Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-218064).

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Received 9 August 2021
Accepted 10 September 2021

To cite: Latronico N, Peli E, Calza S, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2021-218064

ABSTRACT

We report on the outcome of 114 COVID-19-associated acute respiratory distress syndrome (ARDS) survivors evaluated at 3, 6 and 12 months after intensive care unit discharge with assessment of physical, mental and cognitive impairments. Critical illness polyneuromyopathy was diagnosed in 23 patients (39%). Handgrip dynamometry was 70% predicted at 3 months and significantly improved over time, whereas the 6 min walk test (80% predicted) and severe fatigue (27% of patients) did not. Independence in activities of daily living (ADL) was achieved by 98% at 3 months. Cognitive impairment (28% at 3 months) improved over time, whereas depression, anxiety and post-traumatic stress disorder symptoms, present in 9%, 10% and 4% at 3 months, did not. Normalised health-related quality of life was good. COVID-19-associated ARDS leads to persisting impairment in performance-based measures of physical function, while ADL, cognitive and mental health status, and health-related quality of life may be less impaired. Trial registration number NCT04608994.

INTRODUCTION

Survivors of acute respiratory distress syndrome ('classic' ARDS) frequently experience long-lasting physical, cognitive and mental health impairments, referred to as postintensive care syndrome (PICS).[1] Patients with COVID-19-associated ARDS (C-ARDS) may suffer the same long-term consequences as survivors of classic ARDS,[2] but comprehensive studies assessing all three dimensions of PICS are lacking. We aimed to characterise the frequency of PICS-related impairments, along with activities of daily living (ADL) and health-related quality of life (HRQoL) status, in C-ARDS survivors at 3, 6 and 12 months after intensive care unit (ICU) discharge.

METHODS

In this prospective longitudinal study, we report on 114 of 137 (83%) consecutive critically ill adult patients (≥18 years old) with confirmed SARS-CoV-2 infection and ARDS[3] discharged alive from the Spedali Civili University Hospital in Brescia, Italy, during the first pandemic wave in a Western country from 23 February 2020 until 30 June 2020. Written informed consent was obtained from all participants.

FOLLOW-UP PROTOCOL

A detailed presentation of the follow-up protocol is presented in the online supplemental methods. At 3 months, patients were evaluated via a structured telephone interview. We also reviewed chest X-rays (using Brixia score), clinical charts, oxygen and medication prescription, and dyspnoea (using modified Medical Research Council (mMRC) score).

At 3, 6 and 12 months, we performed a standardised assessment at the local follow-up clinic, including physical, cognitive and mental health status, HRQoL (36-Item Short-Form Health Survey (SF-36) version 1), return to work and ADL (via Barthel Index). We assessed muscle weakness (Medical Research Council Sum Score), handgrip dynamometry, nerve muscle function (via simplified peroneal nerve test (PENT)[4] and electromyography (EMG)), activity limitation via 6 min walk test and participation restrictions via SF-36 role limitations. Cognitive impairments were assessed using the Montreal Cognitive Assessment (MoCA), with a maximum score of 30 and a suggested cut-off score for normalcy of 26. When patients scored less than 26, we used the following classification: 18–25=mild cognitive impairment, 10–17=moderate cognitive impairment and less than 10=severe cognitive impairment. We used the Hospital Anxiety and Depression Scale subscales for depression and anxiety, each classified as abnormal if the score was ≥8, and the post-traumatic stress disorder (PTSD) checklist for diagnostic and statistical manual of mental disorders (DSM)-5 for PTSD (range 0–80, cut-off score >32 indicating PTSD). Between 3 and 6 months, we completed chest X-ray and spirometry.

A sample size calculation was not performed a priori with the study sample representing all eligible survivors treated during the study period. Quantitative variables were summarised using median and IQR (Q1–Q3), while categorical variables were reported as count and percentages. To compare the outcomes at 3, 6 and 12 months, linear mixed models with robust variance estimator for continuous variables or cumulative link mixed models for ordinal variables were used. All tests were two-sided, and a p value less than 0.05 was considered statistically significant. Statistical models assumed a fixed effect for follow-up time (coded as three-level factor) and patients as a random factor (random intercept). We included all data available at either 3, 6 or 12 months, assuming a missing at random scenario with no data imputation performed. We used STATA V.17 and R V.4.0.3 statistical packages.

RESULTS

During the study period, 224 patients with C-ARDS were admitted to our ICU (figure 1). Of these, 137

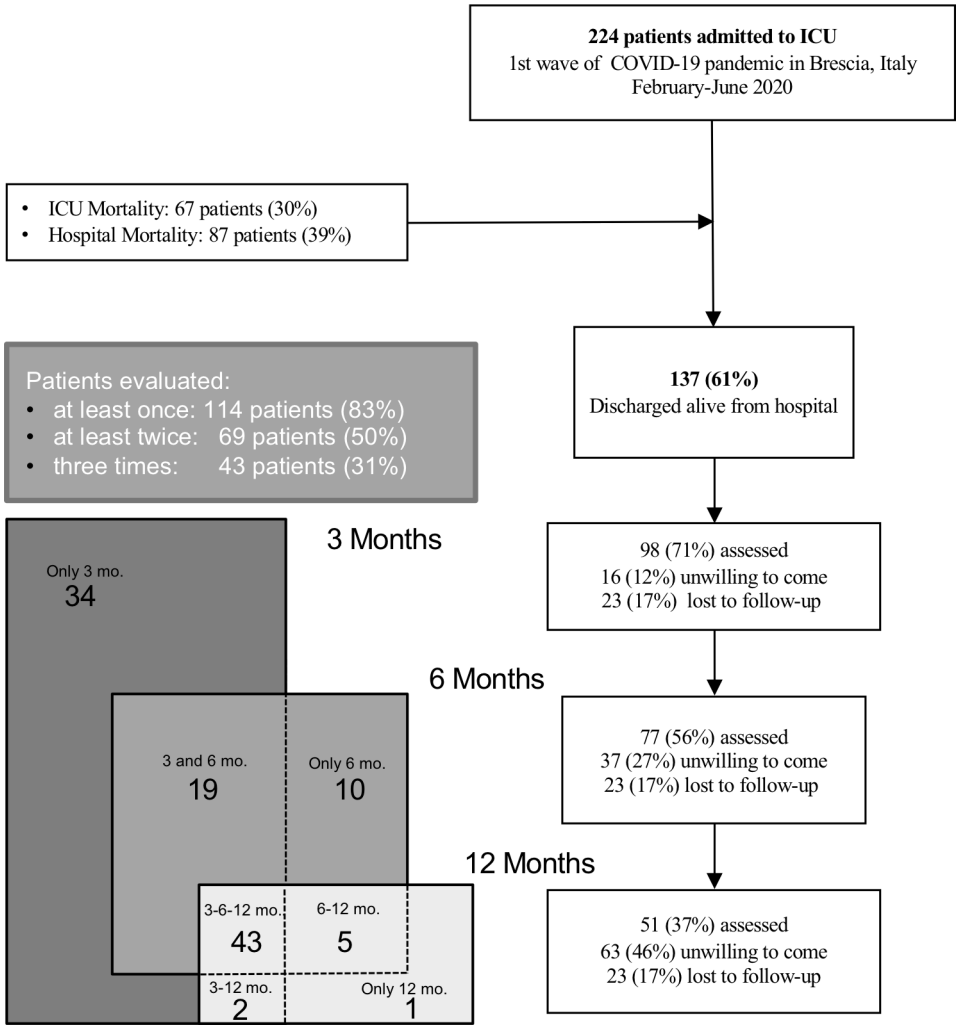

Figure 1 Study flow chart. Of 137 survivors, 23 (17%) were lost to follow-up and 114 (83%) were evaluated inperson at least once. 45 patients were evaluated only once (34 patients at 3 months, 10 at 6 months and 1 at 1 year), 26 twice (19 patients at 3 and 6 months, 2 at 3 and 12 months, and 5 at 6 and 12 months) and 43 three times. ICU, intensive care unit.

patients were discharged alive from the hospital and 114 (83%) were evaluated at least once (figure 1). Demographic and clinical data are shown in online supplemental tables E1 and E2.

At 3 months, the median handgrip strength was 70% of predicted (IQR 63%–83%), with a significant improvement over time (table 1). The median 6 min walk distance was 80% of predicted (IQR 60%–90%) and severe fatigue was reported by 33% of patients, with neither improving over time. Barthel Index demonstrated independence in ADL in 98% at 3 months. PENT (performed in 59 patients) showed critical illness polyneuromyopathy in 23 (39%). Of these, 13 had complete EMG at 6 months, with 9 (69%) having persistent EMG abnormalities. Barthel Index demonstrated independence in ADL in 95 patients (98%) at 3 months up to 100% at 1 year (table 1). Return to work at 3, 6 and 12 months occurred in 66% (65 of 98), 69% (49 of 77) and 86% (44 of 51) of patients.

Most patients had only mild cognitive or mental health impairments (online supplemental table E3) and HRQoL was good relative to Italian norms (table 2).

At 3 months, no patient required supplemental oxygen or reported severe dyspnoea. Chest X-ray (available in 60 patients) was abnormal in 38 (63%); the Brixia score significantly improved compared with hospital discharge (median 2 (IQR 0–3) vs 8 (IQR 4–10); p<0.001). Spirometry (in 59 patients) showed mainly a restrictive pattern and altered diffusing capacity for carbon monoxide (online supplemental table E4).

DISCUSSION

In this prospective longitudinal study of 114 C-ARDS survivors, the main features were impaired handgrip strength and 6 min walk distance and severe fatigue. Cognitive and mental health status were relatively less frequently impaired, with HRQoL similar to population norms.

To date, published studies have relied on a single assessment at 6 months[5] or 4 months,[6] precluding evaluation of the trajectory of recovery. Moreover, muscle weakness was self-reported[5] or the method used to diagnose muscle weakness 'compatible with ICU-related neuromyopathy' was not specified.[6] In our series, critical illness neuromyopathy was diagnosed in 39% of patients using accurate neurophysiological investigations. Handgrip strength was <80% of predicted value in 70% of patients at 3 months, but improved, whereas 6 min walk test remained persistently impaired in 40% at 3, 6 and 12 months. Compared with classic ARDS, the 6 min walk test in our cohort was less impaired (eg, 420 m vs 361 m at 3 months)[7] and fatigue was less prevalent (eg, 34% vs 70% at 6 months)[8] (online supplemental table E5). Chest X-ray was altered in 63% of patients and lung diffusion

Table 1 Physical outcomes* of survivors of COVID-19-associated acute respiratory distress syndrome

	3 months (n=98)	6 months (n=77)	12 months (n=51)	P value†
Body mass index, median (IQR)	27 (24–30)	28 (26–30)	28 (26–31)	0.959
Body mass index gain‡, median (IQR)	−0.7 (−2.1 to 0.6)	−0.4 (−1.7 to 2.6)	0.4 (−1.1 to 0.9)	
Mini Nutritional Assessment Short-Form (MNA-SF)				<0.01
Median (IQR)	13 (11–14)	14 (13–14)	14 (13–14)	
Risk of malnutrition or being malnourished (MNA-SF <12) (%)	31 (32)	10 (14)	5 (9.8)	
Global muscle strength using Medical Research Council Sum Score (MRCss)				>0.99
Median (IQR)	60 (60–60)	60 (60–60)	60 (60–60)	
Abnormal value (MRCss <48), n (%)	3 (3)	1 (1)	1 (2)	
Dominant handgrip strength (kg), median (IQR)	29 (23-34)	32 (24–41)	37 (28–42)	<0.01
Dominant handgrip strength (% predicted)‡	70 (63–84)	81 (71–93)	85 (79–95)	<0.01
6 min walk test (m), median (IQR)	420 (352–487)	420 (385–480)	420 (420–480)	0.802
6 min walk test (% predicted)†, median (IQR)	80 (60–90)	70 (70–80)	80 (70–100)	0.840
6 min walk test, n (%) of abnormal test§	33 (40)	18 (42)	17 (36)	0.884
Fatigue (Fatigue Severity Score), median (IQR)	27 (15–41)	27 (13–38)	20 (13–39)	0.113
Fatigue (Fatigue Severity Score ≥36), n (%) of abnormal test	31 (33)	26 (34)	13 (26)	0.429
Barthel Index, n (%) of patients dependent (<80)	2 (2)	1 (1)	0 (0)	0.094
Return to work, n (%) of patients				0.010
Full employment	63 (64)	49 (64)	44 (86)	
Reduced effectiveness at work	2 (2)	5 (7)	0 (0)	
No return to work	30 (31)	22 (22)	7 (14)	

*Unknown or missing data: body mass index: 2 (3 months), 1 (6 months), 0 (12 months); body mass index gain: 38 (3 months), 18 (6 months), 8 (12 months); MNA-SF: 1 (3 months), 0 (6 months), 0 (12 months); MRCss: 6 (3 months), 29 (6 months), 3 (12 months); handgrip strength: 32 (3 months), 31 (6 months), 21 (12 months); 6 min walk test: 11 (3 months), 34 (6 months), 4 (12 months); Fatigue Severity Score: 5 (3 months), 1 (6 months), 1 (12 months); Barthel Index: 1 (3 months), 0 (6 months), 0 (12 months); return to work: 3 (3 months), 6 (6 months), 0 (12 months).
†P values are calculated for comparisons across the 3-month, 6-month and 12-month assessments using linear mixed models for continuous variables or cumulative link mixed models for ordinal variables.
‡Body mass index gain was calculated as the difference between the body mass index at follow-up and the body mass index at intensive care unit admission.
§Calculated using established reference values provided by Gilbertson *et al*[10]
¶Predicted value for 6 min walk test was calculated according to Enright *et al*[11]

capacity for carbon monoxide (DLCO) reduced in 49%, similar to classic ARDS, warranting assessment at later follow-up.

Compared with the French COMEBAC study in 51 intubated patients,[6] our cohort had a lower incidence of cognitive dysfunction (28% vs 42%), and symptoms of anxiety (9% vs 26%), depression (10% vs 18%) and PTSD (4% vs 10%). Notably, deficits in cognitive function are much more common when investigated using batteries of neuropsychological tests rather than screening tests such as MoCA used in our study and the COMEBAC study;[6] hence, these findings may be understated (online supplemental table E5). The findings appear favourable especially when considered in the context of our other findings regarding ADL and HRQoL and when compared with classic ARDS, where cognitive impairments are described in up to 82% at 3 months and 38% at 6 months (online supplemental table E5). Our findings of 86% return to work at 1 year are also favourable compared with 40% in prior ARDS study[9] (online supplemental table E5). Reasons for these differences remain speculative and are likely multifactorial. We hypothesise that our follow-up clinic, by providing clinical support to patients and serving as a centre to guide referral to other specialists, helped in covering care delivery gaps during transition between points of care, a major problem during the COVID-19 pandemic. Thus, taking responsibility for coordination across the continuum of healthcare might have contributed to improved patient outcome.

Table 2 Health-related quality of life* of survivors of COVID-19-associated acute respiratory distress syndrome

	3 months (n=98) Median (IQR)	6 months (n=77) Median (IQR)	12 months (n=51) Median (IQR)	P value†
Physical functioning	50 (43–55)	52 (46–55)	52 (48–55)	0.082
Role, physical	39 (28–56)	56 (35–56)	56 (35–56)	<0.01
Bodily pain	55 (44–56)	54 (43–56)	56 (48–56)	0.425
General health	54 (44–59)	50 (43–59)	54 (48–59)	0.093
Vitality	53 (46–59)	52 (44–59)	54 (47–59)	0.600
Social functioning	54 (44–60)	49 (44–60)	54 (49–60)	0.364
Role, emotional	56 (39–56)	56 (48–56)	56 (48–56)	0.335
Mental health	55 (51–62)	58 (51–62)	56 (53–62)	0.558
Physical component summary (PCS)	43 (36–51)	50 (39–53)	50 (44–53)	<0.01
Mental component summary (MCS)	52 (46–56)	50 (45–57)	54 (47–60)	0.086

Each of the eight scale measures has been reported as a t-score. The t-scores are a linear transformation of the 0–100 possible range scoring for the SF-36 scales that give every scale a mean of 50 and SD of 10, normed to the Italian general population according to Apolone *et al*[12] . PCS and MCS were calculated according to Taft *et al*[13] using the coefficient from Ware *et al*.[14] PCS and MCS are reported as a t-score metric normed for the Italian general population.
*Unknown or missing data: for all the items of SF-36 version 1: 22 (3 months), 5 (6 months), 2 (12 months).
†P values are calculated for comparisons across the 3-month, 6-month and 12-month assessments using linear mixed models.
SF-36, 36-item Short-Form Health Survey.

The major strengths of this study include its focus on mechanically ventilated patients with C-ARDS, with inperson assessment at 3, 6 and 12 months using a comprehensive multidimensional evaluation. However, this is a single-centre study and may not be generalisable. Moreover, although we could evaluate nearly all patients at least once, repeated assessment was possible in only half due to restricted hospital access and unwillingness of patients to leave their homes during the second and third pandemic waves, thus limiting the strength of our conclusions.

In conclusion, in our single-centre study of patients with C-ARDS from Italy, we found that the inperson performance-based measures of physical status may be impaired in most

patients up to 1 year after ICU discharge. Conversely, patient-reported physical functioning, ADL, return to work, cognitive and mental function, and HRQoL may be relatively less impaired than the performance-based measures of physical status and in comparison with pre-COVID-19 studies of ARDS.

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Acknowledgements We thank Dr Marco Trivelli, former Regional Chief Executive Officer of Lombardy region, Dr Camillo Rossi MD, Chief Medical Officer, and Dr Massimo Lombardo MD, Chief Executive Officer, for supporting the project, Dr Paolo Musatti, Chief Nurse Officer, for providing nurse support to the follow-up clinic, and Mr Michele Guerini, Pulmonary Technician, for pulmonary function testing, all at the Spedali Civili University Hospital in Brescia, Italy. We are grateful to the following residents of the School of Specialty of Anaesthesia and Critical Care Medicine of the University of Brescia for their support in reviewing clinical charts and chest X-ray, material preparation and data collection: Serena Ambrosi, Marta Belleri, Roberto Bolazzi, Federica Bongiovanni, Riccardo Contarino, Laura Ferrari, Alberto Forza, Lucrezia Guadrini, Teresa Iob, Federica Magri, Mattia Marchesi, Silvia Mazzoleni and Vittorio Montini.

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Contributors NL, EP, FAR and SP contributed to the study conception and design. NL was responsible for study supervision. Clinical chart review, chest X-ray analysis, pulmonary function test, material preparation and data collection were performed by all collaborators of the LOng Term Outcome (LOTO) Research Center. SC and SP did the statistical analyses. DMN and JM critically revised the manuscript and contributed important intellectual content. The first draft of the manuscript was written by NL and SP. All authors participated in data interpretation and discussion, and read and approved the final manuscript. NL and SP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The study was funded by Fondazione Alessandra Bono Onlus, a non-profit organisation in Italy (https://www.fondazionealessandrabono.it).

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The Brescia Ethics Committee approved the study (NP 2595).

Provenance and peer review Not commissioned; externally peer reviewed.

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