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Clinical Research Study

Health-Related Quality of Life Improves in Parallel with FEV1 and 6-Minute Walking Distance Test at Between 3 and 12 Months in Critical COVID-19 Survivors

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ABSTRACT

Background: In COVID-19 intensive care unit (ICU)–admitted patients, multiorgan acute complications lead to long-lasting sequelae. The aim of this study was to assess (1) changes in chest CT, pulmonary function test (PFT), functional capacity (6-minute walking distance test (6MWT)), and health-related quality of life (HR-QoL) among ICU COVID-19 survivors at 3, 6, and 12 months after ICU discharge and (2) predictors of persistent impairment/improvement in 6MWT and HR-QoL.

Methods: ICU COVID-19 survivors were prospectively included. Outcomes at 3, 6, and 12 months included PFT, 6MWT, respiratory muscle strength (RMS), HR-QoL (SF-36), Medical Research Council dyspnea scale (mMRC), and post-COVID Functional Status scale.

Results: Eighty-seven survivors were included, from June 3, 2020, to September 2, 2021. At 12 months, 50% of PFT were normal, 46% were restrictive, and 22% showed reduced diffusing capacity for carbon monoxide (DLCO). Impaired DLCO was associated with ICU length of stay and age. In mixed linear model analysis, improvements in RMS and mMRC persisted over time regardless of the adjustments applied ($P \leq .050$). SF-36 improved in parallel with FEV1 and 6MWT between 3 and 12 months ($P \leq .044$), while increment in DLCO correlated with changes in FEV1 and total lung capacity (TLC) ($p \leq 0.026$).

Conclusions: This longitudinal study demonstrated that improvements in SF-36 occur in parallel with improvements in FEV1 and 6MWT between 3 and 12 months post-ICU discharge in a sample of critically ill COVID-19 patients. However, PFT remained, however, abnormal in 50% of patients. Based on continued improvements observed from 3 to 12 months, it is anticipated that COVID-19 ICU patients will continue to recover similarly to ARDS patients.

Introduction

Coronavirus disease 2019 (COVID-19) is the third and global outbreak of coronavirus this century. SARS-CoV-2 is the virus responsible for COVID-19. This outbreak was recognized as a pandemic by the World Health Organization on the 11th of March 2020. As of the 2nd of November 2022, among a total population of approximately 627 million inhabitants who have contracted severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), more than 6.57 million people have died worldwide.[1] The number of patients affected by SARS-CoV-2 is still rising, with striking problems related to emerging variants of concern, despite vaccination rates of up to 86% in European countries and new vaccines including variants omicron BA.1, BA.4, and BA.5.[2]

The presentation of COVID-19 is variable. Among symptomatic COVID-19 patients, an estimated 5% suffer from severe respiratory failure that requires intensive care unit (ICU) admission and fulfills the Berlin definition of acute respiratory distress syndrome (ARDS).[3] These patients experience multiorgan acute complications related to SARS-

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CoV-2 infection (eg, renal, hepatic, thromboembolic, neurologic, cardiac, muscular complications) despite the development of a number of effective treatments. As treatments become more numerous and effective (eg, anticoagulation, glucocorticoids, antiviral therapies, monoclonal antibodies) mortality rate declines.[4] However, this means that more individuals are living with long-term sequelae that can have impacts on their functional capacity and health-related quality of life (HR-QoL).[5]

Persisting symptoms and impaired pulmonary function tests (PFTs) are expected to impair HR-QoL and functional capacity (6-minute walking distance test [6MWT]). Previous studies related to cohorts of hospitalized COVID-19 patients (wards/ICU) followed for up to 12 months have reported improvements in PFT and 6MWT results over time but not in all patients.[6-9] Persisting impaired diffusing capacity for carbon monoxide (DLCO) was related to COVID-19 severity in studies that included both ICU and non-ICU patients.[7,9] HR-QoL also improved over time,[7,8] but not in all domains.

The aim of this study was to assess (1) changes in chest CT, PFT, functional capacity (6MWT), and HR-QoL among ICU COVID-19 survivors at 3, 6, and 12 months after ICU discharge and (2) predictors of persistent impairment/improvement in 6MWT and HR-QoL.

Methods

Design

This was a prospective observational and multicentric study. Patients admitted to the ICU for COVID-19-related ARDS at 2 tertiary reference hospitals (CHU Brugmann and CHU Saint-Pierre, Brussels, Belgium) were included in the study 3 months from ICU discharge.

Participants

Adult participants (>18 years) were included at 3 months from ICU discharge and assessed at 3, 6, and 12 months by chest CT, PFT, and questionnaires. Exclusion criteria included language barrier, refusal, and psychiatric or cognitive disorders known prior to ICU admission.

All included individuals provided written informed consent to participate in the study. The study protocol was approved by ethics committee of the 2 hospitals (references AK/16–01–18/4613 and CE2020/141). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Collection

Baseline Data

Data related to hospitalization were collected from the medical files of the participants, including demographics, Acute Physiologic Assessment and Chronic Health Evaluation Scoring System II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score at ICU admission, biological data, chest CT, COVID-19 treatments, and complications.

Follow-Up

A comprehensive assessment of participants was performed 3 times (3, 6, and 12 months) in each individual, according to a procedure previously described by Truffaut et al. 2021.[10]

PFTs, including spirometry, body plethysmography, and DLCO, were performed. The following values were analyzed: total lung capacity (TLC; in liters and percent predicted value), forced vital capacity (FVC) (in liters and percent predicted value), forced expiratory volume of 1 s (FEV1) (in liters and percent predicted value), Tiffeneau Index (FEV1/FVC), DLCO by single breath test in mmol/minute/kilo Pascal (in percent predicted value, corrected for hemoglobin). GLI reference

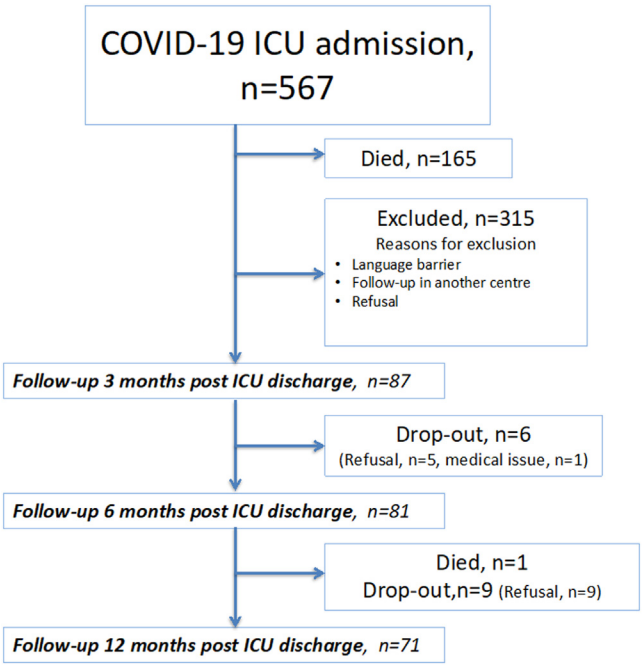

Figure 1. Flowchart of the study. ICU: intensive care unit.

values were used.[11] The maneuvers were performed as follows: in a seated position, with the patient inserting the mouthpiece between the lips while wearing a nose clip. After a few tidal volumes, the patient was asked to inhale as rapidly as possible and then exhale directly without pause, as quickly and completely as possible, with a minimum expiratory time of 6 seconds. The maneuver was repeated at least 3 times, with a maximum of 8 trials, to ensure reproducibility. Reproducibility was calculated on three parameters: peak expiratory flow (PEF), FVC, and FEV1. The measurement was considered nonreproducible if the difference between the 2 highest values of PEF > 10%, FVC > 5%, and FEV1 > 5% or 150 mL. The largest FVC and the largest FEV1 were selected after examining the data from all the usable curves, even if they did not come from the same curve. For DLCO measurements, patients attempted a maximum of 5 maneuvers to obtain 2 acceptable and reproducible measurements. An acceptable maneuver was defined as an inspiratory breath of at least 90% of FVC, a rapid inspiration, and a breath-hold time of 9-11 seconds. Maneuvers are considered reproducible when at least 2 acceptable DLCO measurements are obtained with a difference less than or equal to 0.67 mmol/minute/kilo Pascal.

To assess endurance, the 6MWT with continuous peripheral oxygen saturation monitoring was performed. Respiratory muscle strength (RMS) measurements were performed, following international recommendations: repeated measurements of maximal static respiratory pressures during forceful inspiratory (PI_{max}) and expiratory (PE_{max}) efforts were done to obtain the highest value of 3 inspiratory maneuvers or 3 expiratory maneuvers that vary by less than 10%.[12]

The follow-up assessments also included 3 questionnaires: HR-QoL using the Short Form 36 (SF-36), breathlessness using the modified Medical Research Council dyspnea scale (mMRC), and post-COVID disability using the post-COVID Functional Status scale.[13]

We considered impaired values as below 80% predicted for lung volumes and DLCO,[14] and below 70% predicted for 6MWT.[15]

Chest CT was repeated in each patient, except if normalization occurred. Chest CT scans were reviewed by a single senior radiologist with extensive experience (>20 years). Reported chest CT abnormalities were ground glass opacities, consolidation, and fibrosis (including bronchiolectasies, fibrotic strands, irregular lines, reticulations).

Table 1
Baseline Characteristics of Patients.

Variable (mean, SD or %)	All (n = 87)	Females (n = 55)	Males (n = 32)
Age (years)	56.56 ± 11.52	57.07 ± 10.96	55.69 ± 12.56
Sex (female)	n = 55 (63.2%)	n = 55 (100%)	n = 0 (0%)
BMI ≥30 (kg/m^2)	n = 48 (55.2%)	n = 28 (50.9%)	n = 20 (62.5%)
Current smokers	n = 31 (35.6%)	n = 26 (47.3%)	n = 5 (15.6%)
Medical history			
Cancer	n = 4 (4.5%)	n = 2 (3.6%)	n = 2 (6.2%)
Diabetes	n = 39 (44.8%)	n = 27 (49.1%)	n = 12 (37.5%)
Arterial hypertension	n = 49 (56.3%)	n = 36 (65.5%)	n = 13 (40.6%)
HIV	n = 2 (2.3%)	n = 2 (3.6%)	n = 0 (0%)
Obstructive sleep apnea	n = 6 (16.67%)	n = 2 (3.6%)	n = 4 (12.5%)
COPD	n = 9 (10.3%)	n = 6 (10.9%)	n = 3 (9.4%)
Length of stay (days)			
Hospital	29.24 ± 18.43	29.07 ± 15.91	29.53 ± 22.57
ICU	17.85 ± 14.24	17.51 ± 13.51	18.44 ± 15.83
ICU severity scores			
APACHE II	9.05 ± 4.54	9.18 ± 4.91	8.81 ± 3.88
SOFA	3.43 ± 1.85	3.35 ± 1.98	3.56 ± 1.61
Respiratory support*			
Mechanical ventilation	n = 44 (50.6%)	n = 27 (49.1%)	n = 17 (53.1%)
Mean duration	8.75 ± 11.21	8.36 ± 10.25	9.41 ± 12.85
Neuromuscular blocking drugs	n = 40 (46.0%)	n = 23 (41.8%)	n = 17 (53.1%)
Prone	n = 34 (39.1%)	n = 22 (40%)	n = 12 (37.5%)
ECMO	n = 7 (8.0%)	n = 4 (7.3%)	n = 3 (9.4%)
High flow oxygen	n = 19 (21.8%)	n = 13 (23.6%)	n = 6 (18.8%)
CPAP	n = 4 (4.6%)	n = 2 (3.6%)	n = 2 (6.2%)
BIPAP	n = 17 (19.5%)	n = 11 (20%)	n = 6 (18.8%)
Laboratory data			
Highest D-dimer level (mg/dL)	7115.6 ± 9322.65	7916.8 ± 9622.02	5694.13 ± 8737.02
Lowest lymphocyte count (×10^9/L)	694.26 ± 356.91	680.8 ± 320.97	717.41 ± 416.02
Highest CRP level (mg/dL)	195.04 ± 110.05	196.29 ± 113.37	192.9 ± 105.85
ICU treatments			
Glucocorticoids	n = 71 (81.6%)	n = 41 (74.5%)	n = 30 (93.8%)
Favipiravir	n = 3 (3.4%)	n = 2 (3.6%)	n = 1 (3.1%)
Remdesivir	n = 6 (6.9%)	n = 3 (5.5%)	n = 3 (9.4%)
Anakinra	n = 1 (1.1%)	n = 1 (1.8%)	n = 0 (0%)
Tocilizumab	n = 24 (27.6%)	n = 12 (21.8%)	n = 12 (37.5%)
Broad spectrum antibiotics	n = 67 (77.0%)	n = 42 (76.4%)	n = 25 (78.1%)
Complications			
Thromboembolic event	n = 20 (23.0%)	n = 15 (27.3%)	n = 5 (15.6%)
Critical illness polyneuropathy	n = 10 (11%)	n = 5 (18%)	n = 5 (16%)
Atrial fibrillation	n = 2 (2.3%)	n = 1 (1.8%)	n = 1 (3.1%)

BIPAP = bilevel positive airway pressure; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CRP = C-reactive protein; ECMO = extracorporal membranous oxygenation; HIV = human immunodeficiency virus; ICU = Intensive care unit; SOFA = Sequential Organ Failure Assessment.

* Some patients received more than one modality (consecutive therapies).

Statistical Analysis

Descriptive Statistics

The descriptive statistics included two stages: (1) description of all data for each follow-up (3, 6, and 12 months) and (2) the calculation of changes between each follow-up. For this second stage, all subjects without values at 3 months were excluded. In the case of missing values, the last observation was carried forward (eg, if the 12-month value was missing, the 6-month value was repeated at 12 months). The changes were calculated with delta values: [6-month value – 3-month value], [12-month value – 3-month value], [12-month value – 6-month value].

Descriptive statistics for continuous variables are presented as mean and standard deviation, and as numbers and percentages for categorical variables.

Statistical Analysis

Linear mixed effects models (LME—random intercept model) were used to assess changes over time for repeated measurements of symptoms, functional, and PFT at 3- and 12-month follow-up. LME account for variability between subjects and variability between repeated measurements in the same subject simultaneously. To assess different trajectories for patients, we included the intercept slope effect as a random effect, baseline characteristics and time as fixed effects. The variance–covariance structure was fixed to an unstructured matrix, and the random effects and error terms were assumed to have a normal distribution. Multicollinearity was checked by using variance inflation factors. We gradually added in the potential confounders to observe their effects and a total of five models were developed:

Model 1, no adjustment; Model 2, adjusted for age (quantitative variable) and sex (binomial variable); Model 3, adjusted for age, sex, and obesity (binomial variable) (body mass index [BMI] ≥ 30 kg/m^2); Model 4, adjusted for age, sex, obesity, and comorbidities (binomial variable); Model 5, adjusted for age, sex, symptom duration before admission, ICU length of stay, lower lymphocyte count; higher C-reactive protein (CRP), SOFA, APACHE II scores, lower oxygen level (PaO_2/FiO_2) (quantitative variables) during ICU stay. Indeed, as changes over time for functional variables, dyspnea and HR-QoL can be influenced by different factors such as age, obesity, comorbidities,[16] and characteristics of ICU hospitalization[17] we have decided to adjust for these different parameters.

According to the clinical interpretation of the variables, logistic regression was performed for these dependent variables with a relevant threshold: FEV1 ≥ or < 80% of predicted value; TLC ≥ or < 80% of predicted value; DLCO ≥ or < 80% of predicted value; and 6MWT ≥ or < 70% of predicted value. The independent variables were demographics (SF-36 scores, sex, age, obesity, tobacco use status, diabetes, hyperten-

Table 2
Pulmonary Functional and Symptom Outcomes in 87 COVID-19 ICU Survivors.

Variables (mean, SD or %)	3 months	6 months	12 months	Change 6 months – 3 months	Change 12 months – 3 months	Change 12 months – 6 months
Chest CT						
Normal	*n* = 7 (8%)	*n* = 7 (8%)	*n* = 7 (8%)			
Number affected segments	9.41 ± 7.03	8.75 ± 6.9	8.59 ± 6.84	−0.98 ± 2.73	−1.32 ± 3.58	−0.34 ± 2.01
Ground glass opacities	*n* = 16 (19%)	*n* = 4 (5%)	*n* = 4 (6%)			
Consolidation	*n* = 12 (14%)	*n* = 11 (14%)	*n* = 9 (13%)			
Fibrosis	*n* = 68 (80%)	*n* = 70 (86%)	*n* = 59 (86%)			
Spirometry						
FEV1 (% pred)	83.13 ± 17.86	87.48 ± 17.00	90.35 ± 14.66	3.33 ± 8.81	5.06 ± 10.98	1.73 ± 6.49
<80%	*n* = 32 (36.78%)	*n* = 24 (27.58%)	*n* = 16 (18.39%)			
Body plethysmography						
TLC (% pred)	83.39 ± 18.11	86.6 ± 16.24	89.42 ± 17.22	2.83 ± 11.31	5.58 ± 12.49	2.75 ± 10.03
<80%	*n* = 33 (37.93%)	*n* = 26 (29.88%)	*n* = 20 (22.98%)			
DLCO						
DLCO (% pred)	78.72 ± 20.42	80.22 ± 21.62	82.17 ± 20.87	3.03 ± 15.18	3.83 ± 14.75	0.81 ± 13.55
<80%	*n* = 40 (45.97%)	*n* = 35 (40.23%)	*n* = 38 (43.67%)			
RMS						
IP max (cm H_2O)	81.82 ± 29.43	82.93 ± 29.19	89.73 ± 27.75	2.27 ± 24.54	6.78 ± 23.71	4.51 ± 20.96
EP max (cm H_2O)	65.05 ± 26.08	63.22 ± 22.21	69.03 ± 21.43	−1.48 ± 27.29	1.69 ± 24.97	3.16 ± 18.82
Test of functional capacity						
6MWT distance (% pred)						
<70%	69.53 ± 14.63	72.83 ± 16.83	75.34 ± 15.03	3.49 ± 10.36	4.59 ± 12.42	1.1 ± 7.51
	n = 35 (40.23%)	*n* = 26 (29.88%)	*n* = 20 (22.98%)			
Questionnaires						
SF-36	58.21 ± 20.59	56.18 ± 21.35	58.91 ± 21.40	−2.64 ± 13.98	−1.36 ± 20.38	1.28 ± 16.65
Physical functioning	61.75 ± 27.18	62.44 ± 25.63	60.94 ± 25.12	−0.69 ± 23.14	−0.86 ± 29.75	−0.18 ± 21.18
Pain	60.66 ± 32.21	60.2 ± 29.50	61.67 ± 27.96	−1.67 ± 32.03	−1.44 ± 36.01	0.22 ± 29.25
Role physical	37.62 ± 38.79	52.85 ± 37.31	60.0 ± 34.17	14.56 ± 37.33	21.75 ± 44.55	7.19 ± 36.91
General health	56.91 ± 18.71	52.53 ± 21.65	56.17 ± 21.36	−3.79 ± 15.41	−1.41 ± 20.48	2.38 ± 17.55
Mental health	63.35 ± 21.07	58.1 ± 19.99	62.54 ± 22.65	−5.45 ± 13.82	−4.53 ± 19.68	0.92 ± 16.96
Role emotional	45.83 ± 44.21	53.16 ± 46.70	56.17 ± 43.11	6.67 ± 39.23	7.49 ± 49.72	0.82 ± 43.78
Social	69.38 ± 28.15	67.06 ± 28.98	68.96 ± 26.62	−2.81 ± 25.15	−3.26 ± 28.74	−0.44 ± 22.23
Vitality	49.0 ± 22.0	46.6 ± 21.51	48.71 ± 23.02	−3.19 ± 14.88	−1.62 ± 23.06	1.56 ± 20.67
PCFS				−0.29 ± 0.82	−0.47 ± 1.17	−0.19 ± 0.91
0	*n* = 14 (23.72%)	*n* = 28 (35.89%)	*n* = 28 (40%)			
1	*n* = 19 (32.20%)	*n* = 24 (30.76%)	*n* = 14 (20%)			
2	*n* = 11 (18.64%)	*n* = 13 (16.66%)	*n* = 19 (27.14%)			
3	*n* = 11 (18.64%)	*n* = 10 (12.82%)	*n* = 9 (12.85%)			
4	*n* = 5 (8.47%)	*n* = 3 (3.84%)	*n* = 0 (0%)			
mMRC				−0.23 ± 1.07	−0.26 ± 1.06	−0.02 ± 0.88
0	*n* = 31 (37.80%)	*n* = 39 (48.75%)	*n* = 34 (48.57%)			
1	*n* = 27 (32.92%)	*n* = 28 (35.00%)	*n* = 26 (37.14%)			
2	*n* = 15 (18.29%)	*n* = 8 (10.00%)	*n* = 8 (11.42%)			
3	*n* = 6 (7.31%)	*n* = 1 (1.25%)	*n* = (0.0%)			
4	*n* = 3 (3.65%)	*n* = 4 (5.00%)	*n* = 2 (2.85%)			

6MWT = 6-minute walking distance test; DLCO = diffusing capacity for carbon monoxide; EP = expiratory pressure; FEV1 = forced expiratory volume in one second; IP = inspiratory pressure; mMRC = modified Medical Research Council dyspnea scale; PCFS = post-COVID Functional Status; PFT = Pulmonary function test; RMS = respiratory muscle strength; SF-36 = Short Form 36; TLC = total lung capacity.

sion, and CT scan score) or medical (ICU length of stay and medicines given during ICU stay (glucocorticoids, remdesivir, tocilizumab, antibiotics)).

To assess the links between the changes of variables, Pearson correlations were applied for delta values (6-month – 3-month value; 12-month – 3-month value; and 12-month – 6-month value).

A *P* value of <.05 was considered statistically significant.

All analyses were performed using Python (version 3.9) with the statistics module statsmodels (version 0.13.2). The module is released under the open-source modified BSD license.

Results

Eighty-seven ARDS survivors of the first 3 COVID-19 pandemic waves (variants alpha, alpha, delta) were included in the study. They were admitted to the ICU from March 3, 2020 to June 2, 2021 and included in the study from June 3, 2020 to September 2, 2021. The ICU mortality rate was 29%. The flowchart of the study is presented in Figure 1. Withdrawal of participants was observed in 7% at 6 months and 18% at 12-month follow-up.

Most patients were women (63%), mean age was 57 ± 12 years, and mean ICU length of stay was 18 ± 14 days. Comorbidities were frequent, with 63% being obese, 56% suffering from hypertension, and 45% from diabetes. Baseline chest CT showed 16.8 ± 4.2 affected segments (ground glass opacities, 94%; consolidation, 74%; and fibrosis, 37%).

Demographics and clinical data for the included patients are summarized in Table 1.

Assessments were performed at 3, 6, and 12 months and are summarized in Table 2. About 50% of participants exhibited normal PFT at 12 months, 46% still suffered from restrictive pattern, and 22% from reduced DLCO. Regarding dyspnea, 49% declared they were experiencing no dyspnea after 12 months, while 14% remained breathless (mMRC ≥ 2).

Changes over time related to HR-QoL, measured by SF-36, are illustrated in Figure 2.

Positive changes over time in functional outcomes and symptoms were also analyzed. On the mixed linear model analysis, improvements in RMS and mMRC persisted over time regardless of which of the 5 models with different adjustments was applied (Table 3).

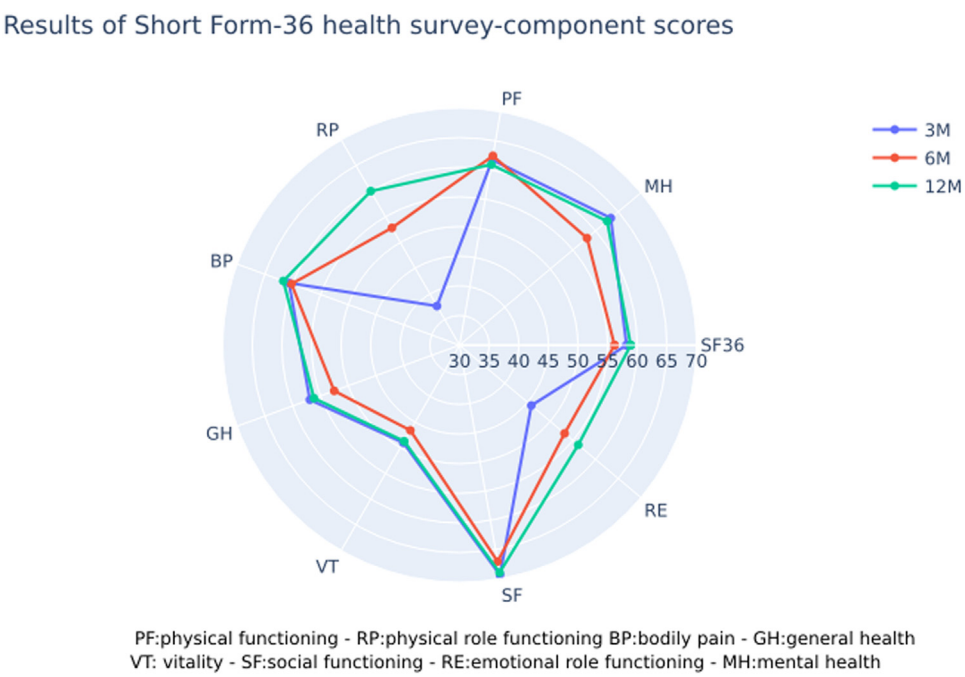

Figure 2. Short Form 36 scores at 3, 6, and 12 months post-ICU discharge.

Table 3
Longitudinal Data Analysis for Mixed Linear Model*.

Variable	Model 1 *(P value)*	Model 2 *(P value)*	Model 3 *(P value)*	Model 4 *(P value)*	Model 5 *(P value)*
PFT					
FEV1 (% pred)	*<.0001*	.7160	.6835	.3979	.8593
FEV1 < 80%, *n* (%)	*<.0001*	.7553	.7538	.7497	.7549
TLC (% pred)	*<.0001*	.1154	.1109	.0755	.0959
TLC < 80%, *n* (%)	*.0008*	.1744	.1209	.0504	.1355
DLCO (% pred)	*.0160*	.1654	.1232	.1259	.2596
DLCO < 80%, *n* (%)	.6879	.6146	.6712	.6273	.5882
6MWT					
distance (% pred)	*<.0001*	.7644	.8562	.7087	.6166
6MWT <70%	*<.0001*	.3824	.2666	.3185	.5479
oxygen desaturation, n (%)	*.2287*	.4400	.4551	.6247	.6554
RMS					
IP max (cm H_2O)	*.0199*	*<.0001*	*<.0001*	*<.0001*	*<.0001*
EP max (cm H_2O)	*.0015*	*<.0001*	*<.0001*	*<.0001*	*<.0001*
mMRC	*.0044*	*.0189*	*.0264*	*.0085*	*.0078*
PCFS	*.0003*	.1120	.1235	.2700	.0918
SF36	.9316	*.0027*	*.0039*	*.0079*	*.0008*
Physical functioning	.8660	*.0140*	*.0210*	*.0165*	*.0054*
Pain	.9443	.2871	.3573	.6408	.2316
Role physical	*<.0001*	.2543	.2628	.5030	.2495
General health	.6228	*.0008*	*.0014*	*.0027*	*.0038*
Mental health	.1733	*.0102*	*.0100*	*.0058*	*.0001*
Role emotional	.0643	*.0166*	*.0251*	.1041	*.0040*
Social	.5713	.0766	.0776	.1718	*.0186*
Vitality	.7031	*.0090*	*.0102*	*.0142*	*.0324*

* *Model 1*, no adjustment; *Model 2*, adjusted for age and sex; *Model 3*, adjusted for age, sex, and obesity (BMI ≥ 30); *Model 4*, adjusted for age, sex, obesity, and comorbidities; *Model 5*, adjusted for age, sex, symptom duration before admission, ICU LOS, lower lymphocyte count; higher CRP, SOFA, APACHE II scores, lower oxygen level (PaO_2/FiO_2) during ICU stay.

6MWT = 6-minute walking distance test; CRP = C-reactive protein; DLCO = diffusing capacity for carbon monoxide; EP = expiratory pressure; FEV1 = forced expiratory volume in 1 second; ICU = Intensive care unit; IP = inspiratory pressure; LOS = length of stay; mMRC = modified Medical Research Council dyspnea scale; PCFS = post-COVID Functional Status; RMS = respiratory muscle strength; SF-36 = Short Form 36; SOFA = Sequential Organ Failure Assessment; TLC = total lung capacity

Correlations between change (delta values) for different variables were also analyzed and are reported in Table 4.

On logistic regression analyses, TLC < 80% predicted value was associated with the number of affected segments on CT scan at 3, 6, and 12 months (*P* values respectively .049, .001, and .010; odds ratio [OR] of 1.102 [95% confidence interval {CI} 1.00;1.21], 1.267 [1.10;1.44] and 1.207 [1.04;1.39]). The only predictor of impaired 6MWT at 12 months was obesity (*P* = .032, OR 6.292 [95% CI 1.17; 33.77]). Impaired TLC at 12 months was associated with female sex (*P* = .015, OR 10.199 [95% CI 1.55; 66.85]) and active smoking (*P* = .005, OR 0.021 [95% CI 0.00; 0.31]), whereas impaired DLCO was associated with ICU length of stay (*P* = .039, OR 1.064 [95% CI 1.00;1.12]) and age (*P* = .01,

Table 4
Predictors of HR-QoL and Functional Capacity.

Associations with HR-QoL	Variable	6 months – 3 months		12 months – 3 months		12 months – 6 months	
		Number of subjects	r *(P value)*	Number of subjects	r *(P value)*	Number of subjects	r *(P value)*
SF-36	FEV1 (% pred)	73	0.11 (.352)	73	*0.29 (.010)*	73	0.09 (.449)
SF-36	TLC (% pred)	73	0.15 (.203)	73	*0.29 (.013)*	73	0.01 (.893)
SF-36	DLCO (% pred)	73	−0.05 (.617)	73	0.00 (.981)	73	−0.04 (.701)
SF-36	6MWT distance (% pred)	73	0.19 (.111)	73	*0.24 (.044)*	73	0.07 (.540)
SF-36	CT Score	73	−0.11 (.335)	73	0.01 (.907)	73	0.20 (.085)
Associations with functional capacity							
FEV1 (% pred)	TLC (% pred)	79	*0.32 (.004)*	79	*0.57 (<.001)*	79	0.13 (.237)
FEV1 (% pred)	DLCO (% pred)	75	*0.32 (.004)*	75	*0.35 (.001)*	75	*0.26 (.026)*
FEV1 (% pred)	6MWT distance (% pred)	73	0.01 (.899)	73	0.05 (.670)	73	0.09 (.427)
FEV1 (% pred)	CT Score	73	−0.10 (.367)	73	0.05 (.671)	73	0.09 (.421)
TLC (% pred)	DLCO (% pred)	75	0.17 (.135)	75	*0.30 (.008)*	75	0.06 (.602)
TLC (% pred)	6MWT distance (% pred)	73	0.12 (.296)	73	0.11 (.346)	73	0.17 (.140)
TLC (% pred)	CT Score	73	−0.06 (.557)	73	−0.06 (.579)	73	−0.05 (.658)
DLCO (% pred)	6MWT distance (% pred)	73	−0.04 (.692)	73	−0.03 (.779)	73	*0.25 (.035)*
DLCO (% pred)	CT Score	73	−0.09 (.406)	73	−0.14 (.248)	73	−0.15 (.204)
6MWT distance (% pred)	CT Score	73	0.14 (.239)	73	*0.26 (.023)*	73	0.01 (.923)

6MWT = 6-minute walking distance test; CT score = number of affected segments on lung CT scan; DLCO = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; HR-QoL = health-related quality of life; SF-36 = Short-Form 36 (global score is used in the present table), TLC = total lung capacity.

OR 1.106 [95% CI 1.02;1.19]). The use of glucocorticoids, tocilizumab, and remdesivir was not associated with better PFT or 6MWT ($P > .05$).

Discussion

In this longitudinal study that assessed 87 ICU COVID-19 patients at 3, 6, and 12 months with repeated measurements, we have highlighted that improvement in HR-QoL, measured by the SF-36, occurs in parallel with FEV1 and 6MWT between 3 months and 12 months follow-up.

Recovery of pulmonary function and radiological abnormalities was largely incomplete at 1 year and still resulted in exertional dyspnea and post-COVID disability in at least half the patients. Thus, patients recovered progressively during the first year following ICU discharge based on objective as well as subjective parameters. The 12-month drop-out rate was acceptable in our study population, 18%, similar to the 14% reported by Eberst et al.[8]

Regarding radiologic features, a large proportion of chest CT scans remained abnormal at 12 months (92%), but with patterns evolving over time: more fibrosis and less ground glass opacities were observed at 12 months compared with 3 months. The same observation was made by Eberst et al.[8] in an ICU survivor cohort and by Wu et al. 2021, in hospitalized patients.[6]

All pulmonary functional parameters improved over time, as previously described in a similar population.[6] Impaired DLCO has been already described as the most common abnormality persisting after coronavirus infection. Indeed, SARS-CoV-2 has some similar features with the 2 first coronavirus outbreaks (SARS-CoV-1 in 2002 and MERS in 2012).[18] In these patients, altered DLCO was also documented, with persisting significant impairment in DLCO in 24%-37% of survivors 1 year after illness onset.[19] In addition, in ARDS (from various etiologies) survivors, DLCO is the most often impaired lung functional marker, averaging 65% after 1 year.[20] Recent studies related to hospitalized COVID-19 patients have reported more positive results, with levels of persistent low DLCO at one year ranging from 11% to 33%.[6-8]

Inspiratory and expiratory muscle strength have also been shown to improve over time after ICU discharge. This is in line with the progressive physical recovery observed in these patients over the first year, through handgrip dynamometry and quadriceps strength, or maximal inspiratory pressure.[7,21] ICU-acquired weakness is a well-known medical complication and has been shown to be associated with the use of neuromuscular blockers and duration of mechanical ventilation in COVID-19 patients.[22] In the present study, RMS, such as dyspnea, improved over time even in different statistical models taking into account demographics, comorbidities, and clinical characteristics of hospitalization.

When adjusting for age, sex, and other parameters (eg, comorbidities, acute ICU variables), SF-36 scores improved over time in the majority of domains. In this study, HR-QoL improved progressively over time in the majority of domains (mainly Role physical and Role emotional). Reduced long-term HR-QoL after ICU stay has been previously well documented.[23,24] Indeed, HR-QoL remains altered 1 year after critical COVID-19 in 75% of patients when measured by the EQ-5D-5L.[25] Comparisons between COVID-19 and non-COVID-19 ICU patients have shown the same degree of impairment at 1 year.[26] Another study that included COVID-19 hospitalized patients (37% ICU) reported, using the SF-12, that reduction of physical and mental health was observed in 49% and 31%, respectively, of patients.[27] In a study from Lorent et al.[7] the authors stated that HR-QoL improved between 3 and 12 months and was not significantly reduced. However, in our series, the scores remained much lower than in healthy middle-aged adults[28] and were overall similar to other ARDS COVID-19 populations.[21] We have also observed, as have other researchers,[7,8] an important improvement in “Role physical” but also, in contrast to other studies, in “Role emotional.” The observed differences could be related to different psychological impacts in these two populations, as anxiety, depression, and posttraumatic stress disorder were not assessed. We have also observed, for Mental Health, Vitality, and General Health, that the scores at 6 months were lower than those at 3 or 12 months. Symptom fluctuation and psychological recovery can vary over time, as reported in a study from Ghosn et al.[27] in which postacute COVID-19 symptoms, in some individuals, were not reported at 6 months but arose at 12 months in a large population of hospitalized COVID-19 patients.

Incremental changes in DLCO over time were correlated with changes in FEV1 and TLC, reflecting overall and active lung repair mechanisms occurring at least during the first year post-ICU discharge.[8,19,20] Sex, age, comorbidities, and current smoking did not influence 6MWT values at 1 year, nor did medications or ICU length of stay, but decreased 6MWT performance was associated, unsurprisingly, with obesity.[29]

In our study, DLCO impairment was associated with age and ICU length of stay at 12 months. Other studies have reported associations with female sex at 6-12 months,[6,7,9] longer hospital stay, preexisting chronic lung disease, and smoking at 1 year[7] or no identified risk factors.[8] However, these last few factors seem to influence other lung volumes, as reduced TLC was associated with current smoking and female sex at 12 months.

Predictors of a better SF-36 were improvements in PFT and 6MWT. The same predictors were reported in the series of Zhou et al., where a correlation between all the SF-36-domain scores and PFT, 6MWT was highlighted in 120 patients assessed 1 year after hospitalization for COVID-19.[30] For 6MWT, the sole predictive factor was the number of affected segments on the chest CT. Villar et al. reported the same findings in 134 patients assessed 3-6 months after hospitalization for COVID-19: patients with abnormal CT at 3-6 months following discharge presented with lower median 6MWT than those with normal CT.[31]

It is disappointing that medications administered in the acute phase did not change PFT outcomes in survivors, despite a proven impact on 28-day mortality for glucocorticoids,[4] tocilizumab, and remdesivir, when given at the right time to the right patient[32,33] but because the study sample size was limited and specific drugs changed with the COVID-19 pandemic, only 6.9% of our patients received remdesivir, so it's difficult to draw conclusions about the impact of medications. The outcome of an often lengthy stay in an intensive care unit is likely to be influenced by a number of factors, such as the clinical severity of ARDS, infectious complications, difficult weaning, etc., all of which lead to sequelae of varying severity. It is very important to recognize these sequelae to help COVID-19 long haulers with pulmonary rehabilitation. This program has been shown, through multiple observational cohorts, benefits in exercise capacity, PFT, and HR-QoL.[34] Psychological support is also essential after COVID-19 critical illness.[35]

To end, patients assessed 12 months after ICU discharge represent only 22% of survivors, which may lead to the possibility of missing-at-random vs missing-not-at-random data and influence the results in one way or another. However, once included, the follow-up of patients over time shows a coherent and homogeneous evolution of the whole cohort.

Limitations

This multicentric cohort lacked a control group of non-ICU hospitalized patients or of ICU non-COVID-19 patients. Moreover, we have observed several disabilities, but we lack precise pre-COVID-19 functional measurements. HR-QoL can be influenced by psychological/psychiatric conditions, and these were not assessed in the present cohort. To assess the associations between changes in HR-QoL and pulmonary functional tests, we used the SF-36 global score, which is not the best way to use the recorded score.[36] However, detailed data for the 8 subscales have been extensively provided in the tables and figures, revealing precisely where the changes occurred. Another source of bias is the change over time in therapeutic treatments and resources availability for ICU patients during the 3 first waves of the pandemic. We have recently shown that, when comparing outcomes of patients handled during these first waves, the use of glucocorticoids, as well as tocilizumab, was associated with improvements in the number of affected segments in chest CT, FEV1, TLC, and DLCO at 3 months.[37] However, due to the small size of the sample, changes over time can be hampered by sparse-data bias. An additional source of limitation is the use of threshold in predicted values and not the Global Lung Initiative (GLI) reference value to interpret PFT. Software was not yet available at the start of the study. It could potentially lead to misclassification of patients, eg, old patients with FEV1< 80% who have normal values when interpreted according to GLI values. Finally, a small proportion of patients was not reassessed at 12 months because of loss of follow-up, leading to a reduction in the number of observations.

Conclusions

This longitudinal study assessed 87 ICU COVID-19 patients at 3, 6, and 12 months after discharge and demonstrated that improvements in HR-QoL, assessed by the SF-36, occur in parallel with FEV1 and 6-minute walking distance test improvements at between 3 and 12 months post-ICU discharge. Pulmonary functional outcomes, SF-36 scores, and dyspnea improved at 3, 6, and 12 months in this sample of critically ill COVID-19 patients, but PFT remained abnormal in 50% of patients and the same proportion still complained of at least exertional dyspnea. Based on continued improvements observed from 3 to 12 months, it is anticipated that COVID-19 ICU patients will continue to recover similar to ARDS patients.[38]

Declarations

Ethics approval and consent to participate

All included patients provided written informed consent to participate in the study. The study protocol was approved by the Saint-Pierre University Hospital ethics committee (AK/16–01–18/4613) and by the Brugmann University Hospital ethics committee (CE2020/141). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for Publication

Not applicable

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Author Contributions

SA, MB, MC, AR, AC, and NDV collected the data; SA, AVB, SAl, MB, DDB, and NDV performed data analyses and prepared the manuscript. SA, AC, AVB, OM, SAl, MB, NDV, MC, and AR have approved the final version of the manuscript.

Declaration of Competing Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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References

1. WHO Coronavirus COVID-19 Dashboard. Available at: https://covid19.who.int/. Accessed February 21, 2022.
2. European Centre for Disease Prevention and Control. COVID-19 vaccination. Available at: https://ecdc.europa.eu. Accessed November 2, 2022.
3. Ranieri VM, Rubenfeld GD, et al.ARDS Definition Task Force Acute respiratory distress syndrome: the Berlin Definition. *JAMA*.. 2012;307(23):2526–2533. doi:10.1001/jama.2012.5669Hor.
4. Horby P, Lim WS, et al.RECOVERY Collaborative Group Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704. doi:10.1056/nejmoa2021436.

5. Zeng N, Zhao YM, Yan W, et al. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. *Mol Psychiatry*. 2023;28(1):423–433. doi:10.1038/s41380-022-01614-7.
6. Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*. 2021;9(7):747–754. doi:10.1016/S2213-2600(21)00174-0.
7. Lorent N, Vande Weygaerde Y, Claeys E, et al. Prospective longitudinal evaluation of hospitalised COVID-19 survivors 3 and 12 months after discharge. *ERJ Open Res*. 2022;8(2):00004–02022. doi:10.1183/23120541.00004-2022.
8. Eberst G, Claudé F, Laurent L, et al. Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia. *Ann Intensive Care*. 2022;12(1):23. doi:10.1186/s13613-022-00997-8.
9. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232. doi:10.1016/s0140-6736(20)32656-8.
10. Truffaut L, Demey L, Bruyneel AV, et al. Post-discharge critical COVID-19 lung function related to severity of radiologic lung involvement at admission. *Respir Res*. 2021;22(1):29. doi:10.1186/s12931-021-01625-y.
11. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324–1343. doi:10.1183/09031936.00080312.
12. Laveneziana P, Albuquerque A, Aliverti A, et al. ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J*. 2019;53(6):1801214. doi:10.1183/13993003.01214-2018.
13. Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J*. 2020;56(1):2001494. doi:10.1183/13993003.01494-2020.
14. Munker D, Veit T, Barton J, et al. Pulmonary function impairment of asymptomatic and persistently symptomatic patients 4 months after COVID-19 according to disease severity. *Infection*. 2022;50(1):157–168. doi:10.1007/s15010-021-01669-8.
15. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J*. 1999;14(2):270–274. doi:10.1034/j.1399-3003.1999.14b06.x.
16. Donini LM, Poggiogalle E, Mosca V, Pinto A, Brunani A, Capodaglio P. Disability affects the 6-minute walking distance in obese subjects (BMI > 40 kg/m^2). *PLoS One*. 2013;8(10):e75491 11. doi:10.1371/journal.pone.0075491.
17. Anastasio F, Barbuto S, Scarnecchia E, et al. Medium-term impact of COVID-19 on pulmonary function, functional capacity and quality of life. *Eur Respir J*. 2021;58(3):2004015 16. doi:10.1183/13993003.04015-2020.
18. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. *J Rehabil Med*. 2020;52(5) jrm00063. doi:10.2340/16501977-2694.
19. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247–2261. doi:10.1378/chest.128.4.2247.
20. Orme Jr J, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2003;167(5):690–694. doi:10.1164/rccm.200206-542oc.
21. Latronico N, Peli E, Calza S, et al. Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax*. 2022;77(3):300–303. doi:10.1136/thoraxjnl-2021-218064.
22. Núñez-Seisdedos MN, Lázaro-Navas I, López-González L, et al. Intensive care unit-acquired weakness and hospital functional mobility outcomes following invasive mechanical ventilation in patients with COVID-19: a single-centre prospective cohort study. *J Intensive Care Med*. 2022;37(8):1005–1014. doi:10.1177/08850666221100498.
23. Pfoh ER, Wozniak AW, Colantuoni E, et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. *Intensive Care Med*. 2016;42(10):1557–1566. doi:10.1007/s00134-016-4530-1.
24. Demoule A, Morawiec E, Decavele M, et al. Health-related quality of life of COVID-19 two and 12 months after intensive care unit admission. *Ann Intensive Care*. 2022;12(1):16 20. doi:10.1186/s13613-022-00991-0.
25. Weihe S, Mortensen CB, Haase N, et al. Long-term cognitive and functional status in Danish ICU patients with COVID-19. *Acta Anaesthesiol Scand*. 2022;66(8):978–986. doi:10.1111/aas.14108.
26. Cavalleri J, Treguier D, Deliège T, et al. One-year functional decline in COVID-19 and non-COVID-19 critically ill survivors: a prospective study incorporating a pre-ICU status assessment. *Healthcare (Basel)*. 2022;10(10):2023. doi:10.3390/healthcare10102023.
27. Ghosn J, Bachelet D, Livrozet M, et al. Prevalence of post-acute COVID-19 symptoms twelve months after hospitalisation in participants retained in follow-up: analyses stratified by gender from a large prospective cohort. *Clin Microbiol Infect*. 2022;29:254.e7–254.e13. doi:10.1016/j.cmi.2022.08.028.
28. Salaffi F, Di Carlo M, Carotti M, et al. The impact of different rheumatic diseases on health-related quality of life: a comparison with a selected sample of healthy individuals using SF-36 questionnaire, EQ-5D and SF-6D utility values. *Acta Biomed*. 2019;89(4):541–557. doi:10.23750/abm.v89i4.7298.
29. Luchesa CA, Mafort TT, Silva RR, et al. Contribution of lung function in predicting distance covered in the 6-min walk test in obese Brazilian women. *Braz J Med Biol Res*. 2020;53(12):e10279. doi:10.1590/1414-431X202010279.
30. Zhou F, Tao M, Shang L, et al. Assessment of sequelae of COVID-19 nearly 1 year after diagnosis. *Front Med (Lausanne)*. 2021;23(8):717194. doi:10.3389/fmed.2021.717194.
31. Villar PME, Mendes PRA, Kiyota TA, et al. Oximetry at admission as a predictor of tomographic and functional impairment after 3-6 months in hospitalized patients with COVID-19. *J Int Med Res*. 2023;51(6):3000605231177187. doi:10.1177/03000605231177187.
32. Klopfenstein T, Gendrin V, Kadiane-Oussou NJ, et al. Tocilizumab in COVID-19 pneumonia: practical proposals based on a narrative review of randomised trials. *Rev Med Virol*. 2022;32(1):e2239. doi:10.1002/rmv.2239.
33. Angamo MT, Mohammed MA, Peterson GM. Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis. *Infection*. 2022;50(1):27–41. doi:10.1007/s15010-021-01671-0.
34. Achkar M, Jamal O, Chaaban T. Post-COVID lung disease(s). *Ann Thorac Med*. 2022;17(3):137–144. doi:10.4103/atm.atm_103_22.
35. Sankar K, Gould MK, Prescott HC. Psychological morbidity after COVID-19 critical illness. *Chest*. 2023;163(1):139–147. doi:10.1016/j.chest.2022.09.035.
36. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. *SAGE Open Med*. 2016;4:2050312116671725. doi:10.1177/2050312116671725.
37. Dusart C, Smet J, Chirumberro A, et al. Pulmonary functional outcomes at 3 months in critical COVID-19 survivors hospitalized during the first, second, and third pandemic waves. *J Clin Med*. 2023;12(11):3712. doi:10.3390/jcm12113712.
38. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293–1304. doi:10.1056/nejmoa1011802.