INTERNAL MEDICINE JOURNAL

doi:10.1111/imj.15345

ORIGINAL ARTICLE

Six-month respiratory outcomes and exercise capacity of COVID-19 acute respiratory failure patients treated with continuous positive airway pressure

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Key words
COVID-19, follow up, acute respiratory failure, exercise capacity.

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Received 8 March 2021; accepted 14 April 2021.

ABSTRACT

Background: COVID-19 long-term sequelae are ill-defined since only a few studies have explored the long-term consequences of this disease so far.
Aims: To evaluate the 6-month respiratory outcome and exercise capacity of COVID-19 acute respiratory failure (ARF) patients treated with continuous positive airway pressure (CPAP) during the first wave of the ongoing COVID-19 pandemic.
Methods: A retrospective observational study included COVID-19 patients with ARF. Interventions included CPAP during hospitalisation and 6-month follow up. Frailty assessment was carried out through frailty index (FI), pO_2/FiO_2 during hospitalisation and at follow up, respiratory parameters, 6-min walking test (6MWT) and the modified British Medical Research Council (mMRC) and Borg scale at follow up.
Results: More than half of the patients had no dyspnoea according to the mMRC scale. Lower in-hospital pO_2/FiO_2 correlated with higher Borg scale levels after 6MWT (ρ 0.27; P 0.04) at the follow-up visit. FI was positively correlated with length of hospitalisation (ρ 0.3; P 0.03) and negatively with the 6MWT distance walked (ρ −0.36; P 0.004).
Conclusions: Robust and frail patients with COVID-19 ARF treated with CPAP outside the intensive care unit setting had good respiratory parameters and exercise capacity at 6-month follow up, although more severe patients had slightly poorer respiratory performance compared with patients with higher PaO_2/FiO_2 and lower FI.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) is a systemic disease with prominent respiratory manifestations.[1,2] Respiratory failure is relatively frequent in patients with COVID-19, implicating recurrent massive increases in the demand for hospitalisation and ventilation support for a wide number of subjects. Healthcare systems in most hit countries have repeatedly proved unable to efficiently fulfil this demand, prompting the identification of alternative treatments.[1] Continuous positive airway pressure (CPAP) ventilation, possibly in combination with respiratory physiotherapy, has been found as an effective alternative to intubation in non-intensive care unit settings.[3] Little is known about the potential sequelae of COVID-19,[4] especially with regard to respiratory performance.[5,6] In this observational study, we evaluated the 6-month respiratory outcomes and exercise capacity of COVID-19 acute respiratory failure (ARF) patients treated with CPAP during the first wave of the COVID-19 pandemic.

Funding: None.
Conflict of interest: None.

Methods

In this retrospective observational study, we analysed the clinical status of patients attending a dedicated post-COVID-19 outpatient clinic 6 ± 1 months after having been hospitalised with COVID-19 and acute respiratory distress syndrome in the Internal Medicine Departments of San Raffaele University Hospital, Milan, Italy. Patients were included within the COVID-BioB protocol (NCT04318366) if they had been treated with CPAP without previous intubation. COVID-19 was diagnosed by the presence of signs and symptoms of SARS-CoV-2 infection in association with a positive reverse-transcriptase polymerase chain reaction test from a nasal and/or throat swab and/or radiological findings consistent with COVID-19 pneumonia.[7,8] Patients who were (i) chronically receiving CPAP for obstructive sleep apnoea; (ii) previously intubated or requiring the intensive care unit (ICU) during the same admission; (iii) enrolled in a concomitant randomised trial on the use of early CPAP; or (iv) with severe contraindications to CPAP (e.g. coma or haemodynamic instability) were excluded.[9,10] After hospital discharge, trained nurses organised follow-up appointments according to patients' discharge dates. In cases of missed follow-up appointments, patients were given the opportunity to reschedule the visits. Follow-up consultations were organised in the outpatient clinic of the hospital and were performed 1, 3 and 6 months after discharge. In the present study, we analysed the data collected during the 6-month follow-up visits. This research complies with the guidelines for human studies. It was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Included subjects have given their written informed consent and that the study protocol was approved by the institute's committee on human research.

Demographics, comorbidities and respiratory parameters including pO_2/FiO_2 ratio (calculated with the Rice equation from SpO_2 when PaO_2 was not available)[11] were recorded on admission and after 6 months. Radiographic Assessment of Lung Edema (RALE) scores were calculated on hospital admission, and scores ≥9 considered indicative of severe lung involvement.[12] A 35-item frailty index (FI) was calculated according to the procedure described by Searle[13] using anamnestic data and baseline evaluation. FI scores above 0.25 were considered indicative of a frailty condition.[13] Follow-up data also encompassed the modified British Medical Research Council (mMRC) dyspnoea scale[14] and a 6-min walking test (6MWT), including measurement of the Borg scale[15] before and after the test.

Descriptive statistics were used to analyse demographic data and long-term health consequences of COVID-19 patients. Spearman correlation was used to explore the association between clinical characteristics during the hospital stay and comorbidities and 6-month outcomes. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences), version 26.0 (SPSS Inc. Chicago, IL, USA). Data are expressed as median (interquartile range) unless otherwise specified.

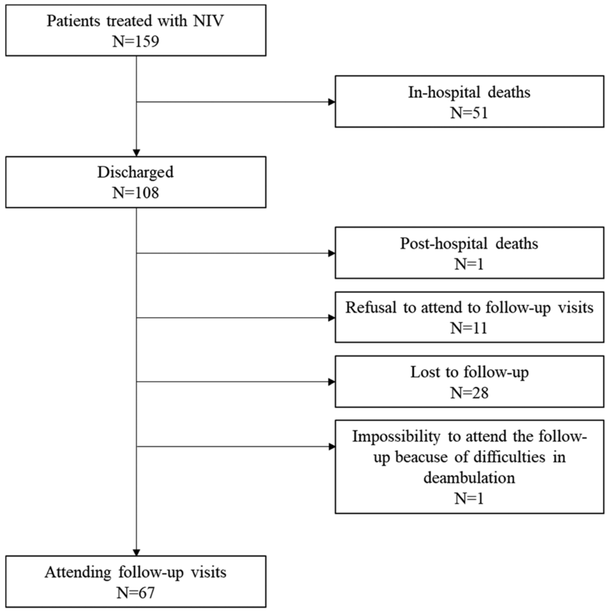

Figure 1 Flow chart of the study.

Results

Of the 108 of 159 patients having been discharged, one died, 11 refused to attend outpatient visits, one was unable to attend the visit and 28 were lost to follow up (Fig. 1). Table 1 illustrates the main characteristics of the sample that was followed up. The majority (85%) of these patients were men and had a mean ± standard deviation (SD) age of 62.8 ± 10.77 years. Despite their relatively young age, 68% were frail (FI values >0.25). However, just a minority of patients suffered from a chronic pulmonary pathology (chronic obstructive pulmonary disease 3%, asthma 3%, other chronic pulmonary diseases 3%). Patients who attended the visits and who were lost to follow up did not differ in terms of demographics, clinical features and respiratory status during hospitalisation.

At hospital admission, the mean RALE score was 11.1 ± 6.72, and 39 (58.2%) patients had an elevated RALE score.

There were 67.2% of patients who had a worse pO_2/FiO_2 during hospitalisation, <100 (median 87.7, IQR 71.25–100.75).

Table 1 Main characteristics of the studied population at hospital admission

Variables	Total sample (n = 67)
Age, mean (SD) (years)	62.8 (±10.77)
Males, *n* (%)	57 (85)
Weight, mean (SD) (kg)	84.7 (±15.88)
BMI, median (IQR) (kg/m^2)	28.5 (25.07–32.04)
Active smokers, *n* (%)	2 (3)
Former smokers, *n* (%)	13 (19)
RALE score at hospital admission, mean (SD)	11 (±6.72)
Hypertension, *n* (%)	28 (42)
Diabetes, *n* (%)	14 (22)
Moderate to severe kidney disease, *n* (%)	2 (3)
Asthma, *n* (%)	2 (3)
COPD, *n* (%)	2 (3)
Other chronic pulmonary diseases, *n* (%)	2 (3)
Ischaemic heart disease, *n* (%)	12 (18)
Congestive heart failure, *n* (%)	0 (0)
Cerebrovascular disease, *n* (%)	1 (2)
Peripheral vascular disease, *n* (%)	7 (11)
Frailty index, mean (SD)	0.27 (±0.07)
Frail patients, *n* (%)	45 (68)
Length of hospital stay, mean (SD) (days)	20.4 (±13.28)
Complications of CPAP treatment, *n* (%), type	1 (2), emesis
Duration of CPAP treatment, median (IQR) (days)	11 (7–17)
24 h CPAP treatment, *n* (%)	5 (8)
Duration of respiratory physiotherapy, median (IQR) (days)	7 (0–14)
Worst pO_2/FiO_2 during hospital stay, median (IQR)	87.7 (71.25–100.75)
Worst pO_2/FiO_2 during hospital stay <100, *n* (%)	45 (67.2)
Patients shifted to invasive ventilations, *n* (%)	15 (23)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; IQR, interquartile range; *N*, number; SD, standard deviation; RALE, Radiographic Assessment of Lung Edema (a method to quantify the degree of radiologic lung alterations observed at chest x-ray; a score ≥ 9 is considered indicative of a severe lung involvement).

CPAP tended to be administered for about half of the hospital stay. One patient manifested a minor CPAP complication (emesis).

No patient needed oxygen supply at 6-month follow up. Oxygen saturation in room air and derived pO_2/FiO_2 were normal and so was the mean respiratory rate. Table 2 shows the respiratory and exercise parameters of patients at the 6-month follow-up visits. Figure 2 illustrates the pO_2/FiO_2 trends for each patient. More than half of the sample had no dyspnoea according to the mMRC scale and the median predicted distance run across the 6MWT was 92% (IQR 84–99). Only four patients manifested strong or somewhat strong dyspnoea after the test.

Table 2 Respiratory and exercise parameters at 6-month follow-up visits

Variables	Total sample (n = 67)
Follow-up visit (from hospital discharge): median (IQR) (months)	6 (6–7)
SpO_2 in room air at follow-up visit, median (IQR) (%)	98 (97–99)
Respiratory rate at follow-up visit, mean (SD)	17 (±4)
pO_2/FiO_2 at follow-up visit, median (IQR)	479.4 (473.7–485.0)
6-min walking test, median (IQR)(%)	460 (427.5–525.0)
Predicted distance at 6-min walking test, median (IQR) (%)	92 (84–99)
SO_2 before 6-min walking test, mean (SD) (%)	97.7 (±1.02)
SO_2 after 6-min walking test, median (IQR) (%)	98 (97–98)
Borg scale before 6-min walking test†, *n* (%)	
No dyspnoea (0)	61 (91)
Extremely weak dyspnoea (0.5)	0 (0)
Very weak dyspnoea (1)	0 (0)
Weak dyspnoea (2)	0 (0)
Moderate dyspnoea (3)	0 (0)
Somewhat strong dyspnoea (4)	0 (0)
Strong dyspnoea (5)	1 (2)
Strong dyspnoea (6)	0 (0)
Very strong dyspnoea (7)	0 (0)
Very strong dyspnoea (8)	0 (0)
Almost maximal (9)	0 (0)
Maximal dyspnoea (10)	0 (0)
Borg scale after 6-min walking test†, *n* (%)	
No dyspnoea (0)	37 (55)
Extremely weak dyspnoea (0.5)	10 (15)
Very weak dyspnoea (1)	4 (6)
Weak dyspnoea (2)	5 (8)
Moderate dyspnoea (3)	1 (2)
Somewhat strong dyspnoea (4)	3 (4)
Strong dyspnoea (5)	1 (2)
Strong dyspnoea (6)	1 (2)
Very strong dyspnoea (7)	0 (0)
Very strong dyspnoea (8)	0 (0)
Almost maximal (9)	0 (0)
Maximal dyspnoea (10)	0 (0)
mMRC score, *n* (%)	
Grade 0	35 (53)
Grade 1	14 (21)
Grade 2	7 (10)
Grade 3	4 (6)
Grade 4	7 (10)
2003Δ pO_2/FiO_2, median (IQR)	380.7 (337.70–404.36)

†Five missing patients. IQR, interquartile range; mMRC, Modified Medical Research Council; SD, standard deviation.

Lower pO_2/FiO_2 correlated with higher Borg scale levels after 6MWT (ρ 0.27; P 0.04) at follow-up visit.

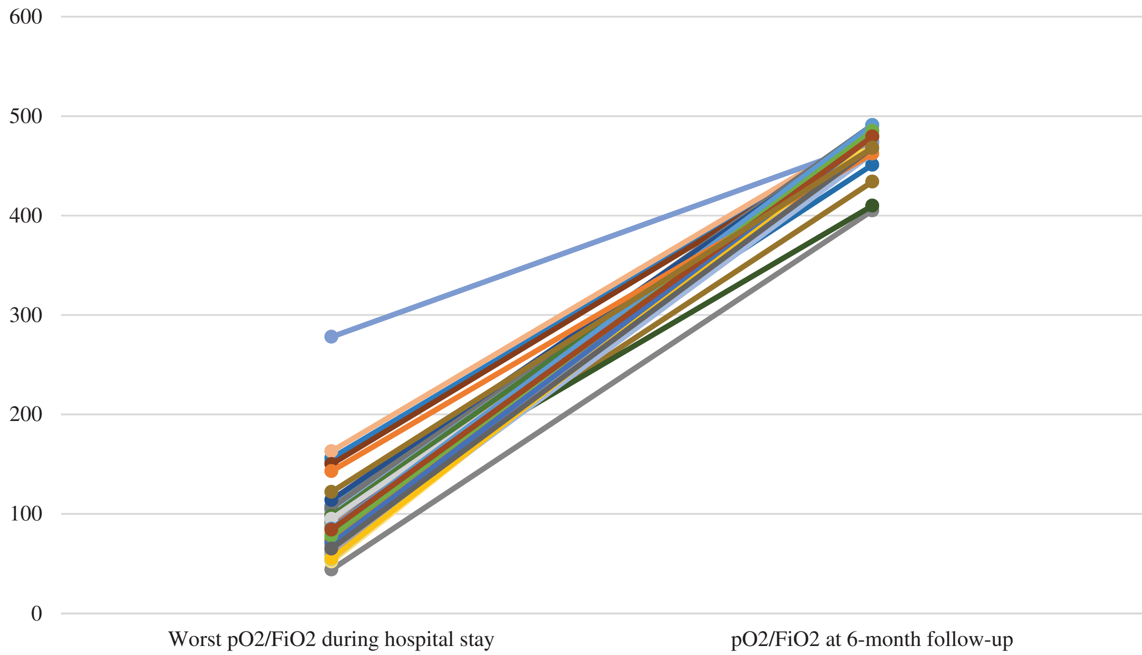

Figure 2 Variations of pO_2/FiO_2 between hospital stay and 6-month follow-up visits.

Moreover, FI was positively correlated with length of hospitalisation (ρ 0.3; P 0.03) and negatively with the 6MWT walked distance (ρ −0.36; P 0.004).

Discussion

In this observational study, we found that patients treated with CPAP for COVID-19 ARF, in spite of the severity of the SARS-CoV-2 infection, displayed good respiratory parameters and exercise capacity 6 months after hospital discharge. Patients who manifested a more severe disease had a greater exertional dyspnoea at 6-month follow up. Frailer patients who had longer hospitalisation had the worst exercise capacity at follow up.

Our results are consistent with those of Huang *et al.* who described a cohort of 1733 patients with COVID-19 and included 122 subjects treated with either high-flow nasal cannula, non-invasive or invasive ventilation. This subgroup had a median 85% completion of the predicted 6MWT distance after 6 months.[6] Patients with severe disease in the cohort by Huang *et al.* tended to be younger (median age 56 years compared with 63 years in our cohort), with a higher representation of women (36% vs 15% in our study) and with lower prevalence of hypertension (37% vs 44%) and diabetes (12% vs 28%). However, they showed longer hospitalisation (median 35 days vs 21 in our cohort).[6] This evidence might suggest that prolonged hospitalisation with potential accrual of complications, such as acute sarcopenia, might have negatively counterbalanced favourable demographic and clinical variables and might have had a prognostic impact on middle-term recovery.[16,17] Consistent with this hypothesis, muscle weakness along with mood disorders was prominently detected by Huang *et al.* and other authors.[6,18] Conversely to other studies,[19–21] our data do not support a clinically relevant role of potential fibrotic complications following COVID-19-related ARF, at least at a functional level. Indeed, previous evidence from SARS survivors suggests that reduced exercise capacity at both 3- and 6-month follow-up time[22,23] was mostly sustained by Critical Illness Myopathy and Neuropathy.[24,25] It has also been demonstrated that a few days of bedrest can impair muscle quantity, strength and performance even in healthy subjects,[26] suggesting *a fortiori* that this phenomenon would be particularly relevant in older people.[17,27] During acute illnesses, catabolic stimuli imbalance muscle homeostasis, increasing muscle degradation.[28] In COVID-19 patients, this process could be particularly pronounced[29] due to the cytokine storm induced by the virus and to the iatrogenic hypercortisolaemia.[30] Therefore, COVID-19 patients are particularly at risk of developing acute sarcopenia. This acute organ insufficiency augments patients' vulnerability to stressors (i.e. it induces frailty)[16,31] and can aggravate a pre-existent frailty condition,[32] thus predisposing to negative clinical outcomes. Moreover, acute sarcopenia could increase the risk of developing chronic sarcopenia.[30,33] Indeed, decreased muscle mass has been demonstrated at 1 year follow up of patients with acute respiratory distress syndrome.[33] The management of the long-term consequences of COVID-19 would therefore require a multidisciplinary follow up including both respiratory and nutritional/physical evaluations.[34,35]

The present study has the merit of having highlighted that robust and frail patients with COVID-19 ARF treated with CPAP outside of the ICU setting had good respiratory parameters and exercise capacity at 6-month follow up, even those receiving CPAP as the ceiling of treatment. CPAP has the advantage of allowing the treatment of a wider range of patients compared with invasive mechanical ventilation (IMV) and probably reduces the length of hospitalisation compared with IMV. Moreover, CPAP avoids barotrauma and other negative consequences of IMV.[36,37]

Some limitations of the present study are worth mentioning. Our study did not encompass systematic spirometry and other pulmonary function tests, which constitutes a limitation to a comprehensive assessment of the course of respiratory recovery after COVID-19. Due to the high number of COVID-19 patients and the limited availability of the machinery for spirometry and diffusion lung carbon monoxide test, we decided to perform these tests as secondary-level exams just in case of alterations at the clinical evaluation or at the walking test.

In a similar way, the lack of information about the degree of baseline dyspnoea and exercise capacity in these patients prevents further considerations about the impact of COVID-19 on pre-morbid respiratory status. Finally, given the observational and monocentric design of the study, the role of CPAP on outcomes remains uncertain and further multicentre randomised studies should be performed to generalise these findings to other contexts.

Conclusion

By describing a relatively large cohort of homogeneous patients surviving severe COVID-19 after treatment with CPAP, we provide additional evidence supporting its use and novel clues about the natural history of COVID-19 after the acute phase. Our results also suggest that multidisciplinary assessment of respiratory and nutritional function of patients with severe COVID-19 both during hospitalisation and during post-discharge follow up might improve patient prognosis and quality of life.

Acknowledgements

The authors acknowledge the following contributors for their support in this work: Lorenzo Dagna MD, Fabio Ciceri MD, Antonella Castagna MD, Emanuele Bosi MD, Carlotta Notte MD, Stefania L. Calvisi MD, Chiara Salmaggi MD, Marta Cilla MD, Mona-Rita Yacoub MD, PhD, Teresa D'Aliberti MD, Massimo Memoli MD, Sabina Martinenghi MD, Amelia Caretto MD, Andrea Laurenzi MD, Renato Finazzi MD, Diana Canetti MD, Chiara Molinari MD, Matteo Impellizzeri MD, Giovanni Guarneri MD, Luca Moroni MD, Piera Angelillo MD, Andrea Assanelli MD, Matteo Bellone MD, Nicola Boffini MD, Elena Brioschi MD, Maria Pia Cicalese MD, Alberto Davalli MD, Giulio Frontino MD, Simona Piemontese MD, Paola Sgaramella MD, Stefano Tentori MD, Mirta Tiraboschi MD, Jubin Abutalebi MD, Stefania Acerno MD, Michele Bailo MD, Laura Cacciaguerra MD, Federica Cerri MD, Filippo Gagliardi MD, Ignazio D. Lopez MD, Roberta Pajno MD, Pietro Panni MD, Marcella Pasetti MD, Antonella Poloniato MD, Francesca Sangalli MD, Eugenio Ventimiglia MD, Chiara Asperti MD, Luca Benassi MD, Ambra Bertola MD, Jacopo Castellani MD, Ludovica Cavallo MD, Elena Cinel MD, Stefania Vadruccio MD, Claudia Frangi MD, Bruno N Germinario MD, Giovanni Gobbin MD, Marco Lanzillotta MD, Emanuela Manzo MD, Andrea Mastrangelo MD, Salvatore Colandonio MD, Raffaele Li Voti MD, Francesco Marcialis MD, Gaia Mancuso MD, Valentina Cantoni MD, Maria Pascali MD, Nicola Farina MD, Annalisa Ruggeri MD, Diego Palumbo MD, Antonio Esposito MD, Sergio Colombo MD, Agnese Gobbi MD, Elena Castelli PT, Clarissa Centurioni MD, Mattia Di Meo PT, Emanuel Della Torre MD, PhD, Flavia Di Scala MD, Anna Morgillo MD, Martina Miglio MS, Paolo Scarpellini MD, Chiara Tassan Din MD, Barbara Castiglioni MD, Chiara Oltolini MD, Marco Ripa MD, Valentina Da Prat MD, Martina Baiardo Redaelli MD, Valentina P. Plumari MD, Elena Moizo MD, Francesco Carcó MD, Paolo Silvani MD and Francesco De Cobelli MD.

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