

RESEARCH ARTICLE

Oxygenation targets in ICU patients with COVID-19: A post hoc subgroup analysis of the HOT-ICU trial

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Abstract

Background: Supplemental oxygen is the key intervention for severe and critical COVID-19 patients. With the unstable supplies of oxygen in many countries, it is important to define the lowest safe dosage.

Methods: In spring 2020, 110 COVID-19 patients were enrolled as part of the Handling Oxygenation Targets in the ICU trial (HOT-ICU). Patients were allocated within 12 h of ICU admission. Oxygen therapy was titrated to a partial pressure of arterial oxygen (PaO₂) of 8 kPa (lower oxygenation group) or a PaO₂ of 12 kPa (higher oxygenation group) during ICU stay up to 90 days. We report key outcomes at 90 days for the subgroup of COVID-19 patients.

Results: At 90 days, 22 of 54 patients (40.7%) in the lower oxygenation group and 23 of 55 patients (41.8%) in the higher oxygenation group had died (adjusted risk ratio: 0.87; 95% confidence interval, 0.58–1.32). The percentage of days alive without life support was significantly higher in the lower oxygenation group ($p = 0.03$). The numbers of severe ischemic events were low with no difference between the two groups. Proning and inhaled vasodilators were used more frequently, and the positive end-expiratory pressure was higher in the higher oxygenation group. Tests for interactions with the results of the remaining HOT-ICU population were insignificant.

Conclusions: Targeting a PaO_2 of 8 kPa may be beneficial in ICU patients with COVID-19. These results come with uncertainty due to the low number of patients in this unplanned subgroup analysis, and insignificant tests for interaction with the main HOT-ICU trial.

Trial registration number: ClinicalTrials.gov number, NCT03174002.

Date of registration: June 2, 2017.

KEYWORDS

intensive care units, oxygen inhalation therapy, randomized controlled trial, respiratory insufficiency, severe acute respiratory syndrome coronavirus 2

Editorial Comment

In this substudy of the HOT-ICU randomized controlled trial comparing two different oxygenation targets for patients with hypoxic respiratory failure, patients with COVID-19 disease who were treated targeting arterial oxygenation of 8 kPa had more days alive without life support. While limited by few patients in the trial with COVID-19, the results, in combination with the main study results, are suggestive that targeting an oxygen level of 8 kPa is both safe and potentially beneficial for patients with COVID-19.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic. The virus causes coronavirus disease 2019 (COVID-19) ranging in severity from fever and mild upper respiratory tract symptoms to acute respiratory distress syndrome (ARDS) with severe hypoxemia requiring advanced respiratory support in the intensive care unit (ICU). Worldwide, the mortality of patients admitted to the ICU with COVID-19 is high, being close to 40%.¹ Supplemental oxygen is the key component of supportive care, but the balance between benefits and harms of different oxygenation targets is unknown for ICU patients with COVID-19.²

In ICU patients with ARDS by any etiology, clinical practice guidelines give no recommendation for oxygenation targets.^{3,4} One oxygenation target that is often referred to as a partial pressure of arterial oxygen (PaO_2) between 7.3 and 10.7 kPa or a SpO_2 of 88 and 95% defined as a standard of care in randomized trials performed by the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.^{5–7} A recent trial, Liberal or Conservative Oxygen Therapy (LOCO₂), in ARDS patients of a similar low target (PaO_2 , 7.3 to 9.3 kPa or SpO_2 , 88% to 92%) versus a higher target (PaO_2 , 12 to 14 kPa or SpO_2 above 95%) was stopped prematurely because 5 of 99 patients had mesenteric ischemia in the lower oxygenation group as compared to none of 102 patients in the higher oxygenation group, and likewise a significant difference in 90-day mortality

between the two groups was found.⁸ In the Handling Oxygenation Targets in the ICU (HOT-ICU) trial, we found no difference in the number of ischemic events nor in 90-day mortality among 2928 patients with moderate to severe acute hypoxaemic respiratory failure acutely admitted to the ICU comparing similar lower and higher oxygenation targets.⁹ Also, no differences in mortality at 90 or 180 days were found in the Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy (ICU-ROX) in which 1000 invasively mechanically ventilated patients were enrolled.¹⁰

During the first wave of the COVID-19 pandemic, 110 ICU patients with COVID-19 were enrolled in the HOT-ICU trial.⁹ The HOT-ICU trial was completed on August 3, 2020, and the primary results have been published.⁹ With the unstable supplies of medical oxygen in many countries and the lack of evidence in this area, we find it important to report key outcomes at 90 days for the subgroup of COVID-19 patients enrolled in the HOT-ICU trial.

2 | METHODS

2.1 | Trial design

Twelve HOT-ICU trial sites in Denmark, Switzerland, Norway, Finland, and the United Kingdom enrolled one or more patients with documented positive SARS-CoV-2 test at baseline or during

the ICU stay. Written informed consent was obtained from the patients or their legal surrogate as per the relevant legislation. The HOT-ICU trial was registered at ClinicalTrials.gov (NCT03174002) before the enrolment of the first patient. The protocol and statistical analysis plan were published before enrolment was completed.^{11,12} The HOT-ICU trial was an investigator-initiated, multicenter, stratified, parallel-grouped, randomized clinical trial with 35 participating ICUs in Denmark, Switzerland, Norway, Finland, the United Kingdom, the Netherlands, and Iceland. The first patient out of 2928 patients was enrolled in the HOT-ICU trial on June 20, 2017, and the last patient on August 3, 2020. Centralized randomization was conducted using a computer-generated concealed allocation sequence, with permuted blocks of variable sizes, in a 1:1 ratio, stratified by site, the presence or absence of chronic obstructive pulmonary disease (COPD), and the presence or absence of active hematological malignancy. No stratification for SARS-CoV-2 status was implemented. The hypothesis of the HOT-ICU trial was that a PaO₂ target of 8 kPa would reduce 90-day mortality, being the primary outcome, as compared with a PaO₂ target of 12 kPa. Results did not confirm this adjusted risk ratio (RR) of 1.02 with a confidence interval (CI) 0.94–1.11.⁹

2.2 | Patients

We screened patients aged 18 years or above who were acutely admitted to the ICU, received at least 10 L of oxygen per minute in an open system or at least a fraction of inspired oxygen (FiO₂) of 0.50 in a closed system, had an arterial line, and were expected to receive supplemental oxygen therapy for at least 24 h in the ICU. We excluded patients that could not be randomized within 12 h of ICU admission; all exclusion criteria are provided in the Supporting Information. In the present subgroup analysis of the HOT-ICU trial, we only include patients who had at least one airway sample positive for SARS-CoV-2 by PCR analysis at randomization or at any time during the ICU admission.

2.3 | Intervention

Patients were randomly assigned to oxygen therapy titrated to achieve a PaO₂ of 8 kPa (lower oxygenation group) or a PaO₂ of 12 kPa (higher oxygenation group) during the entire ICU stay, including re-admissions, to a maximum of 90 days after randomization. To document the intervention, we registered the lowest and the highest PaO₂ in predefined 12-hour intervals with concomitant values for arterial oxygen saturation (SaO₂) and FiO₂. All patients were continuously monitored with SpO₂ to maintain the assigned PaO₂. The oxygenation targets were achieved by adjustments of the FiO₂. All other interventions in the ICU were at the discretion of the clinicians.

2.4 | Outcome measures

We present key outcomes at 90 days as predefined in the HOT-ICU trial including; all-cause mortality; percentage of days alive without the use of life support defined as invasive or non-invasive mechanical ventilation or continuous positive airway pressure treatment, vasopressor or inotropic therapy, or renal replacement therapy; percentage of days alive and out of hospital; and the number of patients with one or more serious adverse events defined as new episodes of shock, myocardial ischemia, intestinal ischemia, or ischemic stroke in the ICU within 90 days, details are provided in the Supporting Information.

2.5 | Statistical analysis

We did no sample size estimation for the analyses reported here. All analyses were conducted according to the intention-to-treat principle¹³ and according to the statistical analysis plan for the HOT-ICU trial.¹² The intention-to-treat population included all randomized patients positive for SARS-CoV-2 in the HOT-ICU trial except for those where follow-up data could not be obtained due to the withdrawal of consent according to national regulations.^{14–16}

We compared 90-day mortality in the two groups using a generalized linear model with a log-link and a binomial error distribution adjusted for the stratification variables site and COPD, but not for active hematological malignancy due to non-convergence in the model. Results are presented as RR and risk differences (RD) with corresponding 95% CI. We also performed a secondary analysis of mortality adjusted for all stratification variables and for baseline parameters; age, presence or absence of active metastatic cancer, type of admission (medical, elective surgical or emergency surgical), and sequential organ failure assessment (SOFA) score calculated on the basis of six organ systems (respiration, coagulation, liver, cardiovascular, central nervous system, and renal) with higher scores indicating more severe organ dysfunction and a maximum score of 24,¹⁷ using a logistic regression model presented as odds ratio with 95% CI. We compared survival times using Kaplan–Meyer curves supplemented with a Cox proportional hazards model adjusted for all stratification variables. Percentages of days alive without life support and of days alive and out of the hospital at day 90 were compared using the van Elteren test with adjustment for the site. The number of patients with one or more serious adverse events in the two groups was compared using a generalized linear model with a log-link and a binomial error distribution adjusted for the stratification variables COPD and active hematological malignancy. The outcomes were tested for interaction with the results of the HOT-ICU trial. We tested a possible interaction on the outcomes between the COVID-19 patients and the remaining non-COVID-19 patients in the HOT-ICU trial. For all tests, a statistical significance was indicated by a *p* value below 0.05. We did not correct for multiple

testing. No imputations for missing values were performed as <5% of data were missing in all parameters. Comparisons of processes during the ICU stay were conducted using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for dichotomous data. All analyses were performed using Stata Statistical Software Release 16 (StataNordic).

3 | RESULTS

From March 3, 2020, to July 20, 2020, 110 patients with COVID-19 were enrolled in the HOT-ICU trial (Figure 1). At baseline, 46 out of 54 patients (85.2%) in the lower oxygenation group and 47 out of 56 patients (83.9%) in the higher oxygenation group had a positive test for SARS-CoV-2, respectively. We obtained 90-day vital status for 109 out of the 110 patients as one patient was lost to follow-up in the higher oxygenation group; 54 patients were randomly assigned to the lower oxygenation group and 56 patients to the higher oxygenation group (Figure 1). The characteristics of the patients were similar at baseline (Table 1).

3.1 | Oxygenation and ICU treatments

During the 90 days of intervention in the ICU, the daily medians of the registered PaO₂ and the corresponding FiO₂ and SaO₂ were lower in the lower oxygenation group as compared to the higher oxygenation group (Figure 2). The patient numbers in the figures are provided in the Supporting Information, as well as the highest and lowest registered PaO₂ with corresponding FiO₂ and SaO₂ (Table S1; Figure S1–S3). Details on the process of care in the ICU for the two oxygenation groups are provided in Table 2.

3.2 | Outcomes and interaction analysis

Ninety days after randomization 22 of 54 patients (40.7%) in the lower oxygenation group and 23 of 55 (41.8%) in the higher oxygenation group had died, implying no significant differences between the two groups in both the unadjusted and the adjusted analyses (Table 2; Figure 3). The percentage of days alive without life support at day 90 was significantly increased in the lower oxygenation group as

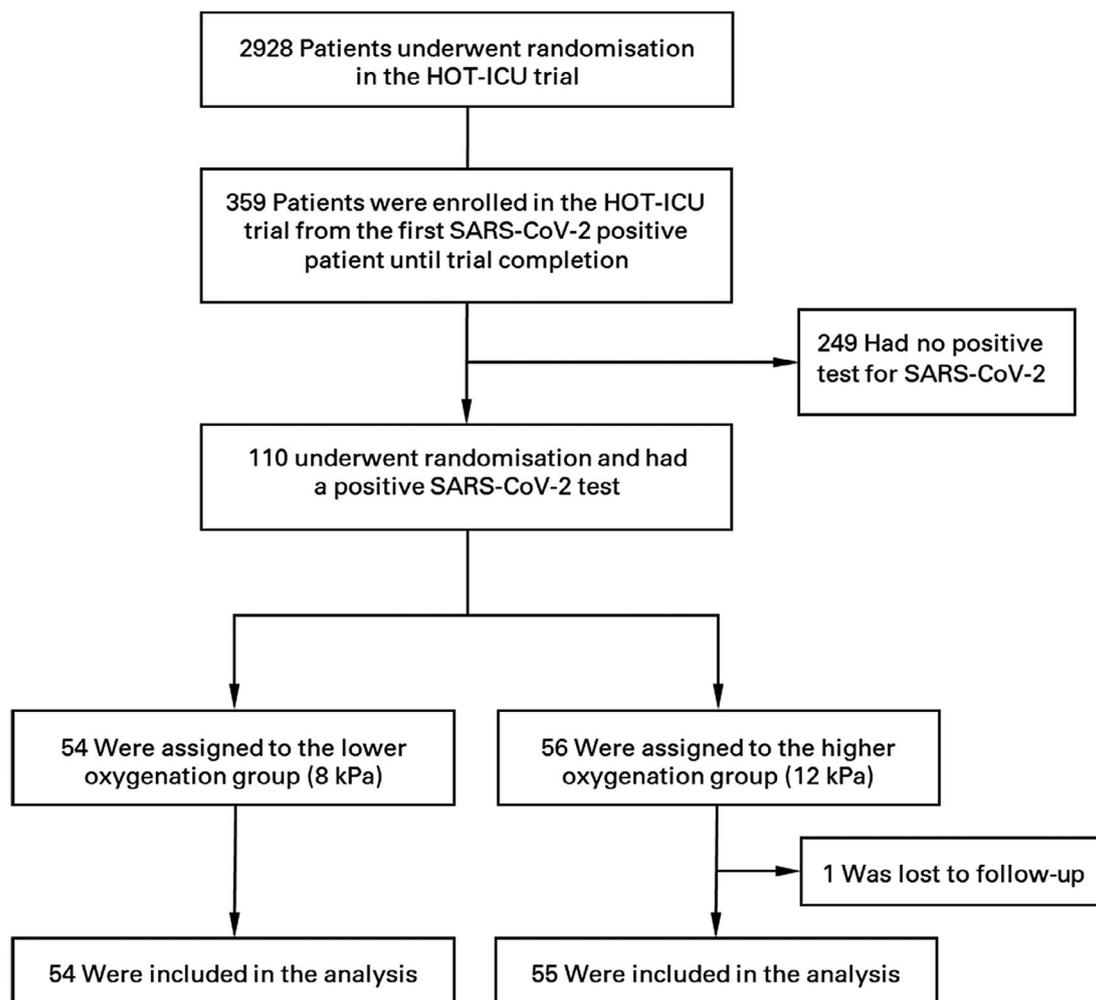


FIGURE 1 Assessment, randomization, and follow-up of COVID-19 patients enrolled in the HOT-ICU trial comparing a lower versus a higher oxygenation target in the ICU

TABLE 1 Baseline characteristics in the two allocation groups

Characteristics	Lower Oxygenation Group (n = 54)	Higher Oxygenation Group (n = 56)
Age—years, median (IQR)	71 (60–76)	69 (60–75)
Male sex—no. (%)	43 (79.6)	43 (76.8)
Time from hospital admission to randomization—days, median (IQR)	2 (1–6)	2 (0–5)
Time from ICU admission to randomization—hours, median (IQR)	4 (1–8)	3 (2–5)
Comorbidities—no. (%)		
Ischemic heart disease	6 (11.1)	6 (10.7)
COPD	6 (11.1)	5 (8.9)
Active hematological malignancy	5 (9.3)	3 (5.4)
Heart failure	2 (3.7)	3 (5.4)
Metastatic cancer	1 (1.9)	2 (3.6)
Chronic dialysis	2 (3.7)	0 (0.0)
Respiratory support at randomization—no. (%)		
Invasive mechanical ventilation	24 (44.4)	31 (55.4)
NIV or CPAP	3 (5.6)	3 (5.4)
Open systems—no. (%)	27 (50.0)	22 (39.3)
Invasive ventilation		
Tidal volume—mL, (IQR)	478 (414–533)	460 (378–570)
End-expiratory pressure—cm H ₂ O, median (IQR)	13 (11–15)	15 (12–15)
Peak inspiratory pressure—cmH ₂ O, median (IQR)	28 (23–30)	28 (23–30)
Non-invasive ventilation or CPAP		
End-expiratory pressure—cmH ₂ O, (IQR)	7 (6–8)	7 (5–10)
Oxygenation parameters at randomization		
PaO ₂ —kPa, median (IQR)	9.7 (8.4–11.3)	9.2 (8.3–10.4)
SaO ₂ —%, median (IQR)	94 (92–97)	93 (90–96)
FiO ₂ —median, (IQR)	0.73 (0.59–0.90)	0.70 (0.59–0.93)
PaO ₂ /FiO ₂ ratio—median (IQR)	13.8 (10.6–19.3)	13.9 (9.5–16.8)
Lactate—mmol/L, median (IQR)	1.2 (0.9–1.9)	1.2 (0.9–1.5)
Use of vasopressor—no. (%)	23 (42.6)	27 (48.2)
SOFA score—median (IQR)	6 (4–8)	6 (4–8)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, non-invasive ventilation; PaO₂, partial pressure of arterial oxygen; SaO₂, arterial oxygen saturation; SOFA, sequential organ failure assessment score.

compared to the higher oxygenation group being 79% and 71%, respectively (Table 2; Table S3). The corresponding days alive without life-support were 57.5 and 61.0, respectively (Table S2). A histogram

of percentages of days alive out of hospital in the two oxygenation groups are provided in the Supporting Information (Figure S4). No significant differences between the two groups were found in the percentage of days alive and out of the hospital or in the number of patients with one or more serious adverse events (Table 2; Table S4).

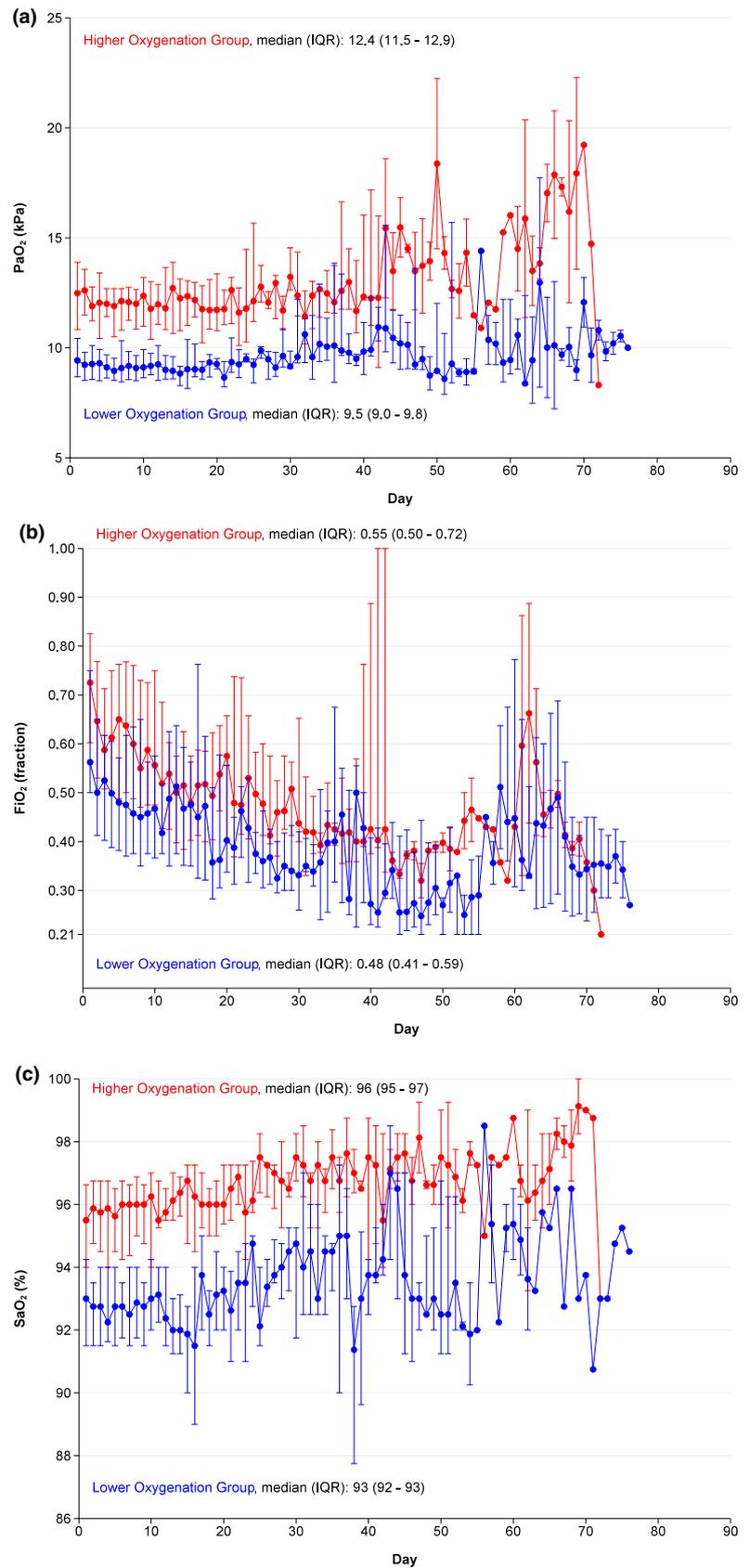
Tests for interaction between COVID-19 patients and the remaining HOT-ICU population without COVID-19 showed no statistically significant heterogeneity effect of the lower oxygenation target versus the higher oxygenation target on 90-day mortality ($p = 0.67$), percentage of days alive without life-support at day 90 ($p = 0.33$), or percentage of days alive out of the hospital at day 90 ($p = 0.33$).

4 | DISCUSSION

In this post hoc subgroup analysis of ICU patients with COVID-19 enrolled in the HOT-ICU trial, targeting a PaO₂ of 8 kPa was not associated with a statistically significant decrease in 90-day mortality as compared with targeting a PaO₂ of 12 kPa. The point estimates of treatment effect favored the lower oxygenation target, however, with wide confidence intervals and an insignificant test for interaction with the results of the main HOT-ICU trial. This emphasizes the importance of conducting larger trials to generate more robust data before a recommendation of oxygenation targets in ICU patients with COVID-19 can be provided.

There is no published randomized clinical trial on oxygenation targets in ICU patients with COVID-19.² Therefore, oxygen therapy in COVID-19 patients is guided by the SSC recommendation of a maximum SpO₂ target of 96%.¹⁸ The sparse evidence is based on data from a retrospective study in critically ill patients with hypoxia being associated with poor outcomes,¹⁹ a systematic review and meta-analysis in acutely ill adults being associated with increased mortality,²⁰ a clinical practice guideline for acutely ill medical patients,²¹ the ICU-ROX trial of mechanically ventilated ICU patients with equipoise between a lower oxygenation target and a higher oxygenation target,¹⁰ and the LOCO₂ trial of ARDS patients with potential harm in the lower oxygenation target group.⁸ The SpO₂ target of a maximum of 96% is maintained in the lower oxygenation group in our subgroup of COVID-19 patients in the ICU. In this subgroup, a higher percentage of days alive without life support, less frequent use of invasive mechanical ventilation, proning and inhaled vasodilators, a lower positive end-expiratory pressure, and a lower number of daily blood gas analyses were observed as compared with the higher oxygenation group. All patients in the subgroup had SARS-CoV-2 pneumonia, while only approximately 60% of the patients in the main HOT-ICU population were diagnosed with pneumonia at baseline,⁹ which may have an impact on the overall outcomes. Importantly, the results of the subgroup of COVID-19 patients are hypothesis generating as it is a pilot study not pre-planned and with a low number of patients. An ongoing randomized clinical trial (HOT-COVID: NCT04425031), which is an extension of the HOT-ICU trial, will potentially provide solid data to generate more valid guidelines.

FIGURE 2 PaO₂, FiO₂, and SaO₂ by allocation group presented in figures (a), (b) and (c), respectively. The medians of daily means of the partial pressure of arterial oxygen (PaO₂), the fraction of inspired oxygen (FiO₂), and the arterial oxygen saturation (SaO₂) in the ICU up until day 90. Daily means were calculated from the 12-h lowest and highest PaO₂ with concomitant values for FiO₂ and SaO₂. Bars represent interquartile ranges (IQR). IQR are missing for some points as there is only one measurement for these particular days, see Table S1 in the supplement for patient numbers by days. SaO₂ values were not available in blood gas analyses from one site and were therefore missing for 19 patients [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]



COVID-19 is a life-threatening condition as it can lead to profound hypoxemia and ARDS.^{22,23} In our COVID-19 subgroup, the patients had severe hypoxaemic respiratory failure at baseline

elucidated by a median PaO₂/FiO₂ ratio <14 kPa and the majority of patients being invasively mechanically ventilated. The high incidence of mechanically ventilated COVID-19 patients may partly be

TABLE 2 Outcomes at day 90 and processes of care during ICU stay in the two allocation groups

Outcomes	Lower oxygenation group (n = 54)	Higher oxygenation group (n = 55)	Risk difference (95% CI)	Risk ratio ^a /Odds ratio ^b (95% CI)	p value
Primary outcome at day 90					
Death by day 90	22 (40.7)	23 (41.8)	-1.08 (-19.56 to 17.41)	0.97 ^a (0.62 to 1.52)	0.91
Adjusted for stratification variables			-0.45 (-17.77 to 16.87)	0.87 ^a (0.58 to 1.32)	0.51
Adjusted for stratification and baseline variables				0.66 ^b (0.26 to 1.70)	0.39
Secondary outcomes at day 90					
Percentage of days alive without life support	79 (0-90)	71 (0-84)			0.03
Percentage of days alive and out of hospital [†]	33.3 (0.0-71.1)	1.0 (0.0-65.6)			0.18
Number of serious adverse events in the ICU	30 (55.6)	30 (53.7)			0.90
Shock	30 (55.6)	29 (51.8)			
Myocardial ischemia	1 (1.9)	0 (0.0)			
Intestinal ischemia	1 (1.9)	0 (0.0)			
Ischemic stroke	0 (0.0)	1 (1.8)			
Processes of care in the ICU					
Daily number of arterial blood gases	7 (6-9)	8 (7-9)			0.04
Respiratory support	47 (87.0)	55 (98.2)			0.03
Invasive MV	45 (83.3)	54 (96.4)			0.03
NIV or CPAP	5 (9.3)	4 (7.1)			0.74
In invasively mechanically ventilated patients					
Tidal volume (mL/kg)	7.0 (6.7-7.6)	7.3 (6.7-7.8)			0.51
PEEP (cm H ₂ O)	12 (10-13)	13 (12-15)			<0.01
PIP (cmH ₂ O)	26 (23-28)	27 (23-30)			0.19
Prone position	15 (27.8)	31 (55.4)			<0.01
Inhaled vasodilators	3 (5.6)	13 (23.2)			0.01
ECMO	1 (1.9)	3 (5.4)			0.62
Vasopressors or inotropes	45 (83.3)	53 (94.6)			0.07
Renal replacement therapy	16 (29.6)	14 (25.0)			0.67
Red blood cell transfusion	14 (25.9)	17 (30.4)			0.67

Note: Data are presented as median (IQR) or n (%), as appropriate.

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; NIV, non-invasive ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

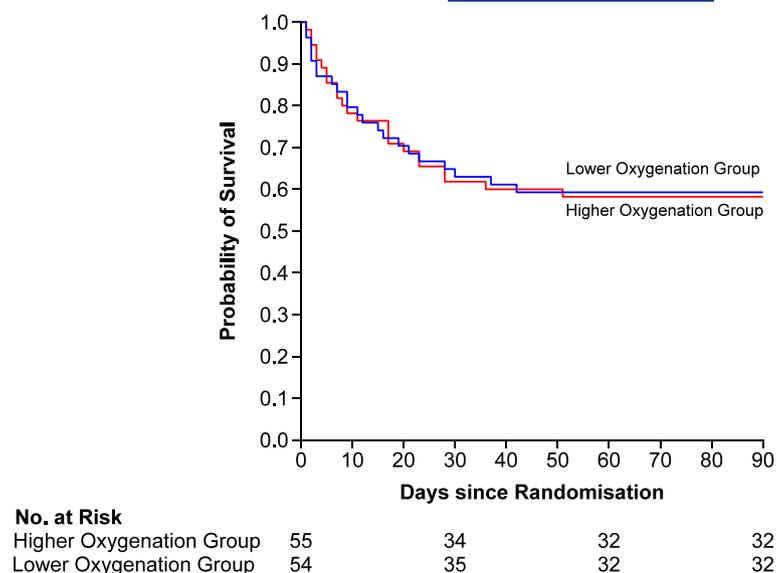
*The seemingly large difference in the two-point estimates is due to a zero-inflated negatively skewed distribution (the histograms are provided in the Supporting Information).

explained by the restricted use of high flow nasal cannula during the first phase of the pandemic.^{22,24} The currently available evidence on targeting oxygen therapy in patients with ARDS is of very low certainty due to lack of data² with only one randomized clinical trial conducted, the LOCO₂ trial.⁸ This trial was stopped prematurely due to a high proportion of intestinal ischemia in the lower oxygenation group,⁸ an observation which could be by chance as no differences in severe ischemic events occurred in neither the main HOT-ICU trial⁹ nor in the present subgroup of COVID-19 patients. Of interest, proning and inhaled vasodilators were used less frequently in the lower oxygenation groups as compared to the higher oxygenation group, similarly to the LOCO₂ trial⁸ and to what was found in the main HOT-ICU trial.⁹ We found no significant difference in mortality at 90 days in the subgroup of COVID-19 patients. The mortality

seen in our subgroup was higher than in the LOCO₂ trial; however, it is consistent with what has been reported worldwide in patients with critical COVID-19.¹ The high mortality may be due to a high frequency of multiorgan dysfunction in critically ill COVID-19 patients^{18,25}; 25% of COVID-19 patients in our study received renal replacement therapy and more than half had at least one episode of shock.

The strengths of the present subgroup analysis are the variety of ICUs and countries involved, the pragmatic protocol maintaining routine practice except for the oxygenation targets, and the clear separations in PaO₂, SaO₂, and FiO₂ between the two groups. The limitations are that patients with COVID-19 were not a pre-planned subgroup in the HOT-ICU trial,⁹ no stratification for a positive SARS-CoV-2 was conducted, the sample size was small, personnel were

FIGURE 3 Kaplan–Meier plots of survival. The unadjusted hazard ratio is 0.98 [(95% CI 0.55–1.75, $p = 0.98$)] and the hazard ratio adjusted for the stratification variables chronic obstructive pulmonary disease, hematological malignancy, and site was 0.82 with 95% CI, 0.45–1.50 ($p = 0.94$) [Colour figure can be viewed at wileyonlinelibrary.com]



not blinded, and data of specific medical treatments for COVID-19 were collected. Also, targeting higher oxygenation may make interventions more likely to occur to achieve this, thus if there is harm in the higher oxygenation group, it may result from the interventions to achieve this and not from the oxygen itself.

In conclusion, in this post hoc subgroup analysis of ICU patients with COVID-19 enrolled in the HOT-ICU trial, a lower oxygenation target did not result in a statistically significant reduction in mortality as compared to higher oxygenation target. With the depleted oxygen resources in the part of the world, our data may justify the present recommendation with a SpO₂ target up to a maximum of 96% until more solid evidence is obtained.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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