

Clinical and long-term outcomes in survivors of critical illness due to COVID-19

M. Egger^{1,2}, J. Reitelbach¹, F. Müller¹, K. Jahn^{1,3}, J. Bergmann^{1,3}

¹ Schoen Clinic Bad Aibling, Department of Neurology, Research Group, Bad Aibling, Germany

² Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany

³ German Center for Vertigo and Balance Disorders (DSGZ), LMU, University Hospital, Munich, Germany

Introduction and Aim: Survivors of critical illness frequently suffer from physical, mental, and cognitive impairments which hinder their independence in daily activities and limit their participation in work and social life [1]. These impairments can be present up to months and years after the critical illness and the health-related quality of life is reduced accordingly [2]. In severe cases of individuals infected by SARS-CoV-2, a treatment on intensive care unit (ICU) was required and long-term impairments were reported in patients after critical COVID-19 disease [3]. The Schoen Clinic Bad Aibling, a center for neurorehabilitation including treatment on ICU, cared for a substantial number of these patients. We aimed to investigate their neurological impairments, clinical progress, and the long-term outcome up to one year after discharge from neurological rehabilitation. In this abstract we give an overview of the study results.

Methods: In this observational prospective cohort study, patients were recruited after admission to rehabilitation. Adult patients with laboratory-confirmed COVID-19 were eligible after the infectious stage and after weaning from mechanical ventilation. Exclusion criteria were (1) insufficient (German) communication skills to complete the questionnaires and (2) patients receiving palliative care. Study visits were conducted at admission to (V1) and at discharge from neurorehabilitation (V2), and 3, 6, and 12 months after discharge. They comprised a comprehensive

set of patient-reported, and clinician-reported outcomes, as well as performance outcomes and questions about personal living and working conditions. The first two study visits were conducted in-person, the study visits after discharge (V3–V5) were conducted via structured telephone interviews and questionnaires sent by regular mail (Figure 1).

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Results: In total, 97 patients (61 ± 12 years, 31% female) were included in the analysis. The median duration of ICU treatment was 52 (interquartile range 36–71) days, the median duration of mechanical ventilation was 39 (22–55) days. As all patients were treated > 8 days on ICU and were ventilated > 96 hours, all fulfilled the criteria for chronic critical illness [4]. Complications during the ICU stay were frequent, including sepsis in 88%, acute respiratory distress syndromes in 82%, dysphagia in 52%, delirium in 32%, and severe encephalopathy in 16%. 84% presented a critical illness polyneuropathy/-myopathy, as measured by electrophysiological measurements during rehabilitation.

In a subgroup of 61 patients we described the clinical course during on average 57 ± 23 days of rehabilitation. Most of the outcome parameters like the Barthel-Index, the Clinical Frailty Scale, handgrip strength, and dyspnoea improved significantly from V1 to V2. Yet, no

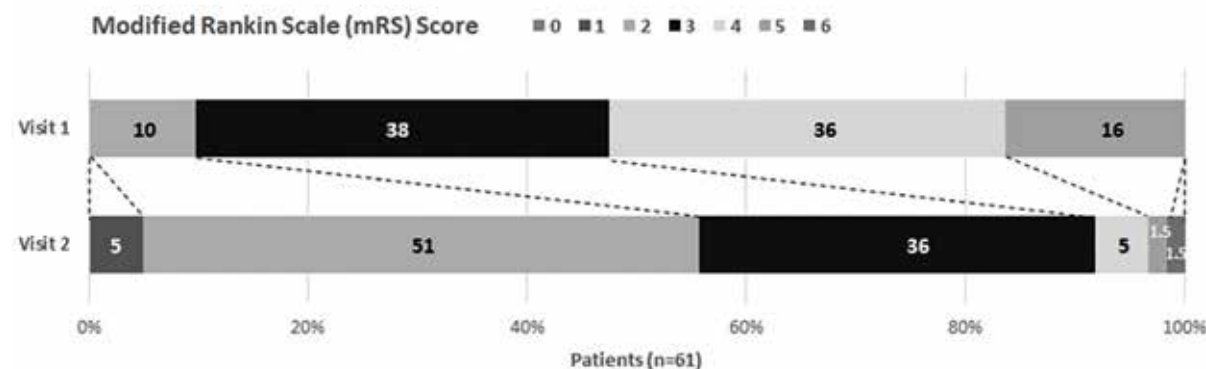


Figure 1. Modified Rankin Scale at visit 1 and 2. A shift of the values can be noticed (depicted with dotted lines) showing improvement between visits (this Figure is a reprint of our own work: Wimmer C, Egger M, Bergmann J, et al. Critical COVID-19 disease: Clinical course and rehabilitation of neurological deficits. *Frontiers in Neurology* 2022; 13, and is used under a CC BY 4.0 licence.)

Table 1. Outcome parameters over the course of the study

	Visit 1 at study onset	Visit 2 at discharge	Visit 3 3 months after discharge	Visit 4 6 months after discharge	Visit 5 12 months after discharge	Friedman-test V1 – V5	Effect size			
							V1–V2	V2–V3	V1–V5	V3–V5
Modified Rankin Scale	4 (3–4)	2 (2–3)	3 (2–3)	2 (1–3)	2 (1–3)	$\chi^2 (4) = 64.06, p < .001$	0.76 ↑	0.07 ↓	0.63 ↑	0.39 ↑
Clinical Frailty Scale	6 (6–7)	5 (4–6)	5 (3–6)	4 (3–5)	4 (3–5)	$\chi^2 (4) = 115.8, p < .001$	0.85 ↑	0.26 →	0.85 ↑	0.57 ↑
Modified Medical Research Council Dyspnea Scale	3 (2–4)	2 (1–2.25)	1 (0–2)	1 (0–2)	1 (0–2)	$\chi^2 (4) = 32.39, p < .001$	0.84 ↑	0.44 ↑	0.80 ↑	0.12 →
FSS-7 Fatigue ≥ 4	2.7 ± 1.5 18 (23.7%)	2.8 ± 1.7 20 (22.5%)	3.8 ± 2.0 34 (44.7%)	3.9 ± 2.0 38 (53.5%)	4.0 ± 1.9 35 (54.7%)	$\chi^2 (4) = 29.38, p < .001$	0.07 ↓	0.47 ↓	0.52 ↓	0.01 ↓
HADS										
Anxiety	5 (2–8)	4 (1–6)	7 (3–10)	6 (3–9)	7 (3–11)	$\chi^2 (4) = 10.95, p = .027$	0.33 ↑	0.54 ↓	0.14 ↓	0.02 →
Anxiety > 7	23 (29.9%)	19 (21.6%)	32 (42.7%)	26 (37.1%)	27 (42.2%)					
Depression	4 (2–8)	3 (1–7)	6 (3–10)	5 (2–9)	6 (3–9)	$\chi^2 (4) = 12.32, p = .015$	0.29 ↑	0.53 ↓	0.26 ↓	0.03 →
Depression > 7	20 (26.0%)	14 (15.9%)	32 (42.7%)	20 (28.6%)	25 (39.1%)					
EQ-5D-5L - Index value	0.53 ± 0.29	0.73 ± 0.20	0.63 ± 0.29	0.64 ± 0.30	0.63 ± 0.33	$\chi^2 (4) = 10.76, p = .029$	0.63 ↑	0.32 ↓	0.26 ↑	0.06 →

Data are n (%), mean ± SD or median (quartile 1 – quartile 3); FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5L = EuroQol – 5 dimensions – 5 level; The effect size was calculated with $r = z/\sqrt{N}$. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), p. 79–81. → Unchanged ↑ Improvement ↓ Deterioration; Due to missing values, sample size included in the Friedman-test for V1 – V5 differs per assessment: modified Rankin Scale n = 56; Clinical Frailty Scale n = 50; Modified Medical Research Council Dyspnea Scale n = 18; FSS-7 n = 38; HADS n = 38; EQ-5D-5L Index n = 43

progress was found for fatigue and anxiety. **Figure 1** displays the improvement according to the modified Rankin Scale, showing that most patients were in categories 3 and 4 at V1, with the majority improving to categories 2 and 3 by discharge. However, the preclinical health state was not regained at discharge, as indicated by the modified Rankin Scale (preclinical median 0 [IQR 0]) or the Clinical Frailty Scale (pre: 2 [1], V2: 5 [2]).

In the following analysis including the total population, we focused on the long-term outcome after rehabilitation [6]. Although the clinician-reported outcomes modified Rankin Scale and the Clinical Frailty Scale improved up to the last study visit, fatigue, depression, and anxiety increased, especially between discharge and the three-month follow-up visit (**Table 1**). During the three follow-up visits, these symptoms did hardly change, and frequency remained on a high, undesirable level. 12 months after rehabilitation discharge, fatigue reached the highest level, with 55% of the participants being affected. Accordingly, health-related quality of life was impaired in most patients, and the mean was substantially lower than in a general German population of the same age (0.92 ± 0.13) [7].

In accordance with the reported impairments, independence in activities of daily living and participation in social and work life were restricted.⁸ Main problems reported six to twelve months after discharge from rehabilitation were fatigue, walking impairments, sensory disturbances, dyspnoea, and problems with internal organs. One year after discharge, 26% required assistance for washing/dressing, 54% needed help with household tasks, and 46% received therapies, with physiotherapy being the most common type. Only 42% were able to resume working under the same conditions (type of work and hours per week) as before COVID-19.

In a final analysis we compared the impairments after critical illness to the post-COVID-19 burden of non-hospitalized individuals with only mild acute infection [9]. We demonstrated that the post-COVID-19 condition can be comparable or even worse than the health status of patients being treated on ICU. Symptoms such as fatigue, anxiety and difficulties in joining in community activities and work activities were significantly more pronounced in the non-hospitalized individuals. According to our analysis only female gender, but not hospitalization, was associated with lower health-related quality of life and lower general disability.

Conclusion: Survivors of critical illness due to COVID-19 suffer greatly from impairments like functional disability, fatigue, anxiety, and depression, even one year after discharge from rehabilitation. These individuals often require assistance in self-care and household tasks, accordingly health-related quality of life, and return to previous employment is often limited. However, the significant symptom burden of post-COVID-19 condition may also manifest in patients who experienced mild acute COVID-19. Therefore, all patients with severe impairments after COVID-19 require adapted therapies and supportive structures even several months after disease onset, with a special attention on mental health.

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