Long-Term Outcomes in COVID-19 ICU Patients: A Prospective Cohort Study

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Research

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Abstract

BACKGROUND

The COVID-19 pandemic causes high rates of intensive care unit (ICU) admissions. After ICU-discharge patients and family members can suffer from persisting impairments known as 'Post Intensive Care Syndrome' (PICS) and PICS-family. Since COVID-19 is relatively new, there is barely any knowledge on the long-term outcomes of COVID-19 ICU-survivors and their family members.

OBJECTIVES

This study aims to gain insight in the long-term physical, social and psychological functioning of COVID-19 ICU-survivors and their family members at three- and six-months following ICU discharge.

METHODS

A single-center, prospective cohort study was conducted in COVID-19 ICU-survivors and their family members. Enrolled participants received questionnaires at three and six months after ICU discharge. The MOS Short-Form General Health Survey, Clinical Frailty Scale, spirometry tests, McMaster Family Assessment Device (FAD-GF6+), the Hospital Anxiety and Depression Scale and return to work were used to evaluate physical, social and psychological functioning.

RESULTS

Sixty COVID-19 ICU-survivors and 78 family members participated. Physical functioning was impaired in ICU-survivors as reflected by a score of 33.3 (IQR 16.7-66.7) and 50 (IQR 16.7-83.3) on the physical functioning subscale at 3- and 6-months follow-up respectively. Diffusion lung capacity was reduced in 69% of patients. Ninety percent of the ICU-survivors reported persistent symptoms after 6 months. Social functioning was impaired as 90% of the COVID-19 ICU-survivors did not reach their pre-ICU employment level, 6 months after ICU-discharge. Psychological functioning in ICU-survivors was normal. Family members experienced worse employment status in 35% and 34% including a decrease in employment rate of 18.3% and 7.4% at 3- and 6-months post ICU-discharge, respectively. Psychologically, 63% of the family members reported ongoing impaired well-being due to the COVID-19 related mandatory physical distance to their relatives.

CONCLUSION

We have shown that COVID-19 ICU-survivors suffer from a prolonged burden of disease, prominent in physical- and social functioning, worse employment status and persisting symptoms in 90%. In addition, family members also report long term effects expressed by a reduction in return to work and impaired well-being. Further research needs to extend the follow up and to study the effects of standardized rehabilitation in COVID-19 patients and their family members.

Introduction

Since December 2019, Coronavirus disease 2019 (COVID-19) has spread rapidly around the world, affecting more than 126 million people so far [1]. Like previous major outbreaks of viral infection in the 21st century, the COVID-19 pandemic is expected to have significant long-term clinical consequences for survivors [2,3,4].
While a majority of infected people with COVID-19 suffer from mild illness with typical respiratory symptoms, a minority of the patients are hospitalized. Of these, 17-26% requires admission to the intensive care unit (ICU). Severe respiratory failure and secondary disabilities, can result in physical, cognitive and mental health disorders after hospital discharge, known as the 'Post Intensive Care Syndrome' (PICS). Many ICU-survivors suffer from PICS, with incidences of 25-80% in the physical, 8-57% in the psychological, and 30-80% in the cognitive domains.

The impact of ICU-admission reaches beyond the patient. Family members of ICU-survivors can also suffer from symptoms such as anxiety, depression, posttraumatic stress disorder (PTSD), and reduced quality of life (QoL). This phenomenon is known as post-intensive care syndrome-family (PICS-F). As family members play an increasingly important role in the support of ICU patients, trust building in the ICU-setting is of paramount importance. However, this seems to be challenged in this pandemic, due to the uncertainties of COVID-19 disease, the limited opportunities for family members to visit their relatives and new ways of digital contact.

Since COVID-19 is relatively new, there is limited data on the long-term effects that can be attributed to this disease. Few studies have assessed the short-term outcomes after hospitalization for COVID-19 patients, mainly focusing on patients who have received ward-based care. Age and comorbidities are associated with severe outcomes in COVID-19 patients. However, there is little knowledge on the outcomes of COVID-19 survivors after ICU-admission. In addition, there is little information on the health consequences of COVID-19 ICU-survivors’ family members. Here we study follow-up data of patients post-ICU discharge.

Patients And Methods

The 'COVID-19 Follow-up Intensive Care Studies' (COFICS) aims to give insight in the long-term physical, social and psychological functioning, of COVID-19 ICU-survivors and their family members. The COFICS is a single-center, prospective cohort study, conducted at the ICU of University Medical Center Groningen (Groningen, The Netherlands). Ethical approval for this study has been given by our hospital's Medical Ethical Committee (METc 201800422) according to Dutch and European legislation. All patients gave their informed consent prior to the data collection.

Study participants

All COVID-19 patients admitted to the ICU between March 19th and September 30th 2020 and their family members were eligible to participate in this study. COVID-19 was diagnosed according to World Health Organization (WHO) definition and was confirmed by RNA detection of the SARS-CoV-2 using the polymerase chain reaction (PCR)-based technique. Family members could be partners, children, other family members, or friends who were identified by the patient as important.

Procedure

All eligible patients were contacted by telephone by experienced research nurses for participation in this study, three months after discharge from the ICU. In addition, patients were asked if they agreed to have their family members contacted for participation. Multiple family members could participate per patient. Questionnaires were sent by ordinary mail at three and six months after ICU discharge. In case of no response, reminders were sent after three weeks. Results of lung function tests were retrieved from local hospitals after obtaining informed consent from the patients for spirometry results.

Outcomes
The outcome is the response to a series of questionnaires and spirometry tests to measure three domains: physical, social and psychological functioning (Figure 1).

Physical functioning was scored with the Dutch version of the 9-point Clinical Frailty Scale (CFS) [22]. The CFS consists of nine pictographs, ranging from ‘very fit’ (1) to ‘terminally ill.’ CFS-scores from 1 till 4 were classified as ‘non-frail’ and from 5 till 9 as ‘frail.’

Additionally, physical functioning was evaluated by requesting the medical data from spirometry tests at six months follow-up. The following respiratory function parameters were measured: forced expiratory volume in 1 second (FEV1); forced vital capacity (FVC); forced expiratory ratio (FEV1/FVC); total lung capacity (TLC) and diffusing lung capacity for carbon monoxide (DLCO %). A measured value of more than 80% of the predicted value was considered as normal.

Symptoms were collected by the question which burden was experienced by the patient at six months follow-up (Supplement 1).

The MOS Short-Form General Health Survey (SF-20) was used to study general health outcomes related to physical and social functioning [23, 24]. The SF-20 measures six QoL domains: physical functioning, role functioning, social functioning, mental health, general health perceptions and pain. The subscale mental health was not part of this study. The SF-20 total score was transformed linearly to a 0-100 scale where 0 represents the lowest and 100 the highest possible score.

Social functioning was evaluated with the general function scale of the McMaster Family Assessment Device (FAD-GF6+) [25]. The FAD-GF6+ is a short validated version of the FAD, which is a quick and effective tool to assess the overall functioning of families [26]. The FAD-GF6+ identifies 6 dimensions of family life which are associated with dysfunctional family. The total score is divided by the number of items on the subscale giving a total score ranging from 1.0 (best functioning) to 4.0 (worse functioning) [27].

Return to work was measured as the proportion of previously employed ICU-survivors reporting return to work after critical illness, including work percentage and change of work activities.

Psychological functioning was measured with the Hospital Anxiety and Depression Scale (HADS) to study anxiety and depression [28]. The HADS contains a seven-item sub-scale for anxiety and a seven-item sub-scale for depression, with a four-point Likert scale for each question. Total scores per subscale range from 0 to 21, with the sums categorized as normal (0-7), mild (8-10), moderate (11-14) and severe (15-21).

Fear of reinfection was questioned on a scale of 0 ('no fear') to 10 ('high level of fear'). Influence of limited visiting possibilities was derived from a description of family members how they felt about the physical distances from their relative and if it had affected their well-being (Supplement 1).

Baseline patient characteristics, including age, gender and clinical data, such as length of hospital stay, comorbidities and delirium, were retrieved from the electronic health record. Patient demographics, such as educational level and marital status, as well as healthcare consumption and family characteristics were addressed in the three-month questionnaire.

Statistical analysis

The Age-adjusted Charlson Comorbidity Index (ACCI) was calculated based on age and comorbidities. ACCI is a simple scoring system in which the factor age is included in the Charlson Comorbidity Index (CCI) [29, 30]. All outcomes
were assessed for the total group of ICU-survivors and divided into three subgroups according to the ACCI (ACCI 0-1, ACCI 2-3 or ACCI ≥4). Outcomes of the family members were assessed for the total group.

Quantitative data is reported as median with interquartile range (IQR), mean with corresponding standard deviation, or number with percentage. Descriptive analyses were performed with SPSS Statistics version 23.0 for Windows. The qualitative data was analyzed by two researchers (NV, IM) using ATLAS TI version 9 for Windows. Firstly, the data was coded inductively where the researcher used the words of the participant as label (in vivo coding). Second, codes were categorized to a list of symptoms.

Results

Baseline characteristics
A total of 94 patients diagnosed with COVID-19 were admitted to the ICU during the study enrolment period. Seventy-three (78%) patients were alive and eligible for inclusion three months post ICU discharge. Sixty (82%) COVID-19 ICU-survivors returned the 3-months questionnaire and 50 (68%) returned the 6-months questionnaire. A total of 102 family members of COVID-19 ICU-survivors were asked to participate in this study, of which 78 (76%) and 67 (66%) completed the 3-months and 6-months questionnaire respectively (Figure 2).

Participant characteristics are given in Table 1.A. Participants are subdivided to ACCI scores 0-1, 2-3 and ≥ 4. Table 1.B shows the characteristics of all family members. The vast majority of ICU-survivors had a BMI above 25 (n=56; 93%) and 55 (92%) ICU-survivors had a ACCI higher than 2. The median length of ICU stay was 19.4 days (IQR 12.3-31.7), of which 16.3 days (10.6-26.5) on mechanical ventilation. Almost 50 percent of the patients suffered a delirium during ICU stay. Most of the family members were partner of the patient, female and the median age was 56 years (IQR 41.0-63.0).

Results on health domains

Physical functioning
Physical functioning of COVID-19 ICU-survivors was low three months post discharge with a median score of 33.3 out of a maximum of 100 (IQR 16.7-66.7) on the physical functioning subscale and 35.0 (IQR 25.0-50.0) on experienced health. Scores slightly improved - but remained low - at six months with a median score of 50 (IQR 16.7-83.3) and 50.0 (IQR 35.0-71.3), respectively. Patients had a median pain score of 50 out of a maximum of 100 at three- and six-months follow-up, but differed between ACCI categories. One third of the ICU-survivors considered themselves ‘mildly frail’ to ‘frail.’ Table 2.A summarizes the 6 months data including FEV1, FVC and DLC0% which were impaired in 18%, 20% and 69% respectively (Table 2.A). At six months, 90% of the ICU-survivors reported symptoms at 6 months, mainly fatigue, worse condition and polyneuropathy (Table 2.A). The bodyweight of ICU-survivors dropped with a median of 6.5 and 5.4 kg at three and six months respectively compared to pre-ICU admission. However, weight differed widely between ACCI categories (Table 2.A).

Family members showed high levels of physical functioning with a median score 100.0 (IQR 83.3-100.0) on physical functioning (Table 2.B).

Social functioning
Role activities were impaired in ICU-survivors with a median of 0 (IQR 0-0) at three and six months. Social functioning scored a median of 60.0 (IQR 40.0-80.0) at three months and 80.0 (IQR 60.0-100.0) at six months. Family functioning showed high median scores of 4.0 (IQR 3.3-4.0) and 3.8 (IQR 3.2-4.0) at three and six months respectively (Table 2A). Three (10%) of the 30 pre-ICU employed survivors fully returned to work whereas 10 (43%) were still too ill to work at
six months post ICU-discharge (Table 1 and Table 2.A). Employment rate was decreased for the vast majority of patients at six months post ICU-discharge (Figure 3A).

Social functioning in family members scored high on role activities (median 100; IQR 50.0-100), social functioning (median 100; IQR 70.0-100) and family functioning (median 3.8; IQR 3.1-4.0). Of the 40 pre-ICU employed family members 26 (65%) fully returned to work at three post ICU discharge whereas nine (23%) were re-integrating or did not returned to work yet. At six months 23 of the 36 (64%) family members fully returned to work and 4 (11%) were re-integrating (Table 2.B). Median employment rate in family members decreased with 18.3% and 7.7% on three and six months respectively compared to pre-ICU admission (Table 1.B and Table 2.B) but differed between family members (Figure 3B).

**Psychological functioning**

Psychological functioning in ICU-survivors was good with median scores $\leq 5.0$ on the anxiety and depression subscales at three and six months (Table 2.A).

Family members showed good psychological functioning as well, with median scores $\leq 4.0$ on the anxiety and depression subscales at three and six months (Table 2.B). The fear of reinfection scored 5.0 and 6.0 for ICU-survivors and family members respectively at six months.

Sixty-three percent of the family members reported impaired well-being due to the mandatory physical distance to their relative at the time of ICU admission (Table 2.B). Fifty-four (68%) family members were distressed by the physical distances, mostly described as ‘very difficult,’ ‘helpless,’ ‘terrible,’ ‘heavy’ and/or ‘terrifying.’ Twelve family members were not distressed and described that ‘the patient was in good hands’ or ‘reasonably well through contact.’ The majority of family members referred to the telephone and video contact as positive and supporting. In contrast, some family members experienced the telephone and video contact negatively, describing this as ‘tense’ or ‘difficult to get in contact’.

Quote family member: “*Saying goodbye to my husband via an iPad before he was put into a coma, was horrible. I had EMDR therapy afterwards. It was a trauma.*”

Quote family member: “*The distance was difficult, but we understood the necessity. The situation was acceptable. In addition, the (digital / telephone) contact with the nurses made up for a lot.*”

**Health care consumption**

All ICU-survivors received care during the follow-up period. The physiotherapist, general practitioner and pulmonologist were mostly visited by ICU-survivors (Table 2.A). The general practitioner and social worker were mostly visited by the family (Table 2B).

**Discussion**

Our results showed that COVID-19 ICU-survivors experienced limitations in physical functioning, reduced diffusion lung capacity and 90% endorsed at least one symptom after six months. Impaired social functioning was present as 90% of ICU-survivors did not reach their pre-ICU employment level at six months. In addition, family members experienced worse employment status 34%. Psychological functioning was normal in ICU-survivors and their family members however 63% of the family members reported ongoing impaired well-being due to the COVID-19 related mandatory physical distances to their relatives.
To our knowledge, this is the first study to assess the health consequences of COVID-19 ICU-survivors at two follow-up times. It is known from previous Corona outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS), that survivors suffer from pulmonary dysfunction, psychological impairment and reduced exercise capacity [2]. Survivors of acute respiratory distress syndrome (ARDS) are also known to experience a high prevalence of functional disability, cognitive impairment, posttraumatic stress disorder, and impaired QoL [31, 32, 33, 34]. Hence, high levels of physical, cognitive and psychosocial impairments among COVID-19 survivors can be expected and require anticipation.

Although a majority of the COVID-19 ICU-survivors in our study were impaired in the physical domain at 3- and 6-months follow-up, only a third of the patients considered themselves as ‘mildly frail’ to ‘frail.’ A possible explanation might be the multidimensional concept of frailty, which includes the social and psychological domain as well [35].

DLCO was lower than 80% from normal values in 69% of ICU-survivors. This percentage is higher than in ward-based COVID-19 patients, where 22-47% had a reduced DLCO [18, 36]. Our findings are in line with a subgroup with severe COVID-19 requiring invasive ventilation, in which 56% had an impaired DLCO [18]. It is likely that the gradual decrease in DLCO among COVID-19 survivors corresponds with the varying degree of severity of disease. Early lung function follow-up is warranted as respiratory rehabilitation can improve respiratory function [37].

The high cumulative incidence of 90% symptoms in our study cohort corresponds with previous studies that reported 74-87% symptoms in ward-patients [14, 18] and 86% symptoms in ICU-patients [18]. New illness related fatigue was the most common reported symptom, which is in line with other studies that had incidences of 53-81% [16, 14, 17, 18]. A reduced condition was the second main symptom in our study, which overlapped with fatigue. Other studies reported breathlessness in 66% [17] and dyspnoea in 42-43% [16, 14] after COVID-19.

Delayed return to work is common after critical illness and is likely a consequence of post-ICU impairments. After ICU-admission, 20%-36% of survivors experiences job loss, 17%-66% changed their occupation and 5%-84% had a worsening of employment status [38]. Pre-existing comorbidities are a potential risk factor for delayed return to work. Although 46% of the pre-ICU employed patients of our study cohort had returned to work at six months, a majority of these patients is not back to their pre-COVID-19 level. Our findings correspond with finding in other studies where 33-47% of ICU-survivors had returned back to work at 3 months follow-up [16, 17]. Burden in the social domain for the family is reflected by one third of the family members that has not fully returned to work yet, at 3 and 6 months. Despite limited evidence on this topic, it is known that 85% of caregivers had returned to their previous work level after one year [39, 40].

Although psychological symptoms are likely to occur in two thirds of survivors of acute respiratory distress syndrome at 12 months follow-up [41], our results showed no impairments in the psychological domain. A possible explanation for this can be a mixture of effective family support, reflected by the high mean family functioning and the relatively high health care consumption. The amount of family care compared to professional care was not studied but this might be interesting for follow-up research.

In our study cohort, 100% and 96% of the patients consumed professional health care at 3 and 6 months follow-up respectively. This is in line with 57% of patients needing healthcare assistance after prolonged mechanical ventilation at 1-year follow-up [42]. It is known that frail patients consume more health care services compared to patients who are not frail [43], but in our study cohort nearly all COVID-19 ICU-survivors consumed health care services post-discharge at 6 months follow-up.
The responses of the family members in this study show that the profound nature of the situation was overwhelming. However, the telephone and video contact were positively evaluated. The majority of the family members (68%) declared that the physical distance was 'very difficult' to handle. However, it is known that experiences of family members are not well represented in existing standardized questionnaires [44].

An easy tool to evaluate the functional outcomes in COVID-19 survivors has been proposed [45]. Several other instruments are also used in COVID-19 studies and studies are therefore difficult to compare. This fact argues in favor of using a standardized set of validated instruments in an international research context [46]. A standardization of follow-up will benefit an organized way of determining functional recovery over time and can improve health care worldwide.

**Strengths and limitations**

A strength of this study is the high response rate at follow-up, from both patients and family members, and the use of validated questionnaires and measurements. In addition, this study includes two follow-up time points after discharge, allowing comparisons over time.

Some limitations are present as well. First, the sample size of this prospective cohort study was limited, increasing the vulnerability for confounding factors. On the other hand, our sample size is larger than the ICU subgroups in other studies [14, 17, 18]. Increasing the cohort size will allow stronger conclusions. A second limitation of this study was that we did not assess the baseline status of patients prior to development of COVID-19. Many ICU-survivors already experience serious limitations in their physical, mental, and cognitive functioning before ICU admission [47]. A third limitation is that the cognitive domain has not been tested in this study. Other studies show the same limitations as comprehensive studies including all three areas of PICS are lacking [48]. Fourth, ICU-survivors were given an open question concerning symptoms instead of a questionnaire with pre-defined symptoms. This might have led to an underestimation of symptoms.

**Conclusion**

COVID-19 ICU-survivors suffer from a prolonged burden of disease, predominantly in physical and social functioning. At six months follow-up, 90% of the ICU-survivors reports symptoms and 90% of the ICU-survivors is not back to their pre-COVID-19 employment level. In family members 34% reported a worse employment status and wellbeing is impaired by the physical distance. These findings may argue for the need for standardization of rehabilitation in COVID-19 patients and their family members.

**Declarations**

**Ethics approval and consent to participate**

The COFICS is a sub study of a larger cohort study: ‘Follow-up Intensive Care Studies (FICS)’. The local medical ethical committee approved the protocol for the FICS study (METc 2018/627) and waived the need for formal evaluation according to the Dutch Law on Scientific Medical Research with Humans. Participants gave written consent by returning the completed follow-up questionnaire. Participants could withdraw from the study at any time without giving a reason. The study is conducted according to the principles of the Declaration of Helsinki.

**Consent for publication**
Availability of data and materials

The datasets generated during and/or analyzed during the current study are available in the UMCG repository.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of the article.

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None to declare.

Authors' contributions

All authors were involved in the design of the study. MO was responsible for data collection and coordinating the research nurses. NV and IM prepared the data for analyses, undertook data analysis and wrote the manuscript. Critical revision of the manuscript for important intellectual content was done by all authors. The manuscript has been seen and approved by all authors.

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Tables
| Variable                                      | Total n = 60 | ACCI 0-1 n = 5 | ACCI 2-3 n = 28 | ACCI ≥ 4 n = 27 |
|-----------------------------------------------|--------------|----------------|-----------------|-----------------|
| Age, years, median (IQR)                      | 62.5 (55.3–68.0) | 37.0 (32.5–46.0) | 61.5 (56.0–66.8) | 65.0 (60.0–71.0) |
| Sex, n (%)                                    |              |                |                 |                 |
| Male                                          | 41 (68)      | 3 (60)         | 9 (32)          | 19 (70)         |
| Female                                        | 19 (32)      | 2 (40)         | 19 (68)         | 8 (30)          |
| Marital status, n (%)                         |              |                |                 |                 |
| Married/living together                       | 51 (85)      | 4 (80)         | 22 (79)         | 25 (93)         |
| Single                                        | 9 (15)       | 1 (20)         | 6 (21)          | 2 (7)           |
| Educational level\(^1,2\), n (%)             |              |                |                 |                 |
| Low                                           | 19 (32)      | 1 (20)         | 9 (32)          | 9 (33)          |
| Middle                                        | 23 (38)      | 2 (40)         | 10 (36)         | 11 (41)         |
| High                                          | 17 (28)      | 2 (40)         | 9 (32)          | 6 (22)          |
| Employment status\(^3\), n (%)               |              |                |                 |                 |
| Employed                                      | 30 (50)      | 4 (100)        | 14 (67)         | 12 (48)         |
| Unemployed                                    | 20 (33)      | 0 (0)          | 7 (33)          | 13 (52)         |
| Work rate, pre-admission (100%=full-time), mean (SD) | 79.0 (28.7) | 77.5 (20.6)   | 81.9 (28.1)     | 76.4 (33.2)     |
| Weight, kg, median (IQR)                      | 92.0 (83.0–104.3) | 108 (79.0–122.0) | 92.5 (83.0–105.0) | 90.0 (82.0–98.0) |
| BMI, kg/m\(^2\), at ICU admission, median (IQR) | 29.4 (26.6–32.4) | 30.8 (28.5–37.3) | 29.2 (25.7–32.4) | 28.7 (26.5–32.7) |
| BMI, at ICU admission, n (%)                  |              |                |                 |                 |
| Normal (18.5–25)                              | 4 (7)        | 0              | 3 (11)          | 1 (4)           |
| Overweight (25–30)                            | 30 (50)      | 2 (40)         | 13 (46)         | 15 (56)         |
| Obese (30–35)                                 | 19 (32)      | 1 (20)         | 11 (39)         | 7 (26)          |
| Extremely obese (>35)                         | 7 (12)       | 2 (40)         | 1 (4)           | 4 (15)          |
| APACHE IV\(^2\), total score, median (IQR)    | 55.0 (45.0–65.3) | 56.0 (28.5–58.5) | 53.0 (44.5–68.8) | 57.0 (10.9–24.0) |
| Variable                      | Total        | ACCI 0-1 | ACCI 2-3 | ACCI ≥ 4 |
|-------------------------------|--------------|----------|----------|---------|
|                               | n = 60       | n = 5    | n = 28   | n = 27  |
| Comorbidities, n (%)          |              |          |          |         |
| Hypertension                  | 20 (33)      | 1 (20)   | 8 (29)   | 11 (41) |
| Diabetes mellitus             | 15 (25)      | 0        | 3 (11)   | 12 (44) |
| Cardiovascular disease        | 12 (20)      | 0        | 3 (11)   | 9 (33)  |
| Cerebrovascular disease       | 1 (2)        | 0        | 0        | 1 (4)   |
| COPD / asthma                 | 6 (10)       | 0        | 3 (11)   | 3 (11)  |
| Chronic kidney disease        | 3 (5)        | 0        | 0        | 3 (11)  |
| Malignancy                    | 3 (5)        | 0        | 1 (4)    | 2 (7)   |
| ECMO, n (%)                   |              |          |          |         |
| Yes                           | 3 (5)        | 2 (40)   | 0        | 1 (4)   |
| No                            | 57 (95)      | 3 (60)   | 0        | 26 (96) |
| Length of ECMO, days, median (IQR) | 21.7 (2.5) | 20.5 (2.1) | 0 | 24.0 |
| Mechanical ventilation, days, median (IQR) | 16.3 (10.6–26.5) | 31.9 (26.7–44.1) | 14.6 (11.6–30.6) | 16.6 (10.9–24.0) |
| Delirium in ICU, n (%)        |              |          |          |         |
| Yes                           | 29 (48)      | 4 (80)   | 13 (46)  | 12 (44) |
| No                            | 31 (52)      | 1 (20)   | 15 (54)  | 15 (56) |
| Length of ICU stay, days, median (IQR) | 19.4 (12.3–31.7) | 39.5 (31.9–49.8) | 16.9 (11.6–30.6) | 19.7 (13.0–28.8) |
| Length of hospital stay, days, median (IQR) | 30.6 (21.9–44.7) | 50.4 (41.7–62.1) | 28.1 (20.4–44.3) | 29.3 (22.0–44.7) |
| Discharge location, n (%)     |              |          |          |         |
| Home                          | 25 (42)      | 0        | 14 (50)  | 11 (41) |
| Other hospital                | 10 (17)      | 0        | 4 (14)   | 6 (22)  |
| Nursing home                  | 4 (7)        | 0        | 1 (4)    | 3 (11)  |
| Rehabilitation center         | 20 (33)      | 5 (100)  | 8 (29)   | 7 (26)  |

Abbreviations: APACHE IV = Acute Physiology And Chronic Health Evaluation; BMI = Body Mass Index; ACCI = Age-adjusted Charlson Comorbidity Index (including age); ICU = Intensive Care Unit

1 According to the ISCED2011 classification
2 Incomplete data
3 Return to work was only evaluated in the 6 months questionnaire; n=50
Table 1

Characteristics of enrolled family members of COVID-19 ICU survivors

| Variable                           | Family n = 78 |
|------------------------------------|---------------|
| Relation to patient, n (%)         |               |
| Partner                            | 49 (63)       |
| Son/daughter                       | 22 (28)       |
| Parent                             | 5 (6)         |
| Sibling                            | 2 (3)         |
| Age¹, years, median (IQR)          | 56.0 (41.0–63.0) |
| Sex¹, n (%)                        |               |
| Male                               | 20 (26)       |
| Female                             | 57 (73)       |
| Marital status, n (%)              |               |
| Married/living together             | 66 (85)       |
| Single                             | 12 (15)       |
| Educational level², n (%)          |               |
| Low                                | 16 (21)       |
| Middle                             | 38 (49)       |
| High                               | 24 (31)       |
| Employment status, n (%)           |               |
| Employed                           | 40 (51)       |
| Unemployed                         | 38 (49)       |
| Employment rate, pre admission (100%=full-time), mean (SD) | 79.9 (26.5) |

¹ Incomplete data

² According to the ISCED2011 classification
Table 2
The physical-, social-, and psychological functioning of COVID-19 ICU survivors 3 and 6 months post ICU discharge

| Domain                      | Variable                        | 3 months | 6 months |
|-----------------------------|---------------------------------|----------|----------|
|                             |                                 | Total (n = 60) | ACCI 0–1 (n = 5) | ACCI 2–3 (n = 28) | ACCI ≥ 4 (n = 27) | Total (n = 50) | ACCI 0–1 (n = 4) | ACCI 2–3 (n = 21) | ACCI ≥ 4 (n = 25) |
| Physical functioning        | Physical functioning¹ (range 0-100) | 33.3 (16.7–66.7) | 0.0 (0.0–66.7) | 33.3 (16.7–62.5) | 33.3 (16.7–66.7) | 50.0 (16.7–83.3) | 0.0 (0.0–50.0) | 33.3 (16.7–58.3) | 33.3 (16.7–66.7) |
|                             | Experienced health¹ (range 0-100) | 35.0 (25.0–50.0) | 35.0 (27.5–62.5) | 35.0 (25.0–53.8) | 27.5 (18.8–50.0) | 50.0 (35.0–71.3) | 32.5 (26.3–42.5) | 35.0 (22.5–52.5) | 27.5 (20.0–50.0) |
|                             | Pain² (range 0-100)             | 50.0 (25.0–75.0) | 75 (37.5–100)   | 40.0 (25.0–75.0) | 50.0 (25.0–75.0) | 50.0 (0.0–75.0)  | 87.5 (75.0–100) | 50.0 (12.5–75.0) | 50.0 (25.0–75.0) |
| Frailty, n (%)              | Not frail (1–3)                 | 40 (67)   | 3 (60)      | 20 (71)       | 17 (63)       | 35 (70)      | 2 (50)       | 15 (71)       | 16 (64)       |
|                             | Mildly frail (4–5)              | 17 (28)   | 2 (40)      | 8 (29)        | 7 (26)        | 14 (28)      | 0           | 6 (29)        | 7 (28)        |
|                             | Frail (6–8)                     | 3 (5)     | 0           | 0            | 3 (11)        | 0           | 0           | 2 (8)         |

All numbers given are the median and interquartile range (IQR), unless otherwise stated.

Abbreviations: ACCI = Age-adjusted Charlson Comorbidity Index (including age); ICU = Intensive Care Unit

¹ A higher score reflects a better functioning

² A higher score represents pain in a greater extent.

³ Data is given for 39 COVID-19 ICU survivors (42 participants underwent a spirometry test of which 1 participant did not consent to collect the data from the hospital. For 2 participants data is missing.)

⁴ > 5% reported health care consumption are presented. Other health care consumption were mentioned for example; social work, occupational therapist, cardiologist, (vascular) surgeon or otorhinolaryngologists.

⁵ n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain              | Variable               | 3 months |             | 6 months |             |             |             |
|---------------------|------------------------|----------|-------------|----------|-------------|-------------|-------------|
|                     |                        | Total (n = 60) | ACCI 0–1 (n = 5) | ACCI 2–3 (n = 28) | ACCI ≥ 4 (n = 27) | Total (n = 50) | ACCI 0–1 (n = 4) | ACCI 2–3 (n = 21) | ACCI ≥ 4 (n = 25) |
|                     |                        | Lung function\(^3\) | - | - | - | 7/39 (18) | 7/35 (20) | 1/36 (3) | 22/32 (69) |
|                     |                        | FEV<sub>1</sub> < 80%, % of predicted | - | - | - | - | - | - | - |
|                     |                        | FVC L < 80%, % of predicted | - | - | - | - | - | - | - |
|                     |                        | FEV<sub>1</sub>/FCV < 70% | - | - | - | - | - | - | - |
|                     |                        | TLC < 80%, % of predicted | - | - | - | - | - | - | - |

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5 n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain | Variable | 3 months | 6 months |
|--------|----------|----------|----------|
|        |          | Total    | ACCI 0–1 | ACCI 2–3 | ACCI ≥ 4 |
|        |          | (n = 60) | (n = 5)  | (n = 28) | (n = 27) |
|        |          |          |          |          |          |
|        |          | Total    | ACCI 0–1 | ACCI 2–3 | ACCI ≥ 4 |
|        |          | (n = 50) | (n = 4)  | (n = 21) | (n = 25) |
|        |          |          |          |          |          |
| Weight, kg | 85.5 | 92.0 | 89.0 | 83.0 | 86.8 | 99.0 | 89.0 | 83.0 |
|            | (80.3–93.5) | (73.5–101.0) | (81.0–94.8) | (78.0–88.0) | (80.5–95.0) | (72.5–114.3) | (82.5–95.0) | (79.0–90.0) |
| Self-reported symptoms<sup>5</sup>, n (%) | - | - | - | - | 44 (90) | 3 (75) | 20 (100) | 21 (84) |
| Any one of the following symptoms | 16 (33) | 1 (25) | 6 (30) | 8 (32) | 12 (25) | 1 (25) | 5 (25) | 6 (24) |
| Fatigue | 9 (18) | 0 | 6 (30) | 1 (4) | 7 (14) | 0 | 5 (25) | 2 (8) |
| Weakened condition | 7 (14) | 0 | 2 (10) | 3 (12) | 7 (14) | 0 | 2 (10) | 3 (12) |
| Cognitive problems | 5 (10) | 0 | 0 | 5 (20) | 5 (10) | 0 | 0 | 5 (20) |
| Polyneuropathy | 5 (10) | 0 | 2 (10) | 3 (12) | 5 (10) | 0 | 2 (10) | 3 (12) |
| Impaired hand functioning | 4 (8) | 2 (10) | 1 (4) | 3 (6) | 1 (5) | 1 (4) | 3 (6) | 1 (5) | 1 (4) |
| All numbers given are the median and interquartile range (IQR), unless otherwise stated. |

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5 n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain                        | Variable                | 3 months        |                      | 6 months        |                      |
|-------------------------------|-------------------------|-----------------|----------------------|-----------------|----------------------|
|                               |                         | Total (n = 60)  | ACCI 0–1 (n = 5)     | ACCI 2–3 (n = 28) | ACCI ≥ 4 (n = 27)    |
| Reduced lung function         |                         | 0.0 (0.0–0.0)   | 0.0 (0.0–0.0)        | 0.0 (0.0–50.0)  | 0.0 (0.0–0.0)        |
| Dyspnoea                      |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 60.0 (20.0–100)     |
| Difficulty walking            |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
| Muscle weakness / stiffness   |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
| Difficulty sleeping           |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
| Shoulder pain                 |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
| Restriction of extremities    |                         | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
| Social functioning            | Role activities¹        | 0.0 (0.0–0.0)   | 0.0 (0.0–0.0)        | 0.0 (0.0–50.0)  | 0.0 (0.0–0.0)        |
|                               | Social functioning¹     | 60.0 (40.0–80.0)| 60.0 (20.0–90.0)     | 60.0 (20.0–80.0)| 80.0 (60.0–100)     |
|                               | Family functioning¹     | 4.0 (3.3–4.0)   | 4.0 (4.0–4.0)        | 3.9 (3.8–4.0)   | 4.0 (3.3–4.0)        |
|                               | Return to work, n (%)   | -               | -                    | -               | -                    |
|                               | No change               | 3 (10)          | 0                    | 2 (14)          | 1 (8)                |
|                               | Reduced employment rate | 4 (13)          | 0                    | 3 (21)          | 1 (8)                |
|                               |                          | 3 (10)          | 0 (0)                | 1 (7)           | 2 (17)               |

All numbers given are the median and interquartile range (IQR), unless otherwise stated.

Abbreviations: ACCI = Age-adjusted Charlson Comorbidity Index (including age); ICU = Intensive Care Unit

¹ A higher score reflects a better functioning

² A higher score represents pain in a greater extent.

³ Data is given for 39 COVID-19 ICU survivors (42 participants underwent a spirometry test of which 1 participant did not consent to collect the data from the hospital. For 2 participants data is missing.)

⁴ > 5% reported health care consumption are presented. Other health care consumption were mentioned for example; social work, occupational therapist, cardiologist, (vascular) surgeon or otorhinolaryngologists.

⁵ n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain | Variable | 3 months | 6 months |
|--------|----------|----------|----------|
|        |          | Total (n = 60) | ACCI 0–1 (n = 5) | ACCI 2–3 (n = 28) | ACCI ≥ 4 (n = 27) | Total (n = 50) | ACCI 0–1 (n = 4) | ACCI 2–3 (n = 21) | ACCI ≥ 4 (n = 25) |
|        |          | 4 (13) | 1 (25) | 2 (14) | 1 (8) | 13 (43) | 3 (75) | 6 (43) | 4 (33) |
|        | Other    | 3 (10) | 0 | 0 | 3 (25) |

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5 n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain                          | Variable                        | 3 months |                      |                       | 6 months |                      |                       |
|--------------------------------|--------------------------------|----------|----------------------|-----------------------|----------|----------------------|-----------------------|
|                                |                                | 3 months |                      |                      | 6 months |                      |                      |
|                                |                                | Total    | ACCI 0–1 (n = 5)     | ACCI 2–3 (n = 28)     | ACCI ≥ 4 (n = 27)    | Total    | ACCI 0–1 (n = 4)     | ACCI 2–3 (n = 21)     | ACCI ≥ 4 (n = 25)    |
|                                |                                | (n = 60) | (n = 5)               | (n = 28)              | (n = 27)         | (n = 50) | (n = 4)              | (n = 21)              | (n = 25)            |
| Employment rate (100%=full-time), mean (sd) | -                              | -        | -                    | -                    | -                | 22.9     | (32.2)               | 10.0                  | (20.0)               | 32.0                 | (39.3)               | 6.7                   | (24.2)               |
| Psychological functioning      | Anxiety (range 0–21)           | 3.5 (1.0–7.8) | 3.0 (2.5–6.0) | 5.0 (2.0–7.8) | 3.0 (1.0–8.0) | 4.5 (0.3–7.0) | 3.5 (2.3–7.0) | 4.0 (1.0–6.5) | 2.0 (1.0–6.0) |
|                                | Depression (range 0–21)        | 4.0 (1.0–6.0) | 4.0 (1.0–6.0) | 4.0 (1.0–6.0) | 2.0 (1.0–6.0) | 3.0 (1.0–5.0) | 4.0 (1.0–5.0) | 4.0 (1.5–6.5) | 4.0 (1.5–6.5) |
|                                | Fear of reinfection (range 1–10)| -        | -                    | -                    | -                | 5.0 (2.0–7.5) | 4.0 (2.3–7.3) | 5.0 (2.3–7.0) | 4.0 (2.0–8.0) |
| Miscellaneous                   | Health care consumption⁴, n (%) | Yes      | 60 (100)             | 5 (100)              | 28 (100)         | 27 (100) | 46 (92)              | 4 (100)              | 21 (100)            | 21 (84)              |
|                                |                                | No       | 0                    | 0                    | 0                | 4 (8)         | 0                | 0                | 4 (16)             |
|                                | Readmission                    | 43 (72)  | 4 (80)               | 22 (79)              | 17 (63)         | 28 (56) | 3 (75)              | 11 (52)             | 14 (56)             |
|                                | General practitioner            | 12 (20)  | 5 (100)              | 5 (18)               | 7 (26)         | 3 (6)          | 0                | 1 (5)             | 2 (8)             |
|                                | Home care                      | 51 (85)  | 4 (80)               | 23 (82)              | 23 (85)        | 43 (86) | 3 (75)              | 19 (91)             | 20 (80)             |
|                                | Physiotherapist                | 42 (70)  | 0                    | 21 (75)              | 17 (63)        | 32 (64) | 0                | 11 (52)            | 18 (72)             |
|                                | Pulmonologist                  | 5 (100)  | 6 (21)               | 10 (37)              | 10 (20)        | 0              | 6 (29)             | 4 (16)             |
|                                | Rehabilitation                 | 0        | 0                    | 0                    | 0              | 0              | 0                | 0                | 0                |

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4 > 5% reported health care consumption are presented. Other health care consumption were mentioned for example; social work, occupational therapist, cardiologist, (vascular) surgeon or otorhinolaryngologists.

5 n = 49 due to one non-response. > 5% reported symptoms are presented. Other burdens were mentioned (< 5%) for example; balance problems, hair loss, smell/taste disorder, skin problems and/or hoarseness.
| Domain | Variable | 3 months | 6 months |
|--------|----------|----------|----------|
|        |          | Total (n = 60) | ACCI 0–1 (n = 5) | ACCI 2–3 (n = 28) | ACCI ≥ 4 (n = 27) | Total (n = 50) | ACCI 0–1 (n = 4) | ACCI 2–3 (n = 21) | ACCI ≥ 4 (n = 25) |
|        | Dietician | 16 (27) | 5 (100) | 11 (39) | 9 (33) | 0 | 4 (15) | 1 (2) | 0 | 0 |
|        |          | 25 (42) | 4 (14) | 8 (13) | | | | | | |

All numbers given are the median and interquartile range (IQR), unless otherwise stated.

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Table 2
The physical-, social- and psychological functioning of family members of COVID-19 ICU survivors 3 and 6 months post ICU discharge

| Domain                  | Variable                               | 3 months (n = 78) | 6 months (n = 67) |
|-------------------------|----------------------------------------|-------------------|-------------------|
| Physical functioning    | Physical functioning\(^1\) (range 0-100) | 100 (83.3–100)    | -                 |
|                        | Experienced health\(^1\) (range 0-100)  | 70.0 (55.0–90.0)  | -                 |
|                        | Pain\(^2\) (range 0-100)                | 25.0 (0.0–50.0)   | -                 |
| Social functioning      | Role activities\(^3\) (range 0-100)     | 100 (50.0-100)    | -                 |
|                        | Social functioning\(^1\) (range 0-100)  | 100 (70.0-100)    | -                 |
|                        | Family functioning\(^1\) (range 1–4)   | 3.8 (3.1-4.0)     | 3.8 (3.2-4.0)     |
| Return to work\(^3\), n (%) | No change                              | 26 (65)           | 23 (64)           |
|                        | Reduced employment rate                | 1 (3)             | 5 (14)            |
|                        | Occupation change                      | 2 (5)             | 1 (3)             |
|                        | Re-integration                         | 5 (13)            | 4 (11)            |
|                        | Not returned to work                   | 4 (10)            | 0                 |
|                        | Job loss                               | 1 (5)             | 0                 |
|                        | Unknown                                | 1 (3)             | 3 (8)             |
|                        | Employment rate (100% = full-time), mean (sd) | 61.6 (38.7)       | 72.5 (27.8)       |
| Psychological functioning| Anxiety (range 0–21)                   | 3.0 (2.0–7.0)     | 4.0 (1.0–8.0)     |
|                        | Depression (range 0–21)                | 2.0 (1.0–6.0)     | 2.0 (1.0–6.0)     |
|                        | Fear of reinfection (range 1–10)       | -                 | 6.0 (4.0–8.0)     |
|                        | Influence no-contact on well-being, n (%) | -               | 42 (63)           |
|                        | Yes                                    |                  |                   |
|                        | No                                     |                  | 21 (31)           |

All numbers given are the median and interquartile range (IQR), unless otherwise stated.

\(^1\) A higher score reflects a better functioning.

\(^2\) A higher score represents pain in a greater extent.

\(^3\) Employed family members at 3 months n = 40 and at 6 months n = 36.

\(^4\) > 5% reported health care consumption at 3 months are presented. Other health care consumption were mentioned for example; home care, physiotherapist, company physician, coach.
| Domain              | Variable                                      | 3 months (n = 78) | 6 months (n = 67) |
|---------------------|-----------------------------------------------|-------------------|-------------------|
| Miscellaneous       | Health care consumption⁴, n (%)               |                   |                   |
|                     | Yes                                           | 40 (51)           | 28 (42)           |
|                     | No                                            | 38 (49)           | 39 (58)           |
|                     | General practitioner                           | 31 (40)           | 19 (28)           |
|                     | Psychologist                                   | 9 (12)            | 8 (12)            |
|                     | Social work                                    | 19 (24)           | 7 (10)            |

All numbers given are the median and interquartile range (IQR), unless otherwise stated.

¹ A higher score reflects a better functioning.

² A higher score represents pain in a greater extent.

³ Employed family members at 3 months n = 40 and at 6 months n = 36.

⁴ > 5% reported health care consumption at 3 months are presented. Other health care consumption were mentioned for example; home care, physiotherapist, company physician, coach.

Figures
Figure 1

Overview of outcome variables per domain of the COFICS at three and six months post ICU discharge. 1 Subscale mental health is excluded 2 Family members received these questions only at 3 months 3 Patients received these questions only at 6 months
Figure 2

COFICS flow diagram: participant recruitment

Figure 3
A Employment rate for each employed COVID-19 ICU survivor (n=29) before ICU admission and six months post ICU discharge. B Employment rate for each employed family member of COVID-19 ICU survivors (n=33) before ICU admission and three and six months post ICU discharge. Only family members with complete data on all measurement points are shown.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalAbstract.pptx
- Supplement1.Overviewofquestions.docx