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

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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

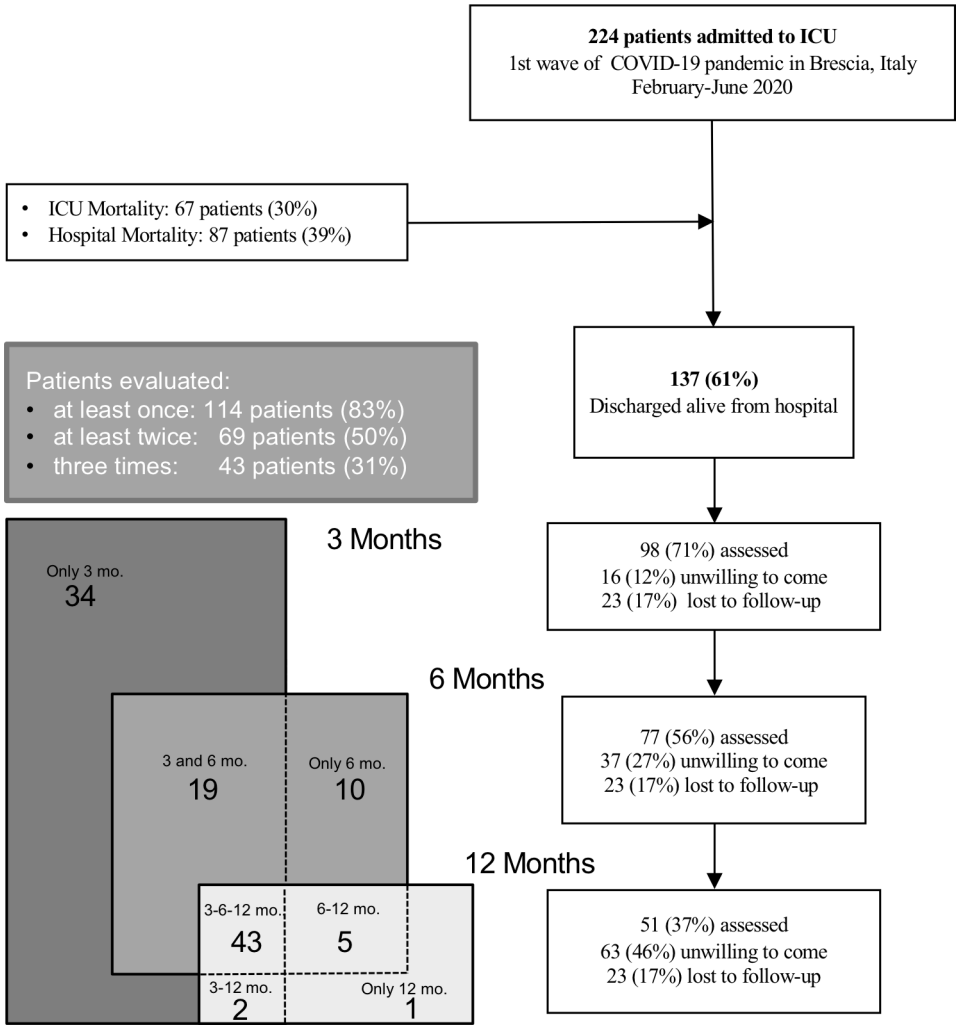

Figure 1 Study flow chart. Of 137 survivors, 23 (17%) were lost to follow-up and 114 (83%) were evaluated inperson at least once. 45 patients were evaluated only once (34 patients at 3 months, 10 at 6 months and 1 at 1 year), 26 twice (19 patients at 3 and 6 months, 2 at 3 and 12 months, and 5 at 6 and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

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REFERENCES

1 Needham DM, Davidson J, Cohen H, *et al*. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502–9.
2 Bangash MN, Owen A, Alderman JE, *et al*. COVID-19 recovery: potential treatments for post-intensive care syndrome. *Lancet Respir Med* 2020;8:1071–3.
3 Acute respiratory distress syndrome. *JAMA* 2012;307:2526–33.
4 Latronico N, Nattino G, Guarneri B, *et al*. Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. *F1000Res* 2014;3:127.
5 Huang C, Huang L, Wang Y, *et al*. 6-month consequences of COVID-19 in patients discharged from Hospital: a cohort study. *Lancet* 2021;397:220–32.
6 Writing Committee for the COMEBAC Study Group, Morin L, Savale L, *et al*. Four-Month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021;325:1525–34.
7 Parry SM, Nalamalapu SR, Nunna K, *et al*. Six-Minute walk distance after critical illness: a systematic review and meta-analysis. *J Intensive Care Med* 2021;36:343–51.
8 Neufeld KJ, Leoutsakos J-MS, Yan H, *et al*. Fatigue symptoms during the first year following ARDS. *Chest* 2020;158:999–1007.
9 Kamdar BB, Suri R, Suchyta MR, *et al*. Return to work after critical illness: a systematic review and meta-analysis. *Thorax* 2020;75:17–27.
10 Gilbertson L, Barber-Lomax S. Power and pinch grip strength recorded using the hand-held Jamar® dynamometer and B+L hydraulic pinch gauge: British normative data for adults. *British Journal of Occupational Therapy* 1994;57:483–8.
11 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384–7.
12 Apolone G, Mosconi P. The Italian SF-36 health survey: translation, validation and norming. *J Clin Epidemiol* 1998;51:1025–36.
13 Taft C, Karlsson J, Sullivan M. Do SF-36 summary component scores accurately summarize subscale scores? *Qual Life Res* 2001;10:395–404.
14 Ware JE, Sherbourne CD. The mos 36-item short-form health survey (SF-36). *I. Conceptual framework and item selection. Med Care* 1992;30:473–83 http://www.ncbi.nlm.nih.gov/pubmed/1593914

ONLINE SUPPLEMENT

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

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SUPPLEMENTAL METHODS

During the first pandemic wave of SARS-CoV-2 in the territory of Lombardy, Italy, the first in a western country, the regional health authorities identified 15 "large hub hospitals" to cohort COVID-19 patients based on expertise in infectious disease and advanced management of acute respiratory distress syndrome (ARDS), including Venous-Venous ECMO [1,2]. After the first case identified on February 20, 2020 [1] and up through March 18, 2020, a total of 17,713 people had tested positive for the new SARS-CoV-2 in Lombardy and 1593 (9%) had been admitted to the ICU [2]. The Spedali Civili University hospital (SCH) in Brescia, one of the largest hospitals in Italy serving a territory of nearly 1.2 million people in the eastern Lombardy, was one of the first first-responder hub hospitals [3] and the ICUs were rapidly saturated by the sharp increase in the number of patients requiring prolonged ventilatory support. Triage for ICU admission proceeded according to the recommendations issued by the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) as of March 6, 2020 [4], which considered age and comorbidities together with the type and severity of the current disease and the presence and reversibility of organ failures as key factors for deciding upon ICU admission. In a preliminary analysis of our data[5], we found no difference in terms of age and a higher proportion of patients with comorbidities in our series compared to the ICU cohort of 3,988 patients admitted by the Lombardy ICU network [2].

The data presented in the current study refer to the activity of the SCH follow-up clinic in assessing the long-term physical (including respiratory), mental and cognitive impairments and their impact on activities of daily living (ADL) and health-related quality of life (HRQoL) in survivors of COVID-19-associated ARDS.

The follow-up clinic

The study is part of a local follow-up program that began in 2014 and is structured to follow critical illness survivors via a specialized team at 6 and 12 months after ICU discharge, providing clinical support and a platform for research on the natural history of PICS and therapeutic interventions and serving as a center to guide patients' referral to other specialists.

The team consists of intensive care physicians and nurses who have been trained in the use of instruments to assess the physical, cognitive and mental health impairments associated with the post-intensive care syndrome (PICS) [6] in addition to measures of ADLs and HRQOL. After waning of the first wave of COVID-19 pandemic in Italy in May 2020, we added a 3-month ambulatory visit to the usual 6-month and 12-month visits to take care of COVID-19 patients at an earlier stage. The follow-up clinic provides clinical support to patients and a platform for research on the natural history of PICS and therapeutic interventions and serves as a center to guide referral to other specialists.

Assessment at hospital discharge

Due to the restrictions and resource limitations imposed by the pandemic, we were unable to follow the patients during the period from ICU discharge to hospital discharge. Thus, we used a structured telephone interview at 3 months to define the

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patients' clinical condition at hospital discharge and the current condition, hospital discharge disposition and current place of residence, along with the patients' willingness to come to the ambulatory clinic for assessment. We also reviewed the medical charts and chest X-ray, patient's oxygen needs, presence of dyspnea (see below, Respiratory symptoms), and drug prescription of antipsychotic drugs, corticosteroids and deep vein thromboprophylaxis at hospital discharge, as described elsewhere[7].

For subjects consenting to participate in follow-up, these data were also used to delineate the trajectory of recovery from the hospital discharge up to the 1-year follow-up visit.

Data collection before ICU admission, at hospital discharge and during telephone interview

A detailed clinical history was taken to define the patient's clinical condition before COVID-19 (pre-existing comorbidities, pharmacological treatments). The patients' clinical condition at hospital discharge was assessed during the telephone interview and/or by reviewing the clinical charts. We collected the following information: patient's oxygen needs, presence of dyspnea, drug prescription, independence in ADL with the Barthel Index [8] and the "Needed physical assistance to stand" item of the Physical Function in Intensive Care Test. The "Needed physical assistance to stand" of the Physical Function in Intensive Care Test was used to assess to categorize sit-to-stand assistance as 0= unable; 1= two people needed; 2= one person needed; and 3= no assistance needed [9]. Family members were interviewed in case of patients' difficulty in reporting their status. The Barthel index, an ordinal scale that measures the subject's capacity to perform 10 basic activities of daily living (ADL), was used to evaluate performance of ADLs [8]. This index gives a quantitative estimation of the patient's level of dependency with scores ranging from 0 and 100, with higher scores indicating increasing independence. We categorized the Barthel Index as: 80-100 (Independent, with a score of 100 indicating full independence); 60-79 (Minimally dependent); 40-59 (Partially dependent); and <20 (Totally dependent).

Chest X-ray evaluation

We used the Brixia Score [10] to assess the chest X-Ray at all follow-up time points. With this score, the lungs are divided into six zones on frontal chest projection, and a score of 0 (no lung abnormalities), 1 (interstitial infiltrates), 2 (interstitial and alveolar infiltrates with interstitial predominance), or 3 (interstitial and alveolar infiltrates with alveolar predominance) is assigned to each zone; the score of each lung zone is summed up the obtain a global score varying from 0 to 18, with higher numbers indicating greater severity.

The follow-up visits at 3, 6 and 12 months

The visit was performed in-person and included the following:

1- The nutritional status at follow-up using the Mini Nutritional Assessment short-form (MNA-SF) [11], and classified as: normal nutritional state (MNA-SF score: 12-14); risk for malnutrition (8-11); malnourished (0-7) [12];

2- The patient's physical functioning was assessed according to the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization using three different constructs: a) impairments at the body or body part level; b) activity limitations (the whole person); and c) restrictions of participation (the whole person in a societal context) [13].

3a) Body function and structure impairments.

We assessed muscle weakness using the Medical Research Council sum score (MRCss) and handgrip dynamometry. With the MRCss, individual scores of six functional limb muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) on each body side are summed up to yield a global estimate of muscle strength [14]. The MRCSss varies between 0 (complete paralysis) and 60 (normal strength), with scores of less than 48 indicating significant weakness (often referred to as "ICU-acquired weakness", ICUAW) and scores of less than 36 indicating severe weakness [15]. With handgrip dynamometry we considered that patients had significant weakness when muscle strength was less than 11 Kg in males and less than 7.5 kg in females [16,17]. We also reported results as percentage of the predicted normal value standardized per age and sex [18].

We assessed the function of peripheral nerves and muscles using the peroneal nerve test (PENT), a simplified neurophysiological technique that has been validated as a screening test for critical illness polyneuromyopathy [19,20]. A compound muscle action potential value <5.4 mV present in both legs was considered abnormal. Patients with abnormal PENT at 3 months were submitted to complete electromyography (EMG) at 6 months.

3b) Activity limitations.

These were assessed using performance-based and patient-reported measures of activity limitations.

For performance-based measure of activity limitations, we used the six-minute walk test, performed in accordance with the American Thoracic Society recommendations [21] with predicted values calculated using an existing equation based on age, sex, height, and body weight [22]. Repeat testing to minimize intra-day variability was not performed.

For self-reported measures of activity limitations, we used the 36-Item Short-Form Health Survey (SF-36 Version 1) physical functioning [23]. It includes 3 possible answers (Not limited; Limited a little; Limited a lot) to 10 items on vigorous and moderate activities; lifting or carrying groceries; climbing one or several flights of stairs; bending, kneeling, or stooping; walking more than a mile, one block or several block; bathing or dressing independently. Scoring method is detailed in the section on health-related quality of life.

We also evaluated the fatigue using the Fatigue Severity Score (FSS), a 9-item scale with questions related to how fatigue affects the person's activities and lifestyle during the past two weeks [24]. Each item consists of statements that are scored on a 7-point Likert-type scale ranging from 1 ("strongly disagree") to 7 ("strongly agree"). The mean score of the items is

used as the FSS score, the higher the score the greater the fatigue severity. An FSS ≥36 was considered as an indicator of severe fatigue.

3c) Participation restrictions.
These were assessed using the SF-36 role limitations.

4) Cognition.
The Montreal Cognitive Assessment (MoCA), a short cognitive screening tool that has been validated as a general cognitive screening test [25] and is recommended by the Society of Critical Care Medicine for ICU patients [26], was administered in-person. MoCA explores different cognitive domains, namely visuospatial and executive functioning (5 points), animal naming (3 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (short-term memory, 5 points), and orientation (6 points). The maximum score is 30, indicating the best possible cognitive performance. The suggested cutoff score for normalcy is 26/30. 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 [25].

5) Mental health.
We assessed depression, anxiety and post-traumatic stress disorder symptoms, which are highly prevalent in ARDS survivors [27]. The Hospital Anxiety and Depression Scale (HADS) subscales for depression and for anxiety were each classified as abnormal if the score was ≥8) [28]. The Posttraumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5) is a 20-item self-report measure that assesses the presence and severity of PTSD symptoms. The 20 items on the PCL-5 correspond with DSM-5 criteria for PTSD and are rated by respondents from 0 ("not at all") to 4 ("extremely"), with a total score ranging from 0 to 80 and a cutoff score >32 indicating PTSD [29].
We also assessed sleep disturbances using the Insomnia Severity Index (ISI ≥8), a brief instrument that is designed to assess the severity of both nighttime and daytime components of insomnia. ISI was classified as follows: No clinically significant insomnia (score: 0–7), subthreshold insomnia (8–14), moderate insomnia (15–21), and severe insomnia (22–28) [30].

6) HRQoL.
We used the SF-36 version 1 [23], an extensively validated generic quality of life measure that consists of the following 8 multiple-item dimensions: PF - Physical functioning ; RP - Role limitations due to physical health problems; SF - Social functioning; BP - Bodily pain; MH - General mental health, covering psychological distress & well-being; RE - Role limitations due to emotional problems; VT - Vitality, energy or fatigue; GH - General health perceptions.

For each of the 8 subscale scores, we calculated the t-score normalizing the value to a 100 point scale[31] and compared it to the Italian normalized reference values[23].
We also calculated two high-order summary scores, the physical component summary (PCS) and the mental component summary (MCS) scores, as described by Taft et al. [32]. First, z-scores were determined for each of the 8 subscale scores by subtracting the subscale means for the Italian general population sample and then dividing the difference by the standard deviation of the Italian general population [23]. Second, the 8 z-scores were multiplied by the corresponding subscale factor score coefficient. Last, T-scores were determined by multiplying the obtained PCS and MCS by 10 and adding 50 to the product, to yield a mean of 50 and a standard deviation of 10 for the Italian norm population [23,32,33].

7) ADL
We used the Barthel Index to measure ADL, as described above [8].

8) Respiratory symptoms.
Dyspnea was defined as present if the patient reported the need to stop "for breath after walking about 100 yards or after a few minutes on the level", corresponding to a modified Medical Research Council Dyspnea (mMRC) scale score ≥3 [34]. We collected the mMRC only as a binary outcome (dyspnea present or absent).

9) The chest X-Ray was assessed using the Brixia Score, as described above [10].

10) Each subject performed spirometry (BIOMEDIN Instruments, Padua, Italy). Slow vital capacity (VC) and inspiratory capacity (IC) were measured twice using a bell spirometer at rest in sitting position. At least three acceptable and reproducible maximal full expiratory maneuvers were performed to measure forced vital capacity (FVC), maximal expiratory volume in the first second (FEV1), and maximal forced expiratory flows at different lung volumes. Lung volumes were measured with a pressure-constant plethysmograph (BIOMEDIN Instruments, Padua, Italy). Three acceptable tracings of mouth pressure versus box volume changes were averaged to achieve a final measurement of functional residual capacity (FRC). Total lung capacity (TLC) and residual volume (RV) were computed subsequently. In each circumstance, the best values were collected for analysis. Lung diffusion capacity for carbon monoxide (DLCO) and its main determinants, alveolar volume and transfer rate for CO (KCO), were measured by single breath technique (BIOMEDIN Instruments, Padua, Italy). DLCO and KCO were adjusted for hemoglobin [35].

FEV1, FVC, TLC, and DLCO were considered abnormal if they were less than 80 of the predicted values. FEV1/FVC was considered abnormal if it was less than 70. Obstructive dysfunction was defined as a FEV1 of less than 80 of the predicted value with a FEV1/FVC of less than 70 of predicted value and FEV1 less than 80 of the predicted value. Obstructive dysfunction was graded as mild (FEV1/FVC 70-99), moderate (50-69) or severe <50. Restrictive dysfunction was defined

as a reduced TLC, and graded as mild (TLC 70-80), moderate (50-69), or severe (<50). DLCO was defined as normal if >80 of predicted value, or mildly (65-80), moderately (50-64), or severely reduced (<49) [35].

SUPPLEMENTAL TABLES.

Table E1: Demographic and clinical characteristics of the study population at hospital discharge.
Definition of abbreviations: IQR= Interquartile Range; ICU=Intensive Care Unit; LOS=length of stay; ECMO= Extra-Corporeal Membrane Oxygenation; SAPS II: Simplified Acute Physiology Score II. NIV= Non-Invasive Ventilation.

	Hospital Survivors N=137	**Died in Hospital N=87**	**Assessed at follow-up N=114**	**Total patients N=224**
Gender, Male - N. (%)	102 (75)	69 (79)	88 (77)	171 (76)
Age, years - Median [IQR]	60 [51-67]	69 [64-73]	60 [52-66]	65 [56-70]
Comorbidities - N (%)				
0	2 (2)	1 (1)	0 (0)	3 (1)
1	89 (66)	43 (49)	73 (64)	132 (60)
2	27 (20)	19 (22)	21 (18)	46 (21)
≥3	17 (13)	24 (28)	18 (26)	5 (18)
Body Mass Index, Kg/m^2 - Median [IQR]	27 [24-30]	26 [24-31]	27 [24-31]	27 [24-30]
SAPS II score - Median [IQR]	28 [22-36]	40 [33-52]	29 [25-35]	32 [26-43]
Use of NIV pre-ICU admission - N (%)	40 (30)	19 (27)	20 (18)	59 (29)
Mechanical Ventilation - N (%)	123 (90)	81 (93)	114 (100)	204 (91)
Duration of Mechanical Ventilation, days – Mean (SD)*	8 (12)	10 (11)	10 (8)	10 (11)
PaO2/FiO2 ratio at ICU admission - N (%)				
>400	15 (11)	2 (2)	9 (8)	17 (8)
300-399	10 (7)	1 (1)	10 (9)	11 (5)
200-299	17 (12)	8 (9)	4 (4)	25 (11)
100-199	57 (42)	42 (48)	50 (44)	99 (44)
<100	38 (28)	34 (39)	41 (36)	72 (32)
Inhaled nitric oxide** - N (%)	5 (4)	6/87(7)	4 (4)	11 (5)
Prone position** - N (%)	20 (15)	21/87(24)	17 (16)	41 (18)
ECMO** - N (%)	0 (0)	1/87(1)	0 (0)	1 (0)
Tracheostomy - N (%)	42 (31)	33/87(38)	36 (32)	75 (34)
Steroids in ICU*** - N (%)	42 (31)	31 (36)	39 (34)	73 (33)
Duration of steroid treatment in ICU, Days - Median [IQR]	6 [4-9]	10 [3-11]	6 [4-9]	8 [4-10]
ICU LOS - Median [IQR]	10 [3-15]	10 [3-19]	12 [7-21]	9 [3-17]
Hospital LOS - Median [IQR]	28 [18-37]	15 [10-25]	29 [20-45]	23 [12-35]
ICU Mortality - N (%)	0 (0)	67 (77)	0 (0)	67 (30)
Hospital Mortality - N (%)	0 (0)	87 (100)	0 (0)	87 (39)

†Unknown or missing data: Comorbidities = 2; SAPS II =102; NIV pre-ICU Admission=20. All data are available for the 114 patients assessed at follow-up.

* Mean was calculated only in patients who received the intervention.
** Ever used in ICU as per internal protocol.
*** Numbers refer to patients that received steroids in the ICU (350 mg of hydrocortisone equivalent dose for 14 days). Most patients received corticosteroids before ICU admission as for internal protocol (dexamethasone 20 mg e.v. for 10 days followed by 10 mg e.v. for other 10 days) [7].

Table E2. Details of the clinical condition, chest X-ray, discharge disposition and prescribed medication at hospital discharge in 114 patients consenting to participate in the in-person follow-up assessment.

Definition of abbreviations: IQR= Interquartile Range; SD=Standard Deviation.

	In-person follow-up visit n=114
Barthel Index — no. (%) patients	
Full independent (100)	23/74 (31)
Independent (80-99)	38/74 (51)
Minimally dependent (60-79)	14/74 (19)
Partially dependent (40-59)	11/74 (15)
Very dependent (20-39)	6/74 (8)
Totally dependent (<20)	5/74 (7)
Sit-to-stand assistance — no. (%) patients	
0 (unable to stand)	4/70 (6)
1 (2 people)	11/70 (16)
2 (1 person)	29/70 (41)
3 (no assistance needed)	26/70 (37)
Chest X-Ray Score - median [IQR]	8.0 [5.0-10.0]
Oxygen Supplementation* - no. (%) patients	19/73 (26)
Dyspnea - no. (%) patients	6/73 (8)
Steroids Therapy* - no. (%) patients	18/73 (25)
Thromboprophylaxis Therapy* - no. (%) patients	49/73 (67)
Antipsychotic Medications* - no. (%) patients	14/73 (20)
Discharge Dispositions - no. (%) patients	
Home	36/79 (46)
Rehabilitation Center	37/79 (47)
Other Hospital	5/79 (6)
Other	1/79 (1)

* Medications at hospital discharge

Table E3: Cognitive and mental health outcomes† of survivors of COVID-19-associated acute respiratory distress syndrome.

Definition of abbreviations: COVID-19 = coronavirus disease; PTSD= post-traumatic stress disorders; PLC-5= PTSD Checklist for DSM-5.

	3 months (N=98)	6 months (N=77)	12 months (N=51)	p**
Montreal Cognitive Assessment (MoCA) - N. (%) of patients				
Normal (MoCA ≥26)	65 (72)	47 (73)	38 (84)	<0.01
Mild Cognitive Impairment (MoCA 18-25)	23 (26)	16 (25)	7 (16)	
Moderate or Severe Cognitive Impairment (MoCA <17) *	2 (2)	1 (2)	0 (0)	
Hospital Anxiety and Depression Scale (HADS), Depression - N. (%) of patients				
Normal (0-7)	72 (91)	60 (86)	40 (89)	0.679
Borderline abnormal (8-10)	5 (6)	5 (7)	4(9)	
Abnormal (11-21)	2 (3)	5(7)	1 (2)	
Hospital Anxiety and Depression Scale (HADS), Anxiety Depression - N. (%) of patients				
Normal (0-7)	71 (90)	61(88)	37 (82)	0.083
Borderline abnormal (8-10)	7(9)	4(6)	5 (11)	
Abnormal (11-21)	1(1)	4(6)	3 (7)	
PTSD (PLC-5) N. (%) of patients with PTDS symptoms (**PLC-5>32)**	4 (4)	6 (8)	3 (6)	0.332
Insomnia Severity Index (ISI), Median [IQR]	1 [0-5]	2.0 [1-7]	2.0 [1-5]	0.073
Insomnia Severity Index N. (%) of patients with insomnia symptoms (ISI>7)	12 (13)	14 (19)	9 (18)	

†Unknown or missing data: MoCA= 8 (3 months), 13 (6 months), 6 (12 months); HADS= 19 (3 months), 7 (6 months) 6 (12 months) ; PTDS=3 (3 months), 2 (6 months), 2 (12 months); ISI= 3 (3 months), 3(6 months) 1(12 months).
* One patient had autism and one had cerebral palsy and epilepsy
**p values are calculated for comparisons across the 3, 6 and 12 month assessments using linear mixed models for continuous variables or cumulative link mixed models for ordinal variables.

Table E4: Pulmonary Function in 59 Patients with COVID-19-associated acute respiratory distress syndrome at 3-6 months after discharge from the intensive care unit.

A mild obstructive pattern was diagnosed in 4 patients (7), and a restrictive pattern in 23 patients (39) (mildly reduced in 15 patients [25] and moderately in 8 [14]). Diffusing capacity of the lungs for carbon monoxide was reduced in 29 patients (49) (mildly reduced in 13 [22] and moderately in 16 [27]).

	N=59
Vital Capacity (% predicted), median [IQR]	96 [85-107]
Forced vital capacity (% predicted), median [IQR]	96 [84-109]
Forced expiratory volume in one second (% predicted), median [IQR]	100 [100-112]
Total lung capacity (% predicted), median [IQR]	84 [76-93]
Residual volume (% predicted), median [IQR]	68 [59-78]
Lung diffusion capacity for carbon monoxide (% predicted), median [IQR]	94 [80-112]

Table E5. Selected clinical studies investigating physical, cognitive and mental health impairments in survivors of COVID-19-associated acute respiratory distress syndrome (ARDS) and classic ARDS.

Numbers in brackets indicate the references. Numbers in red are those of the current study.

Significant muscle weakness: Medical Research Council sum score <48.

Note that the diagnostic instruments and cut-offs used varied between the studies so may not be directly comparable.

	3 MONTHS		6 MONTHS	
	COVID-19-associated ARDS	Classic ARDS	COVID-19-associated ARDS	Classic ARDS
PHYSICAL DOMAIN				
Significant muscle weakness - percentage of patients	3%	22% [36]	1%	8% [37] 15% [36]
Six-minute walking test Mean percentage of normal value – mean distance walked in meters (m)	80 - 420 m	49 – 281 m [38]	80 – 420 m 85 – 479 m [39]	58 – NA [40,41] 64- 368 m [37]
SF-36 Physical functioning – median (normal value)	70 (NA) [42] 85 (84)	40 (86) [43] 35 (90) [38]	90 (84)	36 [44] 49 (86) [43] 55 (90) [38]
Fatigue - percentage of patients	13% [45] 33%	NA	26% 81%** [39]	70% [46] 72% [44]
COGNITIVE DOMAIN				
Cognitive impairment - percentage of patients	28%	59% vs 82%* [47]	27%	15% [44] 25% [48] 36% [41] 37% [49] 38% [46]
MENTAL DOMAIN				
Depression - percentage of patients	9% 37%[#] [45]	26% [50] 37% [51] 41% [52]	14% 32%*** [39]	26% [53] 36% [27] 37% [44]
Anxiety - percentage of patients	10% 37%[#] [45]	38% [50] 38% [54] 46% [52]	12% 32%*** [39]	41% [44] 42% [27]
PTSD - percentage of patients	4% 47%[##] [45]	7% [51] 16% [55] 21% [56] 22% [52]	8%	6% [56] 17% [55] 24% [27,44]
SF-36 HEALTH-RELATED QUALITY OF LIFE				
Physical component summary (PCS) – median (normal value)	43 (50)	29 (NA) [51] 32 (50) [43]	50 (50)	33 (50)[§] [57] 36 (50) [43] 38 (NA) [44] 38 (NA)[§§] [40] 40 (NA)[§§§§] [40]
Mental Component Summary (MCS) - median (normal value)	52 (50)	45 (52) [43] 56 (NA) [51]	50 (50)	45 (NA) [44] 49 (52) [43]

* Numbers indicate the prevalence of cognitive impairments in the treatment group and control group of this randomized clinical trial.

** Self-reported fatigue or muscle weakness assessed using a 3-item symptom questionnaire for current health status (How would you comment your current health status? **1.** Same as prior to COVID-19; **2.** Often feel fatigue, and easier to get tired after activity now than prior to COVID-19; **3.** Better health condition than prior to COVID-19) and muscle strength (How do you feel about your muscle strength compared with the status prior to COVID-19? **1.** Same as before; **2.** Worse than before; **3.** Better than before).

*** self-reported anxiety or depression assessed with the EuroQol five-dimension five-level questionnaire (EQ-5D-5L) for quality of life.

self-reported anxiety or depression assessed with the EQ-5D-5L, ## severe PTSD was reported in 6 of patients.

§ Based on the 12-Item Short-Form Health Survey (SF-12).

§§ ALTOS study, §§§ ICAP study

NA: not available.

Table references: [27,36,45–54,37,55–60,38–44]

References

1 Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy. *JAMA* 2020;**323**:1545. doi:10.1001/jama.2020.4031

2 Grasselli G, Zangrillo A, Zanella A, *et al.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;**323**:1574. doi:10.1001/jama.2020.5394

3 Toniati P, Piva S, Cattalini M, *et al.* Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020;**19**:102568. doi:10.1016/j.autrev.2020.102568

4 Vergano M, Bertolini G, Giannini A, *et al.* Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI). Raccomandazioni di etica clinica per l'ammissione a trattamenti intensivi e per la loro sospensione, in condizioni eccezionali di squilibrio tra necessità e risorse dispon. Published Online First: 2020.https://www.quotidianosanita.it/allegati/allegato2675063.pdf

5 Latronico N, Peli E, Rodella F, *et al.* Six-Month Outcome in Survivors of COVID-19 Associated Acute Respiratory Distress Syndrome. *SSRN Electron J* Published Online First: 2020. doi:10.2139/ssrn.3756865

6 Needham DM, Davidson J, Cohen H, *et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;**40**:502–9. doi:10.1097/CCM.0b013e318232da75

7 Piva S, Filippini M, Turla F, *et al.* Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. *J Crit Care* 2020;**58**:29–33. doi:10.1016/j.jcrc.2020.04.004

8 Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965;**14**:61–5.http://www.ncbi.nlm.nih.gov/pubmed/14258950 (accessed 14 May 2021).

9 Skinner EH, Berney S, Warrillow S, *et al.* Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. *Crit Care Resusc* 2009;**11**:110–5.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L355022451%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=14412772&id=doi:&atitle=Development+of+a+physical+function+outcome+measure+%28PFIT%29+and+a+pilot+exercise+training+pro

10 Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol Med* 2020;**125**:509–13. doi:10.1007/s11547-020-01200-3

11 Kaiser MJ, Bauer JM, Ramsch C, *et al.* Validation of the Mini Nutritional Assessment short-form (MNA-SF): a

practical tool for identification of nutritional status. *J Nutr Health Aging* 2009;**13**:782–8. doi:10.1007/s12603-009-0214-7

12 Kondrup J, Allison SP, Elia M, *et al.* ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003;**22**:415–21. doi:10.1016/s0261-5614(03)00098-0

13 World Health Organization (WHO). *How to use the ICF: A practical manual for using the International Classification of Functioning, Disability and Health (ICF). Exposure draft for comment.* Geneva: 2013. https://www.who.int/classifications/drafticfpracticalmanual.pdf

14 Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol* 2011;**10**:931–41. doi:10.1016/S1474-4422(11)70178-8

15 Hermans G, Clerckx B, Vanhullebusch T, *et al.* Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. *Muscle Nerve* 2012;**45**:18–25. doi:10.1002/mus.22219

16 Gilbertson L, Barber-Lomax S. Power and Pinch Grip Strength Recorded Using the Hand-Held Jamar® Dynamometer and B+L Hydraulic Pinch Gauge: British Normative Data for Adults. *Br J Occup Ther* 1994;**57**:483–8. doi:10.1177/030802269405701209

17 Ali NA, O'Brien JM, Hoffmann SP, *et al.* Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med* 2008;**178**:261–8. doi:10.1164/rccm.200712-1829OC

18 Schlüssel MM, dos Anjos LA, de Vasconcellos MTL, *et al.* Reference values of handgrip dynamometry of healthy adults: A population-based study. *Clin Nutr* 2008;**27**:601–7. doi:10.1016/j.clnu.2008.04.004

19 Latronico N, Bertolini G, Guarneri B, *et al.* Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: the Italian multi-centre CRIMYNE study. *Crit Care* 2007;**11**:R11. doi:10.1186/cc5671

20 Latronico N, Nattino G, Guarneri B, *et al.* Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. *F1000Research* 2014;**3**:127. doi:10.12688/f1000research.3933.3

21 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–7. doi:10.1164/ajrccm.166.1.at1102

22 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;**158**:1384–7. doi:10.1164/ajrccm.158.5.9710086

23 Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. *J Clin Epidemiol* 1998;**51**:1025–36. doi:10.1016/s0895-4356(98)00094-8

24 Krupp LB, LaRocca NG, Muir-Nash J, *et al.* The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**:1121–3. doi:10.1001/archneur.1989.00520460115022

25 McDicken JA, Elliott E, Blayney G, *et al.* Accuracy of the short-form Montreal Cognitive Assessment: Systematic review and validation. *Int J Geriatr Psychiatry* 2019;**34**:1515–25. doi:10.1002/gps.5162

26 Mikkelsen ME, Still M, Anderson BJ, *et al.* Society of Critical Care Medicine's International Consensus Conference on Prediction and Identification of Long-Term Impairments After Critical Illness. *Crit Care Med* 2020;**48**:1670–9. doi:10.1097/CCM.0000000000004586

27 Huang M, Parker AM, Bienvenu OJ, *et al.* Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors: A 1-Year National Multicenter Study. *Crit Care Med* 2016;**44**:954–65. doi:10.1097/CCM.0000000000001621

28 Bjelland I, Dahl AA, Haug TT, *et al.* The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;**52**:69–77. doi:10.1016/s0022-3999(01)00296-3

29 Bovin MJ, Marx BP, Weathers FW, *et al.* Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess* 2016;**28**:1379–91. doi:10.1037/pas0000254

30 Morin CM, Belleville G, Bélanger L, *et al.* The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;**34**:601–8. doi:10.1093/sleep/34.5.601

31 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.http://www.ncbi.nlm.nih.gov/pubmed/1593914

32 Taft C, Karlsson J, Sullivan M. Do SF-36 summary component scores accurately summarize subscale scores? *Qual Life Res* 2001;**10**:395–404. doi:10.1023/a:1012552211996

33 Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in Orthopaedics: A Brief Guide. *J Bone Joint Surg Am* 2015;**97**:1628–34. doi:10.2106/JBJS.O.00030

34 Mahler DA, Wells CK. Evaluation of Clinical Methods for Rating Dyspnea. *Chest* 1988;**93**:580–6. doi:10.1378/chest.93.3.580

35 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38. doi:10.1183/09031936.05.00034805

36 Fan E, Dowdy DW, Colantuoni E, *et al.* Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;**42**:849–59. doi:10.1097/CCM.0000000000000040

37 Needham DM, Wozniak AW, Hough CL, *et al.* Risk Factors for Physical Impairment after Acute Lung Injury in a National, Multicenter Study. *Am J Respir Crit Care Med* 2014;**189**:1214–24. doi:10.1164/rccm.201401-0158OC

38 Herridge MS, Cheung AM, Tansey CM, *et al.* One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;**348**:683–93. doi:10.1056/NEJMoa022450

39 Huang C, Huang L, Wang Y, *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet (London, England)* 2021;**397**:220–32. doi:10.1016/S0140-6736(20)32656-8

40 Chan KS, Aronson Friedman L, Dinglas VD, *et al.* Are physical measures related to patient-centred outcomes in ARDS survivors? *Thorax* 2017;**72**:884–92. doi:10.1136/thoraxjnl-2016-209400

41 Needham DM, Dinglas VD, Morris PE, *et al.* Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. *Am J Respir Crit Care Med* 2013;**188**:567–76. doi:10.1164/rccm.201304-0651OC

42 Valent A, Dudoignon E, Ressaire Q, *et al.* Three-month quality of life in survivors of ARDS due to COVID-19: A preliminary report from a French academic centre. *Anaesthesia, Crit care pain Med* 2020;**39**:740–1. doi:10.1016/j.accpm.2020.10.001

43 Heyland DK, Groll D, Caeser M. Survivors of acute respiratory distress syndrome: relationship between pulmonary dysfunction and long-term health-related quality of life. *Crit Care Med* 2005;**33**:1549–56. doi:10.1097/01.ccm.0000168609.98847.50

44 Brown SM, Wilson EL, Presson AP, *et al.* Understanding patient outcomes after acute respiratory distress syndrome: identifying subtypes of physical, cognitive and mental health outcomes. *Thorax* 2017;**72**:1094–103. doi:10.1136/thoraxjnl-2017-210337

45 Halpin SJ, McIvor C, Whyatt G, *et al.* Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;**93**:1013–22. doi:10.1002/jmv.26368

46 Pfoh ER, Chan KS, Dinglas VD, *et al.* Cognitive screening among acute respiratory failure survivors: a cross-sectional evaluation of the Mini-Mental State Examination. *Crit Care* 2015;**19**:220. doi:10.1186/s13054-015-0934-5

47 Zhao J, Yao L, Wang C, *et al.* The effects of cognitive intervention on cognitive impairments after intensive care unit admission. *Neuropsychol Rehabil* 2017;**27**:301–17. doi:10.1080/09602011.2015.1078246

48 Needham DM, Dinglas VD, Bienvenu OJ, *et al.* One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: Prospective follow-up of EDEN randomised trial. *BMJ* 2013;**346**:1–12. doi:10.1136/bmj.f1532

49 Needham DM, Colantuoni E, Dinglas VD, *et al.* Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: An ancillary study to a randomised controlled trial. *Lancet Respir Med* 2016;**4**:203–12. doi:10.1016/S2213-2600(16)00005-9

50 Jutte JE, Needham DM, Pfoh ER, *et al.* Psychometric evaluation of the Hospital Anxiety and Depression Scale 3 months after acute lung injury. *J Crit Care* 2015;**30**:793–8. doi:10.1016/j.jcrc.2015.04.006

51 Jackson JC, Pandharipande PP, Girard TD, *et al.* Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med* 2014;**2**:369–79. doi:10.1016/S2213-2600(14)70051-7

52 Hatch R, Young D, Barber V, *et al.* Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Crit Care* 2018;**22**:310. doi:10.1186/s13054-018-2223-6

53 Dowdy DW, Bienvenu OJ, Dinglas VD, *et al.* Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? *Crit Care Med* 2009;**37**:1702–7. doi:10.1097/CCM.0b013e31819fea55

54 Stevenson JE, Colantuoni E, Bienvenu OJ, *et al.* General anxiety symptoms after acute lung injury: predictors and correlates. *J Psychosom Res* 2013;**75**:287–93. doi:10.1016/j.jpsychores.2013.06.002

55 Righy C, Rosa RG, da Silva RTA, *et al.* Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. *Crit Care* 2019;**23**:213. doi:10.1186/s13054-019-2489-3

56 Bienvenu OJ, Gellar J, Althouse BM, *et al.* Post-traumatic stress disorder symptoms after acute lung injury: a 2-year prospective longitudinal study. *Psychol Med* 2013;**43**:2657–71. doi:10.1017/S0033291713000214

57 Biehl M, Kashyap R, Ahmed AH, *et al.* Six-month quality-of-life and functional status of acute respiratory distress syndrome survivors compared to patients at risk: a population-based study. *Crit Care* 2015;**19**:356. doi:10.1186/s13054-015-1062-y

58 Chopra V, Flanders SA, O'Malley M, *et al.* Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med* 2021;**174**:576–8. doi:10.7326/M20-5661

59 McCue C, Cowan R, Quasim T, *et al.* Long term outcomes of critically ill COVID-19 pneumonia patients: early learning. *Intensive Care Med* 2021;**47**:240–1. doi:10.1007/s00134-020-06313-x

60 Neufeld KJ, Leoutsakos J-MS, Yan H, *et al.* Fatigue Symptoms During the First Year Following ARDS. *Chest* 2020;**158**:999–1007. doi:10.1016/j.chest.2020.03.059