Conservative oxygen supplementation during helmet continuous positive airway pressure therapy in patients with COVID-19 and respiratory failure: a pilot study

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In patients with COVID-19 pneumonia and respiratory failure, correct oxygen supplementation may be crucial to avoid added lung damage; conservative oxygen therapy was associated to improved survival in patients with COVID-19 and severe respiratory failure https://bit.ly/3KdAxRc

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Abstract

Background Respiratory failure is a severe complication in coronavirus disease 2019 (COVID-19) pneumonia that, in addition to oxygen therapy, may require continuous positive airway pressure (CPAP) support. It has been postulated that COVID-19 lung injury may share some features with those observed in hyperoxic acute lung injury. Thus, a correct target arterial oxygen tension (P_{aO_2}) during oxygen supplementation may be crucial to protect the lung from further tissue damage. The aims of this study were: 1) to evaluate the effects of conservative oxygen supplementation during helmet CPAP therapy on mortality and intensive care unit (ICU) admission in patients with COVID-19 and respiratory failure, and 2) to evaluate the effect of conservative oxygen supplementation on new-onset organ failure and secondary pulmonary infections.

Methods This was a single-centre, historically controlled study of patients with severe respiratory failure due to COVID-19 pneumonia, receiving either conservative or nonconservative oxygen supplementation during helmet CPAP. A cohort receiving conservative oxygen supplementation was studied prospectively in which oxygen supplementation was administered with a target P_{aO_2} <100 mmHg. Results of this cohort were compared with those of a cohort who had received liberal oxygen supplementation.

Results 71 patients were included in the conservative cohort and 75 in the nonconservative cohort. Mortality rate was lower in the conservative cohort (22.5% *versus* 62.7%; p<0.001). Rates of ICU admission and new-onset organ failure were lower in the conservative cohort (14.1% *versus* 37.3%; p=0.001 and 9.9% *versus* 45.3%; p<0.001, respectively).

Conclusions In patients with COVID-19 and severe respiratory failure, conservative oxygen supplementation during helmet CPAP was associated with improved survival, lower ICU admission rate and less new-onset organ failure.

Introduction

Oxygen supplementation is one of the cornerstones in the treatment of hypoxaemic respiratory failure. Unfortunately, it remains unclear what the target oxygenation to strive for is in these patients [1]. Historically, concern has been raised about the potential deleterious effects of excessive oxygen supplementation in terms of pulmonary toxicity [2]. Prolonged hyperoxia, defined as arterial oxygen tension (P_{aO_2}) >100 mmHg or breathing an inspired gas mixture with inspiratory oxygen fraction (F_{IO_2})

>0.7, is associated with an increase in reactive oxygen species (ROS), a reduction of antioxidative defence, an inflammatory state, and endothelial and surfactant damage [3], the latter leading to hyperpermeability, oedema, collagen deposition and fibrosis [4], and absorption atelectasis [5]. In mice, high F_{IO_2} supplementation (*i.e.* F_{IO_2} >0.95) predisposes to lung infections [6]. By contrast, utilising a maximum P_{aO_2} target within a physiological range appears to be safer in humans [7]. In this regard, GIRARDIS *et al.* [8] conducted a randomised clinical trial to assess whether a conservative oxygen therapy protocol could improve survival in patients admitted to the intensive care unit (ICU). They found that conservative oxygen therapy, in which P_{aO_2} was maintained between 70 and 100 mmHg, was associated with decreased mortality [8].

In patients with coronavirus disease 2019 (COVID-19) pneumonia and severe respiratory failure, supplemental oxygen is very often administered for several days to correct hypoxaemia. It has been postulated that COVID-19 lung injury may share some features observed in hyperoxic acute lung injury [9]. It is very likely that a prolonged period of hyperoxia may induce further damage in the already damaged lung affected by COVID-19 pneumonia. Thus, establishing the correct target P_{aO_2} for the treatment of COVID-19 respiratory failure may be crucial in protecting the lung from severe damage.

The aims of the present study were: 1) to evaluate the impact of conservative oxygen therapy on mortality and ICU admissions in patients with severe COVID-19 and respiratory failure receiving helmet CPAP, and 2) to evaluate the effect of conservative oxygen therapy on new-onset organ failure and secondary pulmonary infections.

Methods

We conducted a single-centre, historically controlled study of patients with severe respiratory failure due to COVID-19 pneumonia, undergoing helmet CPAP treatment in a pulmonary subintensive care unit at Policlinico Umberto I Hospital, Sapienza University of Rome (Rome, Italy). The study was approved by the local ethics committee (109/2020).

Conservative cohort

From February 2021 to May 2021, 71 patients were treated with a conservative oxygen supplementation strategy ("conservative cohort"). Inclusion criteria were: age >18 years and COVID-19 with respiratory failure requiring helmet CPAP support. Exclusion criteria were: respiratory acidosis, prompt intubation, ICU admission, pregnancy, or bacterial or fungal pneumonia. Severe pneumonia was defined according to World Health Organization guidelines [7]. Figure 1 shows the management algorithm utilised in the conservative cohort. For CPAP treatment, a helmet device was utilised (Ventukit; StarMed, Teramo, Italy or DIMAR, Medolla, Italy). Conservative oxygen supplementation with helmet CPAP was started in patients who presented with a P_{aO_2}/F_{IO_2} ratio (P/F) <150 under treatment with a Venturi mask at an F_{IO_2} of 0.6. All patients were initially treated with positive end-expiratory pressure (PEEP) set at 7.5 cmH_2O and F_{IO_2} set at 0.6 (figure 1). PEEP was then adjusted according to the P_{aO_2} target. The goal of the

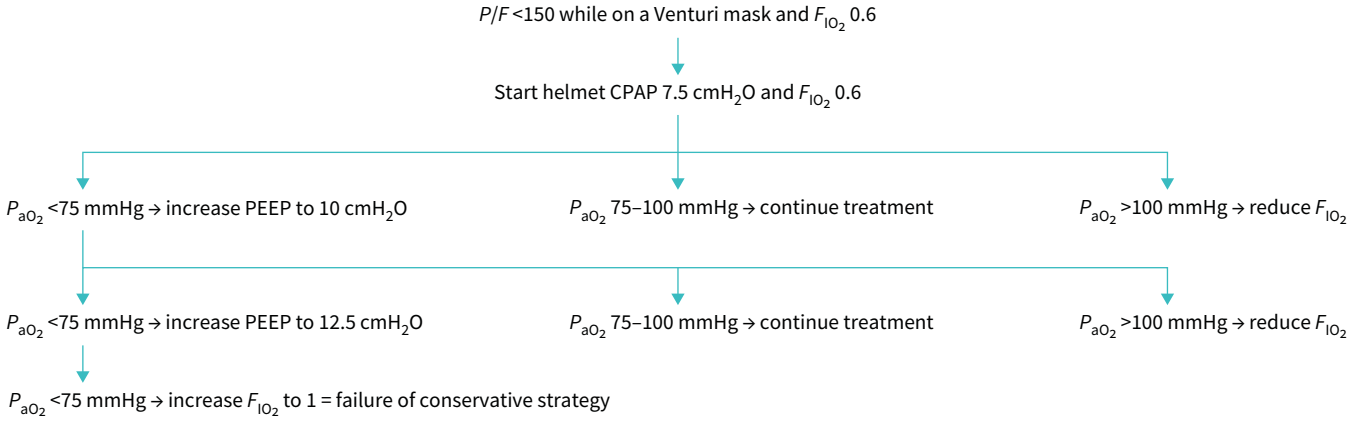

FIGURE 1 Conservative oxygen supplementation strategy during helmet continuous positive airway pressure (CPAP) therapy. Helmet CPAP support was started when the arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio (P/F ratio) was <150 while on a Venturi mask and F_{IO_2} 0.6. Positive end-expiratory pressure (PEEP) and F_{IO_2} were adjusted to maintain a P_{aO_2} between 75 and 100 mmHg (see text for more details). The conservative strategy was considered to have failed if patients required an F_{IO_2} of 1.0 while on a PEEP of 12.5 cmH_2O to maintain the target P_{aO_2}.

conservative approach was to maintain P_{aO_2} values between 75 and 100 mmHg with the use of PEEP and oxygen supplementation while avoiding F_{IO_2} >0.6. If P_{aO_2} was <75 mmHg, PEEP was progressively increased to a maximum of 12.5 cmH_2O. Conversely, if P_{aO_2} was >100 mmHg, F_{IO_2} was progressively decreased to 0.4 and, if P_{aO_2} remained >100 mmHg, PEEP was progressively reduced. Failure of conservative management was defined as the need to increase F_{IO_2} to 1.0 with PEEP of 12.5 cmH_2O in order to maintain the target P_{aO_2}.

Nonconservative cohort

Results obtained in the conservative cohort were compared with those of a previous cohort of 75 patients ("nonconservative cohort"), hospitalised from September 2020 to February 2021 for COVID-19 pneumonia and severe respiratory failure, who received liberal oxygen supplementation and helmet CPAP support. The severity of respiratory failure was equivalent in both cohorts (*i.e.* *P*/*F* ratio <150 while receiving a Venturi mask at F_{IO_2} 0.6 before starting helmet CPAP). In the nonconservative cohort, oxygen and CPAP therapy were administered with a liberal approach, *i.e.* regardless of a P_{aO_2} target.

In both cohorts, all patients were not vaccinated for COVID-19, and received remdesivir for 5 days and dexamethasone for 10 days. Demographic, laboratory and radiological data were collected at baseline. Arterial blood gas measurements were obtained before CPAP therapy, 1–3 h after starting CPAP and at least once daily. We also computed "standard *P*/*F*" by dividing "standard P_{aO_2}" $((1.66\times P_{aCO_2}) + (P_{aO_2} - 66.4))$ by F_{IO_2} [10], as standard *P*/*F* is probably superior to *P*/*F* in predicting in-hospital mortality in COVID-19 [11].

New-onset organ failure and secondary pulmonary infections were diagnosed according to international definitions, and with laboratory tests, microbiological samples and radiological examinations if indicated [12, 13].

Statistical analysis

Summary statistics are presented as frequencies (percentages) for categorical data and mean with standard deviation for normally distributed continuous data. Where continuous data were not normally distributed, the median (interquartile range) was used. Differences in categorical data were compared using the Chi-squared test or Fisher's exact test when expected counts were <5 in any cohort. For continuous normally distributed two-group data, we compared differences using the t-test or Mann–Whitney U-test if data were not normally distributed, whereas a univariable population-averaged generalised estimating equation model with an exchangeable correlation structure was used to compare *P*/*F* and standard *P*/*F* ratio values over time.

The primary outcomes were: 1) all-cause in-hospital mortality, 2) mortality at day 30 and 3) mortality at day 60. We used competing risk modelling (Fine–Gray regression models) with time-on-study as the timescale to explore the effect of the exposure of interest on the outcome incidence considering hospital discharge as the competing event. Cumulative incidence functions were plotted, and crude subdistribution hazard ratios (SHRs) and their associated 95% confidence intervals were calculated. The multivariable analysis was adjusted for factors known at the time of potential exposure that could possibly confound the association of interest to the outcome. These included: age (years), sex (female *versus* male), cardiovascular diseases (yes/no), diabetes (yes/no), malignancy (yes/no), obesity (yes/no), respiratory diseases (yes/no), lung involvement at high-resolution computed tomography (HRCT) (>3 *versus* ⩽3 lobes), D-dimer ($ng\cdot mL^{-1}$), lymphocyte count (μL^{-1}), P_{aO_2} (mmHg), arterial carbon dioxide tension (P_{aCO_2}) (mmHg) and standard *P*/*F* at first arterial blood gas measurements.

Continuous variables were modelled to have a linear effect. The proportional hazards assumption was checked by testing the statistical significance of interaction terms involving failure time, each one at a time.

To further account for potential confounding, the propensity score of being in the conservative cohort based on all of the listed covariates was calculated using a probit model and the derived score was treated as covariate in the Fine–Gray models as a sensitivity analysis.

All statistical calculations were performed using Stata version 17.0 (StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline patient characteristics did not differ between the two cohorts (table 1). Most patients presented with bilateral lung infiltrates involving five lobes (62.0% *versus* 70.7%; p=0.68). In the conservative cohort the management algorithm failed in 18 (25.4%) patients who needed an F_{IO_2} of 1 to maintain the target

TABLE 1 Baseline patient characteristics

	Nonconservative cohort (n=75)	Conservative cohort (n=71)	p-value
Sex			0.69
Male	53 (70.7)	48 (67.6)	
Female	22 (29.3)	23 (32.3)	
Age (years)	71 (61–82)	69 (57–78)	0.22
Diabetes	22 (29.3)	15 (21.1)	0.25
Cardiovascular disease	41 (54.7)	42 (59.1)	0.58
Cancer	10 (13.3)	8 (11.2)	0.70
Chronic respiratory disease	7 (9.3)	7 (9.9)	0.91
Chronic renal failure	8 (10.7)	4 (5.6)	0.27
Obesity	12 (16.0)	16 (22.5)	0.32
Haemoglobin ($g \cdot dL^{-1}$)	13.7 (12.7–15.1)	14.3 (13.4–15.1)	0.11
C_{aO_2} ($mg \cdot dL^{-1}$)	16.76 (14.95–18.88)	18.26 (16.52–18.92)	0.029
Leukocytes ($\times 10^3\ \mu L^{-1}$)	6.675 (4.880–9.430)	6.915 (5.520–9.280)	0.61
Neutrophils ($\times 10^3\ \mu L^{-1}$)	5.150 (3.710–7.350)	5.620 (4.240–8.080)	0.29
Lymphocytes ($\times 10^3\ \mu L^{-1}$)	825 (490–1.030)	800 (550–1.050)	0.78
Platelets ($\times 10^3\ \mu L^{-1}$)	181 (133–226)	196 (163–249)	0.026
D-dimer ($U \cdot L^{-1}$)	754 (507.5–1.558)	755 (489–1.279)	0.75
CRP ($mg \cdot dL^{-1}$)	7.19 (3.70–15.16)	7.07 (3.46–11.49)	0.39
Bilateral pneumonia	72 (96.0)	70 (98.6)	0.99
Lung lobes involved at HRCT			0.68
1	0 (0.0)	1 (1.4)	
2	8 (10.7)	7 (9.9)	
3	4 (5.3)	5 (7.0)	
4	9 (12.0)	13 (18.3)	
5	53 (70.7)	44 (62.0)	
First ABGs in CPAP			
P_{aO_2} (mmHg)	102 (76–138)	108 (83–123)	0.68
P_{aCO_2} (mmHg)	34 (30–38)	35 (32–39)	0.24
Standard P_{aO_2} (mmHg)	82.4 (65.1–136.3)	102.4 (79.7–118)	0.32
pH	7.46 (7.44–7.48)	7.46 (7.43–7.48)	0.70
P/*F* ratio	162 (125–260)	180 (138–214)	0.43
S_{pO_2} (%)	99 (97.7–99.5) (n=66)	99.5 (98.2–100) (n=69)	0.005
Standard *P*/*F* ratio	130 (103–237)	171 (136–197)	0.050
F_{IO_2} (%)	60 (50–60)	60 (60–60)	0.91
PEEP (cmH_2O)	7.5 (7.5–10)	7.5 (7.5–7.5)	0.080
Maximum PEEP (cmH_2O) required during the whole treatment	10 (10–12.5)	10 (7.5–12.5)	0.008

Data are presented as n (%) or median (interquartile range), unless otherwise stated. C_{aO_2}: arterial oxygen content; CRP: C-reactive protein; HRCT: high-resolution computed tomography; ABG: arterial blood gas; CPAP: continuous positive airway pressure; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; *P*/*F* ratio: P_{aO_2}/F_{IO_2} ratio; F_{IO_2}: inspiratory oxygen fraction; S_{pO_2}: oxygen saturation measured by pulse oximetry; PEEP: positive end-expiratory pressure.

P_{aO_2}. In contrast, in the nonconservative cohort an F_{IO_2} of 1 was administered in 54 (72%) patients. The first *P*/*F* ratio and the first standard *P*/*F* ratio during helmet CPAP were greater in the conservative cohort than in the nonconservative cohort (*P*/*F* 180 *versus* 162; p=0.43 and standard *P*/*F* 171 *versus* 130; p=0.05) (table 1). In the following days, only the standard *P*/*F* was greater in the conservative cohort (figure 2).

Compared with the nonconservative cohort, the conservative cohort had a lower mortality (22.5% *versus* 62.7%; p<0.001), fewer ICU admissions (14.1% *versus* 37.3%; p=0.001) and less new-onset organ failure (9.9% *versus* 45.3%; p<0.001). In addition, mortality was lower in the conservative cohort at both 30 and 60 days. Of note, by day 30, 13 patients (18.3%) in the conservative cohort and 40 (53.3%) in nonconservative cohort had died. By day 60, 15 patients (21.1%) in the conservative cohort and 46 (61.3%) in the nonconservative cohort had died (table 2). The unadjusted hazard ratio of death estimated using the Fine–Gray model was 0.259 (95% CI 0.141–0.475; p<0.001) at 30 days and 0.249 (95% CI 0.141–0.439; p<0.001) at 60 days (table 3). When adjusting for confounders, the conservative cohort maintained a lower rate of death (SHR 0.220 (95% CI 0.101–0.478) at 30 days; p<0.001 and SHR 0.227

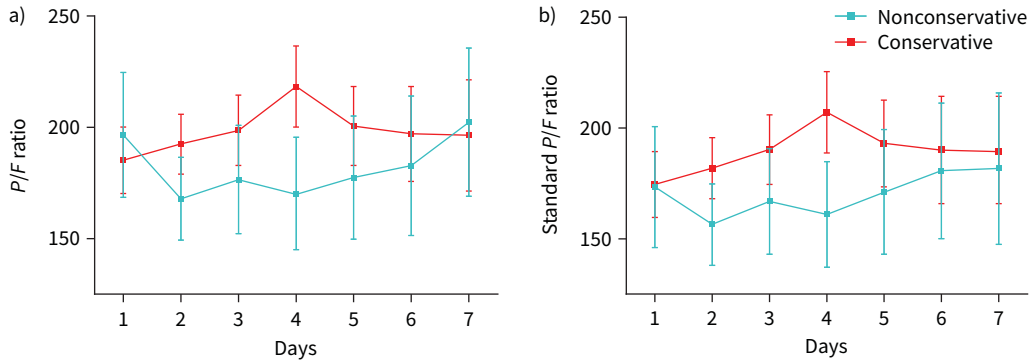

FIGURE 2 Difference in a) arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio (*P*/*F* ratio) and b) standard *P*/*F* ratio in the conservative *versus* nonconservative cohorts. In the conservative cohort the standard *P*/*F* ratio result was higher than in the nonconservative cohort (p=0.01; univariable population-averaged generalised estimating equation model with an exchangeable correlation structure).

(95% CI 0.110–0.470) at 60 days; p<0.001) (table 4). Similar results were observed when propensity score analysis was used to account for cofounders, with a hazard ratio for mortality of 0.256 (95% CI 0.131–0.500) at 30 days and 0.260 (95% CI 0.140–0.482) at 60 days (p<0.001) (table 5).

Discussion

Our major findings were that patients with COVID-19 and severe respiratory failure treated with a conservative oxygen strategy while receiving helmet CPAP support have a lower mortality and fewer ICU admissions than patients treated with a nonconservative oxygen strategy. Moreover, the conservative oxygen strategy was associated with a lower rate of new-onset organ failure.

Hypoxaemic respiratory failure is a common complication in patients with COVID-19 pneumonia and supplemental oxygen is usually administered for several days. Concern has been raised about the possible toxic effects and lung damage induced by prolonged hyperoxia in COVID-19 pneumonia. Short-term hyperoxia is commonly utilised for carbon monoxide poisoning [14], but several studies have previously

TABLE 2 Outcomes

	Nonconservative cohort (n=75)	Conservative cohort (n=71)	p-value
Transfer to ICU	28 (37.3)	10 (14.1)	0.001
All-cause in-hospital mortality	47 (62.7)	16 (22.5)	<0.001
Mortality at 30 days	40 (53.3)	13 (18.3)	<0.001
Mortality at 60 days	46 (61.3)	15 (21.1)	<0.001
New-onset organ failure	34 (45.3)	7 (9.9)	<0.001
Secondary pulmonary infections	21 (28.0)	19 (26.8)	0.87
In-hospital stay (days)	17 (9–28)	20 (16–31)	0.012
Length of CPAP treatment (days)	7 (5–10)	6 (4–8)	0.21

Data are presented as n (%) or median (interquartile range), unless otherwise stated. ICU: intensive care unit; CPAP: continuous positive airway pressure.

TABLE 3 Unadjusted hazard ratio for mortality at 30 and 60 days

	Mortality at 30 days		Mortality at 60 days	
	SHR (95% CI)	p-value	SHR (95% CI)	p-value
Conservative cohort	0.259 (0.141–0.475)	<0.001	0.249 (0.141–0.439)	<0.001

Fine–Gray model. SHR: subdistribution hazard ratio.

TABLE 4 Multivariable analysis

	Mortality at 30 days		Mortality at 60 days	
	SHR (95% CI)	p-value	SHR (95% CI)	p-value
Conservative cohort	0.220 (0.101–0.478)	<0.001	0.227 (0.110–0.470)	<0.001
Age	0.998 (0.964–1.032)	0.887	1.012 (0.977–1.048)	0.509
Sex (female)	1.530 (0.744–3.145)	0.248	1.304 (0.642–2.646)	0.463
Cardiovascular diseases	2.515 (1.031–6.135)	0.043	2.084 (0.856–5.071)	0.106
Respiratory diseases	0.824 (0.379–1.790)	0.625	0.790 (0.308–2.029)	0.624
Diabetes	11.014 (3.225–37.618)	<0.001	1.961 (0.972–3.954)	0.060
Malignancy	2.285 (0.747–6.989)	0.147	1.872 (0.609–5.757)	0.274
Obesity	0.737 (0.308–1.764)	0.494	0.703 (0.275–1.795)	0.461
D-dimer	1.000 (1.000–1.001)	0.049	1.000 (1.000–1.000)	0.220
Lung lobes involved at HRCT	1.355 (0.358–5.118)	0.655	1.043 (0.326–3.335)	0.943
Lymphocytes	0.998 (0.997–0.999)	0.005	1.000 (0.999–1.001)	0.999
P_{aO_2} at first ABGs	1.026 (0.999–1.054)	0.058	1.027 (1.005–1.050)	0.017
Standard *P*/*F* at first ABGs	0.983 (0.970–0.995)	0.008	0.982 (0.971–0.993)	0.001
P_{aCO_2} at first ABGs	0.979 (0.905–1.058)	0.586	0.980 (0.913–1.051)	0.562
Diabetes×time	0.870 (0.782–0.967)	0.010		
Lymphocytes×time	1.000 (1.000–1.001)	<0.001		

Fine–Gray model. SHR: subdistribution hazard ratio; HRCT: high-resolution computed tomography; P_{aO_2}: arterial oxygen tension; ABG: arterial blood gas; *P*/*F* ratio: P_{aO_2}/F_{IO_2} ratio; F_{IO_2}: inspiratory oxygen fraction; P_{aCO_2}: arterial carbon dioxide tension.

argued that a long exposure to high concentrations of oxygen could be dangerous for the lung [15], reporting an association between hyperoxaemia and mortality in ICU critical patients [16, 17].

A recent article on conservative management of COVID-19 patients treated with noninvasive ventilation by CPAP in combination with permissive hypoxaemia suggested that a conservative oxygen supplementation strategy may be feasible and can result in a low intubation rate [18]. This observation is in line with the results of our study in which patients treated with a conservative oxygen supplementation strategy had a lower mortality rate compared with patients treated with a liberal (*i.e.* nonconservative) approach. In particular, our multivariate analysis showed that survival at 30 and 60 days was greater in patients who received conservative than nonconservative oxygen supplementation. It should be noted, however, that consistent with an earlier study [19], comorbidities such as diabetes and cardiovascular diseases may have negatively influenced mortality at 30 days (table 4).

It should be acknowledged that not all previous trials have shown that a conservative oxygen regime is safe. Barrot *et al.* [20] observed that maintaining P_{aO_2} between 55 and 60 mmHg did not increase survival at 28 days among patients with acute respiratory distress syndrome (ARDS) treated in the ICU and predisposed to morbidity including mesenteric ischaemia. In our study, however, we did not observe any adverse effects.

In patients with severe COVID-19, *P*/*F* has been used as a marker of severity of respiratory failure and clinical course; this despite the fact that P_{aO_2} gauges oxygenation more accurately than the *P*/*F* ratio [21]. In a recent study from our group, we reported that the standard *P*/*F* ratio better predicts in-hospital mortality in COVID-19 patients because it better reflects the ability to maintain arterial blood oxygenation in terms of tachypnoea and hyperpnoea [11]. This is why both standard P_{aO_2} and standard *P*/*F* were

TABLE 5 Propensity score analysis

	Mortality at 30 days		Mortality at 60 days	
	SHR (95% CI)	p-value	SHR (95% CI)	p-value
Conservative cohort	0.256 (0.131–0.500)	<0.001	0.260 (0.140–0.482)	<0.001
Propensity score	0.043 (0.006–0.319)	0.002	0.030 (0.005–0.199)	<0.001

Fine–Gray. SHR: subdistribution hazard ratio.

computed in the present study. During hospital stay, standard *P*/*F* was higher with conservative oxygen therapy than with nonconservative oxygen therapy (figure 2). Although it is possible to speculate that this was the cause of the decreased mortality in the conservative cohort, as for classic ARDS, the mechanistic link between hypoxaemia and mortality remains unclear and difficult to establish. Multivariable analysis also confirmed that a higher standard *P*/*F* was associated with a lower hazard of mortality (SHR 0.983 (95% CI 0.970–0.995) at 30 days; p<0.001 and SHR 0.982 (95% CI 0.971–0.993) at 60 days; p<0.001).

The lung parenchyma in severe COVID-19 is characterised by capillary engorgement, capillary thrombosis, alveolar oedema and haemorrhage, and scattered fibrosis [22–25], with resultant ventilation/perfusion mismatch. It has been recently shown that elevated F_{IO_2} increases severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coreceptor expression in respiratory tract epithelium and possibly lung tissue damage [26].

It has also been shown that hyperoxia could lead to new-onset organ failure [5]. In addition, in an experimental model of sepsis, oxygen supplementation may influence the progression to multiple organ dysfunction; and the higher the F_{IO_2}, the greater the number of sites of infection and the increase of inflammatory cytokines released [27, 28]. Indeed, in addition to the negative effects on alveolar wall barrier function, hyperoxia seems to have a detrimental effect on innate immunity and pulmonary host defences. In a mouse model of pneumonia, Baleerio *et al.* [6] reported greater mortality in animals exposed to hyperoxia than in animals exposed to room air, with hyperoxia being associated with a reduction of alveolar macrophage activity and alveolar macrophage killing of Gram-negative bacteria. Some results of our study are in agreement with these reports. Thus, we observed that conservative oxygen therapy was associated with a reduction of new-onset organ failure compared with the nonconservative approach (9.9% *versus* 45.3%; p<0.001). In our study, patients of both cohorts developed secondary pulmonary infections, especially bacterial pneumonia, but we observed no differences between these. We can speculate that the incidence of bacterial pneumonia was not different because of COVID-19-associated lymphopenia and/or steroid treatment utilised in both cohorts of patients.

Our study has some limitations. It is a single-centre, historically controlled study. The number of observations is limited. Patients in the two cohorts were admitted in different pandemic periods. Also, the pathogenicity of different SARS-CoV-2 variants and the improvement in medical staff experience and efficacy over time may have had some impact on patient outcomes. Additional limitations include the uncertainties in computing the *P*/*F* ratio in nonintubated patients [21] and the possibility of residual confounders, such as superinfections.

In conclusion, our retrospective pilot study suggests that in patients with COVID-19 and respiratory failure, conservative oxygen supplementation during helmet CPAP is feasible and safe, and is associated with lower mortality, fewer ICU admissions and less new-onset organ failure.

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References

1 Schjørring OL, Klitgaard TL, Perner A, *et al.* Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 2021; 384: 1301–1311.
2 Chu DK, Kim LH, Young PJ, *et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; 391: 1693–1705.
3 Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care* 2013; 58: 123–141.

4 Kallet RH, Branson RD. Should oxygen therapy be tightly regulated to minimize hyperoxia in critically ill patients? *Respir Care* 2016; 61: 801–817.
5 Tretter V, Zach ML, Böhme S, *et al.* Investigating disturbances of oxygen homeostasis: from cellular mechanisms to the clinical practice. *Front Physiol* 2020; 11: 947.
6 Baleeiro CE, Wilcoxen SE, Morris SB, *et al.* Sublethal hyperoxia impairs pulmonary innate immunity. *J Immunol* 2003; 171: 955–963.
7 World Health Organization. Clinical management of COVID-19: interim guidance 27 May 2020. 2020. https://apps.who.int/iris/handle/10665/332196 Date last accessed: 9 January 2023.
8 Girardis M, Busani S, Damiani E, *et al.* Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA* 2016; 316: 1583–1589.
9 Hanidziar D, Robson SC. Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. *Am J Physiol Lung Cell Mol Physiol* 2021; 320: L12–L16.
10 Mays EE. An arterial blood gas diagram for clinical use. *Chest* 1973; 63: 793–800.
11 Prediletto I, D'Antoni L, Carbonara P, *et al.* Standardizing PaO_2 for $PaCO_2$ in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study. *Eur J Intern Med* 2021; 92: 48–54.
12 American Thoracic Society/Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
13 National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management. NICE guideline 51. 2017. www.nice.org.uk/guidance/ng51 Date last accessed: 9 January 2023.
14 Hafner S, Beloncle F, Koch A, *et al.* Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care* 2015; 5: 42.
15 Singer M, Young PJ, Laffey JG, *et al.* Dangers of hyperoxia. *Crit Care* 2021; 25: 440.
16 Damiani E, Adrario E, Girardis M, *et al.* Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2014; 18: 711.
17 Pala Cifci S, Urcan Tapan Y, Turemis Erkul B, *et al.* The impact of hyperoxia on outcome of patients treated with noninvasive respiratory support. *Can Respir J* 2020; 2020: 3953280.
18 Voshaar T, Stais P, Köhler D, *et al.* Conservative management of COVID-19 associated hypoxaemia. *ERJ Open Res* 2021; 7: 00026-2021.
19 Singh AK, Gillies CL, Singh R, *et al.* Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. *Diabetes Obes Metab* 2020; 22: 1915–1924.
20 Barrot L, Asfar P, Mauny F, *et al.* Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020; 382: 999–1008.
21 Tobin MJ, Jubran A, Laghi F. P_{aO_2}/F_{IO_2} ratio: the mismeasure of oxygenation in COVID-19. *Eur Respir J* 2021; 57: 2100274.
22 Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.
23 Menter T, Haslbauer JD, Nienhold R, *et al.* Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; 77: 198–209.
24 Patel BV, Arachchillage DJ, Ridge CA, *et al.* Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020; 202: 690–699.
25 Yuan S, Jiang SC, Zhang ZW, *et al.* The role of alveolar edema in COVID-19. *Cells* 2021; 10: 1897.
26 Myti D, Gunjak M, Casado F, *et al.* Elevated FiO_2 increases SARS-CoV-2 co-receptor expression in respiratory tract epithelium. *Am J Physiol Lung Cell Mol Physiol* 2020; 319: L670–L674.
27 Carr AC, Spencer E, Mackle D, *et al.* The effect of conservative oxygen therapy on systemic biomarkers of oxidative stress in critically ill patients. *Free Radic Biol Med* 2020; 160: 13–18.
28 Rodríguez-González R, Martín-Barrasa JL, Ramos-Nuez Á, *et al.* Multiple system organ response induced by hyperoxia in a clinically relevant animal model of sepsis. *Shock* 2014; 42: 148–153.