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**Oxygenation targets in ICU patients with COVID-19: a post-hoc sub-group 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 hours of ICU admission. Oxygen therapy was titrated to a partial pressure of arterial oxygen ($PaO_2$) of 8 kPa (lower oxygenation group) or a $PaO_2$ of 12 kPa (higher oxygenation group) during ICU stay up to 90 days. We report key outcomes at 90 days for the sub-group 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). Percentage of days alive without life support was significantly higher in the lower oxygenation group (p=0.03). 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 sub-group 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:** Severe acute respiratory syndrome coronavirus 2, Oxygen Inhalation Therapy, Respiratory Insufficiency, Randomised Controlled Trial, Intensive Care Units

**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 an 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 a oxygen level of 8 kPa is both safe and potentially beneficial for patients with COVID-19.

## 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 hypoxaemia 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 aetiology, clinical practice guidelines give no recommendation for oxygenation targets [3,4]. One oxygenation target that is often referred to is a partial pressure of arterial oxygen ($PaO_2$) between 7.3 to 10.7 kPa or a $SpO_2$ of 88 to 95% defined as standard of care in randomised trials performed by the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network [5-7]. A recent trial, Liberal or Conservative Oxygen Therapy ($LOCO_2$), 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 five of 99 patients had mesenteric ischaemia 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 number of ischaemic 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 Randomised 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 sub-group of COVID-19 patients enrolled in HOT-ICU trial.

## Methods

### 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 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, multicentre, stratified, parallel-grouped, randomised 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. Centralised randomisation 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 haematological malignancy. No stratification for SARS-CoV-2 status was implemented. The hypothesis of the HOT-ICU trial was that a $PaO_2$ target of 8 kPa would reduce 90-day mortality, being the primary outcome, as compared with a $PaO_2$ 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]

**Patients**

We screened patients aged 18 years or above who were acutely admitted to the ICU, received at least 10 litres of oxygen per minute in an open system or at least a fraction of inspired oxygen ($FiO_2$) of 0.50 in a closed system, had an arterial line, and were expected to receive supplemental oxygen therapy for at least 24 hours in the ICU. We excluded patients that could not be randomised within 12 hours of ICU admission; all exclusion criteria are provided in the Supplement. In the present sub-group 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 randomisation or at any time during the ICU admission.

**Intervention**

Patients were randomly assigned to oxygen therapy titrated to achieve a $PaO_2$ of 8 kPa (lower oxygenation group) or a $PaO_2$ of 12 kPa (higher oxygenation group) during the entire ICU stay, including re-admissions, to a maximum of 90 days after randomisation. To document the intervention, we registered the lowest and the highest $PaO_2$ in predefined 12-hour intervals with concomitant values for arterial oxygen saturation ($SaO_2$) and $FiO_2$. All patients were continuously monitored with $SpO_2$ to maintain the assigned $PaO_2$. The oxygenation targets were achieved by adjustments of the $FiO_2$. All other interventions in the ICU were at the discretion of the clinicians.

**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 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 number of patients with one or more serious adverse events defined as a new episodes of shock, myocardial ischaemia, intestinal ischaemia, or ischaemic stroke in the ICU within 90 days, details are provided in the Supplement.

**Statistical analysis**

We did no sample size estimation for the analyses reported here. All analyses were conducted according to the intention-to-treat principle [13] and according to the statistical analysis plan for the HOT-ICU trial.[12] The intention-to-treat population included all randomised patients positive for SARS-CoV-2 in the HOT-ICU trial except for those where follow-up data could not be obtained due to withdrawal of consent according to national regulations.[14-16]

We compared 90-day mortality in the two groups using a generalised linear model with a log-link and a binomial error distribution adjusted for the stratification variables site and COPD, but not for active haematological 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 hospital at day 90 were compared using the van Elteren test with adjustment for site. The number of patients with one or more serious adverse events in the two groups was compared using a generalised linear model with a log-link and a binomial error distribution adjusted for the stratification variables COPD and active haematological 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 less than 5% of data was missing in all parameters. Comparisons of processes during the ICU stay were conducted using 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, Stockholm, Sweden).

## 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, f46 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).

### Oxygenation and ICU treatments

During the 90 days of intervention in the ICU, the daily medians of the registered $PaO_2$ and the corresponding $FiO_2$ and $SaO_2$ 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 Supplement, as well as the highest and lowest registered $PaO_2$ with corresponding $FiO_2$ and $SaO_2$ (Table S1 and Figure S1 to S3). Details on the process of care in the ICU for the two oxygenation groups are provided in Table 2.

### Outcomes and Interaction analysis

Ninety days after randomisation 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 and Figure 3). The percentage of days alive without life support at day 90 was significantly increased in the lower oxygenation group as compared to the higher oxygenation group being 79% and 71%, respectively (Tables 2 and 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 Supplement (Figure S4). No significant differences between the two groups were found in the percentage of days alive and out of hospital or in the number of patients with one or more serious adverse events (Table 2 and 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 hospital at day 90 (P=0.33).

**Discussion**

In this post-hoc sub-group analysis of ICU patients with COVID-19 enrolled in the HOT-ICU trial, targeting a $PaO_2$ of 8 kPa was not associated with a statistically significant decrease in 90-day mortality as compared with targeting a $PaO_2$ of 12 kPa. The point estimates of treatment effect favoured 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 emphasises 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 randomised clinical trial on oxygenation targets in ICU patients with COVID-19.[2] Therefore, oxygen therapy in COVID-19 patients are guided by the SSC recommendation of a maximum $SpO_2$ 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 $LOCO_2$ trial of ARDS patients with potential harm in the lower oxygenation target group.[8] The $SpO_2$ target of a maximum of 96% is maintained in the lower oxygenation group in our sub-group of COVID-19 patients in the ICU. In this sub-group, 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 sub-group 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 sub-group 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 randomised clinical trial (HOT-COVID: NCT04425031), which is an extension of the HOT-ICU trial, will potentially provide solid data to generate more valid guidelines.

COVID-19 is a life-threatening condition as it can lead to profound hypoxaemia and ARDS.[22,23] In our COVID-19 sub-group, the patients had severe hypoxaemic respiratory failure at baseline elucidated by a median $PaO_2/FiO_2$ ratio <14 kPa and the majority of patients being invasively mechanically ventilated. The high incidence of mechanically ventilated COVID-19 patients may partly be 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 data[2] with only one randomised clinical trial conducted, the $LOCO_2$ trial.[8] This trial was stopped prematurely due to a high proportion of intestinal ischaemia in the lower oxygenation group,[8] an observation which could be by chance as no differences in severe ischaemic events occurred in neither the main HOT-ICU trial[9] nor in the present sub-group 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 $LOCO_2$ trial[8] and to what was found in the main HOT-ICU trial.[9] We found no significant difference in mortality at 90 days in the sub-group of COVID-19 patients. The mortality seen in our sub-group was higher than in the $LOCO_2$ 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 sub-group 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 $PaO_2$, $SaO_2$ and $FiO_2$ between the two groups. The limitations are that patients with COVID-19 were not a pre-planned sub-group in the HOT-ICU trial,[9] no stratification for a positive SARS-CoV-2 was conducted, the sample size was small, personnel were not blinded, and data of specific medical treatments for COVID-19 were collected. Also, targeting a 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 sub-group 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 a higher oxygenation target. With the depleted oxygen resources in part of the world our data may justify the present recommendation with a $SpO_2$ 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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**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 randomisation – days, median (IQR) | 2 (1-6) | 2 (0-5) |
| Time from ICU admission to randomisation – hours, median (IQR) | 4 (1-8) | 3 (2-5) |
| Comorbidities – no. (%) | | |
| Ischaemic heart disease | 6 (11.1) | 6 (10.7) |
| COPD | 6 (11.1) | 5 (8.9) |
| Active haematological 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 randomisation – 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 $H_2O$, median (IQR) | 13 (11-15) | 15 (12-15) |
| Peak inspiratory pressure – $cmH_2O$, median (IQR) | 28 (23-30) | 28 (23-30) |
| Non-invasive ventilation or CPAP | | |
| End-expiratory pressure – $cmH_2O$, (IQR) | 7 (6-8) | 7 (5-10) |
| Oxygenation parameters at randomisation | | |
| $PaO_2$ – 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) |

IQR interquartile range, ICU intensive care unit, COPD chronic obstructive pulmonary disease, NIV non-invasive ventilation, CPAP continuous positive airway pressure, $PaO_2$ partial pressure of arterial oxygen, $SaO_2$ arterial oxygen saturation, $FiO_2$ fraction of inspired oxygen, SOFA sequential organ failure assessment score

**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 ischaemia | 1 (1.9) | 0 (0.0) | | | |
| Intestinal ischaemia | 1 (1.9) | 0 (0.0) | | | |
| Ischaemic 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 $H_2O$) | 12 (10-13) | 13 (12-15) | | | <0.01 |
| PIP (cm$H_2O$) | 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: IQR, interquartile range; ICU, intensive care unit; MV, mechanical ventilation; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; ECMO, extra corporeal membrane oxygenation.

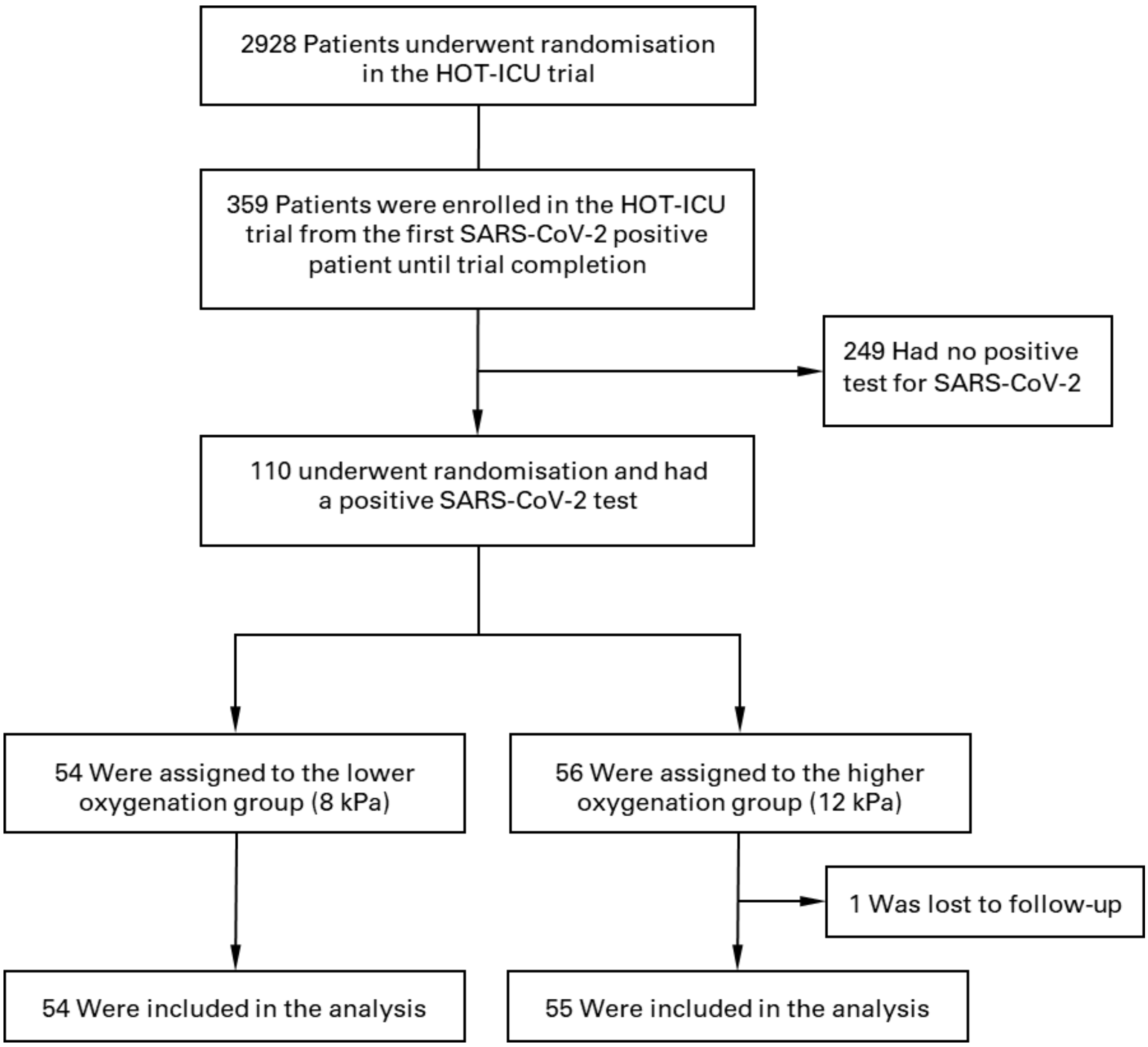
*The seemingly large difference in the two point estimates is due to a zero inflated negatively skewed distribution (the histograms are provided in the supplement)

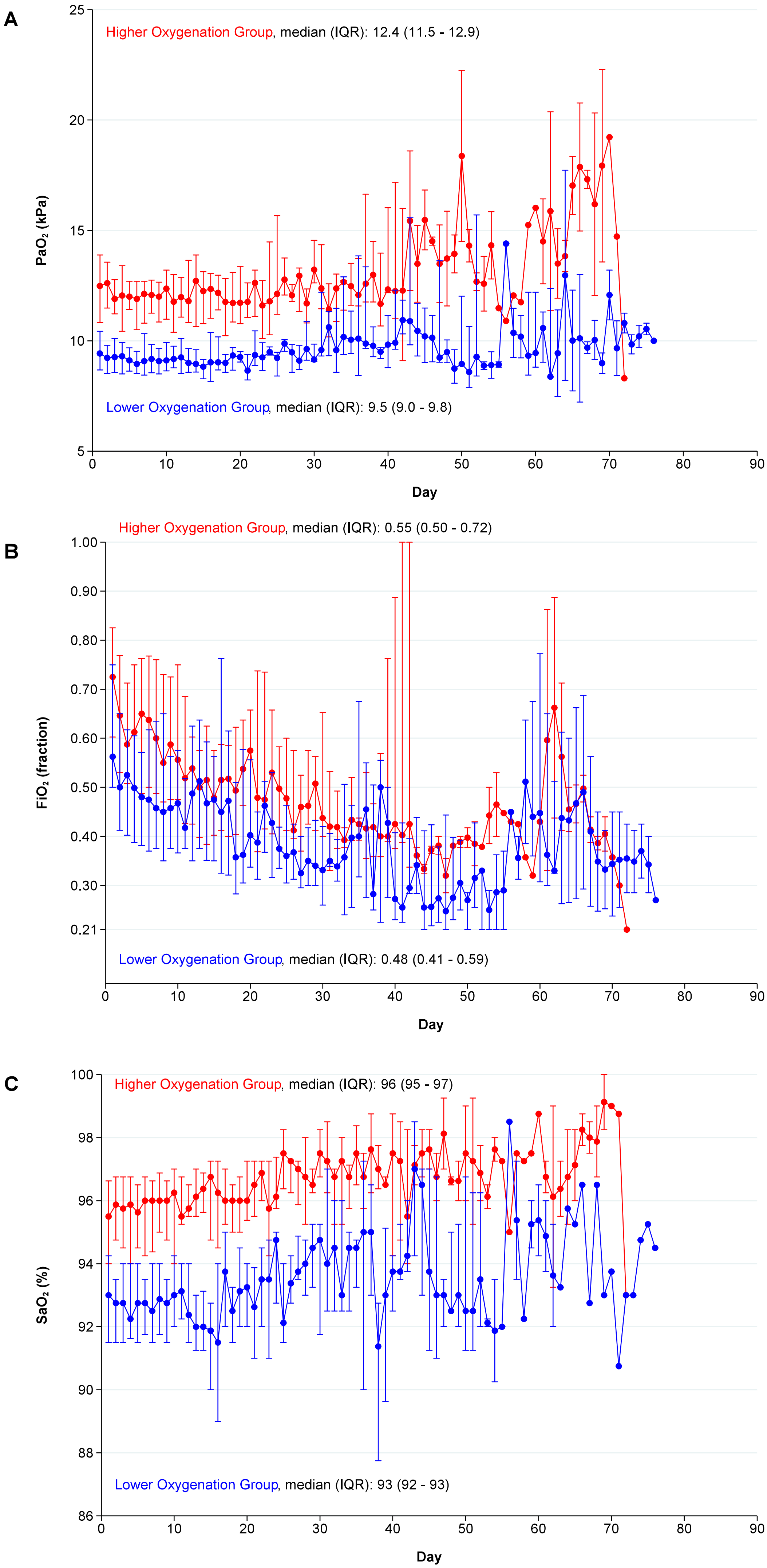
**Figure captions**

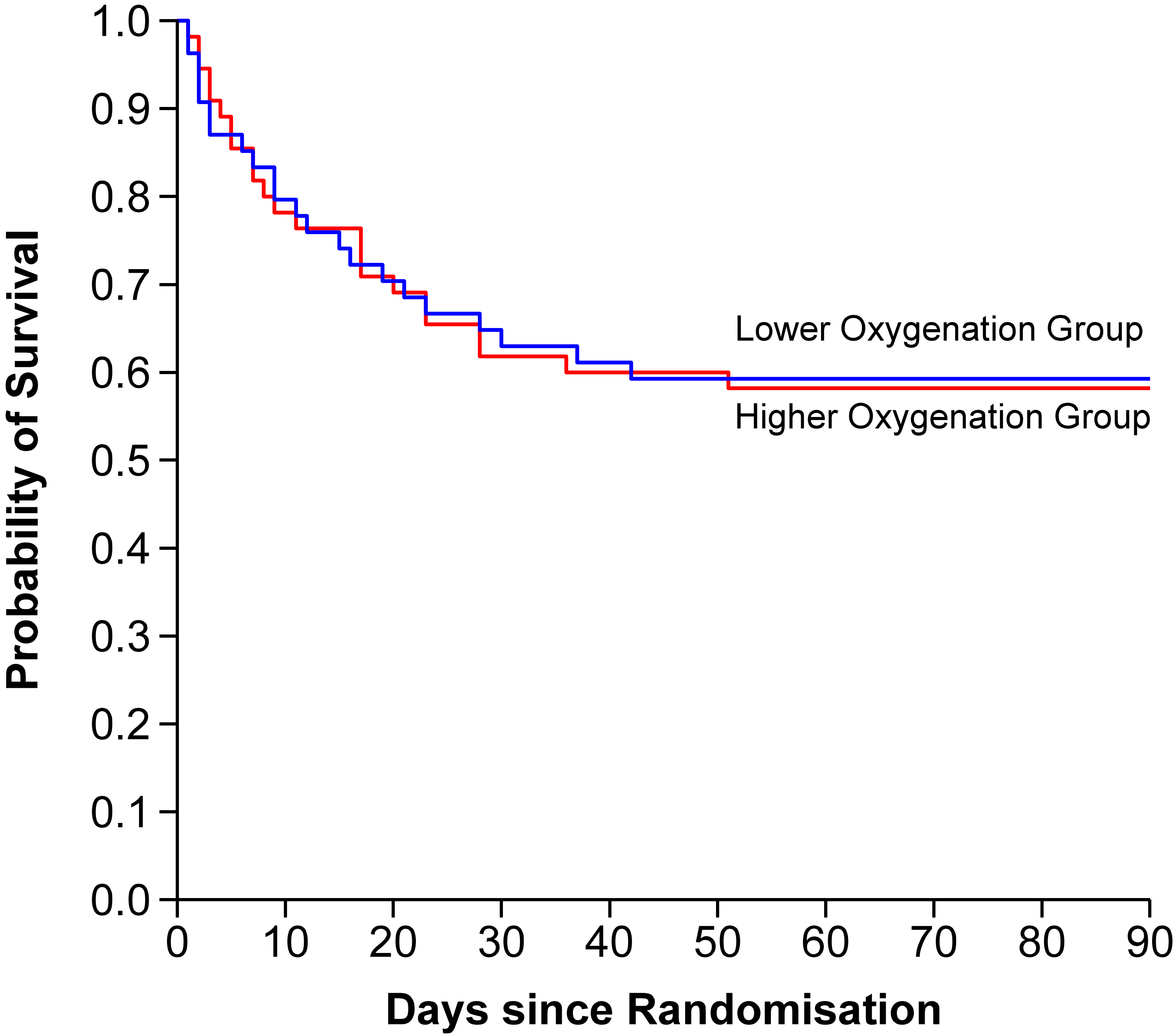
**Figure 1** Assessment, randomisation and follow-up of COVID-19 patients enrolled in the HOT-ICU trial comparing a lower versus a higher oxygenation target in the ICU.

**Fig. 2** $PaO_2$, $FiO_2$ and $SaO_2$ by allocation group. The medians of daily means of the partial pressure of arterial oxygen ($PaO_2$), the fraction of inspired oxygen ($FiO_2$), and the arterial oxygen saturation ($SaO_2$) in the ICU up until day 90. Daily means were calculated from the 12-hour lowest and highest $PaO_2$ with concomitant values for $FiO_2$ and $SaO_2$. 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. $SaO_2$ values were not available in blood gas analyses from one site and were therefore missing for 19 patients.

**Fig. 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, haematological malignancy, and site was 0.82 with 95% CI, 0.45 to 1.50 (P=0.94).


2928 Patients underwent randomisation in the HOT-ICU trial
359 Patients were enrolled in the HOT-ICU trial from the first SARS-CoV-2 positive patient until trial completion
249 Had no positive test for SARS-CoV-2
110 underwent randomisation and had a positive SARS-CoV-2 test
54 Were assigned to the lower oxygenation group (8 kPa)
56 Were assigned to the higher oxygenation group (12 kPa)
1 Was lost to follow-up
54 Were included in the analysis
55 Were included in the analysis


A
Higher Oxygenation Group, median (IQR): 12.4 (11.5 - 12.9)
Lower Oxygenation Group, median (IQR): 9.5 (9.0 - 9.8)
PaO2 (kPa)
Day
B
Higher Oxygenation Group, median (IQR): 0.55 (0.50 - 0.72)
Lower Oxygenation Group, median (IQR): 0.48 (0.41 - 0.59)
FiO2 (fraction)
Day
C
Higher Oxygenation Group, median (IQR): 96 (95 - 97)
Lower Oxygenation Group, median (IQR): 93 (92 - 93)
SaO2 (%)
Day




**No. at Risk**

| | | | | |
|---|---|---|---|---|
| Higher Oxygenation Group | 55 | 34 | 32 | 32 |
| Lower Oxygenation Group | 54 | 35 | 32 | 32 |