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SHORT COMMUNICATION

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Memory impairment and concentration problems in COVID-19 survivors 8 weeks after non-ICU hospitalization: A retrospective cohort study

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Abstract

Studies on the severe acute respiratory syndrome coronavirus 1 have shown long-term effects on health, rehabilitation, and quality of life in patients.To evaluate effects on recovery and mental health in COVID-19 survivors.A single center, retrospective cohort study in (non-ICU admitted) adult patients with COVID-19 infection was conducted. Next to baseline characteristics during hospital admission, data on remaining symptoms and radiographic abnormalities were extracted at the 8-week follow-up at the outpatient clinic. The Hospital Anxiety and Depression Scale (HADS) was used to detect anxiety and depression.Resulting in two hundred and eleven patients were included, median age of 63 years, 61% male, with overweight (average body mass index 28.6 kg/m^2). At the outpatient clinic 13% of the patients were symptom free, whereas 25% reported more than three symptoms. Persisting physical symptoms were mainly fatigue 68%, dyspnea 56%, and cough 26%. Most patients had normalization of chest X-ray (61.1%) and oxygen saturation (89.9%). Interestingly, 33% reported memory impairment and concentration problems 28%. 7.8% scored for anxiety and 7.1% for depression on the HADS. Correlations were found between the number of physical symptoms and scores on the HADS.In conclusion, only 13% had symptom-free recovery after 8 weeks. Besides physical symptoms memory problems were frequently seen. The number of mental and physical symptoms were correlated.

KEYWORDS

COVID-19, mental health, non-ICU patients

1 | INTRODUCTION

The severity of symptoms in acute COVID-19 (coronavirus disease 2019) infection are variable and may affect multiple organ systems. At this moment, being a novel virus, information on long-term effects is limited. In critically ill patients, it is also associated with an increased risk of acute respiratory distress syndrome (ARDS) and thromboembolic complications.[1–3] Furthermore, a substantial part of the admitted patients have comorbidities.[4,5] Because of the variation in symptoms and patients' characteristics, the course of recovery in COVID-19 survivors remains uncertain.

There are long-term effects expected in COVID-19 survivors. Several studies on the former severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) in 2003, have shown long-term effects on pulmonary function, physiological distress, physical ability, chronic fatigue, and quality of life in patients.[6–12] A recent review shows that

a median proportion of 72.5% of the individuals experiences at least one persisting symptom after COVID-19 infection.[13]

Based on the expected long-term symptoms, particularly in the pulmonary system, internal organs and/or neurological and functional and psychological performances, the Jeroen Bosch Hospital (JBZ), The Netherlands, developed its own follow-up system in which pulmonologists, internal medicine physicians, geriatricians, and psychologists were involved.

In this observational cohort study, the outcomes on physical and mental health after COVID-19 infection during outpatient clinic visits to gather knowledge about the effects of COVID-19 at 8 weeks after hospitalization is reported. Data include the resolution of radiographic characteristics and pulmonary function post-COVID-19.

2 | METHODS

2.1 | Study design

A single center, retrospective cohort study in patients 8 weeks after COVID-19- infection hospital admission was performed. Data on remaining symptoms, laboratory finding, and radiographic changes were extracted from the medical records. All is explained in more detail below.

2.2 | Study population

Adults patients with PCR confirmed COVID-19 infection admitted at the Jeroen Bosch Hospital, a large teaching hospital in the Netherlands, between March 1st 2020 and July 1st 2020 were eligible. All patients visited the outpatient clinic 8 weeks after hospital admission. Exclusion criteria were: death, incapacitated patients not able to fill in the questionnaire and/or unable to visit the outpatient clinic, children <18 years and patients post ICU admission. Only those that actually visited the clinic were included in the study. An attendance of >80% was considered high enough to rule out clinically relevant selection bias.

2.3 | Outpatient visit design

The outpatient visit had two main features, namely a questionnaire before visit on which patients were planned on the outpatient clinic of the pulmonologist, internal medicine doctor, or geriatrician, and the design of the visit itself.

First, patients received a questionnaire on their symptoms by mail 4–6 weeks after discharge from the hospital. This questionnaire on expected possible long-term complaints was developed on known data of previous SARS-CoV-1 outbreak in 2003: namely on the pulmonary system, on internal organs and/or on neurological and functional and psychological performances.[6–12] This questionnaire includes the Hospital Anxiety and Depression Scale (HADS).[14] This questionnaire was used as a triage model for follow-up. The questionnaires were assessed by a physician assistant and patients were seen by either the pulmonologist, internal medicine physician, or geriatrician based on the main complaints at 6 weeks after hospital discharge. Visits at the outpatient clinic were scheduled in the following 2 weeks, so around 8 weeks after hospitalization.

Second, the visit at the outpatient clinic was unified for all patient, all underwent laboratory testing and a chest X-ray <48 h before the appointment, mostly at the same day. All physicians used a unified consultation in each patient, that had some general questions in each expected domain, namely the pulmonary system, internal organs and/or neurological and functional, and psychological performances.[6–12] Additional analyses, such as chest CT and pulmonary function test were performed when indicated.

2.4 | Data collection and outcomes measures

Data were automatically extracted from admission files and completed by manual search in the patient medical record. Clinical data on patients age, sex, medical history, comorbidities, duration of hospital stay, discharge location, venous thromboembolic events (VTE), and other events were collected. And from the outpatient clinic visit the questionnaire results, HADS, history taking, physical examination findings, laboratory findings, radiographic changes were extracted. HADS scores of 0–7 were considered normal.

2.5 | Sample size

Being a descriptive study on the outcome of a new pandemic infection, no definite sample size could be estimated.

2.6 | Statistical analysis

Continuous variables were given as means with standard deviation (SD) or medians with ranges depending on their distribution. Categorical variables are shown as percentages and numbers. Correlation coefficients were calculated to analyze the correlation between reported number of symptoms and mental wellbeing (HADS). IBM SPSS statistics version 22 was used for statistical analysis. Significance level was set at 0.05.

2.7 | Ethical approval

The study was conducted according to the principles of the declaration of Helsinki (version November 2013) and the medical ethical review board of the region Noord-Brabant declared that this study fell out of the scope of the Dutch Law on Medical Research (WMO). All collected data were stored and coded according to the agreement on medical treatment act (WGBO) and the Federa (Dutch Federation of Biomedical Scientific Societies) Code of Conduct for medical research.

3 | RESULTS

3.1 | Population

Patients' characteristics are shown in Table 1. Between March 1th and July 1th 2020 423 patients were admitted at the hospital with confirmed COVID-19. Seventy patients were admitted to the ICU and were excluded from the analysis. Of those, 353 were admitted to the medical ward of which 65 died during admission and another 30 patients died after discharge. Of the remaining 258 patients, 211 visited the outpatient clinic (82%). Not all reasons for lost to follow-up were found, however, at least some patients were not invited because these patients were from other areas in the Netherlands and some patients were followed by the primary care physicians after intercollegial consultation.

Table 1 shows that, most patients were male with on average a high body mass index (mean 28.6 kg/m^2). As expected, most cases developed pneumonia at presentation or during hospitalization (89.0%). Only five patients had a pulmonary embolism and one patient had deep venous thrombosis. There were no ischemic cardiac events and no neurological events. The median hospital stay was 5 (1–27) days. The majority of patients were discharged home (82.3%).

3.2 | Symptoms 8 weeks after hospitalization

Table 2 shows the symptoms of the COVID-19 survivors at 8 weeks after hospitalization.

As shown in Table 2, the main complaints at 8 weeks were fatigue (68%), dyspnea (55%), cough (26%) and memory impairment (33%), and concentration problems (28%).

Of the patients, 12.7% were symptom free, 23.5% had one symptom, 20.5% two symptoms, 18.1% three symptoms, and 25.3% experienced more than three symptoms. Most patients had normalization of chest X-ray (61.1%) and oxygen saturation (89.9%).

Table 3 shows that nearly all patients had normalization of laboratory abnormalities. Anemia was the most frequent abnormality. Of the patients with an abnormal CRP 96% had a CRP < 20, 99% <100 Mg/l.

3.3 | Mental health after 8 weeks

Regarding mental health on the HADS questionnaire, median scores were 3 and 2 for anxiety and depression, respectively. Of those, 7.8% of the patients scored >10 points for anxiety and 7.1% of the patients scored >10 points for depression, which is an indication of significant psychological comorbidity. A significant correlation was found between HADS depression scores and HADS anxiety scores (Spearman 0.679, $p < 0.001$). The scores on the HADS depression, anxiety, and sum score were correlated with the number of symptoms (Spearman 0.432, 0.368, 0.434, respectively, all $p < 0.001$).

TABLE 1 Baseline characteristics

Patients characteristics		
Total patients	*n*	211
Age (years)	Median (range)	63 (23–86)
Sex	% male	61.1
Comorbidities		%
Cardiovascular		
Ischemic heart disease		10.0
Coronary heart disease		16.1
Rhythmic heart disease		14.7
Heart failure		4.7
Hypertension		36.5
Internal		
Chronic kidney disease		8.5
Diabetes mellitus		14.7
Rheumatic disorder		12.3
Active malignancy[a]		7.1
Chronic liver disease		0.5
Pulmonary		
Asthma		5.7
COPD		12.3
Geriatric and neurological		
Neurodegenerative and neurological disease		13.3
Smoking		%
Yes		3.4
No		53.2
Quite		43.3
Body mass index (kg/m^2)	Mean (SD)	28.6 (4.7)
Duration hospital stay in days	Median (range)	5 (1–27)
Events during hospital stay		%
Rhythmic cardiac event		6.8
PE or DVT		2.9
Pneumonia		89.0
Urine tract infection		2.6
Delirium		5.7
Discharge location after discharge		%
Home		82.3
Nursing home		13.4
(Geriatric) revalidation		2.9
Other		1.4

[a]Active malignancy or either adjuvant or maintenance therapy.

TABLE 2 Outpatient clinic evaluation

Symptoms at 8 weeks after hospitalization	
Physical symptoms	% (*n*)
Fatigue	68.2 (198)
Dyspnea	55.5 (209)
Cough	25.7 (206)
Night sweats	5.7 (192)
Fever	0.5 (203)
Loss of appetite	18.7 (209)
Persistent weight loss	7.6 (207)
Cardiovascular symptoms	9.9 (203)
Mental health symptoms	% (*n*)
Memory impairment	33.2 (196)
Concentration problems	27.6 (192)
HADS-score (normal 0–7) (*n* = 210)	Median (range)
Anxiety	3 (0–18)
depression	2 (0–18)
Functionality and mobility	% (*n*)
Impaired physical function	9.5 (200)
Tendency to fall	9.6 (198)
Fall	6.7 (209)
Help in daily activities (getting dressed, showering)	11.5 (209)
Examinations	**%**
Low oxygen <95% (*n* = 198)	10.1
Chest ray abnormalities (*n* = 211)	38.9
Unilateral consolidations	13.7
Bilateral consolidations	21.3
Fibrosis	4.3
Atelectasis	1.4
Other	0.5
Referrals after visit	%
Revalidation doctor	2.9
Medical psychologist	5.7
Other doctors	7.1

3.4 | Further examinations after outpatient clinic visit

As shown in Table 2, 2.9% of the patients were referred to a revalidation doctor, 5.7% to a medical psychologist, and 7.2% of the patients to a broad range of other specialties, for example, cardiologist and rheumatologist.

Chest CT was carried out in 22 (10.4%) patients if indicated by the physician. Unilateral (4.5%) or bilateral ground-glass opacities (77.3%) were frequently found, bronchiectasis (unilateral 14.3%, bilateral 38.1%) were the main features on CT.

Spirometry was conducted as appropriate in 22 patients. Diffusion capacity was limited (DLCO < 80%) in 12 of 20 patients tested (mean: 77.5%, range: 39%–125%), despite 25% of these patients had a normal chest X-ray and/or 50% had no abnormalities on CT-scan. In two patients, DLCO was limited before COVID-19 infection.

A 6 min walking distance test was performed in 13 patients. All of them had a normal saturation at the start. Hypoxemia (saturation below 90%) during the test was measured in two patients. Median walking distance was 101.0% (85.5–106.5) of predicted.

4 | DISCUSSION

This study shows remaining symptoms in the majority (87%) of the COVID-19 patient. Besides the known physical symptoms (e.g., fatigue, dyspnea, and cough), a large number of mental symptoms are persisting. The number of physical symptoms and the scores on the HADS for mental symptoms are correlated.

SARS-CoV-2 virus appears to have a serious effect on psychological wellbeing. Previous research reported depression with a median frequency of 14.9%, anxiety with median frequency in 22.1%, loss of memory in 28.3%, and reported difficulty concentrating.[13] Outcomes on mental symptoms were significantly higher in patients with three or more symptoms at follow-up. Memory impairment and/or concentration impairment in approximately 66% (130/197) of patients were found. Based on the HADS questionnaire, about 10% showed signs of either severe anxiety or depression. One in five patients needed counseling by a medical psychologist. And in one extreme case, transfer to psychiatric hospital was necessary because of severe anxiety post-COVID-19 infection, while there was no history of mental instability. Fortunately, the use of a unique questionnaire, partially build on the HADS, allowed us to screen for psychological symptoms and invite a psychologist to the first consult at outpatient clinic visit.

These remarkable outcomes on mental health might partly be explained by the pandemic and novelty of the virus. However, the effects of COVID-19 infection on the brain and psyche are not yet clarified. A recent post-mortal study has shown extensive inflammation of the cerebrum in COVID-19 infected patients (*n* = 9).[15] And numerous case reports associating COVID-19 with neurological illness, for example, encephalitis, have been published. Still, in this study, there were no neurological events related to COVID-19 during admission or follow-up.

A relatively low number of VTE (6/211) was found compared to previous COVID-19 studies. Most likely because ICU patients were excluded. Furthermore, VTE was not a known complication in the beginning of the pandemic, and therefore less noted.

TABLE 3 Outpatient laboratory results

Laboratory results	*n*	Normal range	Median (range)	Abnormal (%)
Hemoglobin (mmol/l)	206			
Female	81	7.5–10.0	8.1 (5.5–9.5)	18.5
Male	125	8.5–11	8.9 (6.3–10.8)	27.2
White blood cell count (x10^9/ml)	207	4–10	7.0 (3.6–19)	10.6
Lymfocyte count (x10^9/ml)	203	1.0–3.5	2.2 (0.8–36.0)	9.9
Thrombocytes (x10^9/ml)	207	150–400	259 (46–696)	7.2
eGFR (CKD-EPI, ml/min/1.73 m^2)	207	>60	85 (8–>90)	15.9
Potassium (mmol/l)	207	3.5–4.8	4.2 (3.2–5.3)	5.7
Sodium (mmol/l)	207	135–145	140 (131–145)	1.4
Creatin Reactive Protein (mg/l)	206	0–8	<3 (<3–330)	14.6
LD (U/l)	205	0–249	222 (136–488)	23.9

Regarding follow-up with radiology examination, minimal bilateral abnormalities were the main finding on chest film and chest CT. Fibrosis was seen in less than 5% on chest X-ray (9/211) and in three patients on CT (3/22) A follow-up CT was not considered standard of care for respiratory infections. As CT-scan was not performed in all patients, the radiographic abnormalities might be underestimated. Since the persisting radiographic changes were relatively mild, no significant hypoxemia was seen and the majority of patients (77.8%) in the cohort were discharged from outpatient treatment, one might question the clinical relevance of these subtle abnormalities. CT-scans and pulmonary function tests were only performed when this was inevitable for good follow-up care. Hence, we do not recommend a chest CT and pulmonary function test as standard follow-up care in non-ICU COVID-19 survivors.

This is one of the studies to describe the recovery of hospitalized COVID-19 survivors at 8 weeks on pulmonary symptoms, internal organs, and mental wellbeing. However, some limitations need to be addressed. First to mention is the single-center design. Other cohorts also show residual symptoms in the majority of the patients[13] Second, we focused on hospitalized non-ICU survivors instead of all COVID-19 patients. This makes that these results are generalizable to this population only. Last, it is still very unknown what COVID-mutations will bring, among that the clinical presentation and recovery. Still our conclusions can help to better understand COVID-19 and the patients' recovery after COVID-19.

5 | CONCLUSION

Although the pulmonary presentation of COVID-19 is well-known, this study shows that other symptoms are also very frequent. Only 13% had symptom-free recovery after 8 weeks: fatigue, cough, dyspnea, and mental symptoms such as memory problems were most frequently seen. This indicates that emphasis on a broad physical scope is needed and that psychological care in post-COVID-19 patients is essential.

AUTHOR CONTRIBUTIONS

Study conception and design: Karen Keijsers, Marielle Broeders, Vania Baptista Lopes, Aryan Klinkert, Lenny Nahar, and Angèle Kerckhoffs. *Data collection*: Karen Keijsers, Vania Baptista Lopes, Aryan Klinkert, and Janwillem van Baar. *Analysis and interpretation of results*: Karen Keijsers, Marielle Broeders, Vania Baptista Lopes, Aryan Klinkert, Lenny Nahar, and Angèle Kerckhoffs. *Draft manuscript preparation*: Karen Keijsers, Marielle Broeders, Vania Baptista Lopes, Aryan Klinkert, Lenny Nahar, and Angèle Kerckhoffs. All authors reviewed the results and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All original data are available from the authors at request.

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