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ORIGINAL RESEARCH

Three-month and six-month outcomes of patients with COVID-19 associated hyperinflammation treated with short-term immunosuppressive therapy: follow-up of the CHIC study

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ABSTRACT

Objectives To prospectively investigate differences in medium-term patient-reported outcome measures and objective functional outcome measures, between patients receiving and those not receiving intensive short-term immunosuppressive therapy for coronavirus disease 19 (COVID-19)-associated hyperinflammation.

Methods Patients previously included in the COVID-19 High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study who received immunosuppressive treatment versus standard of care for COVID-19-associated hyperinflammation were invited for follow-up at 3 and 6 months after hospitalisation. At both visits, patients were assessed by a pulmonologist, completed quality of life (QoL) questionnaires and performed pulmonary and exercise function tests. At 3 months, patients additionally completed questionnaires on dyspnoea, anxiety, depression and trauma. Outcomes were compared between patients receiving and those not receiving intensive short-term immunosuppressive therapy for COVID-19-associated hyperinflammation.

Results 131 (66.5%) patients survived hospitalisation due to COVID-19-associated hyperinflammation and 118 (90.1%) were included. QoL questionnaires, pulmonary- and exercise function tests showed improvement between 3 and 6 months after discharge, which was similar in both groups. Assessed patients reached levels that were close to levels predicted from the normal population. In contrast, diffusing capacity of the lung for carbon monoxide was disturbed in both groups: 69.6% predicted (SD 16.2) and 73.5% predicted (SD 16.5) in control group and treated group, respectively.

Conclusions No differences in medium-term outcomes are demonstrated in survivors of COVID-19-associated hyperinflammation treated or not treated with methylprednisolone with or without tocilizumab during the acute phase. Short-term benefits of this therapy, as showed in the baseline CHIC study analysis, are thus not hampered by medium-term adverse events.

Key messages

What is already known about this subject?
► Short-term immunosuppressive treatment (high dose methylprednisolone with or without tocilizumab) for COVID-19-associated hyperinflammation has proven to improve clinical recovery, to lower intubation rate and to reduce mortality.
► Medium-term outcomes in a general population of patients with COVID-19 are persisting symptoms of dyspnoea, anxiety and fatigue and in particular an impaired diffusion capacity of the lungs 3 until 6 months after the infection.

What does this study add?
► No differences in medium-term outcomes were present in patients with COVID-19-associated hyperinflammation receiving and not receiving short-term immunosuppressive treatment (high dose methylprednisolone with or without tocilizumab) during the acute phase. All patients surviving hospitalisation for COVID-19-associated hyperinflammation showed a remarkable close-to-full recovery over 6 months.

How might this impact on clinical practice or further developments?
► The short-term beneficial effects of methylprednisolone with or without tocilizumab for COVID-19-associated hyperinflammation are not hampered by medium-term adverse events.
► A short-term therapy with methylprednisolone alone with or without tocilizumab for COVID-19-associated hyperinflammation is safe, also on the medium-term.

INTRODUCTION

While the coronavirus disease 19 (COVID-19) pandemic is still ongoing, more questions arise about the medium-term and long-term effects of COVID-19.

The pathophysiology, clinical characteristics and the course of the acute phase of the

disease have been extensively described.[1] A proportion of patients with COVID-19 develop a hyperinflammatory state, which leads to an increased risk of respiratory insufficiency and thromboembolic events, and therefore to a higher mortality.[2] Systemic glucocorticoids are now widely used to prevent the occurrence of immune-mediated damage in COVID-19 and several trials proved their efficacy in lowering mortality.[3–5] Several studies demonstrated that combined therapy of glucocorticoids and tocilizumab for COVID-19-associated hyperinflammation accelerates clinical recovery, lowers intubation rate and reduces mortality.[3 6 7] Furthermore, the use of tocilizumab alone has been shown to improve survival in patients with COVID-19 receiving organ support in the intensive care unit.[8] Hence, glucocorticoids as well as tocilizumab are proven effective in the acute phase of COVID-19-associated hyperinflammation and the WHO recommends their use.[9] However, it remains unknown whether the use of these therapies affects medium-term and long-term outcomes of these patients.

The first 6-month follow-up studies of patients with COVID-19 have been published, showing persisting symptoms of dyspnoea, anxiety and fatigue and, in particular, an impaired diffusion capacity of the lungs until 6 months after the infection.[10–13] Notwithstanding, none of these studies focused on patients with COVID-19-associated hyperinflammation or compared outcomes between patients treated with or without immunosuppression during the acute phase of the disease. In the COVID-19 High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study, patients with COVID-19-associated hyperinflammation were treated with short-term immunosuppression (high dose methylprednisolone with or without tocilizumab) on-top-of standard of care and outcomes were compared with patients who received standard of care only.[3] The CHIC study was one of the first studies that proved the efficacy of a short but intensive course of immunosuppression in these patients. The homogeneous population of this study, including only patients with COVID-19-associated hyperinflammation, makes it an excellent setting for studying medium-term and long-term outcomes of these patients.

The aim of this study was to compare medium-term patient-reported outcome measures (PROMs) and functional outcomes assessed by pulmonary and exercise function tests in patients receiving and those not receiving intensive short-term immunosuppressive therapy for COVID-19-associated hyperinflammation. Additionally, we aimed at comparing the changes in PROMs and functional outcomes between 3 and 6 months between the two treatment groups.

METHODS
Study design and population
The CHIC study is a cohort study that included patients with COVID-19-associated hyperinflammation in the Zuyderland Medical Centre, the Netherlands, between 1 March 2020 and 17 May 2020 that has been previously described in detail.[3] In summary, patient with COVID-19-associated hyperinflammation were included and it was defined according to a set of criteria: patients had to have an oxygen saturation at rest ≤94% (ambient air) or tachypnoea (>30/min); and patients had to meet at least two out of the following three biomarker criteria: C reactive protein >100 mg/L, serum ferritin >900 µg/L at one occasion or a twofold increase of the level at admission within 48 hours and D-dimer level >1500 µg/L.[3] In March 2020, patients were treated with standard of care of the moment, consisting of oxygen support, antibiotics, chloroquine and anticoagulation (control group). After 1 April 2020, patients were treated according to the CHIC protocol, which was added to standard of care (treated group). This protocol included two steps: (1) intravenous methylprednisolone 250 mg on day 1, followed by methylprednisolone 80 mg intravenously on days 2–5 and an option for a 2-day extension; (2) addition of tocilizumab (single dose, 8 mg/kg body weight intravenous, maximum 800 mg) in case of lack of clinical improvement or worsening in respiratory status 48 hours after starting with methylprednisolone. One hundred ninety-seven hospitalised patients were diagnosed with COVID-19-associated hyperinflammation and were included in the CHIC study (before matching of the patients based on age and gender).

A total of 102 patients were treated with standard of care (control group) and 95 patients were treated according to the CHIC protocol (treated group). Among patients included in the last group, 56 patients received methylprednisolone and 39 patients received methylprednisolone plus tocilizumab during hospitalisation. Of all 197 patients, 47 patients in the control group and 19 patients in the treated group died during hospitalisation for COVID-19-associated hyperinflammation.[3] Online supplemental figure S1 shows the flowchart of how many patients were included in the CHIC study. Patients who survived the hospitalisation were invited for standardised ambulatory follow-up according to the Zuyderland's Standard of Care (SoC) post-COVID protocol. One patient in the control group and three patients in the treated group died after hospitalisation, but before the first follow-up visit. Patients were excluded if they were unable to visit the outpatient clinic. All patients provided written informed consent for the use of their data for this study.

Data collection
Patients were monitored at the outpatient clinic at 3 months and at 6 months after hospital discharge. Patients were assessed by a pulmonologist, were asked to complete questionnaires and to perform pulmonary and exercise function tests. Baseline characteristics were derived from the CHIC database of all included patients, including World Health Organisation (WHO) score at baseline and oxygen support at baseline. The WHO score consists of seven stages which are: (1)

Table 1 Baseline demographic and clinical characteristics

	Total (N=118)	Control group (N=52)	Treated group (N=66)	P value*
Age (years)	64 (11)	63 (10)	65 (13)	0.333
Male gender	95 (81)	43 (83)	52 (79)	0.595
BMI (kg/m^2)	28.9 (5.2)	30.3 (5.7)	27.8 (4.6)	0.008
Smoking				0.017
Never smoker	37 (31)	21 (40)	16 (24)	
Ex-smoker	67 (57)	30 (58)	37 (56)	
Current smoker	3 (3)	0	3 (5)	
Hypertension	33 (28)	19 (37)	14 (21)	0.066
Diabetes mellitus	24 (20)	15 (29)	9 (14)	0.042
COPD	14 (12)	5 (10)	9 (14)	0.502
Asthma	8 (7)	3 (6)	5 (8)	0.498
Malignancy	2 (2)	1 (2)	1 (2)	0.689
Haematological malignancy	2 (2)	0	2 (3)	0.311
Cardiovascular disease	18 (15)	6 (12)	12 (18)	0.319
Heart failure	1 (1)	0	1 (2)	0.559
Arrhythmia	12 (10)	4 (8)	8 (12)	0.429
Chronic kidney disease	3 (3)	2 (4)	1 (2)	0.411
Cerebrovascular disease	8 (7)	6 (12)	2 (3)	0.073
Peripheral vascular disease	7 (6)	4 (8)	3 (5)	0.369
Autoimmune disease	13 (11)	7 (14)	6 (9)	0.452
Peptic ulcer	0	0	0	–
Moderate or severe liver disease	0	0	0	–
Charlson Comorbidity Index	0.87 (1.14)	1.02 (1.20)	0.75 (1.09)	0.171
WHO score baseline†				0.012
4: hospitalisation, requiring oxygen	95 (81)	40 (77)	55 (83)	
5: hospitalisation, requiring high-flow nasal oxygen therapy or non-invasive ventilation	14 (12)	4 (8)	10 (15)	
6: hospitalisation, requiring ECMO, invasive mechanical ventilation or both	9 (8)	8 (15)	1 (2)	
Oxygen support at baseline†				0.030
Nasal oxygen	67 (57)	29 (56)	38 (58)	
Oxymask/NRM	28 (24)	11 (21)	17 (26)	
High flow oxygen	14 (12)	4 (8)	10 (15)	
Mechanical ventilation	9 (8)	8 (15)	1 (2)	

Data are presented as N (%) or mean (SD).
*Calculated with independent samples t-test, Mann-Whitney U test or χ^2/Fisher's exact test, as appropriate
†Baseline is at the day on which patients fulfilled the criteria for hyperinflammation during hospitalisation.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; NRM, non-rebreathing mask; WHO, World Health Organisation.

non-hospitalised, able to resume normal activities; (2) non-hospitalised, but unable to resume normal activities; (3) hospitalised, not requiring oxygen therapy; (4) hospitalised, requiring additional oxygen therapy; (5) hospitalised, requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both; (6) hospitalised, requiring extracorporeal membrane oxygenation, mechanical ventilation or both; and (7) death. The scale was used from 2 to 7 in the CHIC study.

Baseline was considered the day on which patients fulfilled criteria for COVID-19-associated hyperinflammation during hospitalisation.

Outcomes
PROMs
The modified Medical Research Council (mMRC) dyspnoea scale was used for assessing patient's perceived functional limitations of breathlessness. The scale consists of

Table 2 Patient-reported outcomes measures at 3 and 6 months of follow-up and their difference between control (ie, standard care/no immunomodulatory therapy) and treated groups (methylprednisolone with or without tocilizumab)

	Three months after discharge			Six months after discharge		
	Control group (N=52)	Treated group (N=66)	P value*	Control group (N=45)	Treated group (N=54)	P value*
mMRC score† (0–4)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.045			
HADS anxiety† (0–21)	3.0 (0.0–8.0)	4.0 (1.0–9.0)	0.455			
HADS anxiety ≥8	26	31	0.603			
HADS depression† (0–21)	3.0 (1.0–8.0)	4.0 (1.0–8.0)	0.811			
HADS depression ≥8	30	27	0.740			
TSQ† (0–10)	1.0 (0.0–2.5)	1.0 (0.0–4.5)	0.700			
TSQ ≥6	8	24	0.056			
EQ VAS (0–100)	65.0 (57.5–75.0)	70.0 (60.0–80.0)	0.063	75.0 (60.0–80.0)	75.0 (65.0–80.0)	0.964
EQ VAS % of predicted population norm	81	90	0.069	90	91	0.943
EQ-5D index (0–1)	0.78 (0.69–0.86)	0.86 (0.69–0.86)	0.141	0.85 (0.78–1.00)	0.89 (0.78–1.00)	0.228
EQ-5D index % of predicted population norm	86	92	0.036	93	97	0.354

Data are presented as % or median (IQR).
The mMRC was completed at 3 months after discharge by 51 control patients and 60 treated patients. The HADS was completed at 3 months after discharge by 50 control patients and 59 treated patients. The TSQ was completed at 3 months after discharge by 37 control patients and 46 treated patients. EQ VAS was completed by 33 control patients and 43 treated patients at 3 months and by 38 control patients and 46 treated patients at 6 months, respectively. EQ-5D index was completed by 53 control patients and 45 treated patients at 3 months and by 40 control patients and 47 treated patients at 6 months, respectively.
*P value of difference between the two groups, calculated by Mann-Whitney U test or χ^2, as appropriate.
†Only measured at 3 months after hospital discharge.
EQ-5D, EuroQol 5-dimensions; EQ VAS, EuroQol Visual Analogue Scale; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; TSQ, Trauma Screening Questionnaire.

five grades of progressive dyspnoea perception. A higher score indicates more dyspnoea perceived. Online supplemental table S1 shows the mMRC scoring system.[14]

The Hospital Anxiety and Depression Scale (HADS) was used for detecting states of anxiety and depression. The questionnaire consists of 14 items with 7 items each for anxiety and depression. A higher score indicates more depression or anxiety symptoms. A score of 8 or more on the subscale anxiety or depression is abnormal.[15 16]

The Trauma Screening Questionnaire (TSQ) was used to screen for symptoms of post-traumatic stress disorder. The questionnaire consists of 10 questions. A higher score indicates more symptoms of post-traumatic stress. A score of 6 or more is abnormal.[17]

The EuroQol 5-dimensions 5-levels (EQ-5D-5L) questionnaire was used for measuring quality of life. The EQ-5D comprises five descriptive system questionnaires and a Visual Analogue Scale (EQ VAS). The descriptive system profile can be linked to a value set which leads to a single summary index for health status.[18] A higher index and EQ VAS indicate a better QoL. Obtained EQ

VAS scores and EQ-5D index scores were compared with Dutch population norms and expressed as a percentage of these norm values.[19]

The mMRC, HADS and TSQ were completed at the 3-month follow-up visit. The EQ-5D-5L questionnaire was completed at the 3-month and at the 6-month follow-up visit.

Pulmonary and exercise function tests

Forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) were tested with a pneumotachograph (Vyaire Medical, Jaeger, Würzburg, Germany) at 3 and 6 months after discharge. According to the SoC post-COVID protocol repeated DLCO measure was not obligatory in case of a normal DLCO at the first visit. DLCO was measured using the single-breath carbon monoxide uptake. These pulmonary function tests were performed according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines.[20 21] Values were calculated using Global Lung Function Initiative network

Table 3 Functional outcomes at 3 and 6 months of follow-up and their difference between control (ie, standard care/no immunomodulatory therapy) and treated groups (methylprednisolone with or without tocilizumab)

	Three months after discharge			Six months after discharge		
	Control group (N=52)	Treated group (N=66)	P value*	Control group (N=45)	Treated group (N=54)	P value†
Pulmonary function tests						
FVC % predicted	91.7 (15.1)	94.8 (17.5)	0.316	96.3 (13.7)	99.4 (19.6)	0.362
FVC <80% predicted	20	17	0.709	11	15	0.538
TLC % predicted	89.2 (14.3)	92.4 (15.0)	0.268	89.0 (14.7)	92.1 (16.4)	0.428
TLC <80% predicted	32	13	0.014	27	20	0.511
DLCO % predicted	73.8 (21.1)	72.7 (17.0)	0.768	69.6 (16.2)	73.5 (16.5)	0.317
DLCO <80% predicted	58	61	0.539	72	73	0.947
Exercise function test						
6MWT (m)	473.4 (124.3)	445.6 (126.6)	0.282	474.3 (119.4)	471.6 (109.8)	0.910
6MWT % predicted distance	74.6 (18.3)	71.4 (19.0)	0.413	75.6 (18.6)	76.2 (16.5)	0.874
6MWT <82 % predicted	65	76	0.243	62	62	0.984
6MWT lowest satO2 (%)	91.2 (4.0)	90.8 (3.0)	0.530	91.3 (4.4)	91.6 (2.9)	0.693
6MWT satO2 <90%	26	28	0.808	21	19	0.789

Data are presented as % or mean (SD).
FVC measurement was performed in 51 control patients and 65 treated patients at 3 months after discharge and in 45 control patients and 52 treated patients at 6 months after discharge. TLC-values were obtained in 50 control patients and 62 treated patients at 3 months after discharge and in 30 control patients and 40 treated patients at 6 months after discharge. DLCO measurement was performed in 51 control patients and 61 treated patients at 3 months after discharge and in 30 control patients and 41 treated patients at 6 months after discharge. 6MWT was performed in 43 control patients and in 54 treated patients at 3 months and in 42 control patients and 47 treated patients at 6 months after discharge.
*P value of difference between the two groups at 3 months after discharge, calculated by independent samples t-test or χ^2, as appropriate.
†P value of difference between the two groups at 6 months after discharge, calculated by independent samples t-test or χ^2, as appropriate.
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; 6MWT, 6-minute walk test; TLC, total lung capacity.

references and expressed as a percentage of predicted values. FVC-values, TLC-values or DLCO-values of <80% predicted were considered abnormal.[20][21]

A 6-minute walk test (6MWT) was performed to objectively evaluate functional exercise capacity at 3 and 6 months after discharge. Saturation with pulse oximetry was continuously measured during the test. 6MWT was performed according to the ERS and ATS guidelines and values were expressed as a percentage of predicted values. A travelled distance of <82% predicted was considered abnormal.[22][23]

Pulmonary and exercise function tests were performed at the 3-month and at the 6-month follow-up visit.

Statistical analysis

Descriptive statistics, namely mean and median values, were used for all outcomes. Differences in outcomes between 3 and 6 months after hospital discharge were computed for each patient and mean values were described. Differences between treatment groups were analysed with the independent samples t-test or Mann-Whitney U test for continuous variables, as appropriate, and with the χ^2 test for categorical variables. Data were analysed with the statistical package SPSS Statistics V.26. A p value ≤0.05 was considered statistically significant.

RESULTS

A total of 118 patients were included in this follow-up, having their follow-up at 3 months (66 treated and 52 control patients) and 99 of them had the 6-month follow-up visit (54 treated and 45 control patients). Two patients died before this second follow-up visit: one patient of the treatment group died because of sudden cardiac death (age 66) and one patient of the control group died of an unknown cause (age 84). Online supplemental figure S1 shows the flowchart of patient inclusion.

Table 1 presents the baseline characteristics of the 118 included patients. The mean age was 63 (SD 10) years in the control group and 65 (SD 13) years in the treated group. Patients were men in 83% of the control group and in 79% of the treated group. Body mass index was higher in the control group and diabetes mellitus was more common in the control group. Hypertension was in both groups the most common comorbidity. At the moment of fulfilment of the criteria for hyperinflammation, 44% of the patients in the control group needed an OxyMask/non-rebreathing mask, high flow oxygen or mechanical ventilation during hospitalisation, versus 43% in the treated group, though more patients in the control group were mechanically ventilated (15% vs 2%).

Table 4 Change in functional and quality of life outcomes between 3 and 6 months and their difference between control (ie, standard care/no immunomodulatory therapy) and treated groups (methylprednisolone with or without tocilizumab)

	Mean absolute difference between 3 and 6 months in control group*	Mean absolute difference between 3 and 6 months in treated group*	P value†
Quality of life			
EQ VAS	+7.61 (10.1)	+2.24 (12.9)	0.077
EQ-5D Index	+0.04 (0.1)	+0.06 (0.2)	0.664
Pulmonary function tests			
FVC % predicted	+4.91 (7.5)	+5.19 (6.8)	0.848
TLC % predicted	+2.17 (10.2)	+2.20 (6.9)	0.989
DLCO % predicted	+4.23 (7.7)	+4.05 (5.5)	0.906
Exercise function test			
6MWT (m)	+19.03 (61.9)	+22.40 (74.1)	0.824
6MWT % predicted distance	+4.43 (11.0)	+3.51 (11.0)	0.703
6MWT lowest satO2	+0.03 (3.0)	+0.98 (3.3)	0.181

Data are presented as mean (SD).
*Difference calculated by subtracting result of 3 months from result of 6 months.
†Calculated with independent samples t-test or Mann-Whitney U test, as appropriate.
DLCO, diffusing capacity for carbon monoxide; EQ-5D, EuroQol 5-dimensions; EQ VAS, EuroQol Visual Analogue Scale; FVC, forced vital capacity; 6MWT, 6-minute walk test; TLC, total lung capacity.

Differences in PROMs between treated and control groups

Table 2 shows the results of the PROMs. The mMRC was higher in the treated group. The absence of dyspnoea after 3 months, reflected in an mMRC of 0, was reported in 43% of the control patients and 35% of the treated patients (p=0.240). The HADS anxiety and depression scores, as well as the TSQ and the EQ-5D, did not differ between the groups.

In both groups, the EQ VAS was more than 80% of the population norm at 3 months after discharge. At 6 months after discharge, the EQ VAS was 90% and 91% of the population norm in the control and the treated groups, respectively. The EQ-5D index was numerically, but not statistically significantly, higher in the treated group compared with the control group at 3 and 6 months after discharge (p=0.141 and p=0.228, respectively). In both groups the EQ-5D index was more than 85% of the population norm at both 3 months and 6 months after discharge.

Differences in pulmonary and exercise function tests between treated and control groups

Table 3 shows the results of the pulmonary and the exercise function tests. Mean values of the FVC % predicted and the TLC % predicted at 3 and 6 months after discharge were within a normal range and did not differ between the two groups. Mean DLCO % predicted was abnormal both at 3 months and 6 months after discharge in both the treated group (72.7% (SD 17.0) and 73.5% (SD 16.5)) predicted) and the control group (73.8% (SD 21.1) and 69.6% (SD 16.2) predicted). Results of the DLCO % predicted did not differ significantly between the two groups.

Results of the 6MWT did not differ between the two groups neither at 3 months nor at 6 months after discharge. At 6 months after discharge, 21% of the control patients and 19% of the treated patients still had a saturation below 90% during the 6MWT. DLCO % predicted was 61.0 (SD 14.8) and 73.0 (SD 15.9) in the group with and without desaturation during 6MWT, respectively.

Differences in PROMs and functional outcomes between 3 months and 6 months between the treated and control groups

Table 4 shows a comparison in the change in QoL, pulmonary function tests and 6MWT between 3 and 6 months between the two groups. QoL, pulmonary function and 6MWT improved in both groups in the time interval between the two consecutive outpatient visits. Improvement did not differ between the control and the treated groups.

DISCUSSION

This prospective comparative cohort study shows that in survivors of hospitalisation due to COVID-19-associated hyperinflammation, patients treated with standard treatment only and patients treated with short-term immunosuppression on top of standard treatment, did similarly well with regard to medium-term subjective and functional outcomes. The beneficial treatment effects of immunosuppression, as described in the baseline data of the CHIC study,[3] are therefore mainly limited to the first weeks after administration. We did not show differences in prognosis in treated and not treated patients after hospital discharge. Importantly, the short-term beneficial

effects of immunosuppression had not been erased by medium-term adverse events.

In the CHIC study, hospital mortality in the control group was higher compared with the treatment group and therefore survivors of the control group in that study were probably less seriously ill. Nevertheless, the current study demonstrated that 6 months after discharge, patients in the treated group and the control group had the same performance in terms of functional and QoL outcomes.

To our knowledge, this is the first study that assesses medium-term outcomes in patients hospitalised for COVID-19-associated hyperinflammation. This is also the first study that assesses medium-term outcome differences between patients who were treated and not treated with high doses of intravenous glucocorticoids and if needed tocilizumab for this hyperinflammatory state during hospitalisation. Recently, our group already demonstrated that antibody response did not differ between these two groups 3 months after hospitalisation.[24]

In comparison to the baseline population of the CHIC study, this study contains younger patients and fewer active smokers. This is likely an example of channelling, due to higher mortality in older patients and in active smokers during hospitalisation in the CHIC study population. Older age and smoking are known risk factors for COVID-19-related mortality.[25]

Main other findings of the study were the considerable proportion of patients with an abnormal DLCO at 3 and 6 months after hospitalisation and the substantial proportion of patients with a desaturation below 90% during the 6MWT. Results of other studies also showed that reduced DLCO was also the most prominent finding 3 to 6 months after hospitalisation for COVID-19.[11–13 26] Results of the 6MWT in the current study were compatible with a multicentre prospective cohort study with 113 patients with COVID-19.[11] SARS-CoV-2 mainly affects the pulmonary alveoli and the surrounding vascular components.[1] The impaired diffusing capacity and the desaturation during 6MWT may be the result of incomplete resolution of this damage. Another possible explanation is that patients had pre-existing diffusion capacity abnormalities, as we did not have baseline pulmonary function tests data.

Remarkable was, despite the abnormalities in pulmonary function and 6MWT, that QoL scores came close to normal population values in both groups. In the first months of 2020, scarce evidence concerning the epidemiology and disease behaviour of COVID-19 and the strict isolation measures confronted the patients with a pronounced psychological burden. A possible explanation for the nearly normal QoL scores could be that these patients were so relieved that they survived hospitalisation, that they put less weight to other outcomes. QoL was assessed in another study with hospitalised patients with COVID-19 6 months after discharge and showed a median EQ VAS of 80, which is slightly higher than in our study. However, the median age in their study was lower and they included also patients with non-severe COVID-19 who did not need supplementary oxygen during hospitalisation.[10] The subjective burden of disease seems limited and therefore, although objective abnormalities in terms of DLCO and 6MWT are still present, long-COVID-19 in terms of reduced QoL appears to be rather infrequent in this group of patients who survived severe COVID-19.

Strengths of our study are the prospective design, the homogeneous population and the combination of PROMs and objective outcomes measures. The homogeneous population is strengthened by focussing on patients with COVID-19-associated hyperinflammation and allowing us to generalise conclusions to this restricted population with serious disease. Also, in our study, patients were treated according to a standard protocol, allowing a better comparison of the outcomes between patients treated and not treated with immunosuppression. Not only addresses this study differences between patients treated and not treated for COVID-19-associated hyperinflammation, but it also gives valuable information about the sequelae of this infection in this group as a whole. Limitations of this study include the absence of baseline data regarding pulmonary and exercise function, anxiety, depression and QoL, which is due to the acute and severe nature of the studied disease. Another well appreciated limitation of this study is that not all potentially eligible patients had visited the outpatient clinic after 3 months (118/127 eligible patients) and 6 months (99/116 eligible patients), and that not all patients who had come had completed all questionnaires and performed all pulmonary and exercise function tests. Whether the missing data are derived from patients who were not able to visit the outpatient clinic because of severe impairment or from patients who were fully recovered and waived to perform the tests, is unknown. It could well be that we have presented a relatively favourable reflection of all patients with severe COVID-19. Still, and in spite of potential completers bias, this study demonstrates similar improvements in both groups, as well as a strong tendency to improve to near premorbid conditions in a significant proportion of the patients.

In conclusion, this study shows that among the survivors of hospitalisation for COVID-19-associated hyperinflammation no differences in medium-term outcomes are present in patients treated or not treated with methylprednisolone with or without tocilizumab during the acute phase. This suggests that the beneficial effects of this therapy including reduced mortality, as showed in the baseline analysis of the CHIC study,[3] are mainly limited to the first 2 weeks and that these short-term benefits of this therapy are not hampered by medium-term adverse events.

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