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]

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