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Short Communication

Acute COVID-19 treatment is not associated with health problems 2 years after hospitalization

Julia C. Berentschot[1,*], L. Martine Bek[2], Majanka H. Heijenbrok-Kal[2,3], Rita J.G. van den Berg-Emons[2], Gerard M. Ribbers[2,3], Joachim G.J.V. Aerts[1], Merel E. Hellemons[1], on behalf of the CO-FLOW Collaboration Group[#]

[1] Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[2] Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[3] Rijndam Rehabilitation, Rotterdam, The Netherlands

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ABSTRACT

Objectives: Various mechanisms, such as immune dysregulation, viral reservoir, and auto-immunity, are hypothesized to underlie the pathogenesis of long-term health problems after hospitalization for COVID-19. We aimed to assess the effect of in-hospital COVID-19 treatments on prominent long-term health problems.

Methods: In this prospective multicenter cohort study, we enrolled patients (age ≥18 years) who had been hospitalized for COVID-19 in the Netherlands between July 2020 and October 2021. We retrospectively collected data on in-hospital COVID-19 treatments, including steroid, anti-inflammatory, and antiviral treatments. Patients completed questionnaires on self-reported recovery, dyspnea, fatigue, cognitive failures, and health-related quality of life and performed the 6-minute walk test at the 2-year follow-up visit.

Results: Five hundred two patients with COVID-19 were included, all were discharged from the hospital between March 2020 and June 2021. The median age at admission was 60.0 (IQR 53.0-68.0) years and 350 (69.7%) patients were male. At hospital admission, 5/405 (1.2%) of the patients had been vaccinated against SARS-CoV-2. Among all 502 patients, the majority (248 [49.4%]) received steroids only, 57 (11.4%) anti-inflammatory treatment, 78 (15.5%) antiviral treatment, and 119 (23.7%) none during hospitalization. Long-term health problems were common in all groups. We found that in-hospital treatments were not significantly associated with health problems at 2 years after hospital discharge, nor after adjusting for confounders.

Conclusion: Many patients with COVID-19 suffer from long-term health problems 2 years after hospital discharge. Acute treatment for COVID-19 is not associated with long-term health problems.

Introduction

COVID-19, caused by SARS-CoV-2, has resulted in a worldwide pandemic, requiring hospitalization for respiratory insufficiency in numerous patients. Many of these patients suffer lingering and debilitating health problems that can persist for months or years [1], commonly referred to as “long COVID” or “post-COVID syndrome.” Long COVID comprises a wide range of symptoms, with dyspnea, fatigue, and neurocognitive symptoms among the most frequently reported, may negatively affect health-related quality of life, and more commonly affects patients after severe COVID-19 [1,2].

During the acute phase, patients hospitalized for COVID-19 commonly exhibit hyper-inflammation and so-called “cytokine storm” [3]. During the pandemic, treatment insights have continued to develop. Several treatments have been recommended to combat the disturbances caused by SARS-CoV-2, including steroids and targeted immunomodulatory (suppressing the inflammatory cytokine storm) and antiviral (suppressing viral replication) treatments in those requiring supplemental oxygen [4]. The immune dysregulation caused by SARS-CoV-2 can persist into convalescence, and such dysregulation has been associated with long COVID [5,6]. Although currently incompletely understood, various mechanisms, including immune dysregulation, persistence of

* Corresponding author. Julia C. Berentschot
E-mail address: j.berentschot@erasmusmc.nl (J.C. Berentschot).
[#] Names and affiliations of the CO-FLOW Collaboration Group members are listed in acknowledgment section.

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SARS-CoV-2 in tissues, and auto-immunity, are hypothesized to underlie long COVID pathogenesis [5]. As such, various in-hospital treatments may affect long-term health outcomes after severe COVID-19. In line with this, nirmatrelvir/ritonavir treatment appeared to reduce the risk of long-term health problems in several cohort studies [7,8]. Regarding in-hospital COVID-19 treatment, our previous study showed that steroid-treated patients are less likely to report muscle weakness up to 1-year post-hospitalization [2]. Another study found no association between steroid or antiviral treatment and symptoms 2 years post-hospitalization for COVID-19 [1]. However, at this time, data are scarce regarding the effect of in-hospital treatment on long-term health outcomes.

Therefore, we aimed to assess the effect of different in-hospital COVID-19 treatments on long-term health problems at 2 years post-discharge. We hypothesized that patients who received immunomodulatory and/or antiviral treatment for COVID-19 may experience fewer health problems than those with steroids only or no treatment.

Methods

The CO-FLOW study is a multicenter prospective cohort study on long-term health outcomes up to 2 years after discharge in adult patients hospitalized for COVID-19 in the Netherlands. The study was conducted in 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities). Patients eligible for the study were those hospitalized for COVID-19 (confirmed by laboratory or clinical diagnosis), aged 18 years or older, had sufficient knowledge of the Dutch or English language, and within 6 months post-discharge. Incapacitated patients (e.g., dementia) were not included. Patient inclusion took place between July 2020 and October 2021 [9]. In this study, we included patients who had completed at least one of our outcomes of interest at the 2-year follow-up and whose data on in-hospital COVID-19 treatment could be retrieved from medical records in the participating hospitals.

We followed national COVID-19 treatment guidelines across the participating hospitals, in line with international recommendations [4,10]. These guidelines evolved due to the initially unknown COVID-19 pathogenesis and treatment effectiveness. At the beginning of the pandemic, no treatment or treatments currently considered ineffective (e.g., (hydroxy)chloroquine and azitromycine), and, more occasionally, immunomodulatory (anti IL-1 or anti IL-6) or antiviral treatments were given. Soon thereafter, patients requiring supplemental oxygen were treated with steroids. Antivirals (remdesivir or convalescent plasma) were initially considered effective for COVID-19 treatment [4]. However, their clinical effectiveness appeared less than anticipated, leading to their discontinuation after the second COVID-19 wave in the Netherlands. During the late second/early third wave, patients with severe illness ($\geq$6 L oxygen and CRP $\geq$75 mg/L) received immunomodulatory treatment (targeting IL-6). Given these various regimes over time, we categorized patients into four groups based on their in-hospital COVID-19 treatment: 1] steroids only (dexamethasone, prednisolone, or methylprednisolone), 2] anti-inflammatory (anti-IL-6 or anti-IL-1) with or without steroids or antivirals, 3] antivirals (remdesivir, oseltamivir, lopinavir, ritonavir, or convalescent plasma) with or without steroids, and 4] none of the previously described treatments or (hydroxy)chloroquine only.

The primary outcome was self-reported recovery from COVID-19 as assessed with the COVID-19 Core Outcome Measure for recovery [11] and was dichotomized into completely recovered and not completely recovered (comprising mostly recovered, somewhat recovered, half recovered, and not recovered at all). Secondary outcomes were assessed with validated patient-reported outcome measures for dyspnea (modified medical research council dyspnea scale, grades 0-4, $\geq$1 indicating dyspnea) [12], fatigue (fatigue assessment scale [FAS], score-range 0-50, cutoff $\geq$22) [13], cognitive failures (cognitive failures questionnaire [CFQ], score-range 0-100, cutoff $>$43) [14], and health-related quality of life (HRQoL) (5-level EuroQoL-5D [EQ-5D-5L] index, score-range 0 [indicating death] to 1 [perfect health]) [15]. Aerobic capacity was assessed with the 6-minute walk test; the 6-minute walk distance (6MWD) was normalized to a percentage of normative value using reference values [16,17].

We assessed differences in baseline characteristics among treatment groups with the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. We first performed univariable Generalized Estimating Equations (GEE) analyses using logistic and linear models to assess the effect of in-hospital COVID-19 treatment on health outcomes at the 2-year follow-up. Subsequently, to control for confounders, age, sex, and baseline characteristics differing among treatment groups were entered as independent variables in multivariable analyses.

Results

Out of the 650 CO-FLOW study participants, 510 patients completed at least one of the outcomes of interest at the 2-year follow-up. From 502 of these patients (median age 60.0 [IQR 53.0-68.0] years; 350 [69.7%] male) data were available on in-hospital treatment and those patients were included in this study. These patients were discharged from the hospital between March 24, 2020, and June 17, 2021. At hospital admission, 5/405 (1.2%) of the patients had been vaccinated against SARS-CoV-2. As for treatment, most patients (248/502 [49.4%]) received steroids only, 57/502 (11.4%) anti-inflammatory, 78/502 (15.5%) antivirals, and 119/502 (23.7%) none during hospitalization. Regarding baseline characteristics, age, sex, body mass index, migration background, and comorbidities did not differ significantly among the treatment groups, while the proportion of ex- or current smokers was higher in the anti-inflammatory group compared to the other groups (Table 1). Moreover, the anti-inflammatory group showed worse in-hospital characteristics, including more frequent thrombosis and delirium, intensive care unit (ICU) admission, and longer hospital stay than the other groups (Table 1); all are related to the indication of this treatment. At the 2-year follow-up (median 731.0 [726.0-740.0] days post-discharge), 427/463 (92.2%) patients reported receiving at least one vaccination against SARS-CoV-2 during follow-up. In the total cohort, 317/435 (72.9%) patients reported that they were not completely recovered from COVID-19. Many patients experienced dyspnea (184/460 [40.0%]), fatigue (220/427 [51.5%]), or cognitive failures (101/432 [23.4%]). Regarding HRQoL, the mean EQ-5D-5L index was .80 (SD .22). Patients reached 94.5% (SD 19.2) of normative 6MWD at 2 years. In univariable GEE analyses, treatment group was not significantly associated with complete recovery, nor with any of the secondary outcomes (dyspnea, total FAS score, total CFQ score, EQ-5D-5L index, or the percentage of normative 6MWD) at 2 years (Table 2). These associations remained non-significant after adjusting for confounders (Table 2).

Discussion

In this cohort study we found that acute COVID-19 treatment did not associate with self-reported recovery or prominent health problems in patients 2 years after hospital discharge. While treatments, especially immunomodulatory, have proven effective in combating immune dysregulation and improving clinical outcomes during the acute phase [4], they did not influence long-term outcomes in our cohort, despite the continued immune dysregulation observed in patients with long COVID [5]. Likewise, antiviral treatment during hospitalization was not associated with favorable

Table 1
Baseline characteristics of patients with COVID-19 at hospital admission.

	None[a] (n = 119)	Steroids only (n = 248)	Anti-inflammatory[b] (n = 57)	Antivirals[c] (n = 78)	*P*-value
Age, years	61.0 (54.0-69.0)	60.0 (54.0-68.0)	62.0 (53.0-68.5)	57.5 (49.8-66.0)	0.18
Sex, male	76 (63.9%)	179 (72.2%)	44 (77.2%)	51 (65.4%)	0.18
BMI, kg/m²	27.9 (25.3-32.0)	28.4 (25.9-32.3)	28.1 (26.3-31.4)	28.7 (25.7-33.0)	0.64
Migration background					
European	92 (77.3%)	191 (78.0%)	42 (73.7%)	57 (73.1%)	0.78
Non-European	27 (22.7%)	54 (22.0%)	15 (26.3%)	21 (26.9%)	
Smoking status					0.01
Never	58 (48.7%)	103 (41.9%)	15 (26.3%)	41 (52.6%)	
Ex or current	61 (51.3%)	143 (58.1%)	42 (73.7%)	37 (47.4%)	
Comorbidities					
Obesity (BMI≥30 kg/m²)	50 (42.0%)	95 (38.3%)	26 (45.6%)	28 (35.9%)	0.62
Diabetes	15 (12.6%)	46 (18.5%)	8 (14.0%)	13 (16.7%)	0.51
Cardiovascular disease	39 (32.8%)	94 (37.9%)	27 (47.4%)	30 (38.5%)	0.32
Pulmonary disease	27 (22.7%)	60 (24.2%)	13 (22.8%)	23 (29.5%)	0.72
In-hospital characteristics					
Vaccination against SARS-CoV-2[d]	0 (0.0%)	3 (1.4%)	1 (1.9%)	1 (2.0%)	NA
Thrombosis	22 (18.5%)	36 (14.5%)	20 (35.7%)	4 (5.1%)	<0.001
Delirium	43 (36.1%)	46 (18.5%)	20 (35.7%)	7 (9.0%)	<0.001
COVID-19 treatment					NA[e]
Steroids					
Dexamethason	-	215 (86.7%)	51 (89.5%)	61 (78.2%)	
Prednisolon	-	32 (12.9%)	2 (3.5%)	3 (3.8%)	
Methylprednisolon	-	19 (7.7%)	9 (15.8%)	1 (1.3%)	
Anti-inflammatory					
Tocilizumab	-	-	55 (96.5%)	-	
Anakinra	-	-	2 (3.5%)	-	
Antivirals					
Remdesivir	-	-	1 (1.8%)	66 (84.6%)	
Oseltamivir	-	-	1 (1.8%)	5 (6.4%)	
Lopinavir/ritonavir	-	-	-	2 (2.6%)	
Convalescent plasma	-	-	1 (1.8%)	7 (9.0%)	
(Hydroxy)chloroquine	5 (4.2%)	1 (0.4%)	-	4 (5.1%)	
None	114 (95.8%)	-	-	-	
Supplemental oxygen	111 (93.3%)	246 (99.2%)	57 (100.0%)	77 (98.7%)	0.002
High flow nasal cannula	23 (19.3%)	76 (30.6%)	40 (70.2%)	16 (20.5%)	<0.001
ICU admission	54 (45.4%)	86 (34.7%)	48 (84.2%)	14 (17.9%)	<0.001
Invasive mechanical ventilation	46 (38.7%)	77 (31.0%)	43 (75.4%)	11 (14.1%)	<0.001
Length of ICU stay, days	20.0 (11.8-36.5)	18.0 (9.0-35.0)	12.5 (8.0-21.3)	13.5 (6.3-31.0)	0.16
Length of hospital stay, days	13.0 (6.0-33.0)	10.0 (5.0-23.0)	23.0 (16.0-34.5)	8.0 (5.0-14.3)	<0.001
COVID-19 wave[f]					<0.001
First	98 (82.4%)	27 (10.9%)	6 (10.5%)	9 (11.5%)	
Second	17 (14.3%)	159 (64.1%)	13 (22.8%)	69 (88.5%)	
Third	4 (3.4%)	62 (25.0%)	38 (66.7%)	-	

Data are presented as the median with interquartile range or number with percentage. Patients were categorized into groups based on their COVID-19 treatment during hospitalization. *P*-values are obtained using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. The variables BMI (n=11 none, n=23 steroids only, and n=13 antivirals groups), migration background (n=3 steroids only group), smoking status (n=2 steroids only group), vaccinated against SARS-CoV-2 at admission (n=26 none, n=39 steroids only, n=4 anti-inflammatory, and n=28 antivirals groups) thrombosis (n=1 anti-inflammatory group), delirium (n=1 anti-inflammatory group), and length of ICU stay (n=2 anti-inflammatory group) contain missing values.
BMI, Body Mass Index; ICU, Intensive Care Unit; NA, Not Applicable.
[a] Comprises patients without steroid, anti-inflammatory, or antiviral treatments, but who may have received (hydroxy)chloroquine.
[b] In addition to anti-inflammatory treatment, patients may have received steroids or antivirals.
[c] In addition to antiviral treatment, patients may have received steroids.
[d] Patient-reported vaccination against SARS-CoV-2.
[e] Group differences in COVID-19 treatment were not assessed; patients were categorized into groups based on these treatments.
[f] We classified patients by discharge date: the first -19 wave (Feb-Jun 2020), second wave (Jul 2020-Feb 2021), and third wave (Feb-Jun 2021).

long-term outcomes. However, the nowadays considered most effective antiviral treatments (e.g., nirmatrelvir/ritonavir) were not given in the acute phase of COVID-19 during this study, which may reduce the risk of long-term health problems [18].

We found that many patients experience persistent health problems 2 years after hospitalization for COVID-19. Although evidence on the association between acute COVID-19 treatment and long-term outcomes is heterogeneous [1,18], studies consistently identified other factors like age, female sex, underlying pulmonary diseases, and increased COVID-19 disease severity as risk factors for long COVID [1,19], consistent with our findings (data not shown).

Currently, there is no effective pharmacological treatment for long COVID. The hypothesized causes of long COVID offer potential treatment options [5], including restoring immune dysregulation and supporting viral clearance. Moreover, long COVID shares similarities with other post-acute infection syndromes (PAISs), such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) [20]. Insights from PAISs may enhance our understanding of the pathophysiologic mechanisms of Long COVID. Despite some studies investigating possible treatment options for long COVID, these findings are pending. These outcomes could represent a significant step in understanding the complexities of long COVID, and may improve long-term health outcomes.

Strengths of our study include its longitudinal and multicenter study design, a large sample size of patients who had been hospitalized for COVID-19, and a high response rate at the 2-year follow-up. Recruitment of study participants occurred independently of

Table 2
Health outcomes at 2 years after hospitalization for COVID-19 per treatment group.

	n	None[a]	Steroids only	Anti-inflammatory[b]	Antivirals[c]	Univariable analysis *P*-value	Multivariable analysis[d] *P*-value
Recovery status (completely recovered)	435	24 (22.6%)	69 (31.9%)	10 (20.4%)	15 (23.4%)	0.16	0.23
Dyspnea (mMRC scale grade≥1)	460	45 (40.9%)	85 (38.1%)	17 (34.0%)	37 (48.1%)	0.37	0.13
Fatigue (total FAS score)	427	23.7 ± 9.1	23.1 ± 8.9	23.8 ± 9.1	25.2 ± 9.0	0.44	0.64
Cognitive failures (total CFQ score)	432	31.6 ± 18.6	30.0 ± 18.8	29.1 ± 16.8	31.2 ± 17.7	0.82	0.49
HRQoL (EQ-5D-5L index)	432	0.78 ± .23	0.80 ± 0.21	0.80 ± 0.19	0.79 ± 0.23	0.85	0.83
6MWT (% of normative 6MWD)[e]	365	96.7 ± 21.8	93.8 ± 17.6	97.9 ± 17.7	91.6 ± 21.2	0.29	0.92

Data are raw test outcomes and are presented as the mean with standard deviation or as a number with percentage. We performed Generalized Estimating Equations (GEE) analysis using logistic (recovery status and dyspnea) and linear (fatigue, cognitive failures, HRQoL, and 6MWT) models to assess the effect of treatment group on health outcomes 2 years after hospitalization for COVID-19. mMRC, Modified Medical Research Council Dyspnea Scale; FAS, Fatigue Assessment Scale; CFQ, Cognitive Failures Questionnaire; HRQoL, Health-Related Quality of Life; EQ-5D-5L, 5-level EuroQoL-5D questionnaires; 6MWT, 6-Minute Walk Test; 6MWD, 6-Minute Walk Distance.

[a] Comprises patients without steroid, anti-inflammatory, or antiviral treatments, but who may have received (hydroxy)chloroquine.

[b] In addition to anti-inflammatory treatment, patients may have received steroids or antivirals.

[c] In addition to antiviral treatment, patients may have received steroids.

[d] Adjusted for age, sex, smoking status, thrombosis, delirium, high flow nasal cannula, intensive care unit treatment, length of stay in the hospital, and COVID-19 wave.

[e] Normative values were calculated according to the method described by Enright and Sherrill [16].

the patients' recovery status, mitigating selection bias. Our study is limited by its observational design in which confounding by indication may play a role, despite our adjustment for multiple confounders. Our national guidelines on COVID-19 treatment may differ from guidelines in other countries, possibly limiting international generalizability of our findings. Moreover, we did not collect information on doses and duration of COVID-19 treatments, and sometimes various treatment regimens could not be clearly separated [4]. Nonetheless, we have analyzed different types of in-hospital COVID-19 treatments, which have been internationally recommended [10], revealing no association with long-term health outcomes.

In summary, we found that many patients who had been hospitalized for COVID-19 suffer from dyspnea, fatigue, cognitive failures, and a decreased HRQoL, while showing good aerobic capacity, 2 years after discharge, irrespective of acute COVID-19 treatment. In light of the public health concerns posed by long COVID, there is an urgent need for a better understanding of the underlying etiology of long COVID and assessment of potential pharmacological treatments.

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Ethical approval

The Medical Ethics Committee of Erasmus MC, University Medical Center Rotterdam, approved this study (MEC-2020-0487). The study has been prospectively registered in the International Clinical Trial Registry Platform (NL8710). Participants provided written informed consent before the start of study measurements.

Declaration of competing interest

All authors have no conflicts of interest related to this work.

Authors' contributions

JB, LB, MHK, RBE, GR, JA, and MH conceptualized the study. JB and LB collected the data. JB, MHK, and MH performed data analysis. JB, LB, MHK, RBE, GR, JA, MH, and the CO-FLOW Collaboration Group interpreted the data. JB, LB, MHK, RBE, GR, JA, MH drafted the manuscript. All authors read and approved the final manuscript.

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CO-FLOW Collaboration Group. (listed in alphabetical order) Joachim G.J.V. Aerts[1], L. Martine Bek[2], Julia C. Berentschot[1], Rita J.G. van den Berg-Emons[2], Sieshem Bindraban[3], Wouter J.B. Blox[4], Jasper van Bommel[5], Shai A. Gajadin[6], Michel E. van Genderen[5], Diederik A.M.P.J. Gommers[5], Majanka H. Heijenbrok-Kal[2,7], Merel E. Hellemons[1], Roxane Heller[8], Erwin Ista[9,10], Stephanie van Loon-Kooij[11], Chantal Luijkx[7], Rutger Osterthun[2,7], Laurien Oswald[3], Gerard M. Ribbers[2,7], Ronald N. van Rossem[11], Herbert J. van de Sande[12], Robert van der Stoep[13], Janette J. Tazmi-Staal[14], Markus P.J.M. Wijffels[7], Eva G. Willems[14]

Affiliations: [1]Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [2]Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [3]Department of Respiratory Medicine, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands. [4]Department of Respiratory Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands. [5]Department of Adult Intensive Care Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [6]Department of Respiratory Medicine, IJsselland Hospital, Capelle aan de IJssel, The Netherlands. [7]Rijndam Rehabilitation, Rotterdam, The Netherlands. [8]Department of Respiratory Medicine, Ikazia Hospital, Rotterdam, The Netherlands. [9]Departments of Pediatrics and Pediatric Surgery, Intensive Care Unit, Erasmus MC Sophia Children's Hospital Rotterdam, The Netherlands. [10]Department of Internal Medicine, section Nursing Science, Erasmus MC, Erasmus University Medical Center Rotterdam, The Netherlands. [11]Department of Respiratory Medicine, Reinier de Graaf Gasthuis, Delft, The Netherlands. [12]Aafje Nursing Home, Rotterdam, The Netherlands. [13]Department of Physical Therapy, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [14]Laurens Intermezzo, Rotterdam, The Netherlands.

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