Rehabilitation needs following COVID-19: Five-month post-discharge clinical follow-up of individuals with concerning self-reported symptoms

Carl Wahlgren,[a] Anestis Divanoglou,[a] Melanie Larsson,[a] Emma Nilsson,[a] Åse Östholm Balkhed,[b] Katarina Niward,[b] Ulrika Birberg Thornberg,[a] Eva Lilliecreutz Gudmundsson,[a] and Richard Levi,[a]

[a]Department of Rehabilitation Medicine and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping S-58185, Sweden
[b]Department of Infectious Diseases and Department of Biomedical and Clinical Sciences, Linköping University, Linköping S-58185, Sweden

eClinicalMedicine 2022;43: 101219
Published online 5 December 2021
https://doi.org/10.1016/j.eclinm.2021.101219

Summary

Background This report describes and objectivizes reported problems among a cohort of previously hospitalized COVID-19 patients by clinical examination and determination of the required level of rehabilitation sevices.

Methods This report forms part of the Linköping COVID-19 Study (LinCoS) that included 745 individuals from one of 21 Swedish healthcare regions, Region Östergötland (RÖ), admitted to hospital for COVID-19 during March 1st–May 31st, 2020. In this descriptive ambidirectional cohort study, all 185 individuals who had reported concerning persisting symptoms were invited to a multi-professional clinical assessment of somatic, functional, affective, neuropsychological status and rehabilitation needs. Rehabilitation needs were assessed using three sub-scales of the Rehabilitation Complexity Scale-Extended.

Findings Among the 158 (85·4%) cases consenting and included in the analysis, we found a broad array of symptoms and signs attributable to COVID-19 involving respiratory, visual, auditory, motor, sensory and cognitive functions that could be confirmed clinically at five months post-discharge. This translated into 16% [95% CI 13–20] of survivors (70/433) of the total regional cohort of hospitalised patients requiring further rehabilitative interventions at follow-up. Weakness in extremities was reported in 28·5% [21·6, 36·2] (45/158). On examination, clinically overt muscle weakness could be corroborated in 15 individuals (10·5%) [6·1, 16·4]. 48% [40, 56] (76/158) reported cognitive symptoms, while the physician noted overt cognitive impairments in only 3% [1·1, 7·5]. In neuropsychological testing, 37% [28–46] (45/122) performed 1.5 SD below the norm, indicating neurocognitive deficits. Fifty-five individuals (34·8%) [27·4, 42·8] reported new or aggravated pain. In three fourths of them, it exerted a 'moderate' or worse detrimental effect on their ability to work.

Interpretation Our study underscores the importance of providing extensive examination of cases with persisting problems after COVID-19, especially since symptoms such as fatigue and breathlessness are highly nonspecific, but may represent significant underlying functional impairments. Robust neurocognitive testing should be performed, as cognitive problems may easily be overlooked during routine medical consultation. In the Swedish context, most rehabilitative interventions could be provided in a primary care setting. A substantial minority of patients should be triaged to specialized rehabilitation services.

Keywords: SARS-CoV-2; Post-COVID-19; PACS; Rehabilitation; Consequences; Residual symptoms; Long-term follow-up

Introduction

As of July 2021, The COVID-19 pandemic has so far resulted in approximately 180 million confirmed cases and 4 million deaths worldwide, and almost 3 billion vaccine doses have been administered.[1]

The acute phase of the disease has been extensively studied,[2] and there is an increasing number of studies on its long-term effects as well.[3,4] The most recent systematic review by the Cochrane Rehabilitation Field[5]

E-mail address: Emma's affiliation would be Medical Faculty, Linköping University.

Research in context

Evidence before this study

We searched MEDLINE with no language restriction for studies exploring long-term consequences after hospitalisation related to COVID-19 up to Jun 30, 2021. We used search terms ("SARS-CoV-2" OR "COVID-19") AND ("hospital*") AND ("consequences" OR "follow-up" OR "long-term" OR "residual" OR "persisting") and their synonyms. Further, we reviewed the REH—COVER series of rapid living systematic reviews from the Cochrane Rehabilitation Field that aims to provide in a timely manner all rehabilitation professionals with the current scientific knowledge on COVID-19 rehabilitation.

Commonly reported presentations at follow-up include dyspnea, mental fatigue, cognitive deficits, muscle weakness, sleep disturbance, anosmia/hyposmia, and affective symptoms such as anxiety and depression.

Most identified studies relied either on self-reported symptoms and/or on patient registries/medical records, or on clinical assessment focused primarily on a single organ or body system. COVID-19 is now considered a heterogeneous entity with a putatively multifactorial aetiology, including viral persistence, inflammatory changes, physical deconditioning and psychological factors. Thus, there is a need for studies employing a holistic approach combining multi-professional clinical assessments, patient reported outcome measures, radiology, functional tests, and laboratory tests.

Added value of this study

The findings of this study are based on a total regional cohort of survivors previously hospitalised for COVID-19, assessing signs and symptoms 5-months post-discharge. Efforts were made to isolate the actual contribution of COVID-19 on outcomes, by assessing premorbid health status, comorbidities, coincidental cases, and by specifically documenting only new or aggravated symptoms occurring during and after COVID-19.

We found that a broad array of symptoms and signs attributable to COVID-19 involving respiratory, visual, auditory, motor, sensory and cognitive functions could be confirmed clinically at five months post-discharge in most patients. Approximately one in five survivors of the total regional cohort of hospitalised patients required further rehabilitative interventions at follow-up.

In conclusion, our study provides important evidence for (a) the need for a thorough assessment of individuals previously hospitalized for COVID-19 as regards persisting rehabilitation needs; (b) inclusion in such assessment of individuals with all degrees of disease severity; and (c) triaging of all individuals according to rehabilitation complexity by a structured, multi-professional approach also including auxiliary testing in addition to screening clinical assessment.

Implications of all the available evidence

Robust neurocognitive testing should be performed, as cognitive problems may easily be overlooked during routine medical consultation. Most rehabilitative interventions could be provided in a primary care setting. A substantial minority of patients should to be triaged to specialized rehabilitation services. Longer-term follow-up studies are also called for, in order to assess the long-term prognosis as regards the sequelae of this disease.

included several studies[6–11] assessing long-term effects after 5–7 months.

Specifically, commonly reported presentations at follow-up include dyspnea,[9,12–18] impaired fitness,[6] mental fatigue[8,13–18] and cognitive deficits,[4] muscle weakness, sleep disturbances,[12,13,15,16,18] anosmia/hyposmia,[12,14,16,18] and affective symptoms such as anxiety and depression.[8,16–18] Neuropathological studies have demonstrated direct and indirect damage from COVID-19 on many organs, such as the heart, lungs and the peripheral and central nervous systems.[19,20] In the first report from the Linköping COVID-19 Study (LinCoS), COVID-19-associated mortality was described, as well as self-reported persisting impairments and limitations in activity and participation among previously hospitalized survivors four months post-discharge.[18] Functional limitations have also been reported in other studies. For instance, Huang and colleagues[16] found decreased FEV1, FVC and TLC, diffusion abnormalities, and impairments in the EQ-5D subscales relating to mobility, pain, usual activities as well as anxiety and depression. All these impairments were more frequently found in patients with severe COVID-19 (CPS 6–9) compared to non-severe COVID-19 (CPS 4–5). Similarly, Zhu and colleagues[21] found that patients with severe COVID-19 had a higher prevalence of anxiety and were more likely to have impairments in instrumental activities of daily life (IADL), compared to non-severe COVID-19. A common finding across studies is that a majority of cases report at least one residual symptom, at 2–6 months follow-up.[13–16,18] In addition, there are some early studies examining effects of interventions targeting specific symptoms.[5]

So far, however, it remains unclear whether or not disease severity influences prevalence of persisting symptoms several months after discharge,[3,5] mandating a further exploration of any such correlation. Further, most studies have relied either on self-reported symptoms and/or on patient registries/medical records,[9] or on clinical assessment focused primarily on a single organ or body system.[6,8,12] COVID-19 is increasingly considered a heterogeneous entity with a putatively multifactorial aetiology, including viral persistence, inflammatory changes, physical deconditioning and psychological factors.[3] Thus, studies that employ a holistic approach combining multi-professional clinical assessments, patient reported outcome measures (PROMs), radiology, functional tests, and laboratory tests are called for. This is important in order to unravel

the complexity of the residual presentations of this new disease and institute comprehensive therapeutic interventions.

The aims of this study were to: (a) describe reported COVID-19-related impairments and activity/participation limitations persisting at five months post-discharge; (b) objectivize and clarify these problems through clinical examination by appropriate rehabilitation professionals, including functional testing and auxiliary investigations; and (c) determine adequate rehabilitation interventions in terms of intensity and complexity.

Methods

Study design and participants

This ambidirectional cohort study covered the county of Östergötland, Sweden. The county has three hospitals, a tertiary care university hospital with 400 beds and two general hospitals with 241 and 76 beds, respectively, and serves a population of approximately 450 000 inhabitants.

In this region, 745 patients with a positive PCR for SARS-CoV-2 were admitted to hospital for COVID-19 during March 1st May 31st, 2020. This report describes the subsequent clinical follow-up of those individuals who reported concerning residual symptoms and limitations in activity and participation at the 4-months screening ($n = 185$, 42·7% of interviewed survivors). Our previous report describes the selection process and criteria in detail.[18]

After exclusion of fatalities, coincidental cases, and cases with premorbid conditions precluding assessment of COVID-19-attributable sequels (e.g. severe dementia or terminal cancer), 433 individuals were screened by rehabilitation professionals using a structured telephone interview four months post discharge. Each telephone interview was evaluated by a multi-professional team as regards indications for further clinical assessment of persisting rehabilitation needs. Based on this assessment, 42·7% of individuals ($n = 185$) reported concerning problems, i.e. problems significantly interfering with daily life activities, and were thus invited for a multi-professional clinical follow-up.

Out of these 185 invited patients, 158 (85·4%) attended the clinical assessment and were included in the analysis (Fig. 1). Prior to the clinical assessment, written informed consent was obtained from all participants. Clinical assessment occurred at a median of 142 (122–165) days post-discharge and a median of 29·5 (21-39) days after the telephone interview.

The clinical follow-up included, as a minimum, an assessment by a physician (100%) and a neuropsychologist (156/158, 98·7%), as well as blood and urine tests. In addition, in cases where the screening interview indicated symptoms suggesting impairments in other organ systems, some patients were also examined by a physiotherapist (78/158, 49·4%), occupational therapist (42/158, 26·6%), speech therapist (18/158, 11·4%) and/or neuro-optometrist (43/158, 27·2%). Auxiliary investigations, e.g. various functional tests and/or radiology, were instituted when clinically indicated.

Following the clinical visit, a series of team conferences were held, during which appropriate further actions were decided. All patients received written feedback as regards test results and on any referrals for further rehabilitative and other medical measures.

The study was performed in accordance with the STROBE statement guidelines.[22]

The blue box in the bottom left corner shows the group of individuals studied in this paper. The 27 individuals who were invited to the clinical assessment but not included in the study consisted of one individual who showed up for the assessment but withdrew consent regarding inclusion in the analysis, and 26 individuals who for various reasons did not show up to the assessment despite several attempts to reschedule the appointment.

Materials

The main focus of this study is on data pertaining to the physician's assessment for new or aggravated impairments related to COVID-19 still persisting at five months post-discharge. This included:

- The pertinent medical history prior to, during and after COVID-19, including current problems. Specifically, symptoms that were *new or aggravated* in relation to COVID-19 *and still present* at the time of the clinic visit were assessed. These are presented as "residual symptoms".
- Physical examination with focus on new or aggravated signs related to COVID-19.
- Laboratory findings (blood and urine), with the aim of identifying persisting pathological findings related to COVID-19.
- Chest and/or brain radiology (when clinically indicated), also with the aim of identifying persisting pathological findings related to COVID-19.

Data corroborating findings on medical examination were also obtained by neuropsychological testing in accordance with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[23] and color Word Interference Test,[24] 6 min walk test (6MWT), spirometry, and/or ophthalmological examination, and are presented in conjunction with the corresponding symptoms and signs. Patient-reported outcome measures (PROMs) were also collected, i.e. the 12 item Short Form Health Survey (SF-12),[25] the Hospital Anxiety and Depression Scale (HADS),[26] and the Multidimensional Fatigue Inventory (MFI).[27] A cut-off

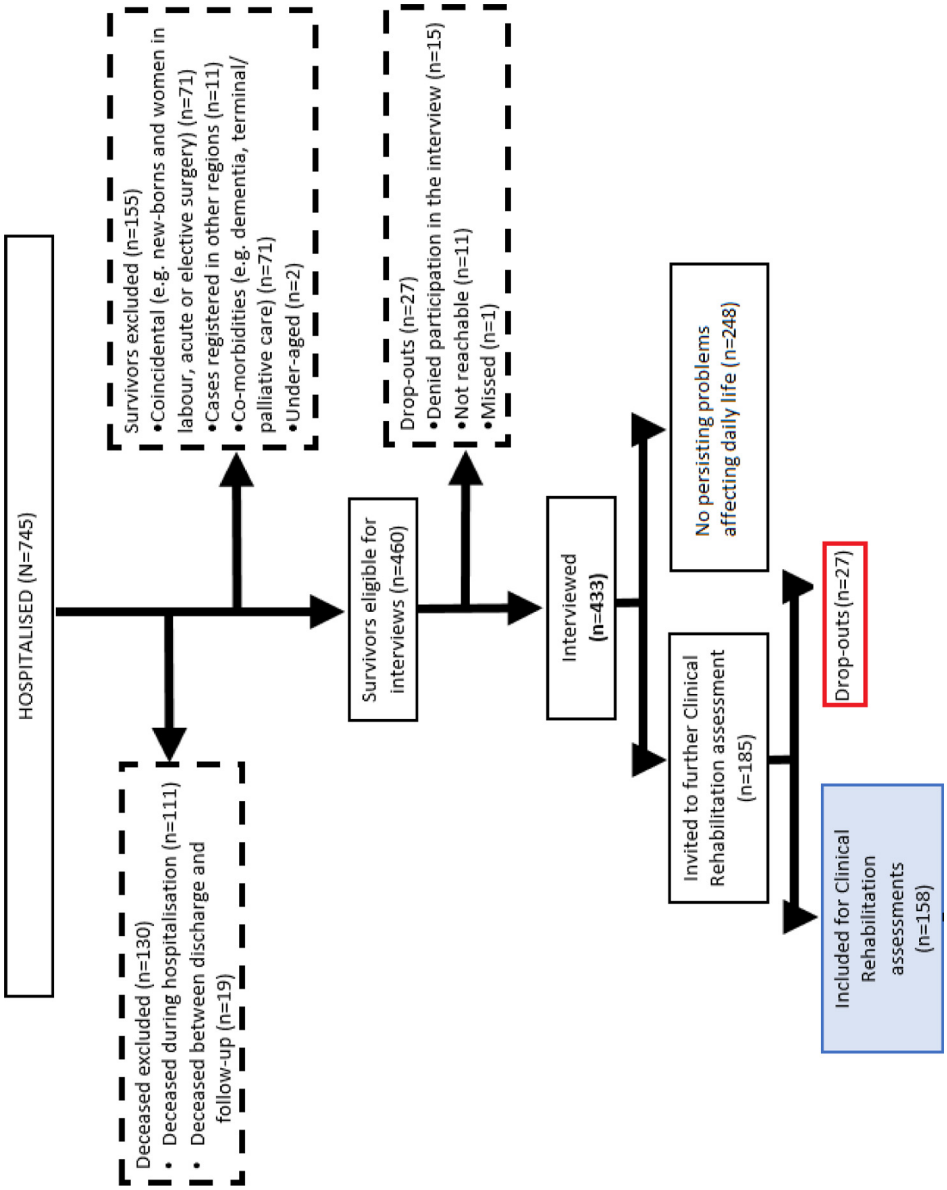

Fig. 1. Participant selection.

of ≥ 8 was used on HADS to indicate potential mild depression/anxiety,[28] and a cut-off of ≥ 53 on MFI for clinically significant fatigue.[29] With regards to RBANS and CWIT, the methodology is described in more detail in another paper from LinCoS.[30]

The highest WHO Clinical Progression Scale (CPS) grade[30] during hospitalization was determined for each patient, as described in our previous paper.[18] According to WHO CPS, patients with grade 4 and 5 were categorized as moderate disease severity and cases with WHO CPS 6–9 as severe.

The following blood and urine tests were obtained at follow-up:

- *Inflammatory parameters:* CRP, leukocyte plasma concentration (LPC), erythrocyte sedimentation rate (ESR)
- *Kidney function:* eGFR, calculated using S-creatinine (MDRD) and S-cystatin C
- Haemoglobin (Hb) - Anaemia was defined in accordance with standards of the hospital laboratory as Hb < 134 (g/L) for males or Hb < 117 (g/L) for females. In case of anaemia, mean corpuscular volume (MCV) is presented as low/normal/elevated.
- *Liver function*: alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (ALP), gamma glutamyl transferase (GT), and/or bilirubin (total)
- *Muscle affection:* creatine kinase (CK)
- *Urine analysis:* U-erythrocytes (present/absent), U-leukocytes (present/absent), U-nitrite (present/absent), U-Albumin/creatinine (< 3 = normal or slightly elevated; 3–30 = moderately elevated; > 30 = markedly elevated)
- P-albumin
- IgG-antibodies against SARS-CoV-2.

The reference values of the Linköping University Hospital laboratory were used. For abnormalities in kidney function, we also refer to Kidney Disease Improving Global Outcomes (KDIGO) 2012.[31] Acute kidney injury was defined according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) definition.[32] Major bleeding as a complication was defined by the International Society on Thrombosis and Haemostasis (ISTH) recommendation.[33] Ventilator associated pneumonia (VAP) was defined using the 2014 Swedish Intensive Care Registry definition.[34] In cases with pathological laboratory findings, results were compared with corresponding results obtained prior to COVID-19, and only new or aggravated findings at five months follow-up were reported as being possibly attributable to this disease.

Rehabilitation needs were assessed using the Therapy Intensity (TI), Therapy Disciplines (TD), and Equipment sub-scales of the Rehabilitation Complexity Scale – Extended (RCS-E).[35]

All obtained data were used for assessment of rehabilitation needs, as well as to issue referrals to relevant rehabilitation providers and/or organ specialists.

Procedures

Clinical assessments were performed between July and December 2020, involving six physicians following a similar structure for clinical assessment. Extensive comparisons were made with corresponding pre-morbid data from medical records, in order to identify and present *new or aggravated* pathology attributable to COVID-19. Any pathological findings attributable to pre-morbid conditions are thus not presented, unless otherwise indicated. With regard to comorbidities, those that prompted an ICD-10 diagnosis in the discharge notes pertaining to the COVID-19 related hospitalisation were retrieved and presented in this paper. Thus, only comorbidities deemed relevant during the patient's hospitalisation were considered.

SF-12 was completed by the patient prior to the visit and later discussed with members of the team involved in the clinical assessment. HADS was completed by the patient at the clinic visit with support from a neuropsychologist. The full version of HADS and item eight of the SF-12 (relating to pain) were extracted and analysed.

Data pertaining to initial presentations, comorbidities, complications, and indicators of disease severity were extracted from the medical record and corroborated by the medical history obtained from the patient at the clinic visit. To identify comorbidities and complications during COVID-19 hospitalisation, the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Swedish version, (ICD-10 SE) codes were extracted from discharge notes pertaining to hospitalisations for all included patients.

The following blood tests performed during hospitalisation for COVID-19 were retrieved retrospectively from medical records: C-reactive protein (CRP), lymphocyte count, D-dimer, Ferritin, estimated glomerular filtration rate using the Modification of Diet in Renal Disease (eGFR MDRD), blood cultures. Bloodstream infection (BSI) was defined as a positive blood culture (excluding contamination). In this paper, we present the 'worst' value observed during hospitalization (i.e. the lowest value for eGFR and lymphocytes, and the highest value of D-dimer, Ferritin, and CRP).

Statistics

Data were presented as mean and standard deviation (SD) for normally distributed continuous variables, as median and inter-quartile range (IQR) for non-

normally distributed numeric variables, and as *n* (%) or *n* (% [95% confidence interval (CI)]) for categorical data. Normality was tested using the Shapiro-Wilks test. Between-group comparisons were performed for participants vs. drop-outs (background data), between groups with different disease severities according to WHO CPS (dichotomized as CPS 4–5 vs. CPS 6–9), between individuals with objectivizable residual sensorimotor impairments vs. those without such impairments, and finally, between individuals reporting a cluster of potentially dysautonomic symptoms and those without such symptoms. These comparisons were performed using a binary logistic regression model using the generalized linear model subroutine in SPSS, with one factor included in the model at a time. In an effort to clarify these presentations, we included the following factors in the analysis: background characteristics (age, sex, premorbid level of function, occupation status before and after COVID-19), disease severity indicators (WHO CPS, CRP during hospitalization, total length of hospital stay), SARS-CoV-2 antibody status at follow-up, and in-hospital complications (AKI, arrhythmia, BSI, VAP, VTE, PE, major bleeding, cerebrovascular event, myocardial infarction and/or critical illness polyneuropathy/-myopathy). Results from the binary logistic regression models were presented as unadjusted odds ratios (OR) with corresponding confidence intervals [95% CI]. Each table presents the exact number of cases contributing data. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) version 27.

Ethics

The Swedish Ethical Review Authority approved the study protocol (Dnr 2020–03029 and 2020–04443).

Role of the funding source

The study was funded by the ALF grant and Region Östergötland. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient and disease severity descriptors

Basic data are presented in Table 1.

In summary, the 158 participants who underwent a clinical assessment had a mean age of 57·4 (± 13·8) years and 38·6% were female (61/158). Median (IQR) length of hospital stay (LOS) was 7[3–19] days. 102 individuals (64·6%) had a moderate disease (CPS 4–5), 16 (10·1%) had severe disease that did not require mechanical ventilation (CPS 6), and 40 (25·3%) had severe disease that required mechanical ventilation (CPS 7–9). Out of the 90 individuals that were working or studying prior to contracting COVID-19, 21 (23%) were on sick leave four months after discharge from hospital.

The group of 27 individuals who dropped out was largely similar to the group of participants as regards patient and disease severity descriptors with a few exceptions (Appendix Table 3). Firstly, a higher proportion of the drop-outs were female (67%, 18 of 27), compared to 39% (61 of 158) of participants (OR 3·18, 95% CI [1·34, 7·53]). Secondly, the individuals who dropped out were more likely to be unemployed at the time of the clinical assessment (5·60 [1·66, 18·85]) as compared to participants. Finally, individuals with African ethnicity (excluding Middle Eastern or North African) (9·00 [1·40, 57·9]) or 'other' ethnicity (8·00 [1·64, 38·9]) were also more likely not to attend. Appendix Table 3 contains background data for: (a) the entire cohort of patients hospitalized for COVID-19 in the healthcare region during the time frame described in this paper (March 1st through May 31st, 2020), *n* = 734, (b) those survivors deemed eligible for screening telephone interview at 4 months post-discharge (*n* = 460), (c) those who attended clinical assessment (*n* = 158), and finally (d) those who were invited to the clinical assessment but denied inclusion or did not attend (*n* = 27).

As a complementary measure of disease severity, we present the worst laboratory test results from hospitalisation (Appendix Table 1). Two thirds (70·1%) had lymphopenia (P-lymphocytes < 1·1) at some point during their hospital stay. The majority (62·9%) had at least one value of CRP >100. Further, ferritin and D-dimer values were available in between half and two thirds of individuals. Ferritin was elevated in 92 (89·3% 95% CI [81·7, 94·6]) and D-dimer in 57 (69·5% [58·4, 79·2]) tested individuals. The median values were 1010 (450–1970) and 0.62 (0.20–1.48), respectively.

Thirty percent had at least one complication during hospitalization for COVID-19 (Appendix Fig. 1). The most common complication was acute kidney injury (AKI, 24/158, 15%), followed by venous thromboembolism (9/158, 6%). Twenty-five percent (40/158) received mechanical ventilation, for 15·5 (9·3–24·3) days. Among those, eight (20% [9·1, 35·7]) suffered critical illness polyneuropathy/-myopathy (CIP/CMP) and ten (25% [12·7, 41·2]) ventilator-associated pneumonia (VAP).

Residual presentations at five-month clinical follow-up

Of the 158 individuals attending clinical follow-up five months post-discharge, only 6 (3.8% [1·4, 8·1]) reported full recovery. Residual clinical presentations are presented in detail in Tables 2–4 and are hereby categorised into higher cerebral and affective, and somatic and functional. Presentations are typically presented as reported by the patient, followed, when obtainable, by findings from the medical examination, and/or standardised testing.

Background data	
Age (mean, SD)	57·4 (13·8) years
Sex, females (n,%)	61 (38·6%)
Length of stay (median, IQR)	7 (3—19) days
Mechanical ventilation (median, IQR), *n* = 40	15·5 (9·5—23·5) days
WHO CPS (n,%)	
4—5	*102 (64·6%)*
6	*16 (10·1%)*
7—9	*40 (25·3%)*
Education, *n* = 150	
Primary or lower	*33 (22·0%)*
Secondary	*63 (42·0%)*
Tertiary or higher	*54 (36·0%)*
Occupation prior to COVID-19, *n* = 155	
Work/studies	*90 (58·1%)*
Pensioner	*52 (33·5%)*
Unemployed	*7 (4·5%)*
Sick leave	*6 (3·9%)*
Occupation after COVID-19, *n* = 155	
Work/studies	*64 (41·3%)*
Pensioner	*54 (34·8%)*
Unemployed	*10 (6·5%)*
Sick leave	*27 (17·4%)*
Ethnicity*	
Swedish	*102 (64·6%)*
Other Europe	*19 (12·0%)*
Middle East/North Africa	*30 (19·0%)*
Other Africa	*2 (1·2%)*
Other	*3 (1·9%)*
Unknown	*2 (1·2%)*
Premorbid level of function,[18] *n* = 157	
No or mild frailty	*79 (50·3%)*
Moderate frailty	*51 (32·5%)*
Considerable frailty	*26 (16·6%)*
Severe frailty	*1 (0·6%)*
Comorbidities	
Hypertension	*64 (40·5%)*
Diabetes mellitus	*38 (24·1%)*
Respiratory disease	*33 (20·9%)*
Cardiovascular disease	*31 (19·6%)*
Psychiatric condition	*19 (12·0%)*
Obesity	*13 (8·2%)*
Chronic kidney disease	*10 (6·3%)*
Cancer	*5 (3·2%)*
None of the above	*48 (30·4%)*
Typical presenting symptoms	154 (97·5%)

***Table 1*: Background data.**
158 cases, unless otherwise specified. * = Ethnicity was determined by considering relevant entries in the medical record and primary language. Additionally, interpreter was used in 22 (13·9%); typical presenting symptoms = at least one of: fever, cough, anosmia, and/or shortness of breath.

Somatic and functional presentations

Weakness in one or several extremities was reported in 28·5% [21·6, 36·2] (45 of 158 participants), most commonly bilaterally. On medical examination, clinically overt muscle weakness could be corroborated in 16 individuals (10·5% [6·1, 16·4]). Furthermore, 12 individuals (7·6%) received walking aids after COVID-19 that they still needed at the 5-month follow-up. Forty-three individuals (27·2% [20·4, 34·9]) reported anaesthesia/hypaesthesia and/or paraesthesia, with 23 (14·6% [9·5, 21·0]) also showing signs of new or aggravated sensory disturbance upon physical examination. Our analysis (Appendix Table 5) showed that for every day of hospitalization, the odds for developing sensory and/or motor impairments as evidenced by clinical examination was 3% higher (OR 1·03, 95% CI [1·02, 1·05]). Further, there were higher odds for such impairments in those with higher disease severity, (3·17 [1·43, 7·00]), as well in those with any of the following complications: acute kidney injury (3·58 [1·40, 9·16]), bloodstream infection (5·12 [1·59, 16·49]), ventilator-associated pneumonia (6·44 [1·70, 24·43]), stroke (5·38 [1·14, 25·37]), and/or critical illness polyneuropathy/-myopathy (13·11 [2·51, 68·55]). No such association was seen for arrhythmia, major bleeding, venous thromboembolism, myocardial infarction, age, sex, level of CRP during hospitalization, presence of SARS-CoV-2 antibodies at follow-up or presence of pathological chest radiology at follow-up.

Fifty-five individuals (34·8% [27·4, 42·8]) reported new or aggravated pain, with three out of four of these indicating that it exerted a 'moderate' detrimental effect or worse on their ability to work (question eight of SF-12). Nociceptive-type pain (49/158, 31·0% [23·9, 38·8]) was considerably more common than neuropathic-type pain (8 of 158 individuals, 5·1% [2·2, 9·7]). For nociceptive pain, headache was the most common pain localization.

New or aggravated shortness of breath and/or breathing discomfort were reported by 64 individuals (40·5% [32·8, 48·6]), and cough by 11 (7·0% [3·5, 12·1]), totalling 69 individuals with residual respiratory symptoms. For these individuals, results of the spirometry, 6MWT, and follow-up chest radiology were analysed and are shown in Table 4. Further clarifications of Table 4 are described in the Supplementary material. Pathological results likely attributable to COVID-19 were seen in one third, one fourth and one fifth of these individuals, respectively. Isolated cardio-circulatory symptoms such as peripheral coldness in extremities, palpitations, thoracic dysesthesia or discomfort (excluding breathing discomfort) were reported by nine individuals (5·7% [2·6, 10·5]). Twenty-two individuals (13·9% [8·9, 20·3]) reported a cluster of symptoms suggestive of dysautonomia, i.e. a combination of visual disturbances, dizziness, intermittent nocturnal hyperhidrosis/fever, palpitations, heat sensitivity, cold sensitivity, and cold peripherals. Compared to the rest of the cohort (*n* = 136), the group presenting with dysautonomic symptoms was younger (OR 1·08, 95% CI [1·04, 1·12]), more often female (OR 4·19 [1·60, 11·00]), were less likely to have SARS-CoV-2 antibodies at follow-up (OR

Phenomenon	MHx (*n* = 158)	Physician's Ax (*n* = 153)	Testing
Higher cerebral functions	76 (48·1% [40·1, 56·2])	5 (3·3% [1·1, 7·5])	Neurocog. Ax 45* (37·1% [30·6, 48·1])
Memory impairment	*52 (32·9% [25·7, 40·8])*		
Language related disturbances	*26 (16·5% [11·0, 23·2])*		
Other cognitive	*34 (21·5% [15·4, 28·8])*		
Fatigue	83 (52·5% [44·4, 60·5])		MFI 106 (73·1% [65·1, 80·1])
Mental fatigue	*40 (25·3% [18·7, 32·8])*		
Physical fatigue	*23 (14·6% [9·5, 21·0])*		
Unspecified fatigue	*30 (19·0% [13·2, 26·0])*		
Weakness in extremities	45 (28·5% [21·6, 36·2])	16 (10·5% [6·1, 16·4])	
Upper only	9 (5·7% [2·6, 10·5])	4 (2·6% [0·7, 6·6])	
Lower only	13 (8·2% [4·5, 13·7])	5 (3·3% [1·1, 7·5])	
Upper and lower	23 (14·6% [9·5, 21·0])	6 (3·9% [1·5, 8·3])	
Unilateral	8 (5·1% [2·2, 9·7])	5 (3·3% [1·1, 7·5])	
Bilateral	37 (23·4% [17·1, 30·8])	10 (6·5% [3·2, 11·7])	
Altered sensation	43 (27·2% [20·4, 34·9])	23 (15·2% [9·9, 22·0])	
Extremities	42 (26·6% [19·9, 34·2])	23 (15·2% [9·9, 22·0])	
Upper only	11 (7·0% [3·5, 12·1])	3 (2·0% [0·4, 5·6])	
Lower only	17 (10·8% [6·4, 16·7])	14 (9·2% [5·1, 14·9])	
Upper and lower	14 (8·9% [4·9, 14·4])	6 (3·9% [1·5, 8·3])	
Unilateral	13 (8·2% [4·5, 13·7])	12 (7·8% [4·1, 13·3])	
Bilateral	29 (18·4% [12·7, 25·3])	11 (7·2% [3·6, 12·5])	
Axial	6 (3·8% [1·4, 8·1])	4 (2·6% [0·7, 6·5])	
Affective symptoms	41 (25·9% [19·3, 33·5])	11 (7·1% [3·6, 12·4])	
Visual problems	27 (17·1% [11·6, 23·9])	10 (6·6% [3·2, 11·8])	Optometrist's Ax*** (7 (25·9%)/7**)
Clumsiness	7 (4·4% [1·8, 8·9])	5 (3·3% [1·1, 7·5])	
Poor balance	5 (3·2% [1·0, 7·2])	4 (2·6% [0·7, 6·6])	

***Table 2*: Residual neurological symptoms with corresponding clinical findings.**
95% confidence intervals are shown in hard brackets. MHx = medical history (during physician's consultation); Ax = assessment; *n* varies between assessment and medical history because some of the patients could not be physically examined (or that this was not documented properly in the medical records). Affective symptoms = depression, anxiety, decreased motivation etc.; Altered sensation = hypaesthesia, anaesthesia and/or paraesthesia; * = total score at least 1.5 SD below norm; *** = Out of 27 individuals reporting visual symptoms at clinical assessment, 16 were assessed the by optometrist. Out of those 16, 44% underwent visual rehabilitation; ** = 7 individuals *who did not report* visual symptoms at the clinical assessment later underwent visual rehabilitation; Other cognitive symptoms = impaired attention, difficulty concentrating, light or sound sensitivity etc.; Language related symptoms = difficulties formulating or understanding language. MFI = Multidimensional Fatigue Inventory score of at least 53.

0·21 [0·08, 0·55]) (Appendix Table 4). They had lower disease severity according to the WHO CPS (OR 0·15 [0·03, 0·68]), lower CRP during hospitalization (OR 0·13 [0·03, 0·49]), and a shorter length of initial hospital stay (OR 0·85 [0·76, 0·96]). No association was seen for dysautonomia with any complication during hospitalization (acute kidney injury, arrhythmia, bloodstream infection, ventilator-associated pneumonia, venous thromboembolism, major bleeding, stroke, CIMP or myocardial infarction) or with presence of pathological chest radiology at follow-up.

In total, persisting smell or taste disturbance was reported by 33 people (20·9% [14·8, 28·1]). Further, new or aggravated visual problems were reported by 27 individuals (17·1% [11·6, 23·9]) including photosensitivity on eye examination and eye pain on oculomotor testing. Of these 27 individuals, 16 were also assessed by an optometrist, with seven cases displaying significant neuro-ophthalmological disturbances. An additional seven persons were found to have significant problems related to vision. These problems were not reported or observed during medical examination, but were noted by other healthcare professionals at the clinical visit, e.g. during neuropsychological testing. Nine individuals (5·7% [2·6, 10·5]) reported new or aggravated hearing loss. Audiometry was performed in eight of these patients, and six subsequently received hearing aids for the first time. Voice abnormalities (most commonly hoarseness) were reported by 22 individuals (13·9% [8·9, 20·3]).

Cognitive and affective symptoms and fatigue

Seventy-six (48·1% [40·1, 56·2]) individuals reported at least one persisting symptom related to higher cerebral dysfunction (excluding fatigue). The most common symptom was impaired memory (52/158, 32·9% [25·7, 40·8]). Twenty-two individuals (13·9% [8·9, 20·3]) reported speech problems, such as impaired word finding or speech comprehension. During medical consultation, only five individuals (3·3% [1·1, 7·5]) showed overt

Symptom, *n* = 158	N (% [95% CI])
Pain	55 (34·8% [27·4, 42·8])
Neuropathic type pain	*8 (5·1% [2·2, 9·7])*
Nociceptive type pain	*49 (31·0% [23·9, 38·8])*
Headache	*28 (17·7% [12·1, 24·6])*
Extremities (excludes generalized)	*16 (10·1% [5·9, 15·9])*
Generalized	*6 (3·8% [1·4, 8·1])*
Trunk	*4 (2·5% [0·7, 6·4])*
Smell/taste disturbance	33 (20·9% [14·8, 28·1])
Sleep disturbances	29 (18·4% [12·7, 25·3])
Voice/speech abnormality	22 (13·9% [8·9, 20·3])
Integumentary symptoms	21 (13·3% [8·4, 19·6])
Dysphagia	13 (8·2% [4·5, 13·7])
Dizziness	13 (8·2% [4·5, 13·7])
Hearing impairment/tinnitus	9 (5·7% [2·6, 10·5])
Decreased appetite	7 (4·4% [1·8, 8·9])
GI symptoms	6 (3·8% [1·4, 8·1])
Ocular pain	3 (1·9% [0·4, 5·4])
Urogenital symptoms	2 (1·3% [0·2, 4·5])
No residual symptoms	6 (3·8% [1·4, 8·1])

***Table 3*: Residual symptoms based on subjective reporting.**
Integumentary symptoms = hair loss, dry skin and similar; GI symptoms = bowel pain, abnormal stool consistency; sleep disturbances = insomnia, fragmented sleep, frequent nightmares etc.; voice/speech abnormality = hoarseness, dysarthria etc.; dizziness = excludes typical vestibular pattern (vertigo); urogenital symptoms = frequent urination, difficulty urinating, sexual dysfunction; dysphagia = difficulty swallowing; Neuropathic type pain = pain characterized by a burning, prickling or electrical sensation.

signs of cognitive impairment (such as disorientation). By contrast, formal neurocognitive testing showed that 45 individuals (37% [31, 48]) out of 122 with valid neurocognitive testing performed at least 1·5 standard deviations (SD) below norm values, indicating neurocognitive deficits. Fatigue was reported at the physician's assessment in 83 individuals (52·5% [44·4, 60·5]), and was further characterized by the patient as predominantly mental (40 of 158 individuals, 25·3% [18·7, 32·8]), predominantly physical (32/158, 14·6% [9·5, 21·0]) or mixed or unable to specify (30/158, 19·0% [13·2, 26·0]). On the MFI, 106 individuals (73·1% [65·1, 80·1]) scored over the cut-off for clinically significant fatigue. Affective symptoms were reported by 41 individuals (25·9% [19·3, 33·5]) and included increased irritability, stress sensitivity, emotional lability, depression and/or anxiety. Clinically overt affective disturbances (i.e. obvious depressed mood or agitation) were noted in 11 individuals (7·1% [3·6, 12·4]) during medical consultation. Results from HADS indicated anxiety and depression in 43% [35, 52] (60/140) and 29% [22, 38] (41/140), respectively.

Laboratory findings

Results from laboratory tests (urine and blood) at follow up are shown in Appendix Table 2. Overall seropositivity for SARS-CoV-2 antibodies was 76·5% [68·9, 83·1] (114/149). Anaemia was seen in eight individuals (5·4% [2·4, 10·4]) and was typically mild. In 28 individuals (18·9% [13·0, 26·2]) laboratory signs of mild inflammation were found, defined as elevation of at least one of the following values: erythrocyte sedimentation rate (ESR), CRP, P-Leukocytes. None had leukopenia. Significant new or aggravated impairment in kidney function (eGFR) was seen in 19 individuals (12·8% [7·9, 19·3]). Twenty individuals (13·5% [8·5, 20·1]), exhibited elevated liver enzymes and/or bilirubin. Microscopic haematuria was seen in 17 individuals (12·2% [7·3, 18·9]).

Radiological findings

Out of 119 cases with chest radiology (X-ray and/or computed tomography) showing signs of viral pneumonia during hospitalisation, 27 (22·9% [15·7, 31·5]) were still pathological at 5 months; 52 (43·2% [34·1, 52·7]) were normalized radiologically and 40 (33·9% [25·4, 43·2]) were not assessed with follow-up radiology. Three out of four (28/39) individuals who lacked follow-up chest radiology were asymptomatic as regards persisting respiratory symptoms, and most of the remaining (9/11) showed normal results in 6 min walk test and spirometry.

Brain MRI at follow-up was performed in a minority of the cohort. About two thirds of those examined showed multiple white matter lesions. Elaboration of these findings together with corresponding neuropsychological testing are presented in separate report from LinCoS.[36]

Rehabilitation needs at five months post-discharge

Table 5 shows persisting rehabilitation needs according to three subscales of the Rehabilitation Complexity Scale-Extended (RCS-E[35]). In total, 70 individuals (44·3% [36·4, 52·4]) presented with persisting rehabilitation needs at the five month clinical visit. In terms of therapy intensity, all individuals were deemed to require less than daily interventions (typically 1–3 sessions/week), thus allowing for outpatient rehabilitation. In terms of required therapy disciplines, most individuals required one or two disciplines (typically a physiotherapist and/or an occupational therapist), thus allowing for rehabilitation in most instances to be performed in primary care. Eleven individuals (7% [3·5, 12·1]) required several disciplines (i.e. TD grade 3 and 4) typically addressed in specialized rehabilitation centres.

In terms of assistive equipment, 17 individuals needed technical aids due to persisting COVID-19-related problems at five months post discharge. These comprised 12 instances of walking aids (cane, walker or wheelchair), and six instances of hearing aids. This type of equipment is categorized according to RCS-E as "basic", typically available through primary care sources.

Phenomenon	MHx (*n* = 158)	Clinical axe (*n* = 153)	6MWT (*n* = 69)	Spirometry (*n* = 69)	Chest radiology (*n* = 69)
Resp.	69 (44% [36, 52])	Low SpO2 (***): 8 (5% [2, 10])	D: 8 (12% [5, 22])	P: 24 (35% [24, 47])	P: 14 (20% [12, 32])
SOB and/or breathing discomfort	64 (41% [33, 49])	Inc. RF (**): 1 (1% [0, 4])	SD: 9 (13% [6, 23])	N: 18 (26% [16, 38])	N: 35 (51% [38, 63])
Cough	11 (7% [4, 12])	W: 5 (3% [1, 8])	N: 17 (25% [15, 37])	N/P: 19 (28% [18, 40])	N/P: 20 (29% [19, 41])
			I: 14 (20% [12, 32])	I: 8 (12% [5, 22])	
			N/P.: 21 (30% [20, 43])		
Dysautonomic symptoms	22 (14% [9, 20])	Tach.: 8 (5% [2, 10])			
		HT: 2 (1% [0, 5])			
Isolated circulatory symptoms (*)	9 (6% [3, 11])	Oedema: 3 (2% [0, 6])			
		PC: 2 (1% [0, 5])			

***Table 4*: Residual cardiopulmonary and dysautonomic symptoms with corresponding clinical findings.**
Resp. = respiratory symptoms; MHx = symptoms found in the medical history; Ax = assessment; SOB = shortness of breath; crep. = crepitation; 6MWT = 6 min walk test; *n* varies between assessment and medical history because some of the patients could not be physically examined (or that this was not documented properly in the medical records). * = Cardiopulmonary symptoms includes all of the sub-categories in the table *except* dysautonomic symptoms; Dysautonomic symptoms = Describes a pattern including multiple of the following symptoms: recurring fever, sweating, feeling warm, increased temperature sensitivity, blurred vision, dizziness; Isolated cardio circulatory symptoms = peripheral coldness, palpitations, chest pain or discomfort (excluding breathing correlated chest pain), excludes individuals included in 'dysautonomic symptoms'; *** = (95% or lower at rest *and* self reportedly symptomatic).; HT = hypotension, defined as systolic blood pressure < 100, sitting); ** = respiratory frequency 25 at rest. Results from 6MWT, spirometry and radiology are presented only for individuals with residual respiratory symptoms (*n* = 69); *D* = indicates desaturation > 4% compared to the resting measurement; SD = short distance on the 6MWT; N/*P* = not performed; *N* = normal; *P* = pathological; *I* = indicates an inconclusive result; *W* = wheezing or crepitations heard on pulmonary auscultation; Tach. = tachycardia (> 100 heartbeats per min) at rest; PC = peripheral coldness observed during physical examination.

Stratifying these results based on disease severity, as assessed by the WHO CPS, shows a greater need for equipment (OR 7.4 [2·3, 24·0]) and rehabilitation (OR 3·19 [1·62, 6·29]) in patients with severe disease (CPS 6–9), compared to those with moderate disease (CPS 4–5).

Referrals were provided in 70·3% [62·5, 77·3] of cases (111 of 158 individuals), most commonly to primary care facilities for further rehabilitation and/or medical follow-up. Patients requiring highly specialized and multiprofessional neurological rehabilitation (TD grade 3 and 4) were referred to a specialized rehabilitation department. Eight percent were referred to a specialist in otorhinolaryngology.

Discussion

In the previous paper of LinCoS, we evaluated 433 hospitalised cases and found that 185 cases reported persisting problems to a concerning degree 4 months after discharge. Based on a multi-professional clinical assessment that included relevant auxiliary investigations, the current study confirmed that most of the participants

Sub scales (grade)	Total (*n* = 158)	WHO CPS 4–5 (*n* = 102)	WHO CPS 6–9 (*n* = 56)	Odds ratio [95% CI]
Therapy intensity (TI)				
1 (less than daily)	70 (44·3% [36·4, 52·4])	34 (33·3% [24·3, 43·4])	36 (64·3% [50·3, 76·6])	3·19 [1·62, 6·29]
2+ (daily or more)	0	0	0	
Therapy disciplines (TD)				
1 (1 therapist)	29 (18·4% [12·7, 25·2])	13 (12·7% [7·0, 20·8])	16 (28·6% [17·3, 42·2])	3·93 [1·63, 9·48]
2 (2–3 therapists)	30 (19·0% [13·2, 26·0])	13 (12·7% [7·0, 20·8])	17 (30·4% [18·8, 44·1])	3·65 [1·53, 8·69]
3 (4–5 therapists)	9 (5·7% [2·6, 10·5])	7 (6·9% [2·8, 13·6])	2 (1·3% [0·1, 4·5])	0·91 [0·18, 4·73]
4 (6+ therapists)	2 (3·6% [0·4, 12·3])	1 (1·0% [0·0, 5·3])	1 (1·8% [0·0, 9·6])	3 (2·9% [0·6, 8·4])
Equipment (E)				
1 (basic specialist eq)	17 (10·7% [6·4, 16·7])	3·19 [0·19, 53·2]	14 (25·0% [14·4, 38·4])	7.41 [2·28, 24·0]
2 (highly specialist eq)	0	0	0	

***Table 5*: Rehabilitation Complexity Scale – Extended.**[35]
The table shows three sub scales of the RCS-E: Therapy intensity (TI), Therapy disciplines (TD), and Equipment (E). TI: grade 1 denotes less than daily therapy interventions; TD: grade 1: 1 therapist, grade 2: 2–3 therapists, grade 3: 4–5 therapists, grade 4: 6 or more therapists.; E: grade 1: basic special equipment (walking aid, wheelchair and/or hearing aids), grade 2: highly specialist equipment. Odds ratios are given for the WHO CPS 6–9 group, with the CPS 4–5 group as reference.[1]

who had reported concerning problems suffered a broad array of deficits involving respiratory, visual, auditory, motor, sensory and cognitive functions at 5 months after acute illness. This translated into 16% [12·8, 20·0] of survivors (70/433) of the total regional cohort of hospitalised patients requiring further rehabilitative interventions at the time of 5-month follow-up. Our findings underscore the necessity to develop structured programs for routine screening of rehabilitation needs after COVID-19, including adequate triage in terms of rehabilitation complexity. Results of this study indicate that rehabilitation providers in primary care may serve as a sufficient level of care for many patients, but also that a substantial minority of patients may indeed need more advanced resources.

Of particular concern is the clinical assessment, which needs to be sophisticated enough to capture impairments easily overseen in routine encounters, such as neurocognitive impairments, as well as cardiopulmonary and dysautonomic problems. Such problems are common and potentially debilitating if not properly addressed.[5,37] As a case in point, 48% [40·1, 56·2] (76/158) of cases reported experiencing cognitive symptoms, with memory impairment being most common, but the physician noted overt cognitive impairments in only 3% [1·1, 7·5] (5/153) of cases. Formal neuropsychological testing by a neuropsychologist, however, showed that 37% [31, 48] (45/122) performed 1.5 SD below the norm indicating neurocognitive deficit. These findings indicate that objectifiable neurocognitive deficits are common after hospitalization for COVID-19 and can persist for 5 months after discharge.[38] In order to identify and quantify any such deficits, neurocognitive testing should be performed, as such problems may be overlooked during medical consultation. Robust neurocognitive testing constitutes a valuable aid in delivering adequate health care services and allocating resources.[4] Exactly because of the critical interplay of neurocognitive functions with daily living, early detection of neurocognitive dysfunction will be critical for independent functioning and improved quality of life for many COVID-19 survivors.[4]

Forty percent complained of residual respiratory symptoms at the 5-months follow-up, with a significant portion showing pathological results in 6MWT and spirometry, suggesting functional impairment of respiratory function. Persisting dyspnoea and other respiratory symptoms were prevalent in our cohort, and were corroborated by functional testing and pathological chest radiology. Dyspnoea has been linked both with a persistent breathing disorder (overall high equivalents at VO2 peak and ventilatory inefficiency for those hospitalized in the ICU) [6] and muscle deconditioning.[6,7] Respiratory impairment is an important area with implications for functional ability and needs to be adequately addressed.[5] As a case in point,[39] after three weeks of in-patient multidisciplinary rehabilitation, participants exhibited improved respiratory muscle strength, increased independence and markedly improved walking distance. Liu and colleagues[40] showed that a 6-weeks respiratory rehabilitation program consisting of, among other things, respiratory muscle training, cough exercise and stretching exercises, led to enhanced pulmonary function, increased quality of life and reduced anxiety.

In many instances, subjective complaints could be substantiated and differentiated by auxiliary examinations and tests. This is clearly of importance, as many common symptoms, such as fatigue,[41] are highly unspecific and may be related to impairments in cardiopulmonary, cerebral,[4] autonomic and/or visual functions. More than 50% (83/158) of cases in this cohort reported persisting fatigue at 5 months follow-up and almost three out of four scored over the cut-off on the MFI. Other studies have estimated the prevalence of fatigue post-COVID-19 to 38–64%.[3,13–17,41] Fatigue has been shown not to be associated with age, type of treatment or length of hospitalisation, but rather with factors such as breathlessness and anxiety.[8,41] Because of the complex nature of fatigue, it has been recommended that its management requires multidisciplinary intervention. A correct and early diagnosis is necessary to provide relevant interventions and to prevent such problems from becoming chronic.[3] Since COVID-19 is a novel disease, it is all the more relevant to complement mere symptom enumerations with a search for root causes.

It is noteworthy that the subgroup presenting with symptoms suggestive of dysautonomia were significantly younger, more frequently of female gender, had much shorter hospital length of stay and a substantially lower frequency of SARS-CoV-2 antibodies as compared to the rest of the individuals. It has been theorized,[42,43] that this is characteristic of the subgroup of COVID-19 patients most prone to develop such symptoms in general. Thus, dysautonomic problems may be more common among *non-hospitalized* COVID-19 patients, as such persons are less likely to be admitted to hospital in contrast to those with more pronounced respiratory symptoms.

The possible link between fatigue and autonomic dysfunction was examined by Townsend et al.[8] who compared 20 individuals with residual fatigue, 6 months post COVID-19, with 20 similar individuals without fatigue. Although 70% of the fatigued group and 0% in the control group reported orthostatic intolerance (defined as at least one of: palpitations, dizziness, feeling lightheaded, or chest discomfort upon standing), they found no major objective differences with regards to autonomic function between the groups. However, they found a strong correlation between fatigue and anxiety. Additionally, they reported differences in regard to return to work, with 35% of the fatigue group and 0% of the control group being on sick leave at the time of the study (all worked prior to COVID-19), suggesting that

fatigue has a strong negative effect on the ability to work.

Problems such as persisting sensorimotor impairments were more frequent among individuals with more severe disease (WHO CPS 6–9) mostly treated in intensive care units (ICU). This reflects the higher incidence of critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) among such patients,[44,45] but motor and sensory impairments were also seen in non-ICU treated patients. Other problems, such as cardiorespiratory, cognitive and affective symptoms, were common across all WHO CPS subgroups, underscoring the need for post-acute screening also of patients with moderate disease severity. The current study and recent systematic reviews[3,5] show that therapeutic interventions should be targeted primarily towards improving fatigue, muscle weakness and cognitive symptoms. Dyspnoea, impairments to the senses (touch, taste, smell, vision and hearing), sleep disorders and affective symptoms also need to be addressed. Some interventions have been evaluated in pilot-controlled and randomized controlled trials. For instance, in a 4-week pilot controlled intervention in 14 patients recently discharged from the ICU, Mateo and colleagues[46] evaluated the addition of functional electrical stimulation of the legs during cycling, leading to a reduction in sedentary behaviour compared to the control group. In a randomized controlled trial of 140 patients with mild COVID-19,[47] a combination of pulmonary rehabilitation and a group psychological intervention, significantly reduced anxiety and improved sleep quality, compared to the control group receiving standard nursing care.

As mentioned, 70 individuals (44%) had residual rehabilitation needs at the five month assessment, corresponding to about one fifth of the total cohort of survivors. For a significant majority of these individuals, outpatient rehabilitation involving one or two professions for 1–3 sessions per week was sufficient. Further, our analysis showed that residual rehabilitation needs, as assessed using the WHO CPS at five months post-discharge, were more common in patients with severe disease (CPS 6–9) compared to moderate disease (CPS 4–5), both in terms of equipment (walking and hearing aids) and personnel resources. However, when looking solely on the 11 individuals with the greatest rehabilitation needs (requiring support from four or more professions), there was no difference in terms of disease severity. Indeed, some neurological symptoms have been estimated to be more common in patients with lower disease severity.[3]

When interpreting the results, some methodological factors should be considered. First, this study is based on a total regional population hospitalized for COVID-19 during the first wave of the pandemic in the spring of 2020. All hospitalizations coincidental to a positive SARS-CoV-2 test were excluded, as were all cases which, due to severe premorbid conditions (e.g. severe dementia, terminal cancer), were precluded from assessment of rehabilitation needs. By covering a whole region and by covering all disease severities within the hospitalized COVID-19 population, we believe results to be representative of the impact of this disease. A limitation of our study was that non-hospitalized cases were not included. The primary reason for this was that at the time of the first pandemic wave in Sweden, diagnostic testing was not available for this group, thus precluding definite COVID-19 diagnosis.

Second, this paper reports findings in the subgroup of survivors (185/433, 43%) who were identified by screening at 4 months as having persisting problems significantly hindering daily life. This corresponds well with other studies,[14,48] suggesting significant residual morbidity. Additionally, as only 13% (56/433) of screened survivors reported to be fully recovered, with another 44% (192/433) reporting persisting problems but not hindering daily life, this study is likely underestimating the total rehabilitation needs. Furthermore, it is possible that some symptoms were not reported during the screening telephone interview despite being present. As regards false positives: first, this is inevitable in a proper screening procedure and second, any false positives could be identified during the clinical assessment and thus did not influence our estimation of rehabilitation needs.

Third, the findings of the current study are the result of a comprehensive multi-professional clinical assessment involving physicians and neuropsychologists, and where relevant physiotherapists, occupational therapists, neuro-opticians, and speech pathologists, which included a combination of clinical tests, PROMs, laboratory tests and radiological assessments. Such an approach has allowed us to present a relatively broad overview of the magnitude and diversity of sequels of COVID-19, as opposed to a compartmentalized approach to individual organ systems. When conducting the clinical assessment and analysing the data, care was taken to refine and isolate health problems attributable to COVID-19 in contradistinction to pre- and comorbid conditions unrelated to COVID-19. Thus, only symptoms, signs, laboratory findings and results of auxiliary investigations reflecting new or aggravated and persisting problems related to COVID-19 are reported. More sophisticated auxiliary investigations will no doubt sometimes be called for, but were beyond the scope of this study. Specifically, cardiac and autonomic dysfunctions have recently been highlighted,[49–51] and would surely benefit from a more extensive evaluation than was possible within the scope of this study.

Finally, this study reports *residual* rehabilitation needs at five months, regardless of interventions provided during hospitalization and/or post discharge. Since such interventions as well as a tendency towards spontaneous improvements over time are likely to

decrease residual rehabilitation needs, assessments of such needs performed during earlier stages post-discharge would most likely show greater and more complex needs. By considering these precautions when discussing the results, we believe our study to present a conservative estimate of the sequels of this disease.

The broad array of symptoms post COVID-19, as reflected in screening interviews performed at 4 months post-discharge were verified by a multi-professional clinical assessment at five months. Our study underscores the importance of providing a comprehensive assessment of cases with persisting problems after this novel disease, precisely because many symptoms, such as fatigue and breathlessness, are highly nonspecific. As many as 16% [13, 20] of the total regional cohort of hospitalised patients during the first wave of the pandemic were found to have residual rehabilitation needs at 5 months post-discharge. In a majority of cases, rehabilitative services could be performed under the auspices of primary care. However, cases found to have serious neurocognitive, cardiopulmonary and/or sensorimotor impairments qualify for complex multiprofessional rehabilitation, typically provided by specialized rehabilitation centers.

Contributors

RL with aid from AD conceptualized the idea, designed the study and acquired funding. CW with aid from RL and AD wrote the original draft, and EN, KN, ELG, UBT and ÅÖB reviewed and edited the manuscript. CW analysed most of the data, aided by AD, EN and ML. Data curation was performed by ML, CW, ELG, RL and UBT, aided by ÅÖB and KN. AD administered the project. CW and AD were responsible for the raw data associated with the study. CW, AD and RL took the decision to submit the manuscript for publication.

Data sharing

As subsequent follow-up investigations related to LinCoS are in progress, data presented in this report will not be made available to others at this stage. After completion of LinCoS, data can be made available upon request and after an individualized assessment by the LinCoS Project Group.

Funding

The study was funded by an ALF grant and RÖ.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Dr Christer Andersson and Professor Emeritus Rune Sjödahl for their active involvement in LinCoS and for providing feedback on this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101219.

References

1 WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: 5 Jul 2021)
2 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. *JAMA* 2020;**323**(16):1574–81.
3 Rogers JP, Watson CJ, Badenoch J, Cross B, Butler M, Song J, et al. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. *J Neurol Neurosurg Psychiatry* 2021.
4 Kumar S, Veldhuis A, Malhotra T. Neuropsychiatric and Cognitive Sequelae of COVID-19. *Front Psychol* 2021;**12**:577529.
5 Negrini F, de Sire A, Andrenelli E, Lazzarini SG, Patrini M, Ceravolo MG, et al. Rehabilitation and COVID-19: update of the rapid living systematic review by cochrane rehabilitation field as of april 30th, 2021. *Eur J Phys Rehabil Med*. 2021;**57(4)**:663–7.
6 Debeaumont D, Boujibar F, Ferrand-Devouge E, Artaud-Macari E, Tamion F, Gravier FE, et al. Cardiopulmonary exercise testing to assess persistent symptoms at 6 months in people with COVID-19 who survived hospitalization-a pilot study. *Phys Ther* 2021;**101(6)**: pzab099.
7 Rinaldo RF, Mondoni M, Parazzini EM, Pitari F, Brambilla E, Luraschi S, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J* 2021;**58 (2)**:2100870.
8 Townsend L, Moloney D, Finucane C, McCarthy K, Bergin C, Bannan C, et al. Fatigue following COVID-19 infection is not associated with autonomic dysfunction. *PLoS One* 2021;**16**(2):e0247280.
9 Taboada M, Carinena A, Moreno E, Rodriguez N, Dominguez MJ, Casal A, et al. Post-COVID-19 functional status six-months after hospitalization. *J Infect* 2021;**82**(4):e31–e3.
10 Liu M, Lv F, Huang Y, Xiao K. Follow-up study of the chest CT characteristics of COVID-19 survivors seven months after recovery. *Front Med* 2021;**8**:636298. (Lausanne).
11 Walle-Hansen MM, Ranhoff AH, Mellingsaeter M, Wang-Hansen MS, Myrstad M. Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19. *BMC Geriatr* 2021;**21**(1):199.
12 Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. *Eur Respir J* 2021;**57** (4):2003481.
13 Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect* 2021;**27**(1):89–95.
14 Carfì A, Bernabei R, Landi F. Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;**324** (6):603–5.
15 Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;**81**(6):e4–6.
16 Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;**397**(10270):220–32.
17 Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2021;**93**(2):1013–22.
18 Divanoglou A, Samuelsson APK, Sjodahl PER, Andersson C, Levi PR. Rehabilitation needs and mortality associated with the COVID-19 pandemic: a population-based study of all hospitalised and

home-healthcare individuals in a Swedish healthcare region. *E Clin Med* 2021;**36**:100920.
19 Fisicaro F, Di Napoli M, Liberto A, Fanella M, Di Stasio F, Pennisi M, et al. Neurological sequelae in patients with COVID-19: a histopathological perspective. *Int J Environ Res Public Health* 2021;**18**(4):1415.
20 Mansueto G. COVID-19: brief check through the pathologist's eye (autopsy archive). *Pathol Res Pract* 2020;**216**(11):153195.
21 Zhu S, Gao Q, Yang L, Yang Y, Xia W, Cai X, et al. Prevalence and risk factors of disability and anxiety in a retrospective cohort of 432 survivors of coronavirus disease-2019 (COVID-19) from China. *PLoS One* 2020;**15**(12):e0243883.
22 Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;**147**(8):573–7.
23 Randolph C, Tierney MC, Mohr E, Chase TN. The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* 1998;**20**(3):310–9.
24 Delis DCK, Kramer E, Delis-Kaplan JH. Executive function system (D-KEFS), examiner's manual. San Antonio, TX, USA: The Psychological Corporation; 2001.
25 Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. International quality of life assessment. *J Clin Epidemiol* 1998;**51**(11):1171–8.
26 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**(6):361–70.
27 Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;**39**(3):315–25.
28 Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 2002;**52**(2):69–77.
29 Hinz A, Fleischer M, Brahler E, Wirtz H, Bosse-Henck A. Fatigue in patients with sarcoidosis, compared with the general population. *Gen Hosp Psychiatry* 2011;**33**(5):462–8.
30 W. H. O. Working Group on the Clinical Characterisation and Management of Covid-infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020;**20**(8):e192–e7.
31 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
32 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative Workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care* 2004;**8**(4):R204–12.
33 Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**(4):692–4.
34 Swedish Intensive Care Registry. SIR:s riktlinje för registrering av negativa händelser och komplikationer inom intensivvård i Sverige. 2014 [updated 1 Dec 2019]. Available online: https://www.icuregswe.org/globalassets/riktlinjer/komplikationer_21.pdf. (last cited: 7 Jul 2021).
35 Turner-Stokes L, Scott H, Williams H, Siegert R. The rehabilitation complexity scale—extended version: detection of patients with highly complex needs. *Disabil Rehabil* 2012;**34**(9):715–20.
36 Hellgren L, Birberg Thornberg U, Samuelsson K, Levi R, Divanoglou A, Blystad I. Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study. *BMJ Open* 2021;**11**(10):e055164.
37 Brugliera L, Spina A, Castellazzi P, Cimino P, Tettamanti A, Houdayer E, et al. Rehabilitation of COVID-19 patients. *J Rehabil Med* 2020;**52**(4):jrm00046.
38 Ferrucci R, Dini M, Groppo E, Rosci C, Reitano MR, Bai F, et al. Long-lasting cognitive abnormalities after COVID-19. *Brain Sci* 2021;**11**(2).
39 Puchner B, Sahanic S, Kirchmair R, Pizzini A, Sonnweber B, Woll E, et al. Beneficial effects of multi-disciplinary rehabilitation in post-acute COVID-19: an observational cohort study. *Eur J Phys Rehabil Med* 2021;**57**(2):189–98.
40 Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. *Complement Ther Clin Pract* 2020;**39**:101166.
41 Shendy W, Ezzat MM, ELaidy DA, Elsherif AA. Prevalence of fatigue in patients post COVID-19. *Eur J Mol Clin Med* 2021;**8**(3):1330–40.
42 Olshansky B, Cannom D, Fedorowski A, Stewart J, Gibbons C, Sutton R, et al. Postural orthostatic tachycardia syndrome (POTS): a critical assessment. *Prog Cardiovasc Dis* 2020;**63**(3):263–70.
43 Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res* 2021;**31**(3):385–94.
44 Frithiof R, Rostami E, Kumlien E, Virhammar J, Fallmar D, Hultstrom M, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: a prospective study. *Clin Neurophysiol* 2021;**132(7)**:1733–40.
45 Cabanes-Martinez L, Villadoniga M, Gonzalez-Rodriguez L, Araque L, Diaz-Cid A, Ruz-Caracuel I, et al. Neuromuscular involvement in COVID-19 critically ill patients. *Clin Neurophysiol* 2020;**131**(12):2809–16.
46 Mateo S, Bergeron V, Cheminon M, Guinet-Lacoste A, Pouget MC, Jacquin-Courtois S, et al. Functional electrical stimulation-cycling favours erectus position restoration and walking in patients with critical COVID-19. A proof-of-concept controlled study. *Ann Phys Rehabil Med* 2021;**64(6)**:101516.
47 Liu Y, Yang YQ, Liu Y, Pei SL, Yang HH, Wu JJ, et al. Effects of group psychological intervention combined with pulmonary rehabilitation exercises on anxiety and sleep disorders in patients with mild coronavirus disease 2019 (COVID-19) infections in a Fangcang hospital. *Psychol Health Med* 2021;**26**(4):1–11.
48 Taboada M, Moreno E, Cariñena A, Rey T, Pita-Romero R, Leal S, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. *Br J Anaesth* 2021;**126**(3):e110–e3.
49 Moody WE, Liu B, Mahmoud-Elsayed HM, Senior J, Lalla SS, Khan-Kheil AM, et al. Persisting adverse ventricular remodeling in COVID-19 survivors: a longitudinal echocardiographic study. *J Am Soc Echocardiogr* 2021;**34**(5):562–6.
50 Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**(3):e048391.
51 Johansson M, Stahlberg M, Runold M, Nygren-Bonnier M, Nilsson J, Olshansky B, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep* 2021;**3**(4):573–80.