Long-term impact of COVID-19 requiring elevated oxygen support and safety of prolonged positive pressure ventilation

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ABSTRACT

In this study, we analyzed long-term sequelae in patients hospitalized at Montichiari Hospital (Brescia, Italy) during the COVID-19 acute phase, who needed a high-flow oxygen treatment. The follow-up evaluation has been performed after more than one year from discharge through a quality-of-life phone interview, standard laboratory tests, chest computed tomography, and global spirometry with an evaluation of the diffusing capacity of the lungs for carbon monoxide (DLCO). In our analysis, we found that patients who needed high FiO2 support during the acute phase, independently from the device used to administer it, showed a long-term heavy burden of pulmonary consequences: more than half of patients presented radiological alterations and persistent dyspnea or DLCO alterations; about 17% of them had alterations compatible with pulmonary fibrosis. Further analysis included a comparison of long-term consequences in patients treated with different devices. An interesting result was that prolonged positive pressure ventilation treatment didn't seem to cause persistent pulmonary damage and thus could be considered a safe approach. In conclusion, this study confirms the heavy quality-of-life impact of moderate to severe COVID-19 and highlights the importance of recognizing patients who will benefit from rehabilitative programs and customized follow-up depending on the acute phase disease severity.

Introduction

Many efforts for COVID-19 are directed towards prevention, early diagnosis, and effective treatment, but the puzzle of long-lasting effects observed in patients who recovered from the disease's acute phase is yet to be completely elucidated.

The follow-up of COVID-19 patients showed that one or more symptoms of the acute phase infection persist or new different symptoms appear in a substantial percentage of people, even weeks or months after the disease.[1,2]

The most common symptoms reported in many studies are fatigue and dyspnea; other persistent symptoms may include cognitive and mental impairment, chest and joint pain, palpitation, myalgia, smell and taste dysfunction, cough, headache, and gastrointestinal and cardiac issues.[3,4]

An univocal definition for this condition is lacking and various authors have used different names like "Long COVID-19", "Long haulers", "Long-term COVID-19 effects", "persistent COVID-19 symptoms", and "post COVID-19 syndrome".[1] In the present retrospective analysis, we agree to use the term "Long COVID" to describe the long-lasting effects of COVID-19. Long COVID can be categorized into two stages depending on the duration of prolonged symptoms: "post-acute COVID" which includes those cases in which symptoms last from 3 to 12 weeks and "chronic COVID" in which symptoms last more than 12 weeks.

The majority of those with Long COVID show biochemical and radiological recovery.[5]

It has been hypothesized that Long COVID may be driven by long-term tissue damage and pathological inflammation. Factors from the acute phase like endotheliopathy, antigen-antibody reaction, and aberrant immune response might elicit secondary manifestations.[3,5]

The aim of this retrospective analysis is to investigate long-term consequences mainly on lung structure and function as well as on quality-of-life of moderate to severe SARS-CoV2-related pneumonia requiring hospitalization and treatment with high oxygen flows.

Patients and Methods

A total of 374 patients were hospitalized in the Internal Medicine ward of Montichiari Hospital, ASST Spedali Civili of Brescia, Italy for SARS-CoV2 infection from November 2020 to April 2021, during the so-called "second/third wave".

For each patient, we collected demographic data (such as date of birth, sex, weight, height), comorbidities [heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease (CKD), neoplasm] ongoing home therapy [angiotensin converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs), statins, anti-platelet or anti-coagulant drugs, immunomodulatory drugs, steroids], length of hospital stay, type of oxygen supply, presence of radiological alterations and biochemical laboratory tests data.

Overall, 41 died of COVID-19; 214 had a mild clinical course, while 119 developed a moderate to severe disease with necessity of administration of a fraction of inspired oxygen (FiO2) higher than 40% delivered with Venturi mask (VM) or pressure-positive devices [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP)].

We planned a follow-up program to assess long-term consequences on the group of patients that needed higher oxygen supplementation that was scheduled:

- a quality-of-life phone interview for the investigation of persistent symptoms: anxiety, asthenia, dysgeusia, dyspnea, fever, insomnia, loss of appetite;
- standard laboratory tests: white blood count [10^3/µl], Neutrophils [10^3/µl], Lymphocytes [10^3/µl], Monocytes [103/µl], Hemoglobin (Hb) [g/dl], Platelets (Plt) [10^3/µl], CRP [mg/L], AST [U/L], ALT [U/L], Ferritin [µg/L], Creatinine [mg/dl];
- chest computed tomography (CT), performed at the Radiology department of Montichiari Hospital;
- spirometry with an evaluation of the diffusing capacity of the lungs for carbon monoxide (DLCO), performed at the pneumology clinic in Montichiari Hospital.

Of all the patients contacted, 43 accepted to undergo the present follow-up program. The evaluation was conducted after a mean of 382±47 days from hospital discharge. Two patients were excluded from the final analysis due to the impossibility of performing the full follow-up program.

We then compared the data of these subjects with information gathered from a group of patients that did not need a high FiO2 (from ambient air to 35%) during their hospital stay. The scheduled approach was the same, but the follow-up time was shorter (82±17 days from the discharge).

Specific main objectives of this study were therefore: i) to better understand respiratory long-term sequelae of COVID-19 on patients needing high oxygen support during the acute phase of the disease; ii) to compare outcomes with patients that did not need high flow oxygen supplementation during their hospital staying; iii) to focus on the possible correlation between the use of prolonged positive pressure oxygen supplementation and worse outcome (due to possible barotrauma); iv) to analyze the long-term impact on the quality-of-life of a moderate to severe disease.

Statistical analysis

Statistical analyses have been conducted with SPSS software version 25.0 (Chicago, IL, USA) and the statistical significance level has been set to 0.05.

We reported categorical variables as percentages (%) and continuous variables as means±standard deviation when data were normally distributed, and as medians and interquartile range when data were not normally distributed (*i.e.*, lymphocytes, procalcitonin, ferritin values). Statistical significance between

groups was assessed by means of Student's t-test for quantitative variables and χ^2 test for qualitative ones, by means of one-way analysis of variance (ANOVA) or by Mann-Whitney U test when appropriate.

Results

One-year follow-up in COVID-19 patients with high oxygen support

The mean age was 63±10 years, 27% were female and 73% were male, 49% of the sample was obese (defined as a body mass index >30 Kg/m^2), 37% of the patients suffered from heart diseases, 59% were hypertensives, 24% had diabetes, 12% had CKD and 5% had an active neoplasm.

A total of 20% of patients were on ACE inhibitors, and 20% on ARBs. Statins were taken by 39%; antiplatelets agents by 22%, and anticoagulants by 2% as reported in Table 1.

As far as oxygen support is concerned, 23 patients needed at least a 40% FiO2 provided by VM, and 18 patients needed positive pressure support. The mean FiO2 support was 48±12%.

The follow-up evaluation has been made at a mean of 382±47 days after hospital discharge.

While standard laboratory tests showed a substantial normalization of all measured indexes, as reported in Table 2, we found persistence of CT radiological alterations (*i.e.*, ground-glass opacities, irregular linear/reticular opacities) in 70.7% of patients and 41% of patients showed a mild to moderate DLCO reduction at spirometry.

More than half of patients (53.7%; 22/41) had both radiological alterations (honeycombing with or without bronchiectasis) and persistent dyspnea or DLCO alterations. The three conditions together were described in 7 patients (17.1%). For those patients, it is possible to hypothesize pulmonary fibrosis, as described in the literature.[6]

Moreover, we evaluated the quality of life through a structured questionnaire: 65.9% of the patients had dyspnea for mild to moderate efforts, 61% asthenia, 22% showed loss of appetite, 31.7% had persistent dysgeusia or anosmia, 31,7% insomnia and 43.9% anxiety. No one had persistent fever (Table 2).

Outcome with different oxygen delivery devices: positive pressure ventilation versus Venturi mask

For the reasons presented in the discussion section, during the 2020 and 2021 outbreaks of the SARS-CoV-2 pandemic, there was a wide use of positive pressure ventilation prolonged for several days as never happened before.

This prolonged use of positive pressure ventilation raised some concerns about its safety.

Table 1. Main demographic data, comorbidities, and ongoing therapies of COVID-19 patients with high oxygen support, included in the follow-up program.

Population	
Age [years]	63±10
Sex (m/f) [n° of patients]	30/11
Days of follow-up	382±47
Comorbidity	
Heart disease	37% (15/41)
Hypertension	59% (24/41)
Diabetes	24% (10/41)
COPD	2% (1/41)
CDK	12% (5/41)
Neoplasm	5% (2/41)
Obesity	49% (20/41)
CCI	2.6±1
Chronic therapy	
ACE-i	20% (8/41)
ARBs	20% (8/41)
Statin	39% (16/41)
Antiaggregant	22% (9/41)
Anticoagulant	2% (1/41)
Steroid	2% (1/41)
Insulin	0% (0/41)
Hypoglycemic therapy	24% (10/41)

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CCI, Charlson comorbidity index; ACE-I, angiotensin converting enzyme-inhibitors; ARBS, angiotensin receptor blockers.

Table 2. One-year follow-up laboratory tests, radiological imaging, spirometry, and quality of life evaluated through a phone interview.

Biochemistry	
WBC [10^3/mL]	7.2±2.2
Neutrophils [10^3/mL]	3.8±1.6
Lymphocytes [10^3/mL]	2.5±0.9
Monocytes [10^3/mL]	0.6±1.4
Hb [g/dL]	14.9±1.3
Platelets [10^3/mL]	243±65.8
CRP [mg/L]	1.6±5.4
AST [u/L]	22±8.5
ALT [u/L]	28±12.9
Creatinine [mg/dL]	0.9±0.2
Instrumental data	
Radiological alterations	70.7% (29/41)
Radiological alterations + dyspnea/DLCO alterations	53.7% (22/41)
Radiological alterations + dyspnea + DLCO alterations	17.1% (7/41)
DLCO alterations	39% (16/41)
Quality of life	
Anxiety	43.9% (18/41)
Asthenia	61% (25/41)
Dysgeusia	31.7% (13/41)
Dyspnea	65.9% (27/41)
Fever	0% (0/41)
Insomnia	31.7% (13/41)
Loss of appetite	22% (9/41)

WBC, white blood cells; CRP, c-reactive protein; Hb, hemoglobin; DLCO, diffusing capacity of the lungs for carbon monoxide.

In our study: 23 patients (56.1%) used VM, and 18 patients (43.9%) needed positive pressure support. The mean CPAP/BiPAP duration was 9±5 days. The two groups, although small, were homogeneous as reported in Table 3.

We didn't find any statistically significant difference related to a different oxygen delivery device neither in radiological alterations nor in spirometry abnormalities at follow-up.

In particular, the simultaneous presence of radiological alterations, persistent dyspnea, and DLCO alterations (and consequently the diagnosis of pulmonary fibrosis) wasn't different between the two groups (Table 3).

Relationship between long-term sequelae and different degrees of fraction of inspired oxygen oxygen support

We then analyzed outcomes in patients who needed different FiO2 support during the acute phase.

The first group included 42 patients who needed to be treated with up to 35% FiO2 through nasal cannulas or VM (when not on ambient air) during the acute phase.

The second group included 41 patients who needed at least 40% FiO2 treatment provided by VM or positive pressure ventilation.

No significant differences in age, sex, comorbidities, and ongoing home therapy were found between the two groups (Table 4).

Standard laboratory tests showed a substantial normalization of all measured indexes in both groups. Follow-up radiological alterations were present in 30.9% of the first group and in 70.7% of the second group. No patients in the first group presented concomitant radiological alterations, persistent dyspnea, and alteration of DLCO, while 17.1% presented the three conditions together in the second group.

As far as symptoms are concerned, they were similar between the two groups except for dyspnea for mild to moderate efforts (30.8% patients of the first group and 65.9% of the second one) and anxiety (12.8% *vs*. 43.9%), as reported in Table 4.

Discussion

COVID-19 characteristics, morbidity, and mortality regarding the first and second/third waves have been analyzed in a previous study.[7]

We focused instead on the Long COVID impact and on the role of possible related risk factors. There is still a scarcity of available data to identify the predictors of post-recovery phase. It has been suggested that the symptoms observed in Long COVID may be associated with lasting inflammation, hospitalization with intensive care unit (ICU) admission, and emotional distress during isolation.[5]

In our retrospective analysis, we found that pa-

Table 3. Demographic data, radiological imaging, spirometry, and laboratory tests in Venturi mask vs. continuous positive airway pressure/bilevel positive airway pressure.

Population			
Data	**VM**	**C-PAP/Bi-PAP**	**Significance**
Age [years]	63±10	64±11	NS
Sex (m/f) [n° of patients]	17/6	12/6	NS
Days of follow-up	393±50	371±40	NS
Comorbidities (CCI)	2.7±1.5	3±1	NS
Instrumental data			
Radiological alterations	69.6% (16/23)	52.9% (9/18)	NS
Radiological alterations + dyspnea/DLCO alterations	52.2% (12/23)	58.8% (10/18)	NS
Radiological alterations + dyspnea + DLCO alterations	21.7% (5/23)	11.8% (2/18)	NS
DLCO alterations	43.5% (10/23)	64.7% (11/18)	NS
Biochemistry			
WBC [10^3/mL]	7.5±2.3	7.6±2.1	NS
Neutrophils [10^3/mL]	4±1.8	4±1.1	NS
Lymphocytes [10^3/mL]	2.6±0.8	2.7±1.1	NS
Monocytes [10^3/mL]	0.6±0.3	0.6±0.2	NS
Hb [g/dL]	14.6±1.3	14.6±1.5	NS
Platelets [10^3/mL]	243.3±77.3	251.4±48.2	NS
CRP [mg/L]	5.3±6.8	1.8±1.7	NS
AST [u/L]	25±9.8	23.8±6.9	NS
ALT [u/L]	33±14	26.9±11.2	NS
Creatinine [mg/dL]	1±0.3	1±0.2	NS

VM, Venturi mask; C-PAP, continuous positive airway pressure; Bi-PAP, bilevel positive airway pressure; CCI, Charlson comorbidity index; DLCO, diffusing capacity of the lungs for carbon monoxide; WBC, white blood cells; CRP, c-reactive protein; Hb, hemoglobin.

tients who needed high FiO2 support during the COVID-19 acute phase showed a long-term heavy burden of pulmonary consequences, not only in terms of pulmonary fibrosis diagnosis, but even in terms of radiological, clinical, or functional alterations.

This finding is interesting for its implications: a higher number of patients may develop pulmonary fibrosis over time.

Our study couldn't clearly distinguish whether the pulmonary damage was a consequence of the disease itself (with its inflammatory damage), of high FiO2 prolonged treatment, or both; it anyway points out how a more severe acute disease is related to heavier burden in terms of pulmonary disease and to a poorer quality of life.

Interestingly enough, the prolonged use of positive pressure ventilation didn't relate to a higher incidence of pulmonary fibrosis or isolated functional, structural, clinical alterations.

The use of positive pressure ventilation had mainly been reserved for patients affected by cardiogenic pulmonary edema (CPAP) or by chronic pulmonary disease exacerbation. This treatment is usually applied for a limited time, ranging from a few hours to 1-2 days.

Starting from March 2020, positive pressure ventilation was extensively used for COVID-19-associated respiratory failure: at the very beginning, this condition was considered an acute respiratory distress syndrome and consequently treated. The lack of ICU resources made it very difficult to treat properly all patients needing orotracheal intubation (OTI), especially during the first and, to a minor degree, during the second/third wave. This forced doctors to make hard choices, excluding OTI patients with less chance of survival. Moreover, there was a significant number of patients that had no indication of OTI, due to age or comorbidity but didn't respond to standard oxygen treatment.

This led to extensive use of positive pressure ventilation both as a bridge therapy in patients waiting for ICU admission (and eventually for OTI) as well as a *per se* treatment of COVID-19 patients who needed oxygen support higher than a VM but were not eligible for OTI.[8]

In time, positive pressure ventilation was accepted as a treatment strategy in patients with high-oxygen need.[9-11]

The prolonged use of positive pressure ventilation raised some concerns about its safety and possible long-term consequences related to barotrauma.

An interesting finding of our study was that a prolonged positive pressure ventilation treatment (for a mean time of 9 days) wasn't related to an increase in persistent pulmonary damage compared to patients treated with standard oxygen therapy.

For this reason, although data need to be confirmed with larger numbers, our results suggest that

Table 4. Demographic data, comorbidities, radiological imaging, spirometry, and quality of life in two different fraction-of-inspired oxygen groups.

Population			
Data	**FIO2 ≤35%**	**FIO2 ≥40%**	**Significance**
Age [years]	65±12	63±10	0.5
Sex (m/f) [n° of patients]	24/18	30/11	0.1
Heart disease	14.3% (6/42)	37% (15/41)	0.02
Hypertension	50% (21/42)	59% (24/41)	0.44
Diabetes	14.3% (6/42)	24% (10/41)	0.2
COPD	7.1% (3/42)	2% (1/41)	0.3
Comorbidities (CCI)	2±2	2.6±1	0.6
Instrumental data			
Radiological alterations	30.9% (13/42)	70.7% (29/41)	0.002
Radiological alterations + dyspnea/DLCO alterations	23.8% (10/42)	53.7% (22/41)	0.005
Radiological alterations + dyspnea + DLCO alterations	0% (0/42)	17.1% (7/41)	0.006
DLCO alterations	38.1% (16/42)	39% (16/41)	0.71
Quality of life			
Anxiety	9.5% (4/42)	43.9% (18/41)	<0.001
Asthenia	47.6% (20/42)	61% (25/41)	0.2
Dysgeusia	14.3% (6/42)	31.7% (13/41)	0.06
Dyspnea	33.3% (14/42)	65.9% (27/41)	0.003
Fever	0% (0/42)	0% (0/41)	/
Insomnia	30.9% (13/42)	31.7% (13/41)	0.9
Loss of appetite	9.5% (4/42)	22% (9/41)	0.1

FIO2, fraction of inspired oxygen; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; DLCO, diffusing capacity of the lungs for carbon monoxide.

treating patients with positive pressure devices could be safe even for a prolonged time and may represent an alternative treatment for respiratory failure in COVID-19 patients with not only absolute but even relative contraindication to OTI.

A prolonged high FiO2 oxygen treatment (related to disease severity) had a huge impact on patients' quality of life: previous studies reported the presence of fatigue, muscle weakness, sleep difficulties, anxiety, or depression in COVID-19 survivors at 4 to 6 months after the acute infection.[11,12]

In our study, many patients suffered from dyspnea for mild to moderate efforts and asthenia, almost half of them reported anxious symptoms and a third insomnia or dysgeusia after more than one year from the discharge.

The negative impact on quality of life in the long term resulted even more evident when data were compared to patients with a milder disease course and a lower FiO2 support.

Dyspnea and anxiety were more frequent in patients who needed higher FiO2 oxygen support; on the other hand, asthenia, loss of appetite, insomnia, and dysgeusia were similar between the groups. This confirms that Long COVID symptoms may go beyond improvements in pulmonary examinations (both functional and radiological) and normalization of biochemical exams.[13]

Another objective of our study was to compare patients treated with FiO2 ≥40% with those treated with FiO2 ≤35% (including no oxygen need) who had been analyzed in a previous short-term follow-up study.[12]

Although the different follow-up length could be a limitation for the analysis, it is interesting to observe how radiological alterations and persistent dyspnea for mild to moderate efforts resulted in significantly less frequent in the group treated with FiO2 ≤35%, even if considering a shorter follow-up period (about four months *vs*. more than one year in the FiO2 ≥40% group).

As described in the results section, there wasn't any statistically significant difference in spirometry and DLCO between the two considered groups; anyway, this could be explained by the different follow-up periods.

It is possible and even reasonable to suppose that a longer follow-up period for the low-FiO2 group would have resulted in a higher percentage of normalized spirometry data; however, this observation remains speculative because we weren't able to perform control spirometry at a one-year follow-up in this group of patients.

Limitations of the study

Our study has some limitations. In the first instance, it may be regarded as a monocentric one since it included patients hospitalized and observed at follow-up in Montichiari Hospital, Italy. Moreover, the sample size was limited: further analyses with a higher number of patients' sample should be performed to confirm our findings.

Finally, as discussed in the previous section, different timelines in follow-up were considered in the analyses of low *vs*. high FiO2 groups.

Conclusions

Our data suggest that patients treated with higher FiO2 (which is related to a more severe respiratory disease) show persistence of significant radiological, clinical, and functional alterations after more than one year from discharge. In at least 7 of them (17% of the sample) pulmonary fibrosis can be diagnosed.

These results are in agreement with previous literature data: patients who were critically ill during their hospital stay show more severe impaired pulmonary diffusion capacities and chest imaging abnormalities.[14] A recent analysis of the UK Interstitial Lung Disease Consortium described residual lung abnormalities in up to 11% of patients hospitalized for COVID-19, within 240 days from discharge.[15]

Interestingly, in our study alterations are not related to positive pressure oxygen administration, even prolonged for more than one week: this suggests that this treatment approach is safe in patients who cannot be transferred to intensive care units for any reason. More and wider studies will be needed to confirm this result.

In conclusion, this study confirms the heavy quality of life impact of moderate to severe COVID-19.

We think that it is very important to recognize patients who will benefit from rehabilitative programs and customized follow-up in relation to the acute phase severity.

Further studies are necessary to better understand the Long COVID spectrum with all its risk factors, markers, and pathophysiology, in order to improve patients' outcomes.

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Appendix A

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