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Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19

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IMPORTANCE One-year outcomes in patients who have had COVID-19 and who received treatment in the intensive care unit (ICU) are unknown.

OBJECTIVE To assess the occurrence of physical, mental, and cognitive symptoms among patients with COVID-19 at 1 year after ICU treatment.

DESIGN, SETTING, AND PARTICIPANTS An exploratory prospective multicenter cohort study conducted in ICUs of 11 Dutch hospitals. Patients (N = 452) with COVID-19, aged 16 years and older, and alive after hospital discharge following admission to 1 of the 11 ICUs during the first COVID-19 surge (March 1, 2020, until July 1, 2020) were eligible for inclusion. Patients were followed up for 1 year, and the date of final follow-up was June 16, 2021.

EXPOSURES Patients with COVID-19 who received ICU treatment and survived 1 year after ICU admission.

MAIN OUTCOMES AND MEASURES The main outcomes were self-reported occurrence of physical symptoms (frailty [Clinical Frailty Scale score ≥5], fatigue [Checklist Individual Strength—fatigue subscale score ≥27], physical problems), mental symptoms (anxiety [Hospital Anxiety and Depression {HADS} subscale score ≥8], depression [HADS subscale score ≥8], posttraumatic stress disorder [mean Impact of Event Scale score ≥1.75]), and cognitive symptoms (Cognitive Failure Questionnaire—14 score ≥43) 1 year after ICU treatment and measured with validated questionnaires.

RESULTS Of the 452 eligible patients, 301 (66.8%) patients could be included, and 246 (81.5%) patients (mean [SD] age, 61.2 [9.3] years; 176 men [71.5%]; median ICU stay, 18 days [IQR, 11 to 32]) completed the 1-year follow-up questionnaires. At 1 year after ICU treatment for COVID-19, physical symptoms were reported by 182 of 245 patients (74.3% [95% CI, 68.3% to 79.6%]), mental symptoms were reported by 64 of 244 patients (26.2% [95% CI, 20.8% to 32.2%]), and cognitive symptoms were reported by 39 of 241 patients (16.2% [95% CI, 11.8% to 21.5%]). The most frequently reported new physical problems were weakened condition (95/244 patients [38.9%]), joint stiffness (64/243 patients [26.3%]) joint pain (62/243 patients [25.5%]), muscle weakness (60/242 patients [24.8%]) and myalgia (52/244 patients [21.3%]).

CONCLUSIONS AND RELEVANCE In this exploratory study of patients in 11 Dutch hospitals who survived 1 year following ICU treatment for COVID-19, physical, mental, or cognitive symptoms were frequently reported.

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Supplemental content

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The COVID-19 pandemic resulted in a surge of critically ill patients who required treatment in intensive care units (ICUs), with many survivors of critical illness at risk of experiencing long-term impairments.[1] Post-ICU symptoms can be divided within the physical, mental, and cognitive domain and are associated with increased 1-year mortality, higher health care costs, and lower quality of life (QoL).[2-4]

Recent studies have demonstrated that patients who required ICU treatment for COVID-19 experience short-term symptoms in all 3 domains.[5-7] Long-term consequences are yet largely unknown but are likely substantial given the presence of known risk factors for post-ICU problems, circumstances of the pandemic, and the occurrence of symptoms in hospitalized non-ICU patients with COVID-19.[8-10] In view of the long duration of ICU treatment among patients with COVID-19, worse long-term outcomes would be expected compared with ICU patients without COVID-19.[1] Additionally, patients who survive acute respiratory distress syndrome (ARDS) (which is clinically similar to severe COVID-19) frequently experience long-term symptoms.[11,12] Insight into the long-term outcomes among patients with COVID-19 who received ICU treatment is important for providing adequate care and aftercare tailored to the clinical needs of these patients.[13]

The aim of the present study was to assess the occurrence of physical, mental, and cognitive symptoms in patients with COVID-19 at 1 year following receipt of ICU treatment.

Key Points

Question What are the 1-year outcomes among patients who survive intensive care unit (ICU) treatment for COVID-19?

Findings In this exploratory multicenter prospective cohort study that included 246 patients who were alive 1 year following ICU treatment for COVID-19, 74.3% reported physical symptoms, 26.2% reported mental symptoms, and 16.2% reported cognitive symptoms.

Meaning Physical, mental, and cognitive symptoms were frequent 1 year after ICU treatment for COVID-19.

Methods

Study Design, Setting, and Population

This exploratory prospective cohort study is part of the MONITOR-IC study, a multicenter study in ICU survivors.[14] The study protocol has been previously described[15] and approved by the local research ethics committee (CMO region Arnhem-Nijmegen, the Netherlands, No. 2016-2724).

Briefly, ICU patients treated for COVID-19 were recruited from 11 Dutch hospitals (3 university hospitals, 5 teaching hospitals, and 3 nonteaching hospitals). Eligible patients were recruited for participation after ICU discharge (either before hospital discharge or as soon as possible after). Written informed consent was obtained from all patients or their legal representatives. ICU patients (aged 16 years or older and alive after hospital discharge) admitted to the ICU during the first COVID-19 surge in the Netherlands (March 1, 2020, until July 1, 2020) with confirmed COVID-19 infection (by laboratory or clinical diagnosis [eg, computed tomography]) were eligible. Exclusion criteria were an ICU admission of less than 12 hours, having a life expectancy of less than 48 hours, or receiving palliative care.

Study Outcomes

The main outcomes were physical, mental, and cognitive symptoms 1 year after ICU admission, which were measured with self-reported, recommended and validated questionnaires, completed by patients or a proxy if the patient was unable.[15,16] Nonresponders received 2 reminders. The questionnaires could be completed online or on paper, based on the patients' preference.

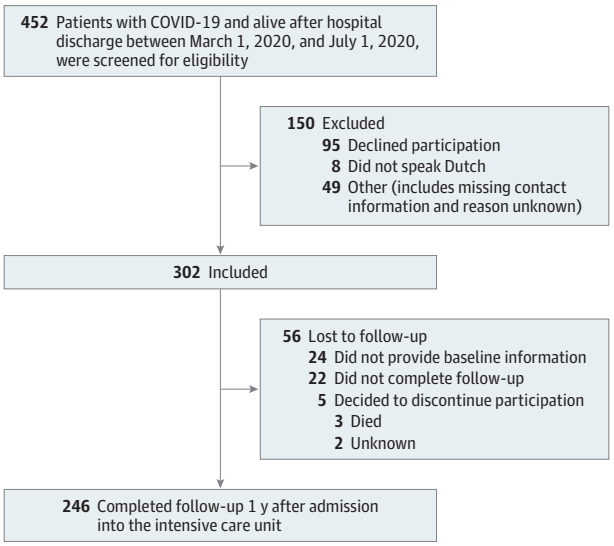
Physical symptoms were measured using the Clinical Frailty Score (incremental scale objectifying frailty; score range, 1 [very fit] to 9 [terminally ill], with a score of ≥5 indicating a person as frail)[17,18] and the Checklist Individual Strength—fatigue subscale (a 7-point rating subscale of the CIS-20 measuring fatigue severity and consisting of 8 statements; score range, 8-56 [cutoff value of ≥27 indicates abnormal fatigue]).[19,20] Moreover, the study questionnaire included a list of 30 physical problems of which presence was rated with a 4-point Likert scale (no problems, mild problems, moderate problems, or severe problems). Physical problems were present if at least 1 problem was rated as moderate or severe.

Mental symptoms of anxiety, depression, and posttraumatic stress disorder were measured using the Hospital Anxiety and Depression Scale (HADS; the HADS-Anxiety [HADS-A] and the HADS-Depression [HADS-D] components each consist of 7 questions with a 4-point Likert scale [0-3], with a cutoff value of ≥8 indicating the presence of symptoms of anxiety or depression for both subscales)[21,22] and the Impact of Event Scale—6 (IES-6; consists of 6 questions derived from the IES—Revised [IES-R], with a 5-point Likert scale ranging from 0 [not at all] to 4 [extremely], with a mean cutoff value of ≥1.75 over all questions indicating presence of posttraumatic stress disorder symptoms).[23,24]

Cognitive symptoms were measured using the abbreviated Cognitive Failure Questionnaire-14 (14 questions with a 5-point Likert scale measuring daily life cognitive failures ranging from 0 [never] to 4 [very often] resulting in a factored score ranging from 0-100, with a score of ≥43 indicating cognitive symptoms).[25]

The ability to return to work was assessed by a question with multiple options regarding the patient's level of recovery (from full recovery "working as before admission" to incapacity "completely stopped working because of the consequences of the critical illness episode"). Additionally, after inclusion, patients were asked to report their level

Figure. Participant Flowchart of Patients With COVID-19 Treated in the Intensive Care Unit



of education and racial and ethnic background and dichotomized by high education level (indicating higher vocational or university education) and ethnicity (having Dutch ancestry or not). Patients' other demographics and information concerning ICU admission were retrieved from medical records and the NICE (Dutch National Intensive Care Evaluation) registry.[26]

Statistical Analysis

Continuous variables were presented as mean (SD) or median (first and third IQR), and categorical variables were presented as proportions. Outcome scores were presented as median (IQR). Outcome scores were dichotomized using the previously mentioned thresholds and presented as proportion with 95% CIs. The occurrence of symptoms in a domain (physical, mental, cognitive) was positive if there was at least 1 symptom present in that particular domain.

Patients who completed the 1-year follow-up questionnaires were included in the analysis. Baseline characteristics were compared between responders and nonresponders (ie, included patients with available baseline information but who did not complete the 1-year follow-up questionnaires) using the independent sample I test or Mann-Whitney *U* test, depending on the distribution of the continuous variables, and the χ^2 test was used for categorical variables.

Missing data in the CIS-8 and the HADS questionnaires were imputed using a participant's means score if at least half of the items were answered (the half rule), and missing data in the IES-6 were replaced with the individual mean if at least 5 of 6 questions were answered.[27] For the Cognitive Failure Questionnaire-14, only fully completed forms were included. All statistical tests were 2-sided and statistical significance was defined as a $P < .05$. Data were analyzed using SPSS version 25.

Table 1. Demographic and Clinical Characteristics of Patients With COVID-19 Treated in the Intensive Care Unit (N = 246)

	COVID-19 ICU survivors, No./total (%)
Patient characteristics[a]	
Age, mean (SD), y	61.2 (9.3)
Men	176/246 (71.5)
Women	70/246 (28.5)
Questionnaire completed by patient	221/246 (89.8)
Ancestry other than Dutch	26/233 (11.2)
High education level[b]	78/240 (32.5)
Body mass index, mean (SD)[c]	28.0 (4.5)
Body mass index ≥30	62/239 (25.2)
Chronic condition, ≥1[d]	58/246 (23.6)
ICU characteristics	
APACHE IV score, mean (SD)[e]	58.9 (16.6)
Patients received IMV[f]	132/162 (81.5)
Duration of IMV, median (IQR), d	14 (8-22)
Duration of ICU stay, median (IQR), d	18.5 (11-32)
Duration of hospital stay, median (IQR), d	30 (20-46)

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IMV, invasive mechanical ventilation.

[a] Patients were admitted to the ICU between March 1, 2020, and July 1, 2020 (the first COVID-19 surge in the Netherlands).

[b] Higher vocational education and university education were classified as high education level dichotomized vs lower education levels.

[c] Body mass index was calculated by the weight in kilograms divided by height in meters squared. Cutoff value of ≥30 for obesity was based on the World Health Organization's definition.

[d] Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, and chronic dialysis or kidney failure.

[e] The APACHE IV scale measures severity of illness in critically ill patients (score range, 0-286, with higher scores indicating worse outcomes). For example, a patient in the ICU treated for COVID-19 with an APACHE IV score of 60 who is already in the hospital for 5 days prior to ICU admission without a chronic health condition has an estimated mortality rate of approximately 16%.

[f] Of the 11 participating hospitals, 4 were not able to provide data regarding use of mechanical ventilation.

Results

Patient and ICU Characteristics

During the study period, 452 patients with COVID-19 who received ICU treatment survived to hospital discharge, of whom 302 (66.8%) were included (**Figure**). Of the included patients, 246 (81.5%) completed the 1-year follow-up questionnaires. ICU patients with COVID-19 had a mean (SD) age of 61.2 (9.3) years, 176 (71.5%) were men, and the mean body mass index (calculated as weight in kilograms divided by height in meters squared) was 28.0 (4.5) (**Table 1**). The median length of ICU stay was 18.5 days (IQR, 11 to 32).

There were no differences in patient and pre-ICU characteristics between responders and nonresponders except

Table 2. Prevalence of Symptoms in Patients at 1-Year Survival Following Intensive Care Unit Treatment for COVID-19 (N = 246)

	Values at 1-y follow-up, No./total (%) [95% CI]
Physical symptoms	
Reported ≥1 physical symptom	182/245 (74.3) [68.3-79.6]
Clinical Frailty Scale score, median (IQR)[a]	2 (2-3)
Exceeded frailty cutoff[a]	15/245 (6.1) [3.5-9.9]
Checklist Individual Strength-8—fatigue subscale score, median (IQR)[b]	29 (18-39)
Exceeded fatigue cutoff[b]	138/246 (56.1) [49.7-62.4]
New or worsened physical problems, No. of problems, median (IQR)[c]	2 (0-5)
Reported ≥1 physical problem	165/246 (67.1) [60.8-72.9]
Mental symptoms	
Reported ≥1 mental symptom	64/244 (26.2) [20.8-32.2]
HADS scale-anxiety score, median (IQR)[d]	3 (1-6)
Exceeded anxiety cutoff[d]	44/246 (17.9) [13.3-23.3]
HADS scale-depression score, median (IQR)[d]	3 (1-5)
Exceeded depression cutoff[d]	45/246 (18.3) [13.7-23.7]
Impact of Event Scale-6 score, median (IQR)[e]	0.5 (0.2-1.2)
Exceeded posttraumatic stress disorder cutoff[e]	24/244 (9.8) [6.4-14.3]
Cognitive symptoms	
Cognitive Failure Questionnaire-14 score, median (IQR)[f]	24.8 (12.8-37.0)
Exceeded cognitive failure cutoff[f]	39/241 (16.2) [11.8-21.5]

Abbreviation: HADS, Hospital Anxiety and Depression Scale.

[a] Score range, 1 (very fit) to 9 (terminally ill), with a score of 5 or greater indicating frailty. A score of 2 describes a person who is fit, and higher scores indicate being more frail.

[b] A 7-point rating subscale of the Checklist Individual Strength-20 (score range, 8-56, with a score of 27 or greater indicating abnormal fatigue) and consisting of 8 statements.

[c] Physical problems were objectified by a list of 30 symptoms and were present if at least 1 symptom was moderate or severe.

[d] Score range, 0 (best) to 21 (worst), with higher scores indicating worse symptoms, with the presence of anxiety or depression symptoms defined by a subscale score of 8 or greater.

[e] Score range, 0 (not at all symptomatic) to 4 (extremely symptomatic), with a score of 1.75 or greater indicating presence of symptoms.

[f] Score range, 0 (never) to 100 (very often), with a score of 43 or greater indicating symptoms of daily life cognitive failure.

Table 3. Symptoms Experienced by Patients With COVID-19 1 Year After Intensive Care Unit Treatment[a]

	No./total (%) of patients with 1-y outcomes		
Domain	1 Domain	2 Domains	All 3 domains
Physical[b]	107/245 (43.5)	35/246 (14.2) + Mental	26/246 (10.5)
Mental[c]	1/244 (0.4)		
Cognitive[d]		15/246 (5.9) + Physical	

[a] Percentages will not sum to 100% because 25.5% of patients experienced no symptoms at 1 year. Percentages may differ from 1-year outcomes presented in Table 2 because only patients without any missing outcome variable were included in the analysis (N = 239). Empty cells indicate that zero patients fulfilled the category.

[b] Physical symptoms were defined as either being frail (Clinical Frailty Scale score of ≥5), fatigued (Checklist Individual Strength score of ≥27), or having at least 1 new or worsened physical problem.

[c] Mental symptoms were defined as either experiencing symptoms of anxiety (Hospital Anxiety and Depression Scale—anxiety subscale score of ≥8), depression (Hospital Anxiety and Depression Scale—depression subscale score of ≥8), or posttraumatic stress disorder (mean Impact of Event scale-6 score of ≥1.75).

[d] Cognitive symptoms were defined as having a Cognitive Failure Questionnaire score of 43 or greater.

for ethnicity as 11.2% of the responders had other than Dutch ancestry compared with 30.0% of the nonresponders (P = .004) (eTable in the Supplement).

Physical, Mental, and Cognitive Outcomes 1 Year After ICU Treatment

At 1 year following ICU treatment, physical symptoms were reported by 74.3% (182/245) of patients, mental symptoms by 26.2% (64/244), and cognitive symptoms by 16.2% (39/241) (**Table 2**). Overall, 30.6% of the survivors reported symptoms in at least 2 domains, and 10.5% experienced symptoms in all 3 domains 1 year after ICU treatment (**Table 3**). Additionally, 57.8% of the survivors who were employed before ICU admission reported work-related problems (eg, working less hours than before or still on sick leave).

Physical Outcomes

One year after ICU treatment for COVID-19, 6.1% (15/245) of the survivors reported being frail and 56.1% (138/246) reported experiencing fatigue. Two-thirds reported new physical problems as a result of ICU treatment for COVID-19 (Table 2). Most frequently reported physical problems were weakened condition (38.9%), joint stiffness (26.3%), joint pain (25.5%), muscle weakness (24.8%), myalgia (21.3%), and dyspnea (20.8%) (**Table 4**).

Mental Outcomes

Symptoms of anxiety were reported by 17.9% (44/246) of the survivors and by 18.3% (45/246) for depression 1 year after ICU treatment for COVID-19 (Table 2). In addition, 9.8% of survivors (24/244) reported symptoms of posttraumatic stress disorder.

Cognitive Outcome

The median Cognitive Failure Questionnaire-14 score was 24.8 (IQR, 12.8 to 37.0) and cognitive symptoms were reported by 16.2% (39/241) of the survivors (Table 2).

The median scores and distributions of all outcome variables are presented in Table 2 and the eFigure in the Supplement.

Discussion

In this exploratory prospective cohort study including patients of 11 Dutch hospitals who survived 1 year following ICU treatment for COVID-19, physical, mental, or cognitive symptoms were reported frequently. In addition, many survivors experienced a weakened condition or musculoskeletal problems and had work-related problems as a result of the critical illness episode.

Studies in patients who survived ICU treatment for COVID-19 with outcomes up to 6 months follow-up showed comparable prevalence rates of fatigue and musculoskeletal problems, eg, ICU-acquired weakness.[5,28,29] However, the reported prevalence rates for symptoms of anxiety 4 months after ICU treatment (23.4%)[30] and for anxiety (33%) and depression (36%) at 6 months after ICU treatment,[31] all measured with the HADS outcome measure and thresholds, are higher compared with the 1-year outcomes reported in the present study, which could possibly be attributed to the recovery of mental health over time. However, these short-term studies[5,25,30,31] had smaller sample sizes, included less than half of the number of COVID-19 ICU survivors as in the present study, and only 1 study analyzed all 3 domains of post-ICU outcomes. In other viral outbreaks, for instance SARS in 2003 or MERS in 2012, approximately one-third of the ICU survivors reported mental health problems beyond 6 months after discharge, which is slightly higher than the 1-year rate of 26.2% for mental health symptoms reported in the present study.[32]

A recent study of ICU patients without COVID-19 and also the MONITOR-IC study, with similar questionnaires and cutoff values, reported prevalence rates among ICU survivors with a medical admission 1 year after ICU treatment (N = 649) of 77.0% for physical symptoms, 35.5% for mental symptoms, and 14% for cognitive symptoms.[14,15,33] Compared with the present study, prevalence of physical (74.3%) and cognitive symptoms (16.2%) was similar. However, prevalence rates of mental symptoms (26.2%) were lower among patients who survived ICU treatment for COVID-19 compared with patients treated for another medical admission reason.[33] A total of 58% of the ICU survivors with COVID-19 in the present study reported problems with return to work, compared with 43% among ICU survivors without COVID-19.[33]

Limitations

This study has several limitations. First, patient-reported outcome measures were assessed, which cannot be used as diagnostic tools. In addition, cognitive problems were assessed by self-report, which may differ from findings at formal neuropsychological testing.[34] Second, important information about ICU treatment, such as the use sedation, prone positioning, and occurrence of delirium, was not available. Furthermore, information about post-ICU treatment, such as the use of rehabilitation programs, was also not available. This information could have been valuable to better interpret 1-year outcomes.

Third, physical symptoms are likely to be overrepresented in relation to mental and cognitive symptoms because more self-reported outcome measures were used to assess physical symptoms. Fourth, we did not study ICU patients with non–COVID-19 diagnoses, and we therefore cannot conclude that the symptoms at 1 year were specific for COVID-19.

Table 4. Prevalence of New Physical Problems in Patients With COVID-19 1 Year After Intensive Care Unit Admission

New physical problems[a]	No./total (%) [95% CI]
Weakened condition	95/244 (38.9) [33.0-45.1]
Joint stiffness	64/243 (26.3) [21.1-32.1]
Joint pain	62/243 (25.5) [20.3-31.2]
Muscle weakness	60/242 (24.8) [19.6-30.5]
Myalgia	52/244 (21.3) [16.5-26.7]
Dyspnea	51/245 (20.8) [16.1-26.2]
Tingling or numb sensation in limbs	50/243 (20.6) [15.8-26.0]
Lung disease	45/243 (18.5) [14.0-23.7]
Neuropathic pain	42/242 (17.4) [12.9-22.5]
Voice problems (eg, hoarseness)	29/244 (11.9) [8.2-16.3]
Dizziness or balance problems	28/243 (11.5) [7.9-15.9]
Hypotension or hypertension	28/245 (11.4) [7.9-15.8]
Sexual problems	18/240 (7.5) [4.6-11.3]
Skin problems	18/245 (7.3) [4.5-11.1]
Hair loss	17/243 (7.0) [4.2-10.7]
Loss of smell	17/245 (6.9) [4.2-10.6]
Loss of taste	15/245 (6.1) [3.6-9.6]
Headache	13/243 (5.3) [3.0-8.7]
Heart disease, chest pain	13/244 (5.3) [3.0-8.6]
Vision problems	12/244 (4.9) [2.7-8.1]
Loss of hearing	10/244 (4.1) [2.1-7.1]
Bowel problems	9/245 (3.7) [1.8-6.5]
Urinary problems	8/244 (3.3) [1.5-6.0]
Wound pain	5/245 (2.0) [0.7-4.3]
Pressure ulcers	5/243 (2.1) [0.7-4.4]
Abdominal pain	4/245 (1.6) [0.5-3.8]
Dysphagia	3/243 (1.2) [0.3-3.2]
Menstrual problems	1/200 (0.5) [0.0-2.2]
Other pain	13/206 (6.3) [3.5-10.2]
Other physical problems	22/194 (11.3) [7.4-16.3]

[a] New physical problems were selected from a list of 30 problems, and a condition or symptom was considered present if it was at least moderate or severe.

Conclusions

In this exploratory study of patients in 11 Dutch hospitals who survived 1-year following ICU treatment for COVID-19, physical, mental, or cognitive symptoms were frequently reported.

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