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

Nicola Latronico, Elena Peli, Stefano Calza, Federica Rodella, Maria Paola Novelli, Andrea Cella, John Marshall, Dale M Needham, Frank Antony Rasulo, Simone Piva, LOTO Investigators

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.

INTRODUCTION

Survivors of acute respiratory distress syndrome (‘classic’ ARDS) frequently experience long-lasting physical, cognitive and mental health impairments, referred to as post-intensive care syndrome (PICS). Patients with COVID-19-associated ARDS (C-ARDS) may suffer the same long-term consequences as survivors of classic ARDS, 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 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).

RESULTS

During the study period, 224 patients with C-ARDS were admitted to our ICU (figure 1). Of these, 137
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<.0001). 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 months5 or 4 months,6 precluding evaluation of the trajectory of recovery. Moreover, muscle weakness was self-reported5 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...
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, 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; 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 (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. 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

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

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

*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 value metric normed for the Italian general population.
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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Competing interests None declared.

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