementia, n (%)	1(0.4)	2(0.3)	0.7		
Autoimmune, n (%)	11(4.2)	45(6.2)	0.2		
Gastrointestinal, n (%)	15(5.8)	65(8.9)	0.1		
Endocrine, n (%)	17(6.5)	58(7.9)	0.4		

Data are mean (SD) or number of patients (%) for the univariate analysis and estimated ORs (95% CIs) of the explanatory variables in the persistent post-COVID-19 symptoms group for the multivariable analysis. The OR represents the odds that the presence of persistent post-COVID-19 symptoms will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure; for continuous predictors, the OR represents the increase in odds of the outcome of interest with every one unit increase in the input variable. The p-value for the multivariable analysis is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). Abbreviations: OR: Odds ratio. CI: Confidence interval. SD: Standard deviation. SOFA: Sequential Organ Failure Assessment. CHF: congestive heart failure. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. BMI: Body Mass Index. HIV: human immunodeficiency virus. NIVM: Non Invasive Mechanical Ventilation. IMV: Invasive Mechanical Ventilation. ICU: Intensive Care Unit. ECMO: Extracorporeal membrane oxygenation. CRRT: Continuous renal replacement therapy. NMB: Neuromuscular blockade. CPR: Cardiopulmonary resuscitation. ICUAP: Intensive Care Unit acquired pneumonia. ARDS: Acute respiratory distress syndrome.

	Univariate		Multivariable(n = 991)		
Obesity (BMI > 30 kg/m ²), n (%)	98(37.7)	293(40.1)	0.5		
Diabetes Mellitus, n (%)	46(17.7)	140(19.2)	0.6		
Haematological disease, n (%)	13(5)	39(5.3)	0.8		
Solid cancer, n (%)	8(3.1)	21(2.9)	0.8		
Transplant, n (%)	2(0.8)	9(1.2)	0.7		
HIV, n (%)	0	4(0.5)	0.5		
Oxygen requirement, n (%)	248(99.2)	723(99.7)	0.2		
NIV, n (%)	68(26.5)	280(38.9)	0		
IMV, n (%)	155(59.6)	510(70.2)	< 0.01		
Prone, n (%)	136(52.3)	431(59.4)	0.04		
Tracheostomy, n (%)	52(20)	260(35.8)	< 0.01		
ICU length of stay, mean (SD), days	14.3(12.2)	22.2(18.2)	< 0.01	1.03(1.01–1.05)	0.002
ECMO, n (%)	52(2(0.8)	16(2.2)	0.1		
CRRT, n (%)	7(2.7)	47(6.5)	0.02		
Shock, n (%)	132(51.6)	46(64.3)	0		
NMB, n (%)	124(48.2)	430(59.6)	< 0.01		
Corticosteroids, n (%)	207(80.5)	543(75.3)	0.1		
CPR, n (%)	2(0.8)	5(0.7)	0.9		

Data are mean (SD) or number of patients (%) for the univariate analysis and estimated ORs (95% CIs) of the explanatory variables in the persistent post-COVID-19 symptoms group for the multivariable analysis. The OR represents the odds that the presence of persistent post-COVID-19 symptoms will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure; for continuous predictors, the OR represents the increase in odds of the outcome of interest with every one unit increase in the input variable. The p-value for the multivariable analysis is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). Abbreviations: OR: Odds ratio. CI: Confidence interval. SD: Standard deviation. SOFA: Sequential Organ Failure Assessment. CHF: congestive heart failure. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. BMI: Body Mass Index. HIV: human immunodeficiency virus. NIVM: Non Invasive Mechanical Ventilation. IMV: Invasive Mechanical Ventilation. ICU: Intensive Care Unit. ECMO: Extracorporeal membrane oxygenation. CRRT: Continuous renal replacement therapy. NMB: Neuromuscular blockade. CPR: Cardiopulmonary resuscitation. ICUAP: Intensive Care Unit acquired pneumonia. ARDS: Acute respiratory distress syndrome.

	Univariate			Multivariable(n = 991)	
ICUAP, n (%)	41(15.9)	219(30.2)	< 0.01	1.73(1.03–2.92)	0.03
ARDS, n (%)	175(68.4)	564(77.6)	< 0.01		
NTX, n (%)	9(3.5)	36(5.0)	0.38		
COP, n (%)	11(4.3)	35(4.9)	0.86		
PE, n (%)	33(13)	64(9)	0.08		
Delirium, n (%)	52(20.1)	182(25.1)	0.1		
<p>Data are mean (SD) or number of patients (%) for the univariate analysis and estimated ORs (95% CIs) of the explanatory variables in the persistent post-COVID-19 symptoms group for the multivariable analysis. The OR represents the odds that the presence of persistent post-COVID-19 symptoms will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure; for continuous predictors, the OR represents the increase in odds of the outcome of interest with every one unit increase in the input variable. The p-value for the multivariable analysis is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). Abbreviations: OR: Odds ratio. CI: Confidence interval. SD: Standard deviation. SOFA: Sequential Organ Failure Assessment. CHF: congestive heart failure. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. BMI: Body Mass Index. HIV: human immunodeficiency virus. NIVM: Non Invasive Mechanical Ventilation. IMV: Invasive Mechanical Ventilation. ICU: Intensive Care Unit. ECMO: Extracorporeal membrane oxygenation. CRRT: Continuous renal replacement therapy. NMB: Neuromuscular blockade. CPR: Cardiopulmonary resuscitation. ICUAP: Intensive Care Unit acquired pneumonia. ARDS: Acute respiratory distress syndrome.</p>					

Discussion

The present study analysed a multicentre cohort of patients admitted to the ICU with COVID-19. Few data are currently available on the follow-up of survivor patients with COVID-19 after discharge. Interestingly, we found that more than 70% of patients discharged from the ICU had persistent post-COVID-19 symptoms after three months passed since hospital discharge; however, the hospital re-admission rate within this period remained low and only 15% needed to visit the emergency department. There was also a poor correlation between abnormal radiologic findings and persistent post-COVID-19 symptoms in critically ill patients after three months passed since hospital discharge. Factors associated with persistent post-COVID-19 symptoms included female sex, duration of ICU stay, and the onset of ICUAP.

With respect to the burden of follow-up on the healthcare system, x-rays and CT scans were performed in 4 of 10 ICU-admitted patients after three months since hospital discharge. As expected, normal x-rays were frequent in patients with good clinical resolution; interstitial patterns were more often seen in chest CT scans of patients with persistent post-COVID-19 symptoms. Recently, patients with previously undiagnosed fibrotic lung abnormalities have been reported to face the possibility of ARDS onset [19]. In a cohort of 114 survivors of severe COVID-19 monitored for six months, chest CT scans revealed fibrotic-

like changes in the lungs in more than one-third of cases [20]. In contrast, only 2.5% of our cohort presented with an interstitial lung pattern. In our view, an important issue is to determine patients' need for resources after hospital discharge. More than 15% of our cohort patients discharged from the ICU required oxygen; yet at the time of writing this manuscript, only a minority (5%) continued receiving supplementary oxygen at home. Interestingly, nebulizers were less frequently used than supplementary oxygen after hospital discharge. To the best of our knowledge, this is a novel finding. Few data are, however, available regarding additional therapy in patients with COVID-19 discharged from the ICU; this is a point that warrants further exploration. Investigators Banerjee et al. [21] followed 621 discharged patients receiving oxygen at home and reported a 30-day hospital re-admission rate of 8.5%. Readmission rate in our cohort was much lower than that in that study (3.1%), although more patients (15%) visited the emergency department after discharge.

The symptoms most frequently observed in patients with post-COVID-19 included dyspnoea, asthenia, and weakness. After analysis of the therapy provided, we found that oxygen therapy was provided significantly more often to patients with persistent post-COVID-19 symptoms. In a previous study in China, patients monitored for three months after hospital discharge presented with considerable radiologic and physiologic abnormalities [22]. In another Chinese study [23] including over 1000 patients, survivors of COVID-19 presented with fatigue, sleep difficulties and anxiety or depression at 6-month follow-up. However, as in the previous study, no detailed data about the functional status of the patients were provided. In our study, we did not perform any analysis related to depression or anxiety.

A strength of our research includes the prospective follow-up of a detailed list of lung function parameters. Soriano et al. [24] recently wrote an editorial suggesting more studies be done in clinical research assessing the post-COVID-19 condition. Our study integrates an extremely sizeable cohort and evaluates a relevant subgroup of the population, i.e., critically ill patients. A French study found that patients with COVID-19 had some symptoms not previously present before their disease [25]. These findings can complement our report, as most of the patients included in our cohort had a critically ill condition. Moreover, in our cohort, ICU-admitted patients with no clinical resolution had worse forced expiratory volume in the first second (FEV1) than those who did not present with persistent post-COVID-19 symptoms. Some studies—the majority from China and some from Europe, with limited patient samples—have also found substantial differences in LFT; however, most patients included were not critically ill [26][27]. In addition to FEV1, FEV1/FVC and DLCO presented significant differences. In a study done in Sweden, investigators Ekbom et al. [28] found that over half of patients with COVID-19 treated in the ICU had impaired lung function during follow-up, suggesting further follow-up studies including DLCO. In their cohort, a mean DLCO of 62% was reported as predicted amongst those with abnormal DLCO. These figures are like ours. We observed a significant correlation between abnormal DLCO and poor health post-COVID-19 in our cohort. The presence of decreased DLCO might reflect microvascular or alveolar capillary damage and be expected in patients with no clinical resolution [29]. Very little is known about the pathophysiology of poor health post-COVID-19. COVID-19 causes lung damage due to a marked inflammatory response to the virus. As is known, the disease may damage endothelial cells in the lung parenchyma. Therefore, identifying pathways may prove as a key point in determining this damage.

Ward et al. [30] found that increased plasma levels of von Willebrand factor antigen (VWF:Ag) and pro-coagulant factor VIII (FVIII) were seen in patients with SARS-CoV-2 infection. In our cohort, we found only elevated levels of fibrinogen in patients with persistent post-COVID-19 symptoms; this observation could help determine the role of endothelial activation in pathophysiology of the disease.

Additionally, we aimed to determine an association between ventilatory parameters in patients with invasive mechanical ventilation and persistent post-COVID-19 symptoms at the 3-month follow-up since hospital discharge. Our assessment of different respiratory parameters such as $\text{PaO}_2/\text{FiO}_2$ ratio and pCO_2 showed a significant correlation across two variables: compliance at the time of intubation and PCO_2 at day 3. Both parameters clearly reflect the damage caused to the respiratory system by a COVID-19 infection. It is interesting that compliance, albeit not the $\text{PaO}_2/\text{FiO}_2$ ratio, was a predictor of persistent post-COVID-19 symptoms. A recent study found that median time to intubation was twice as long in the very-low compliance group than in the low-normal compliance group [31]. Reported higher levels of PaCO_2 in patients in the very-low lung compliance group in that study correlated strongly with our findings. Furthermore, some authors [32] have suggested that compliance in COVID-19-related ARDS is higher in non-COVID-19-related ARDS; our finding could find explanation by the fact that patients with low compliance were those with more severe ARDS. Recently, Gonzalez et al. found that abnormal results were present in CT scans of more than two-thirds of patients with COVID-19-related ARDS[33].

The last and perhaps most important finding of our study is the identification of independent risk factors for persistent post-COVID-19 symptoms.

The first risk factor is female sex. This is an intriguing finding, given that male patients are more widely reported to be admitted to the ICU[34][35] for COVID-19. Further, a systematic review found that COVID-19 may be associated with worse outcomes in males than in females [36]. Whilst most ICU-admitted patients in our cohort were male (67%), more female patients had persistent post-COVID-19 symptoms at 3-month follow-up. The PHOSP-COVID study conducted in the United Kingdom observed that 70% had not fully recovered a mean follow-up period of five months after hospital discharge, with women being more than men [37].

In addition to female patients, another group who presented with poor recovery included critically ill patients with a longer duration of ICU stay. After applying for adjustment, we found that tracheostomy was not an independent risk factor for poor recovery. This finding challenges the recommendation that early tracheostomy may reduce recovery time in critical COVID-19[38].

Lastly, the onset of pneumonia during the ICU stay proved to be an independent risk factor at 3-month follow-up. This is a very especially important finding given the high incidence of nosocomial pneumonia in critically ill patients, especially than those that needed invasive mechanical ventilation. This finding stresses the importance of the prevention ICUAP in COVID-19 critically ill patients. The hypothesis behind this finding is that a second hit (ICUAP) after COVID-19 increased lung damage and consequently increased the risk of respiratory symptoms persistence at follow-up. Some multicentre, European

manuscripts suggest that ventilator-associated lower respiratory tract infections (VA-LRTI) were more frequent in patients with COVID-19 than in patients admitted to the ICU with another virus (influenza) or in patients without viral infections [39]. To the best of our knowledge, our finding has not been reported elsewhere, and other studies should be carried out to confirm or refute it.

Our study has several limitations. Samples obtained from the centres may not be representative, given that hospital units selected all had the research resources necessary to participate. We included an acceptable number of variables for follow-up analysis; however, certain functional tests were not recorded, including the six-minute walk test (6MWT), an excellent tool for assessing sub-maximal exercise aerobic capacity and endurance. We preferred to determine LFT and imaging, as detailed extensively in this manuscript, and felt that the 6MWT might not be reproducible as a measure for oxygen desaturation. A strength of this manuscript is the availability of many data points from the acute period and including data of day 1 and day 3 to determine risk factors of Long-Covid 19 syndrome.

Conclusion

In conclusion, we evaluated many critically ill patients with COVID-19 after three months passed since hospital discharge. Persistent post-COVID-19 symptoms occurred in more than two-thirds of patients; however, the hospital readmission rate remained low. There was not clinical association between such symptoms and persistently abnormal chest x-rays. Also, more than 10% of these patients still required oxygen at home. Female sex, duration of ICU stay, and the onset of ICUAP were independent risk factors for persistent post-COVID-19 symptoms in critically ill patients at 3-month follow-up. Prevention of ICUAP could have beneficial effects in poor health post-Covid 19 syndrome.

Declarations

- Ethics approval and consent to participate: The study received approval by the institution's Internal Review Board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370).
- Consent for publication: All authors listed on the title page have read the manuscript, attest to the validity, and legitimacy of the data and its interpretation, and agree to its submission to Critical Care.
- Availability of data and material. Data and material are available.
- Competing interests. The authors declare that they have no competing interests.
- Funding: CIBERESUCICOVID. CIBER enfermedades respiratorias
- Authors' contributions. IML and AT designed the study. All other authors contributed to data acquisition and approved the manuscript.
- Acknowledgements. To all the patients and families

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Figures

Figure 1. Flow chart and the percentage of patients with persistent post-COVID-19 symptoms.

Figure 1

See image above for figure legend

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