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The predictive role of fatigue and neuropsychological components on functional outcomes in COVID-19 after a multidisciplinary rehabilitation program

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Abstract

Objective: To verify the impact of altered cognitive functioning and higher levels of mental fatigue, both reported after coronavirus disease 2019 (COVID-19), on rehabilitation treatment outcomes.

Methods: In this real-practice retrospective pre–post intervention cohort study, cognitive functioning, measured through standardized neuropsychological measures, and individual levels of fatigue, depression and anxiety symptoms, were evaluated at admission to a rehabilitation program in individuals who had been hospitalized for COVID-19. The rehabilitation program effectiveness was measured through the Functional Independence Measure.

Results: Among the patient sample ($n = 66$), 87.88% reported experiencing high levels of fatigue at admission, while 16.67% reported depressive symptoms, and 22.73% reported anxiety symptoms. After rehabilitation, the sample displayed a significant decrease in the level of disability, in both the motor and cognitive subscales. Neuropsychological and psychological functioning did

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not play a predictive role. The 45 patients who received mechanical ventilation during intensive care, representing 68.18% of the sample, benefited more from rehabilitation treatment.
Conclusions: The results support the importance of an early rehabilitation program after COVID-19 infection, independent of the initial neuropsychological and psychological functioning. Respiratory assistance may represent a crucial factor for short-term neuropsychological disease after-effects. Future studies on the long-term neuropsychological effect of COVID-19 infection on individual levels of disability are necessary.

Keywords
COVID-19, multidisciplinary rehabilitation, Functional Independence Measure, neuropsychological assessment, mechanical ventilation, cognitive functions.

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Introduction

Cumulative evidence collected from the start of the coronavirus disease 2019 (COVID-19) pandemic suggests that altered cognitive function is a short- and long-term side-effect of the disease.[1] In their 2021 review,[1] Vanderlind and colleagues recognized the domains of attention, executive function and memory as the most impaired after COVID-19, despite the substantial heterogeneity of samples, methods, and results in published studies. Cognitive impairments were associated with anxiety and depressive symptoms, and also with fatigue,[1,2] which is a complex symptom composed of three main factors: asthenia/daytime tiredness, pathological exhaustibility, and worsening of symptoms due to stress.[3] In a study by Almeria et al., 2020,[4] 88.6% of patients reported fatigue at 10–35 days after hospitalization, however, other studies have reported lower rates (12.7–16.7%) at 1 month after discharge.[5,6] Cognitive and psychological alterations may impact COVID-19 rehabilitation treatment, particularly in terms of lower engagement, resulting ultimately in diminished therapeutic benefit,[7] mirroring evidence regarding altered cognitive dysfunction associated with a poor rehabilitation outcome in other clinical conditions.[8–11] Overall, there is a paucity of evidence regarding the effectiveness of COVID-19 rehabilitation programs; moreover, evidence about the role of neuropsychological and psychological alteration on rehabilitation treatment outcomes following COVID-19 is even more scarce.[12] However, evidence in the field may facilitate effective tailoring of rehabilitative interventions.

The aim of the present retrospective study was to verify the impact of cognitive functioning and psychological components (depression, anxiety, and fatigue) on the short-term effectiveness of a multidisciplinary patient-tailored rehabilitation program,[13] in terms of reducing the level of COVID-19 disability in a sample of individuals who recovered in a Swiss rehabilitation center.

Patients and methods

This real-practice retrospective pre–post intervention cohort study was conducted without a control group, as, in the context of the COVID-19 pandemic, a clinical trial

of rehabilitation versus 'sham rehabilitation' controls was considered unethical. Post-acute care patients who overcame COVID-19 and were included in a rehabilitation protocol at the Clinica Hildebrand – Centro di Riabilitazione Brissago (Switzerland) were recruited between May 2020 and December 2021. Data collected for the present study were obtained as part of the included institutions' clinical procedures. The study was approved by the Swiss Association of Research Ethics Committees (2022-00805; Rif.CE 4101), and oral and written informed consent was obtained from participants, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The reporting of this study conforms to STROBE guidelines,[14] and all patient details were de-identified.

Study population

Previously published inclusion/exclusion criteria were adopted in the present study.[13] All included patients came directly from an acute care setting, which may have been an intensive care unit (ICU), a respiratory high dependency care unit, or an infectious diseases unit of a local hospital. Patients were consecutively admitted for the rehabilitation protocol according to the following inclusion criteria. For patients with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive nasopharyngeal swab: (i) a recent chest computed tomography scan or X-ray with evidence of significant improvement versus baseline (e.g. reduction of lesion load by at least 50%, and/or improvement of the ground-glass picture); (ii) arterial oxygen partial pressure (PaO2)/fractional inspired oxygen (FiO2) ratio (P/F ratio) >300 with FiO2 35% during recovery in the ICU (this index is used for evaluating the extent of damage to the lungs when diagnosing acute respiratory distress syndrome [ARDS]);[15] (iii) apyretic for at least 3 days; and (iv) 90 mmHg < systolic blood pressure <140 mmHg; 60 mmHg < diastolic blood pressure < 90 mmHg. For patients with a negative nasopharyngeal swab for SARS-CoV-2: (i) apyretic for at least 3 days, and (ii) at least two consecutive negative swabs with an interval of at least 48 h between swabs. Patients who were under psychotropic drugs prior to study inclusion, those with COVID-19 encephalitis, patients with signs of dementia, or patients with pre-COVID 19 history of neurological or psychiatric diagnosis were excluded from the study.

At admission into the rehabilitation program, the presence of multiple pathologies and their cumulative severity in the study participants was assessed using the version provided by Mistry et al.[16] of the Cumulative Illness Rating Scale (CIRS).[17] The scale consists of 14 health domain-related categories. Each item is scored on a 5-point ordinal scale, ranging from a score of 0 (no impairment to that organ or system no problem) to 4 (extremely severe). The Severity Index (SI) was computed as the mean of scores for all categories (excluding psychiatric or behavioral factors), with a higher score of 5; and the Comorbidity Index (CI) was computed as the number of all categories (except for the psychiatric category) in which participants reported a score ≥3 (higher score 13). Thus, the score relative to the psychiatric component was independently reported (score from 0 to 4). In addition, the body mass index (BMI) was computed for each participant, and, in the first 24 h after admission, the nutritional status of all patients was recorded through the Nutritional Risk Screening-2002 (NRS-2002) system,[18] which scores patients regarding two components of undernutrition and disease severity. Scores range from 0 to 6, and a score ≥3 suggests malnutrition.

Neuropsychological assessment

Participants underwent neuropsychological assessment on the day after admission.

In order to verify global cognitive functioning, all participants were assessed with the Mini Mental State Examination.[19,20] Verbal memory was tested, specifically the short-term component through the Digit Span Forward task,[21] and the long-term component through the Story-Recall test.[22] Global executive-frontal functioning was tested through the Frontal Assessment Battery,[23,24] and verbal working memory was assessed through the Digit Span Backward task.[21]

Psychological assessment

Participants underwent psychological assessment immediately after neuropsychological assessment. Individual levels of anxiety and depression during hospitalization were analyzed with the Hospital Anxiety and Depression Scale (HADS).[25] This questionnaire was created specifically avoiding reliance on aspects of these conditions that are also common somatic symptoms of illness, such as fatigue. A cut-off point of 8/21 for both the scales of anxiety (with a specificity of 0.78 and sensitivity of 0.9) and depression (with a specificity of 0.79 and sensitivity of 0.83) is conventionally used.[26] The severity of tiredness in fatiguing illnesses was measured with the 11-item Chalder Fatigue Scale,[27] in the physical and mental domain,[28] following the procedure score suggested by Morriss et al.,[29] thus, a score $\geq$4 in the total score is used as a significant threshold. The questionnaire has been shown to have good internal consistency, as indicated by a split half reliabilities of 0.85,[27] and a Cronbach alpha that ranges between 0.86 and 0.92.

The rehabilitation program

The rehabilitation program was conducted as described previously,[13] following the indications of Crisafulli et al.,[30] using different strategies between patients who were either positive or negative for SARS-CoV-2. This was necessary in order to avoid further risk of contagion, particularly during respiratory rehabilitation sessions, typically characterized by a greater production of droplets.

Respiratory domain . For this domain, the initial aim was to reduce breathing difficulties and perception of dyspnea, as well as reducing the incidence of complications, such as bacterial superinfections of the airways. Procedures were conducted in parallel with weaning from oxygen therapy or, when this was not feasible, with the aim of obtaining the greatest possible oxygen therapy reduction, optimizing the flows for home therapy. Patients who remained positive for SARS-CoV-2 underwent a rehabilitative protocol that included respiratory exercises, such as deep, slow breathing, and chest expansion combined with shoulder expansion in order to reduce the spread of droplets. Breathing exercise helped patients to fully re-expand the lungs and to further the progression of airway secretions from small to large airway, thus reducing alveolar dead space. Once negative for SARS-CoV-2, aerosol therapy could be introduced and active breathing, as well as training with positive expiratory pressure, were started. The rehabilitation sessions occurred daily, with a duration ranging from 30 to 45 minutes, according to individual tolerance.

Neuromotor domain. Neuromotor rehabilitation aimed at the preservation of joint mobility and prevention of muscle wasting. Patients were trained in the passage from supine position to sitting, bed to wheelchair transfer and sitting to standing. The intervals of time spent standing were gradually increased and, when the standing position was deemed safe, gait training was started, initially with assistance and aids, and afterwards independently. The last steps of the motor rehabilitation process, also useful for

evaluating improvement in respiratory performance, were training in climbing and descending stairs and proprioceptive exercises to improve balance and postural reactions. The program included daily sessions of about 30 minutes, provided 5 days per week. The rehabilitation setting changed as recovery progressed: initial sessions were delivered at the patient's bed, then in the rehabilitation gym, according to individual tolerance.

Psychological domain. All participants received psychological support to address the emotional and traumatic issues related to the disease itself and to the prolonged isolation faced before and during hospitalization. The number of sessions per week varied in accordance with individual needs.

For individuals who received mechanical ventilation, speech and nutritional session therapy was also included in order to improve speech skills and swallowing, which may have been compromised after orotracheal intubation or tracheostomy. Each session occurred daily, with a duration ranging from 30 to 45 minutes, according to individual tolerance.

Primary outcome: Functional Independence Measure

The short-term effect of multidisciplinary rehabilitation was verified using the Functional Independence Measure (FIM),[31] the most widely used disability and dependence assessment instrument in rehabilitation medicine, for a variety of clinical populations and diagnoses. The FIM score, measured at admission (T0) and at the end of rehabilitation (T1), has been well validated to predict functional ability during rehabilitation periods.[32] As described previously,[13] it consists of an 18-item, seven-level, ordinal scale intended to be sensitive to changes over the course of a comprehensive inpatient medical rehabilitation program. The 18 items are grouped into two subscales: motor and cognition. The motor subscale includes eating, grooming, bathing, dressing upper body, dressing lower body, toileting, bladder management, bowel management, bed/chair/wheelchair transfers, toilet transfers, bath/shower transfer, walk/wheelchair, and stairs. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 (total assistance or not testable) to 7 (complete independence). The motor subscale is the sum of individual motor subscale items, with a possible value of between 13 and 91. The cognition subscale includes: comprehension, expression, social interaction, problem solving, and memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 (total assistance or not testable) to 7 (complete independence). The sum of individual cognition subscale items results in the cognition subscale score, with a possible value of between 5 and 35. Finally, a total FIM score may be calculated as the sum of the two subscale scores, with a possible value of between 18 and 126. The higher the score, the more independent the patient is in performing the task associated with that item.

Statistical analyses

All neuropsychological and psychological measures were scored according to the relevant seminal articles. Differences in parameters between patients who did or did not receive mechanical ventilation were analyzed by Mann–Whitney *U*-test.

Efficacy of the rehabilitation treatment. Changes in the motor and cognition FIM subscales, and the total FIM score, used to evaluate the efficacy of rehabilitation treatment on improving the level of disability, were analyzed by comparing the scores reported at baseline (T0) and after treatment (T1) using Wilcoxon signed–rank test. The Rehabilitation Effectiveness (REs) index was successively computed for each FIM

score, representing the percentage of potential functional improvement eventually achieved after the rehabilitation program.[33] The REs index for each FIM score was computed as:

$$REs = 100\% \ x \ \frac{DC\,(x) - adm\,(x)}{Max\,(x) - adm\,(x)}$$

where, x represents the score; DC, the discharge; adm, the admission; and max, the maximum possible score. Moreover, the DREs was computed by dividing the REs by the number of days that the patient engaged in the rehabilitation program.

Role of neuropsychological and psychological components in predicting treatment efficacy. To investigate whether changes in FIM scores observed after the rehabilitation program (T1) may be associated with participants' cognitive and psychological functioning at admission, linear regression analysis was performed.[34] As a preliminary analysis, the correlation and directionality of the data were assessed to formulate the statistical model, using Pearson's correlation coefficient to obtain Pearson's r for continuous factors; and Spearman's rank correlation coefficient to obtain Spearman's ρ for categorical factors. Those factors significantly associated with the main outcome score ($P \leq 0.05$) were further investigated with the linear regression model, for which the R^2 value was reported as a goodness-of-fit measure. In addition, the significance of the model was evaluated through the F-value and the P-value. Finally, the relative contribution of factors included in the statistical model was verified with the independent variable (i.e., the outcome score). For each factor, the variance inflation factor (VIF) was reported as a measure of multicollinearity.

Data are presented as n (%) prevalence or mean ± SD, and range, and were analyzed using SPSS Statistics software for Windows, version 26.0 (IBM, Armonk, NY, USA). A P value ≤0.05 was considered to be statistically significant.

Results

Study population

A total of 66 patients (27 females; 39 males) were recruited. Forty-five participants (68.18% of the sample) received mechanical ventilation in ICUs. According to the P/F ratio registered at the ICUs, all included participants reported a severe level of ARDS (i.e., P/F > 100 mmHg). Participant demographic and clinical data are summarized in Table 1.

Neuropsychological and psychological functioning

Comparison of neuropsychological tests scores reported for the current study population with normative data available in the corresponding seminal articles (described above), showed that 17 participants (25.76%) scored below the normative cut-off in the Mini Mental State Examination; seven (10.61%) scored below the Digit Span Forward; eight (12.12%) scored below the Story-Recall test; 24 (36.36%) scored below the Frontal Assessment Battery, and seven (10.61%) scored below the Digit Span Backward.

The majority ($n = 58$ [87.88%]) of the current sample scored higher than the cut-off of 4 for the Chalder Fatigue Scale total score. Regarding the HADS questionnaire (with cut-off of 8 on both scales), 11 participants (16.67%) scored higher than the cut-off on the depression scale, and 15 participants (22.73%) scored higher than the cut-off on the anxiety scale. Further detailed results regarding neuropsychological and psychological assessment are reported in Supplementary Tables S1–S3.

Table 1. Demographic and clinical characteristics for the study population overall, and patients grouped according to whether they received mechanical ventilation.

Characteristic	Overall $n = 66$	No mechanical ventilation $n = 21$	Mechanical ventilation $n = 45$	Statistical significance[a]
Age, years	70.14 ± 10.82 (35–87)	75.95 ± 8.76 (53–86)	67.42 ± 10.7 (35–87)	U = 233; **P = 0.001**
Duration of rehabilitation treatment, days	41.83 ± 25.29 (8–146)	37.62 ± 20.98 (8–98)	43.93 ± 27.19 (15–146)	U = 493.5; P = 0.44
Body mass index, kg/m^2	28.92 ± 6.91 (20–51)	26 ± 4.48 (20.4–35.6)	29.93 ± 7.38 (22.1–51.2)	U = 161.5; P = 0.93
NRS-2002 score	4.58 ± 1.03 (3–7)	3.78 ± 0.83 (3–5)	4.81 ± 0.98 (3–7)	U = 217; **P = 0.01**
Cumulative Illness Rating Scale				
Severity Index (0–56)	1.76 ± 0.57 (0–3)	1.66 ± 0.62 (0.46–2.77)	1.8 ± 0.56 (0.54–3.00)	U = 526.5; P = 0.36
Comorbidity Index (0–12)	7.68 ± 2.35 (3–11)	7.24 ± 2.36 (3–11)	7.89 ± 2.35 (3–11)	U = 536.5; P = 0.29
Psychiatric index (0–4)	1.42 ± 1.84 (0–4)	1.29 ± 1.15 (0–4)	1.48 ± 1.21 (0–4)	U = 536.5; P = 0.29
Mini Mental State Examination (0–30)	25.02 ± 5.84 (3–30)	25.21 ± 5.86 (8–30)	24.93 ± 5.9 (3–30)	U = 426; P = 0.98
Digit Span Forward (0–9)	5.25 ± 1.23 (3–9)	5.58 ± 1.26 (3–8)	5.11 ± 1.17 (3–9)	U = 324.5; P = 0.11
Story-Recall test (0–24)	12 ± 5.76 (0–24)	11.63 ± 5.61 (0–18.5)	12.16 ± 5.89 (1–23.5)	U = 434; P = 0.81
Frontal Assessment Battery (0–18)	13.3 ± 3.35 (6–18)	13.42 ± 3.45 (6–17)	13.57 ± 3.33 (3–18)	U = 409; P = 0.79
Digit Span Backward (0–7)	3.7 ± 1.23 (2–7)	3.89 ± 1.33 (2–7)	3.62 ± 1.19 (2–6)	U = 381; P = 0.48
11 item – Chalder Fatigue Scale total score (0–13)	6.29 ± 2.3 (0–13)	5.76 ± 2.64 (0–10)	6.55 ± 2.12 (3–13)	U = 514-5; P = 0.45
HADS-Anxiety (0–21)	5.26 ± 4.18 (0–17)	5.62 ± 4.83 (0–16)	5.09 ± 3.88 (0–17)	U = 456.5; P = 0.93
HADS-Depression (0–21)	4.57 ± 3.49 (0–17)	4.57 ± 4.25 (0–17)	4.57 ± 3.12 (0–14)	U = 493.5; P = 0.65

Data presented as mean ± SD (range).

NRS-2002, Nutritional Risk Screening-2002 system; HADS, Hospital Anxiety and Depression Scale.

[a]Mann–Whitney *U*-test.

Rehabilitation treatment efficacy

Significantly higher scores at T1 were registered for the three FIM scales (motor, cognitive and total) compared with those registered at T0 (all $P < 0.001$; Table 2), suggesting that the level of functionality globally increased in the sample following rehabilitation.

Predictive role of neuropsychological and psychological components on rehabilitation treatment efficacy

The relationship between scores relative to the primary outcome and all of the collected measures was assessed, with the results summarized in Table 3.

Age was significantly inversely related with FIM motor REs and DREs scores, and the FIM total REs scores ($P < 0.05$), in agreement with our previous study.[13] The CIRS comorbidity index score was significantly inversely related with the DREs motor score ($P = 0.03$), moreover, a higher psychiatric index by CIRS was significantly related with a lower DREs cognitive score ($P = 0.008$). In the neuropsychological and psychological assessment, only the Story-Recall test score was found to be significantly related with the DREs motor score; with a positive association. Crucially, the use of mechanical ventilation significantly correlated with all investigated parameters (all $P < 0.001$).

Linear regression models were run according to the results of correlation analyses, and age and the use of mechanical ventilation were found to be significant predictors of the motor and total FIM REs scores. The variance inflation factor (VIF) values for age and use of mechanical ventilation prior to rehabilitation were both 1.14. The model relative to the motor REs score was statistically significant ($R^2 = 0.55$; $F[2,61] = 37.08$; $P < 0.001$); and mechanical ventilation ($B = 40.65$; $t = 7.92$; $P < 0.001$), but not age ($B = –0.07$; $t = –0.32$; $P = 0.74$) was found to significantly predict the motor REs score. Similarly, mechanical ventilation ($B = 38.99$; $t = 7.53$; $P < 0.001$), but not age ($B < –0.001$; $t < 0.001$; $P = 1$), significantly predicted the total REs score ($R^2 = 0.52$; $F[2,61] = 32.16$; $P < 0.001$). Successively, the predictive role of mechanical ventilation on cognitive REs score was analyzed; the model was statistically

Table 2. Functional Independence Measure (FIM) scores obtained at T0 (before starting the rehabilitation program) and T1 (at the end of rehabilitation) in the present sample of 66 patients, together with REs and DREs scores for each FIM, calculated at the end of rehabilitation.

FIM	Study timepoint		Statistical significance[a]	REs	DREs
	T0	T1			
Motor score	34.34 ± 19.84 13–85	66.27 ± 16.45 27–90	Z=1953; $P < 0.001$; $\eta^2 = 3.21$	54.08 ± 26.4 4–98	1.73 ± 1.27 0–5
Cognitive score	21.37 ± 8.01 5–33	27.55 ± 5.52 10–35	Z = 1018; $P < 0.001$; $\eta^2 = 6.75$	37.58 ± 34.32 –29–100	1.04 ± 1.26 –2–5
Total score	55.42 ± 25.97 18–116	93.82 ± 20.83 38–125	Z = 1953; $P < 0.001$; $\eta^2 = 3.21$	51.88 ± 25.75 4–94	1.63 ± 1.19 0–5

Data presented as mean ± SD and range.
REs, Rehabilitation Effectiveness index; DREs, REs per day.
[a]Wilcoxon signed–rank test.

Table 3. Relationship between participant characteristics and three scales (motor, cognitive, and total) from the Functional Independence Measure (FIM).[a]

	REs			DREs		
	Motor	Cognitive	Total	Motor	Cognitive	Total
Characteristic						
Age, years	r = –031	r = –0.45	r = –0.25	r = –0.26	r = 0.12	r = 0.23
	P = 0.01	P = 0.72	**P = 0.04**	**P = 0.03**	P = 0.35	P = 0.06
Sex, male/female	ρ = 0.2	ρ = 0.16	ρ = 0.22	ρ = 0.23	ρ = 0.14	ρ = 0.24
	P = 0.1	P = 0.2	P = 0.07	P = 0.07	P = 0.25	P = 0.059
Body mass index, kg/m^2	r = –0.32	r = 0.22	r = –0.32	r = –0.19	r = 0.23	r = –0.2
	P = 0.07	P = 0.21	P = 0.07	P = 0.29	P = 0.19	P = 0.26
NRS-2002 score	r = 0.15	r = 0.15	r = 0.16	r = 0.15	r = 0.11	r = 0.15
	P = 0.34	P = 0.35	P = 0.34	P = 0.36	P = 0.49	P = 0.37
Mechanical ventilation	ρ = 0.71	ρ = 0.45	ρ = 0.69	ρ = 0.49	ρ = 0.4	ρ = 0.48
	P < 0.001	**P < 0.001**	**P < 0.001**	**P < 0.001**	**P = 0.001**	**P < 0.001**
Cumulative Illness Rating Scale						
Severity index	r = 0.01	r = –0.07	r = 0.05	r = –0.15	r = –0.03	r = –0.12
	P = 0.88	P = 0.55	P = 0.65	P = 0.22	P = 0.79	P = 0.33
Comorbidity index	r = –0.005	r = 0.12	r = –0.05	r = –0.27	r = –0.57	r = –0.22
	P = 0.96	P = 0.31	P = 0.66	**P = 0.03**	P = 0.66	P = 0.06
Psychiatric component	ρ = –0.23	ρ = –0.29	ρ = –0.21	ρ = –0.23	ρ = –0.41	ρ = –0.21
	P = 0.14	P = 0.06	P = 0.18	P = 0.15	**P = 0.008**	P = 0.17
Neuropsychological and psychological assessment						
Mini Mental State Examination	r = 0.01	r = 0.14	r = 0.05	r = 0.13	r = 0.11	r = 0.14
	P = 0.88	P = 0.28	P = 0.65	P = 0.31	P = 0.39	P = 0.27
Digit Span Forward	r = –0.08	r = 0.07	r = –0.05	r = 0.1	r = 0.16	r = 0.12
	P = 0.53	P = 0.55	P = 0.65	P = 0.44	P = 0.21	P = 0.33
Story-Recall test	r = 0.1	r = 0.04	r = 0.93	r = 0.27	r = 0.09	r = 0.25
	P = 0.41	P = 0.72	P = 0.48	**P = 0.03**	P = 0.49	P = 0.051
Frontal Assessment Battery	r = 0.11	r = 0.18	r = 0.13	r = 0.17	r = 0.11	r = 0.17
	P = 0.4	P = 0.15	P = 0.3	P = 0.19	P = 0.39	P = 0.18
Digit Span Backward	r = –0.03	r = 0.08	r = –0.03	r = 0.15	r = 0.12	r = 0.15
	P = 0.78	P = 0.52	P = 0.79	P = 0.23	P = 0.34	P = 0.22
Chalder Fatigue	r = 0.12	r = 0.05	r = 0.1	r = 0.02	r = 0.09	r = 0.03
Scale – total score	P = 0.35	P = 0.7	P = 0.44	P = 0.83	P = 0.47	P = 0.76
HADS-Anxiety	r = –0.03	r = –0.05	r = –0.04	r = 0.04	r = –0.03	r = 0.03
	P = 0.77	P = 0.68	P = 0.74	P = 0.71	P = 0.77	P = 0.76
HADS-Depression	r = 0.01	r = –0.06	r = –0.001	r = 0.04	r = 0.03	r = 0.04
	P = 0.92	P = 0.61	P = 0.99	P = 0.74	P = 0.8	P = 0.74

REs, Rehabilitation Effectiveness index; DREs, REs per day; NRS-2002, Nutritional Risk Screening-2002 system; HADS, Hospital Anxiety and Depression Scale.

[a]Statistically significant *P* values ($P \leq 0.05$) in bold (Pearson's correlation coefficient for continuous factors or Spearman's rank correlation coefficient for categorical data).

significant ($R^2 = 0.18$; $F[1,61] = 13.54$; $P = 0.001$), and mechanical ventilation (VIF = 1; B = 30.87; t = 3.68; $P = 0.001$) was found to be a significant predictor.

The role of age, mechanical ventilation, the comorbidity index of CIRS, and the Story-Recall test score (i.e., long-term verbal memory) in predicting the DREs

motor score was assessed. The model was statistically significant ($R^2 = 0.31$; F[4,58] = 6.27; $P < 0.001$); mechanical ventilation (VIF = 1.15; B = 1.08; t = 3.49; $P = 0.001$) and the CIRS comorbidity index (VIF = 1.22; B = –0.14; t = –2.21; $P = 0.03$) were found to significantly predict the motor DREs score, however, neither age (VIF = 1.36; B = –0.009; t = –0.63; $P = 0.53$] nor the Story-Recall test score (VIF = 1.42; B = 0.02; t = 0.92; $P = 0.35$] were significant. Thus, higher levels of comorbidities and the use of mechanical ventilation during ICU hospitalization predicted less change in the FIM motor scale after rehabilitation treatment.

Crucially, mechanical ventilation (VIF = 1.01; B = 0.79; t = 2.02: $P = 0.05$), but not the score for the psychiatric component of CIRS (VIF = 1.01; B = –0.27; t = –1.44; $P = 0.15$), significantly predicted changes in the cognitive DREs score ($R^2 = 0.15$; F[2,39] = 3.43; $P = 0.04$). Mechanical ventilation (VIF = 1; B = 1.11; t = 3.83: $P < 0.001$) also significantly predicted changes in the total DREs score ($R^2 = 0.19$; F[1,61] = 17.73; $P < 0.001$).

Subgroup analyses of the role of mechanical ventilation

Overall, the results suggested a crucial role for mechanical ventilation during ICU care on the residual level of disability and dependence after rehabilitation treatment. Because of this clear-cut, but not a-priori expected, result, data were further analyzed focusing on the subgroup of participants ($n = 45$) who received mechanical ventilation in the ICU.

Participant subgroup. Patients received mechanical ventilation treatment for a mean of 17 ± 13.42 days (range, 5–87 days). The mean P/F ratio was 12.22 ± 3.9 days (range, 6–22 days). Thirteen patients required ventilation via tracheostomy while in the ICU, for a mean of 15.38 ± 8.18 days (range, 4–31 days). According to Mann– Whitney *U*-test, patients who received mechanical ventilation ($n = 45$) were younger ($P < 0.001$) and showed a higher risk of malnutrition (according to Kondrup NRS-2002 scores, $P < 0.01$) compared with those who did not receive mechanical ventilation ($n = 21$) (Table 1). No other between-group differences were observed. Moreover, at the beginning of rehabilitation treatment (T0), patients who had received mechanical ventilation reported significantly lower scores in the motor and total FIM scale; and numerically lower scores in the cognitive domain, although the result did not reach statistical significance (Table 4).

Neuropsychological and psychological functioning in mechanical ventilation subgroup. Of the mechanical ventilation subgroup, 12 patients (26.67%) reported a lower score than the normative cut-off for the Mini Mental State Examination, with lower than normative cut-off scores reported in five patients (11.11%) for the Digit Span Forward, six patients (13.33%) for the Story-Recall test; 17 patients (37.78%) for the Frontal Assessment Battery, and six patients (13.33%) for the Digit Span Backward. Moreover, 39 patients (86.67% of this subgroup) reported a score lower than the normative cut-off for the Chalder Fatigue Scale – total score. In addition, scores above the normative cut-off were reported in five patients (13.33% of the subgroup) for the depression scale and seven patients (15.56%) for the anxiety scale of HADS. Crucially, this mechanical ventilation subgroup showed significantly larger changes in all main outcomes (REs and DREs score) registered through the FIM scale (Table 4).

Predictive role of neuropsychological and psychological components on rehabilitation treatment efficacy in mechanical ventilation subgroup. For the mechanical ventilation subgroup, the relationship between

Table 4. Differences in motor score, cognitive score, and total score from the Functional Independence Measure (FIM) scale registered before the rehabilitation program (T0), and the corresponding REs and DREs scores between patients who had received mechanical ventilation and those who had not.

Characteristic	No mechanical ventilation $n = 21$	Mechanical ventilation $n = 45$	Statistical significance[a]
T0 – FIM Motor score	42.95 ± 19.81 (16–83)	30.23 ± 18.72 (13–85)	U = 270; **P = 0.007**
T0 – FIM Cognitive score	23.9 ± 7.29 (10–33)	20.16 ± 8.14 (5–33)	U = 323.5; P = 0.052
T0 – FIM Total score	65.9 ± 24.74 (32–113)	50.41 ± 25.31 (18–116)	U = 292.5; **P = 0.017**
Motor REs score	26.8 ± 18.8 (4.48–66.67)	68.06 ± 17.15 (21.92–97.5)	U = 806.6; **P < 0.001**
Cognitive REs score	17.16 ± 27.96 (–21.43–100)	48.03 ± 32.8 (–28.57–100)	U = 669; **P < 0.001**
Total REs score	29.06 ± 18.47 (3.9–62.2)	65.08 ± 17.7 (17.17–93.62)	U = 796.5; **P < 0.001**
Motor DREs score	0.97 ± 0.92 (0.14–3.33)	2.11 ± 1.27 (0.31–5.29)	U = 589; **P < 0.001**
Cognitive DREs score	0.44 ± 0.67 (–0.32–1.92)	1.35 ± 1.38 (–2.04–4.76)	U = 643; **P = 0.001**
Total DREs score	0.89 ± 0.78 (0.12–2.63)	2 ± 1.2 (0.33–5.24)	U = 684; **P < 0.001**

Data presented as mean ± SD (range).
REs, Rehabilitation Effectiveness index; DREs, REs per day.
[a]Statistically significant *P* values ($P \leq 0.05$) in bold (Mann–Whitney *U*-test).

psychological/neuropsychological characteristics and the scores relative to the FIM are summarized in Table 5, in addition to the P/F ratio registered at T0. Regression analyses were then performed in this subgroup to verify the role of factors, found to be significantly related to the main scores, in predicting rehabilitation outcomes.

The psychiatric component, assessed through the CIRS (VIF = 1), was significantly related to the cognitive REs score, however, when introduced as a predictor in the regression model, it was found not to be statistically significant ($R^2 = 0.02$; F[1,40] = 1.1; $P = 0.3$). Regarding the motor DREs score, the parameters of age, Digit Span Backward score (which refers to verbal working memory), the Story-Recall test (i.e., verbal long-term memory), and the comorbidity index from CIRS, were introduced as predictors in the regression analyses. The model was statistically significant ($R^2 = 0.28$; F[4,39] = 3.46; $P = 0.01$); however, no parameter emerged to be a significant predictor of the motor DREs score (age VIF = 1.24; B = –0.03; t = –1.71; $P = 0.09$; Digit Span Backward VIF = 1.23; B = 0.25; t = 1.61; $P = 0.11$; Story-Recall test VIF = 1.57; B = 0.01; t = 0.32; $P = 0.74$; and CIRS comorbidity index VIF = 1.27; B = –0.1; t = –1.33; $P = 0.19$). Regarding the total DREs score, age, the Digit Span Backward Test score, and the Story-Recall test score were introduced as predictors. The model was statistically significant ($R^2 = 0.21$; F[3,39] = 3.34; $P = 0.03$), however, no parameter emerged to be a significant predictor of the total DREs score (age VIF = 1.24; B = –0.02; t = –1.62; $P = 0.11$; Digit Span Backward VIF = 1.17; B = 0.28; t = 1.85; $P = 0.07$; and Story-Recall test VIF = 1.42; B = 0.02; t = 0.58; $P = 0.56$). Overall, the results from supplementary subgroup analyses showed that none of the clinical, neuropsychological and psychological parameters investigated in this research predicted the rehabilitative outcomes of those individuals who received mechanical ventilation in ICUs.

Discussion

The aim of this retrospective observational study was to verify the role of neuropsychological and psychological factors, including fatigue, in predicting significant changes in the level of disability after a multidisciplinary rehabilitation program following COVID-19.

Table 5. Relationship between the three scales (motor, cognitive, and total) from the Functional Independence Measure (FIM) and clinical, psychological, and neuropsychological characteristics in the subgroup of patients who received mechanical ventilation ($n = 45$).[a]

	REs			DREs		
	Motor	Cognitive	Total	Motor	Cognitive	Total
Characteristic						
Age, years	r = 0.24	r = 0.23	r = –0.15	r = –0.39	r = 0.1	r = –0.36
	P = 0.12	*P* = 0.41	*P* = 0.34	***P* = 0.01**	*P* = 0.5	***P* = 0.01**
Sex, male/female	ρ = –0.08	ρ = –0.02	ρ = –0.98	ρ = 0.14	ρ = 0.01	ρ = 0.13
	P = 0.61	*P* = 0.87	*P* = 0.54	*P* = 0.35	*P* = 0.91	*P* = 0.38
Body mass index, kg/m^2	r = 0.27	r = 0.22	r = 0.28	r = 0.38	r = 0.35	r = 0.39
	P = 0.19	*P* = 0.3	*P* = 0.18	*P* = 0.07	*P* = 0.09	*P* = 0.06
NRS-2002 score	r = –0.27	r = –0.05	r = –0.25	r = 0.1	r = –0.008	r = 0.06
	P = 0.16	*P* = 0.76	*P* = 0.19	*P* = 0.6	*P* = 0.96	*P* = 0.72
P/F pascal	r = –0.13	r = 0.05	r = –0.13	r = –0.008	r = 0.03	r = –0.02
	P = 0.44	*P* = 0.75	*P* = 0.42	*P* = 0.96	*P* = 0.83	*P* = 0.9
Cumulative Illness Rating Scale						
Severity index	r = –0.11	r = 0.18	r = –0.02	r = –0.17	r = –0.01	r = –0.15
	P = 0.48	*P* = 0.25	*P* = 0.88	*P* = 0.26	*P* = 0.94	*P* = 0.33
Comorbidity index	r = –0.13	r = 0.21	r = –0.02	r = –0.33	r = –0.05	r = –0.29
	P = 0.41	*P* = 0.18	*P* = 0.86	***P* = 0.03**	*P* = 0.75	*P* = 0.057
Psychiatric component	ρ = –0.14	ρ = –0.31	ρ = –0.19	ρ = –0.17	ρ = –0.28	ρ = –0.16
	P = 0.36	***P* = 0.04**	*P* = 0.21	*P* = 0.28	*P* = 0.06	*P* = 0.29
Neuropsychological and psychological assessment						
Mini Mental State Examination	r = 0.15	r = 0.16	r = 0.18	r = 0.2	r = 0.14	r = 0.22
	P = 0.33	*P* = 0.31	*P* = 0.23	*P* = 0.19	*P* = 0.35	*P* = 0.16
Digit Span Forward	r = 0.1	r = 0.21	r = 0.15	r = 0.25	r = 0.3	r = 0.28
	P = 0.5	*P* = 0.18	*P* = 0.36	*P* = 0.11	*P* = 0.052	*P* = 0.07
Digit Span Backward	r = 0.22	r = 0.05	r = 0.18	r = 0.34	r = 0.17	r = 0.33
	P = 0.15	*P* = 0.75	*P* = 0.25	***P* = 0.02**	*P* = 0.28	***P* = 0.03**
Story-Recall test	r = 0.25	r = –0.08	r = 0.18	r = 0.35	r = 0.04	r = 0.32
	P = 0.11	*P* = 0.6	*P* = 0.26	***P* = 0.02**	*P* = 0.78	***P* = 0.04**
Frontal Assessment Battery	r = 0.3	r = 0.14	r = 0.89	r = 0.22	r = 0.08	r = 0.22
	***P* = 0.05**	*P* = 0.36	***P* = 0.05**	*P* = 0.16	*P* = 0.6	*P* = 0.16
Chalder Fatigue	r = –0.1	r = –0.06	r = –0.02	r = –0.02	r = 0.03	r = –0.02
Scale – total score	*P* = 0.94	*P* = 0.67	*P* = 0.86	*P* = 0.89	*P* = 0.83	*P* = 0.88
HADS-Anxiety	r = –0.005	r = –0.13	r = –0.04	r = 0.83	r = 0.04	r = 0.08
	P = 0.97	*P* = 0.41	*P* = 0.8	*P* = 0.61	*P* = 0.79	*P* = 0.62
HADS-Depression	r = –0.16	r = –0.11	r = –0.16	r = 0.05	r = –0.06	r = 0.4
	P = 0.31	*P* = 0.48	*P* = 0.31	*P* = 0.73	*P* = 0.67	*P* = 0.79

REs, Rehabilitation Effectiveness index; DREs, REs per day; NRS-2002, Nutritional Risk Screening-2002; P/F, arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio; HADS, Hospital Anxiety and Depression Scale.
[a]Statistically significant *P* values ($P \leq 0.05$) in bold (Pearson's correlation coefficient for continuous factors or Spearman's rank correlation coefficient for categorical data).

First, the results of the present study underlined that the participants reported a significant decrease in the level of disability, in both motor and cognitive components, after the rehabilitation program. This result, which mirrored previously published results by our group,[13] confirmed the efficacy of the proposed multidisciplinary

treatment in the context of COVID-19. The result also concurred with other previous evidence addressing the overall efficacy of rehabilitation programs for patients who have spent time in acute and post-acute care settings.[1]

Secondly, results regarding the predictive role of neuropsychological and psychological factors, particularly the level of fatigue, on functional outcomes following the multidisciplinary rehabilitation program, were assessed. At admission to the program, some participants reported altered cognitive functioning: a lower performance, meaning an altered functioning, was observed in multiple tests but with different degrees of severity, in line with previous, though rare, evidence.[1] Crucially, the majority of the present study population reported experiencing fatigue, particularly in the physical domain, in line with a previous study.[4] However, according to the present statistical analyses, the level of neuropsychological and psychological functioning registered at admission to the program following COVID-19 did not impact on the rehabilitative outcome, in disagreement with our preliminary hypothesis that altered cognitive dysfunction may be associated with a poor rehabilitation outcome, as reported in other clinical conditions.[8–11] However, it should be noted that multiple published studies have reported that altered cognitive functioning does not hamper the outcomes of rehabilitative efforts,[35–37] supporting the clinical practice to offer a complete multidisciplinary rehabilitation to individuals including those with higher cognitive impairment at rehabilitation admission. In the present study overall, a specific role was not observed for the investigated neuropsychological and psychological components in predicting the overall positive change following the rehabilitation program; and this result remained when the duration of rehabilitation was taken into account (DREs score). Nevertheless, certain methodological considerations should be addressed. The present work adopted a restricted number of neuropsychological tests, mostly focusing on verbal (and not visuospatial) domains. This limitation was due to the difficulty in performing an extended assessment, which is time-consuming, and altering conventional procedures within clinical settings is difficult, particularly in the context of COVID-19. Thus, the emergence of other cognitive alterations in other, untested, domains cannot be excluded, particularly in those relative to higher cognitive levels, such as strategic reasoning or ability to inhibit interference. Nevertheless, a value of the present study was the inclusion of ad-hoc single function neuropsychological testing, rather than cognitive screening measures exclusively, as performed in other studies.[1] Regarding psychological assessment of the level of depressive and anxiety symptoms, self-reported measures were employed, as traditionally used in clinical settings. It should be observed that the present results mirrored previously reported rates;[1] thus, as found elsewhere, it was suggested that individuals may experience 'a survivor syndrome', which decreases the presence of negative psychological outcome, and thus its impact on the level of therapeutic compliance, compared with those individuals who were not hospitalized due to COVID-19 symptoms. Finally, it should be highlighted that the level of fatigue was also measured through a self-report measure, which may not directly mirror the physical engagement in rehabilitation activities. Nevertheless, self-reported questionnaires on fatigue are the most common and possibly the most effective way of evaluating fatigue in research and clinical settings.[38] Indeed, multiple questionnaires on fatigue may be found in the published literature, such as the Functional Assessment of Chronic Illness Therapy-Fatigue Scale,[39] and the Fatigue Severity Scale.[40] The present study employed the

Chalder Fatigue Scale,[27] to assess the level of fatigue in COVID-19, in line with other studies in the field,[2,41] in light of its optimal statistical properties. Moreover, this questionnaire, as with all others included in the present work, forms a permanent part of assessments at the institutions involved in the study.

A further clear-cut result emerged during the present study – the role of mechanical ventilation. Crucially, mechanical ventilation was observed to be the only statistically significant factor that predicted a significant decrease in the level of disability in the sample, following rehabilitative treatment. When individuals who received mechanical ventilation in ICUs were compared with the rest of the study population, they were observed to be younger, as reported elsewhere,[42] and they were at a higher risk of malnutrition. Also, they seemed to benefit more from rehabilitation treatment (i.e., REs score), including when treatment duration was accounted for (DRes score), even though they registered a higher level of disability at admission, particularly in the motor domain. No differences in neuropsychological and psychological functioning were found between individuals who received mechanical ventilation and the rest of the study population, in line with previous evidence,[42] but in disagreement with others.[4] If mechanical ventilation was considered to be an implicit clinical index of a very critical health state, the present results and those collected by Alemanno et al.,[42] showing no decreased cognitive efficiency in this group, appear counterintuitive. However, Alemanno et al.[42] highlighted the possible protective role of sedation, which might have spared patients from the inflammatory stress that such a critical illness might have induced in otherwise conscious patients, reducing the disease impact on cognitive and psychological functioning. Nevertheless, it cannot be excluded that patients who received mechanical ventilation in ICUs may experience cognitive difficulties in other, untested, domains, as previously stated, or they may experience significant long-term alterations, as suggested by Ritchie et al.,[43] in their 2020 report: in the context of ARDS, it was observed that a significant proportion of individuals who have spent time receiving mechanical ventilation in ICUs experience lasting cognitive impairment, such as memory failure, which persists for 1 or 2 years following discharge. Further studies are required to clarify whether a similar pattern of alteration may be registered in the context of COVID-19.

Despite the limitations of the present study (i.e., limited size of the study population, a limited number of neuropsychological tests used to assess cognitive functioning due to context limitations, and the absence of radiological parameters or positive end expiratory pressure values, other than the P/F ratio registered at the ICU, to define ARDS), the present results, in conjunction with those reported by Barbieri et al.[13] highlight the efficacy of a multidisciplinary rehabilitative program in reducing the short-term level of disability after COVID-19. Moreover, the present study underlined the crucial role played by respiratory assistance on the short-term neuropsychological after-effects of the disease, as also suggested by Negrini et al.[44] Nevertheless, future data collection regarding the long-term effect of COVID-19 infection on individual levels of disability, as well as on cognitive and psychological functioning, through a more comprehensive assessment, are necessary. Future investigations should consider whether patients needed the mechanical ventilotherapy in the acute and post-acute settings, in light of evidence showing that a significantly lower quality of life level is often registered at 1 year after discharge.[45–47]

Author contributions

Conception and design: NC, LB, LS, PL, and PR; data acquisition: NB, VB, LS, LB; data analysis: LS and FS; data interpretation: NC, LB, VB, FS, and PR; article drafting: NC, LB and FS; and final approval of the version to be published: LS, LB, PL and PR.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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Supplementary material

Supplementary material for this study is available online.

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