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The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study

Gregory L. Calligaro*[1,2] , Usha Lalla*[3], Gordon Audley[4], Phindile Gina[1], Malcolm G. Miller[2], Marc Mendelson[5], Sipho Dlamini[5], Sean Wasserman[5,6], Graeme Meintjes[6,7], Jonathan Peter[8], Dion Levin[9], Joel A. Dave[10], Ntobeko Ntusi[7], Stuart Meier[1], Francesca Little[11], Desiree L. Moodley[3], Elizabeth H. Louw[3], Andre Nortje[3], Arifa Parker[12], Jantjie J. Taljaard[12], Brian W. Allwood[3], Keertan Dheda*[1,2,13] and Coenraad F.N. Koegelenberg*[3].

* These authors contributed equally.

1 Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute and South African MRC/UCT Centre for the Study of Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa.

2 Division of Critical Care, Department of Anaesthesia and Perioperative Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

3 Division of Pulmonology, Department of Medicine, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

4 Division of General Medicine, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

5 Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

6 Wellcome Centre for Infectious Disease Research in Africa (CIDRI-Africa), Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

7 Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

8 Division of Clinical Immunology and Allergology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

9 Division of Gastroenterology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

10 Division of Endocrinology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

[11] Department of Statistical Sciences, University of Cape Town, Cape Town, South Africa.

[12] Division of Infectious Diseases, Department of Medicine, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa.

[13] Faculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author:

A/Professor Gregory Calligaro
Division of Pulmonology, Department of Medicine, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa
Tel: +27 21 404 4435 Fax: +27 21 404 7651
E-mail: greg.calligaro@uct.ac.za

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ABSTRACT

BACKGROUND: The utility of heated and humidified high-flow nasal oxygen (HFNO) for severe COVID-19-related hypoxaemic respiratory failure (HRF), particularly in settings with limited access to intensive care unit (ICU) resources, remains unclear, and predictors of outcome have been poorly studied.

METHODS: We included consecutive patients with COVID-19-related HRF treated with HFNO at two tertiary hospitals in Cape Town, South Africa. The primary outcome was the proportion of patients who were successfully weaned from HFNO, whilst failure comprised intubation or death on HFNO.

FINDINGS: The median (IQR) arterial oxygen partial pressure to fraction inspired oxygen ratio (P_aO2/FiO_2) was 68 (54-92) in 293 enrolled patients. Of these, 137/293 (47%) of patients [P_aO2/FiO_2 76 (63-93)] were successfully weaned from HFNO. The median duration of HFNO was 6 (3-9) in those successfully treated versus 2 (1-5) days in those who failed (p<0.001). A higher ratio of oxygen saturation/FiO2 to respiratory rate within 6 hours (ROX-6 score) after HFNO commencement was associated with HFNO success (ROX-6; AHR 0.43, 0.31-0.60), as was use of steroids (AHR 0.35, 95%CI 0.19-0.64). A ROX-6 score of ≥3.7 was 80% predictive of successful weaning whilst ROX-6 ≤2.2 was 74% predictive of failure. In total, 139 patents (52%) survived to hospital discharge, whilst mortality amongst HFNO failures with outcomes was 129/140 (92%).

INTERPRETATION: In a resource-constrained setting, HFNO for severe COVID-19 HRF is feasible and more almost half of those who receive it can be successfully weaned without the need for mechanical ventilation.

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RESEARCH IN CONTEXT

Evidence before this study: The utility of high-flow nasal oxygen (HFNO) for severe Coronavirus disease 2019 (COVID-19)-related hypoxaemic respiratory failure (HRF), particularly in settings with limited access to intensive care unit (ICU) resources, remains unclear. We searched PubMed and Google Scholar for articles published in all languages up to 25 July 2020 using the search terms “HFNO”, “HFNC”, “COVID-19”, “respiratory failure”, “ARDS”, “ICU”, “mechanical ventilation”, and “outcomes”. We identified only 4 studies (2 in non-peer-reviewed preprint format) that evaluated HFNO in COVID-19-related HRF. The four studies together included a total of 312 patients, all were retrospective, and only one study enrolled patients from a resource-limited setting (China). Significantly, none were from HIV-endemic or resource-poor (African) settings, and none evaluated the effect of steroids in modulating outcomes, which is now the standard of care.

Added value of this study: To our knowledge this is the largest prospective observational study to evaluate HFNO for severe COVID-19 pneumonia. We showed that HFNO in combination is feasible and can successfully be utilised to provide respiratory support to a significant proportion of patients with COVID-19-related HRF. Moreover, this approach avoided mechanical ventilation even in patients with profound hypoxaemia. A higher ROX index measured at 6 hours after HFNO initiation (ROX-6), along with treatment with steroids, independently predicted success. A generalised model was fit to the data to determine the relative weighting and importance of each predictor including individual components of the ROX score. The majority of our patients received HFNO in a ward-based non-critical care environment, demonstrating

the feasibility of HFNO outside of the ICU using affordable pulse oximetry-based monitoring.

Implications of all the available evidence: In a resource-constrained setting, HFNO for severe COVID-19 HRF is feasible and more almost half of those who receive it can be successfully weaned without the need for mechanical ventilation.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially fatal infection caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. The highly contagious nature and exponential spread of SARS-CoV-2, coupled with its potential for a rapid progression to acute respiratory distress syndrome (ARDS), has overwhelmed health care systems globally, contributing to the high mortality rates in early reports[1,2].

The initial approach for respiratory support for severe COVID-19 pneumonia centred around invasive mechanical ventilation and the standard lung protective strategy recommended for ARDS[3]. This may have been detrimental to a proportion of patients due to ventilator induced lung injury (VILI) and associated systemic inflammation[4]. Furthermore, other strategies to improve oxygenation may be more appropriate in patients with hypoxemic respiratory failure who do not require ventilatory support[4].

High-flow nasal oxygen (HFNO) is delivered by an air/oxygen blender, an active humidifier, a single heated circuit, and a nasal interface. It delivers adequately heated and humidified medical gas at flow-rates of up to 60 L/min, and is considered to have a number of physiological benefits, including the reduction of anatomical dead space and work of breathing, the provision of a constant fraction of inspired oxygen with adequate humidification and a degree of positive end-expiratory pressure (PEEP)[5,6]. Although HFNO was originally utilised in neonatology, its use has extended to adult critical care[6].

The Western Cape Province was the initial epicentre of the outbreak in South Africa, the country which by early September 2020 had recorded the seventh highest number of confirmed COVID-19 cases worldwide [7]. The ratio of ICU to hospital beds in the

public health sector in South Africa is only ~4%[8]. In April 2020, in anticipation of the rapid saturation of the existing critical care capacity resources, the two major tertiary centres in Cape Town adopted the use of HFNO, both inside the intensive care unit (ICU) and in non-critical care environments, in an effort to increase the capacity to manage patients with severe respiratory failure secondary to COVID-19[9].

To date, few retrospective studies with limited sample sizes, one of which is from a relatively resource-limited setting (China), have evaluated HFNO in COVID-19-related HRF[10-13]. However, to what extent HFNO is feasible in a more resource-poor, HIV-endemic, and non-ICU setting, remains unclear. Moreover, the predictors of treatment failure and the modulating effect of steroids thereon remain unclarified. We hypothesised that a significant proportion of patients with hypoxemic respiratory failure could be supported with HFNO as initial support, thereby decreasing the burden on our healthcare system's intensive care during the COVID-19 pandemic. Thus, the main aim of this study was to assess the impact of HFNO in avoiding mechanical ventilation in patients with severe respiratory failure secondary to COVID-19. As secondary objectives, we aimed to identify potential physiological parameters or biomarkers that may predict HFNO failure and assessed overall survival to hospital discharge.

METHODS

Study design

We conducted a prospective multi-centre observational study within the public health system in Cape Town, South Africa. The study was approved by the local ethics committees at each site (UCT HREC 295/2020 and SU HREC S20/05/001_COVID-19), and informed consent was waived in acknowledgement that the intervention was

being assessed within the routine service. The study is reported in accordance with the STROBE statement for cohort studies[14] (Supplementary Appendix).

Setting

The study was conducted at two urban tertiary academic hospitals in Cape Town, South Africa [Groote Schuur Hospital (GSH) and Tygerberg Hospital (TBH)], servicing a population of ~4.5 million with high tuberculosis and HIV prevalence[15]. Patients were enrolled from the 19th of April to the 30th of June 2020. During this period, each hospital admitted ~15-20 COVID-19 positive patients per day. At the end of the study period, GSH had admitted 1342 patients with COVID-19, and had increased ICU bed capacity three-fold to 55 beds, admitting ~25-30 ventilated patients to ICU per week during the peak (all HFNO being offered in repurposed medical wards)[16,17]; at TBH, 1016 patients with COVID-19 were admitted during the study period, ICU bed capacity had tripled to 45 beds, and ~25 patients were admitted to ICU (both ventilated and for HFNO) per week during the peak (personal communication, Directorate of Health Impact Assessment, Western Cape Government: Health).

Participants

Eligible participants were consecutive adult patients (aged ≥18 years) with severe respiratory failure, and laboratory-confirmed COVID-19 pneumonia [detection of SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) on any respiratory sample] who were treated with HFNO during hospitalisation. Severe respiratory failure was defined as a respiratory rate ≥30 breaths per minute with oxygen saturations ≤92% despite oxygen at 15L/min via reservoir bag, and/or arterial oxygen partial pressure to fractional inspired oxygen (P_aO_2/FiO_2) ratio<150. The decision to initiate HFNO was at the discretion of the treating clinical team based on a

protocol for the stepwise escalation of oxygen therapy, and was contraindicated in patients with exhaustion or confusion. Likewise, the decision on the timing of intubation and mechanical ventilation was not protocolised, but determined by the treating clinical team on a composite assessment of respiratory effort, patient exhaustion, rising arterial partial pressure of carbon dioxide ($PaCO_2$) or altered mental state rather than a single measure of oxygenation such as saturation or P_aO_2. Awake prone positioning was encouraged at every clinical encounter and reinforced by nursing staff according to a shared clinical protocol.

Therapeutic interventions like anticoagulation strategy and the use of steroids (both physician directed) were also recorded. No other SARS-CoV-2 directed therapy was provided to any patient, either off-label or as part of a clinical trial, at either hospital during the study period. The start of the study predated the preliminary report of the efficacy of dexamethasone by RECOVERY[18], and prescription of corticosteroids prior to this date was by physician preference. After the 16th of June, all patients on HFNO received either dexamethasone 6mg intravenously daily, or prednisone 40mg daily for 10 days.

HFNO

Heated and humidified HFNO was exclusively provided within the ICU at TBH, and within designated medical wards (non-ICU) at GSH where patients were cohorted. Patients wore surgical masks and all personnel were supplied with personal protective equipment, including N95 masks and visors. HFNO was delivered either by a Hamilton C1 ventilator (Hamilton Medical AG, Bonaduz, Switzerland), Airvo™ 2 (Fisher & Paykel Healthcare, Irvine, California, USA) or Inspire™ O^{2}FLO (Vincent Medical, Hong Kong,

China) machine. Flow was initiated at 50-60L/min with FiO_2 0.8-1.0, titrated to aim for an oxygen saturation (SpO_2) ≥92%.

Procedures

Demographic and clinical variables, and if available, contemporaneous peripheral blood differential counts and inflammatory biomarkers (D-dimer and C-reactive protein) were recorded on commencement of HFNO. HFNO settings (FiO_2 and flow rate) along with heart rate, respiratory rate and peripheral oxygen saturations were recorded at 6 hours post-initiation of HFNO. Using these variables, we calculated the validated ROX score[19] (ratio of oxygen saturation/FiO2 to respiratory rate) at 6 hours (ROX-6) and modified ROX score[20] (ROX score divided by heart rate) at 6 hours (mROX-6) score. For patients who were intubated before 6 hours, the variables at the time that the decision was made that HFNO was failing were recorded.

Outcomes

The primary endpoint was the proportion of patients with a successful outcome (weaned off HFNO). Failure was defined as composite of the need for intubation or death whilst on HFNO. Of secondary interest were predictors of HFNO failure, and survival to hospital discharge (percentage of patients discharged home alive, or transferred to a rehabilitation facility, excluding patients still admitted and undergoing treatment).

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and were compared using Pearson's χ^2 tests or Fisher's exact tests. Continuous variables were expressed as means with standard deviations, or medians with inter-quartile ranges.

Non-parametric data was compared using Wilcoxon rank-sum tests. A CONSORT diagram reported the flow of patients in the study (Figure 1). The crude cumulative proportion of HFNO success was calculated. Predictors of intubation were primarily analysed using a Cox proportional hazards model, incorporating clinically important variables selected *a priori* for the model. The index date was the date of initiation of HFNO, with censoring occurring upon intubation, death, or the end of the study (30th June 2020). Receiver operating characteristic (ROC) curves were constructed using the software program GraphPad Prism (version 8, GraphPad Software, USA) and Youden's index was calculated to determine the cut-off that maximised sensitivity and specificity for ROX-6 and mROX-6[21]. Descriptive statistics, comparisons between parametric and non-parametric samples, and Cox proportional hazards regression were performed using Stata (V.12.1, Stata Corp, College Station, Texas, USA)[22].

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first and last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patient population

During the enrolment period of our study, each hospital admitted between 30 to 60 COVID-19 positive patients per day. GSH admitted 1288 patients with COVID-19, increasing ICU bed capacity three-fold to 55 beds, admitting ~25-30 ventilated patients to ICU per week (all HFNO being offered in repurposed medical wards). At TBH, 1244

patients with COVID-19 were admitted, ICU bed capacity had also been tripled to 45 beds, and ~35 patients were admitted to ICU (both ventilated and for HFNO) per week.

Two hundred and ninety-three patients were enrolled between the 16th of April and 30th of June 2020: 105 (36%) were admitted to the ICU for HFNO, while 188 (64%) received HFNO in the designated COVID-19 ward (non-ICU). The median (IQR) age was 52 (44-58) years; 163/292 (56%) were males. Every patient was on via reservoir face mask at 15L/min prior to initiation of HFNO; the median (IQR) ratio of P_aO2/FiO_2 pre-HFNO was 68 (54-92). The median (IQR) duration of symptoms prior to treatment with HFNO was 7 (4-9) days. Comorbidities were highly prevalent: 134/293 (46%) patients were diabetic (with 79/134 (59%) having an HbA1c>8%); 131/293 (45%) were hypertensive, 153/293 (52%) were obese (body mass index≥30), and 45/292 (15%) were HIV positive (Table 1). Therapeutic anticoagulation with enoxaparin at 1mg/kg 12-hourly was almost universal (281/293, 96%), and 222/293 (76%) received steroids (dexamethasone or prednisolone / hydrocortisone dose-equivalent). Most patients (188/293, 64%) were treated with HFNO outside of the ICU. At any point during the study period, between 25 and 40 patients were being treated with HFNO at each of the participating hospitals.

Primary outcome

Successful treatment with HFNO was achieved in 137/293 (47%) of patients (Figure 1); of these, the majority (128/137, 93%) were subsequently discharged from hospital. At the time of writing, 8 patients (6%) had been weaned off HFNO but were still in hospital. The median (IQR) duration of HFNO was 6 (3-9) days in those successfully treated versus 2 (1-5) days in those who failed (p<0.001 (Figure 2). Of the latter, time

to intubation was 2 (0.5-5) days, whilst time to death on HFNO was 4 (2-6) days (p=0.02).

Predictors of HFNO failure

Differences in demographics, clinical characteristics and inflammatory marker profiles between patients with a successful outcome on HFNO and those with HFNO failure are summarised in Table 1. Patients who had a successful outcome on HFNO had higher oxygen saturations, lower respiratory and heart rates, and lower oxygen requirements (FiO_2) within 6 hours of commencement of HFNO (Table 2). ROX-6 and mROX-6 were also significantly different among patients with HFNO failure vs. success: 2.41 (2.06-3.05) vs. 3.26 (2.72-4.10) for ROX-6 (p<0.001) and 2.33 (1.92-3.12) vs. 3.44 (2.67-4.20) for mROX-6 (p<0.001), respectively (Figure S1, Supplementary Appendix). 17/293 (6%) patients failed HFNO before 6 hours, and had ROX-6 and mROX-6 scores recorded at the time of intubation.

ROX-6 and mROX-6 were very closely correlated (r^2=0.870), and both had virtually identical hazard ratios for outcome in univariable analysis (Table 3), so ROX-6 was chosen for the multivariable analysis as it includes one less observation and is easier to calculate. In this model, only poorly-controlled diabetes (HbA1c>8%) (adjusted HR 1.56, 95% CI 1.06-2.28), treatment with steroids (adjusted HR 0.25, 95% CI 0.18-0.37,), ROX-6 score (adjusted HR 0.42, 95% CI 0.33-0.54) were significantly associated with the relative hazard of treatment failure. The association between treatment with steroids and ICU setting was significant (p=0.004), suggesting that the influence of setting on outcome was largely explained by the increased use of steroids in ICU.

Diagnostic performance of ROX-6 for HFNO failure

The area under the ROC curve (AUC) was 0.75 (Figure 3A). A ROX-6 below 3.7 (cut-off A, maximising sensitivity) was 90% sensitive (true positives) whilst ROX-6 above 2.2 (cut-off B, maximising specificity) was 90% specific (true negatives) (Figure 3B). The corresponding positive predictive values (PPV) and negative predictive values (PPV) are shown in the table below Figure 3. The single cut-off that maximised sensitivity and specificity (Youden's index) was 2.7; the PPV and NPV at Youden's index was 72% and 73%, respectively.

Survival to hospital discharge

At the time of analysis, 10/293 (3%) patients were still in the ICU and ventilated, and 14/293 (5%) were still in hospital after either successful HFNO treatment or ICU discharge. Overall survival to hospital discharge for patients treated with HFNO (denominator excluding those still in hospital or ventilated in ICU) was 139/269 (52%), and mortality was 130/269 (48%). In patients successfully treated with HFNO, one patient (1/137, 1%) died after successfully being weaned off HFNO. Of the patients who failed HFNO, 111/156 (71%) were intubated after failing HFNO, and 45/156 (29%) died whilst receiving the therapy. Of the deaths prior to intubation, 26/45 (58%) died unexpectedly before intubation could be considered, and the remaining 19/45 (42%) were assessed as requiring intubation but were declined as non-ICU candidates due local facility protocols, or in a few cases, had pre-specified their preference not to be intubated. Survival to hospital discharge was 128/129 (99%) and 11/140 (7%) in the HFNO success and failure groups respectively ($p<0.0001$).

DISCUSSION

This prospective observational study of HFNO for severe COVID-19 pneumonia is the largest reported to date. Our study showed that HFNO can successfully be utilised to provide respiratory support to patients with COVID-19 pneumonia and HRF, and avoided mechanical ventilation even in patients with profound hypoxaemia. However, HFNO failed in just over half of our cohort, and the mortality in this group of patients who received mechanical ventilation was very high. Although these poorer ventilation outcomes may be the consequence of a patient population suffering from socioeconomic deprivation, multiple comorbidities and high tuberculosis and HIV prevalence, it also raises the possibility that persistence with HFNO in certain patients may delay the inevitable requirement for intubation, which could jeopardise clinical outcomes[23]. This further highlights the need for early differentiation of patients who may benefit from HFNO from those who will require mechanical ventilation, although in our resource-limited setting access to the latter was not unrestricted. We showed that a higher ROX index measured at 6 hours after HFNO initiation (ROX-6), along with treatment with steroids, independently predicted success. Moreover, poorly controlled diabetes was associated with HFNO failure. Importantly, treatment with HFNO outside of the ICU, and HIV positive status, did not portend worse outcome.

Most of our patients received HFNO in a non-critical care ward-based environment, demonstrating the feasibility of HFNO outside of the ICU. This potential to increase the capacity to manage severe COVID-19 pneumonia in resource-constrained settings has important implications. In settings where firstly, access to the infrastructure and/or expertise of ICU care is limited, or, secondly, transport of clinically unstable patients to a facility with a designated ICU is potentially hazardous and undesirable, HFNO may be considered as an appropriate mode of respiratory support. While adequate PPE is mandatory for all health care workers attending to patients on HFNO, evidence

suggest that the risk of airborne transmission is no greater than the use of face mask oxygen[24]. The degree to which HFNO can be scaled up as a treatment for large numbers of patients with HRF would, however, be highly dependent on local oxygen capacity, the delivery infrastructure within individual hospitals, and the robustness of the supply chain.

Evidence of efficacy of HFNO in reducing the requirement for intubation is consistent with previous studies, albeit in patients with HRF of other causes[25,26]. A meta-analysis of 9 randomised controlled trials of acute HRF in the pre-COVID-19 era found HFNO resulted in lower intubation rates without affecting survival[27]. Preliminary data, mainly case reports and small case series, have also described its potential utility in patients with COVID-19 pneumonia[9,10,28-32], and usually in combination with awake proning[33,34]. The finding that ROX and mROX can be used as a prediction tool is also consistent with studies of early predictors of HFNO outcome in other forms of respiratory failure[19,20]. We found that ROX performed equivalently to mROX, and thus favoured it, as it comprised fewer input variables. In a 2-year multicentre prospective observational cohort study of 191 patients with pneumonia (not related to COVID-19) treated with HFNO, Roco *et al*. found that 68 (35.6%) required intubation[15]. The prediction accuracy of the ROX index increased over time (area under the ROC curve 2 h, 0.679; 6 h, 0.703; 12 h, 0.759). ROX ≥4.88 measured at 2 (hazard ratio, 0.434; 95% CI, 0.264-0.715; P = 0.001), 6 (hazard ratio, 0.304; 95% CI, 0.182-0.509; P < 0.001), or 12 hours (hazard ratio, 0.291; 95% CI, 0.161-0.524; P < 0.001) after HFNO initiation was associated with a lower risk for intubation. A ROX <2.85, <3.47, and <3.85 at 2, 6, and 12 hours of HFNO initiation, respectively, were predictors of treatment failure. They found that among components of the index, oxygen saturation as measured by pulse oximetry/FiO2 had a greater weight than respiratory rate.

A recently published letter from France (n= 62)[11], two pre-print reports from the same centre in the USA (n=104 and n=129) and a study from China (n=17)[10] evaluated COVID-19 pneumonia treated with HFNO. They found intubation rates of between 31% and 66%, and that ROX (measured within the first 4 hours) predicted success[11]. Compared to our study, there were several important differences in the published French study: the median ROX score that predicted survival was 1.5 times higher than ROX-6; time to intubation was much shorter (10 hours), and ICU mortality was much lower i.e. 17%. The obvious distinction was the severity of HRF: the mean SPO_2 was substantially lower (90 vs 96%) and respiratory rate higher (37 vs 25 per minute) in our study population.

The main strengths of this study are the prospective, multi-centre design, the relatively large sample size with completed outcomes collected over a relatively short period of time, and the reporting predictors and outcomes within the context of corticosteroids, which is now the standard of care. The latter is an important point because it will likely impact thresholds for intubation and outcomes including death. In addition, we also clarified the relative importance of the different predictors including the components of the ROX score. It is also the only study from a population with high HIV prevalence, and the first report of the large-scale use of HFNO outside of a standard ICU. The compromise of providing non-invasive respiratory support outside of a conventional ICU setting has been made in other places (such as in Italy[35] – however, these patients were still cared for by intensivists in designated “level 2” ICU beds).

Some limitations of this study deserve emphasis. We could not adequately control for differences in physician experience and judgement around the timing of intubation. However, well-outlined protocolised provincial guidelines for intubation and mechanical ventilation, including score-based risk stratification (based on SOFA

score, pre-morbid status, comorbidities and age) were followed[36]. Studies utilising composite physiological scores to determine predictors for the need for intubation inherently suffer from confirmation bias[19,20,37,38], as even if the ROX index is not formally calculated, the individual components (SpO_2, FiO_2 and respiratory rate) are incorporated in a Bayesian-type reasoning by the clinician in making the intubation decision. Nevertheless, an objective measure that crystallises the current respiratory parameters, and can potentially reassure the clinician about the safety of continuing with HFNO, is still useful. Biomarker data was incomplete, thus reducing the power of the multivariable prediction model. However, this was a pragmatic 'real-world' study where blood sampling was clinically driven rather than protocolised outside the ICU. Our study was also not randomised (with a "usual care" as an alternative) but this would have been impractical and given the scale of the pandemic and the limited intensive care resources. Lastly, intermittent proning was routinely performed, making it impossible to determine the impact of HFNO without prone positioning.

In conclusion, in a resource-constrained setting where access to ICU care and mechanical ventilation is limited, HFNO for severe COVID-19 HRF is feasible and deliverable even in a ward-based non-critical care environment, and more almost half of those who receive it can be successfully weaned without the need for mechanical ventilation. Conversely, mortality in patients who fail HFNO is high.

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Contributors

GC, UL, GA, MGM, KD and CK were involved in the conception and design. GC, UL, GA, DM and CK were involved in study implementation and data collection. GC, SM, and FL did the analysis. GC, UL, MGM, JP, KD and CK interpreted the data and provided important intellectual input. GC, UL, KD and CK wrote the first draft. All authors read and commented on the manuscript.

Data sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Declaration of interest

BA has received speakers fees from Novartis, and CK has served on an advisory board from AstraZeneca, both outside the submitted work.

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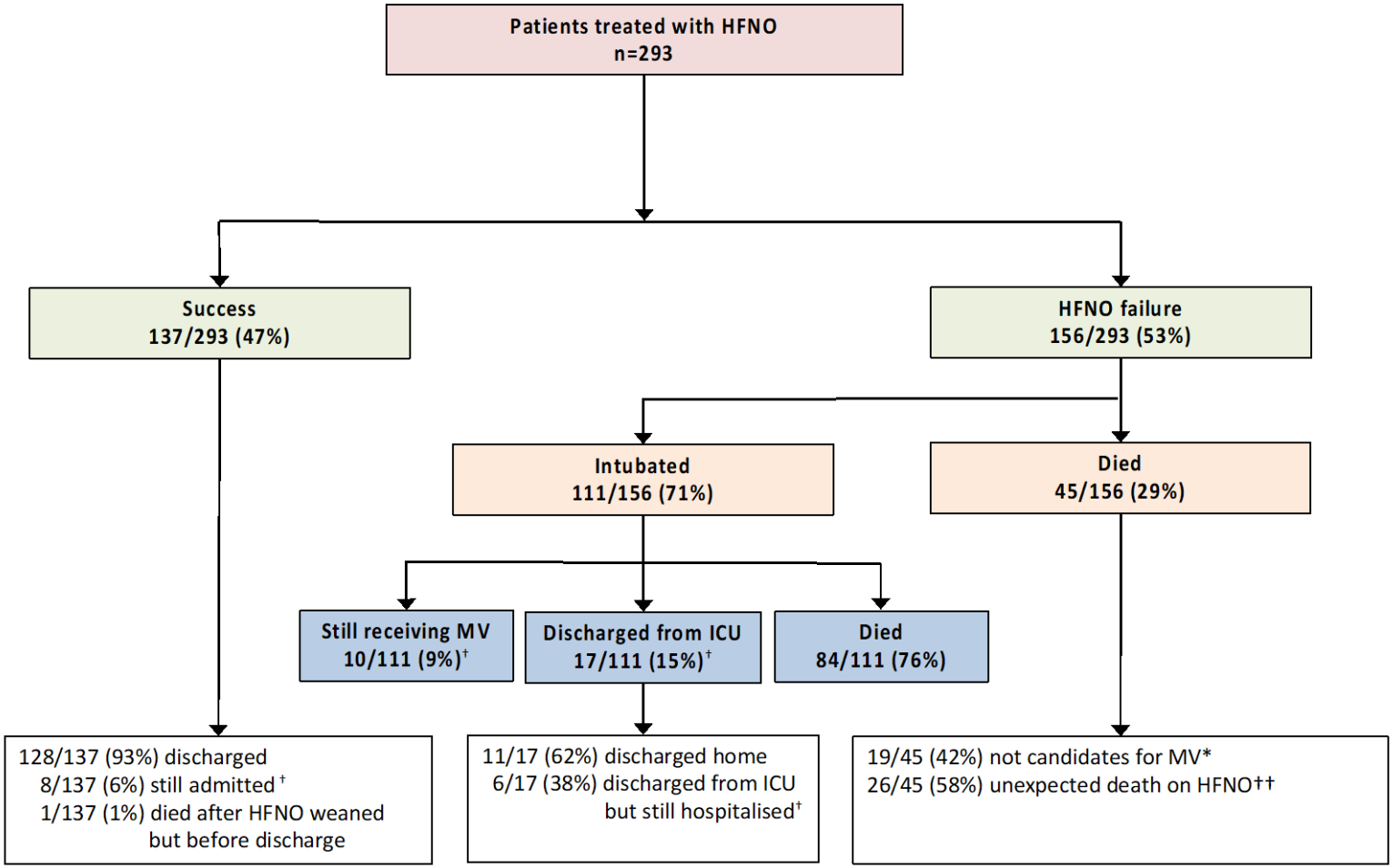


Figure 1. CONSORT diagram showing outcomes of HFNO and survival to discharge.
HFNO: high-flow nasal cannula oxygen; ICU: intensive care unit; MV: mechanical ventilation, DNR: do not resuscitate.
Success = weaned from HFNO; Failure= need for intubation or death.
* Triaged due local facility protocol, DNR order or pre-specified patient preference.
† Survival to hospital discharge = 139/269 (52%): denominator excludes those still in hospital or ventilated in ICU (n=24).
†† Sudden death = abrupt unexpected death on HFNO (intubation was not being considered at the time).

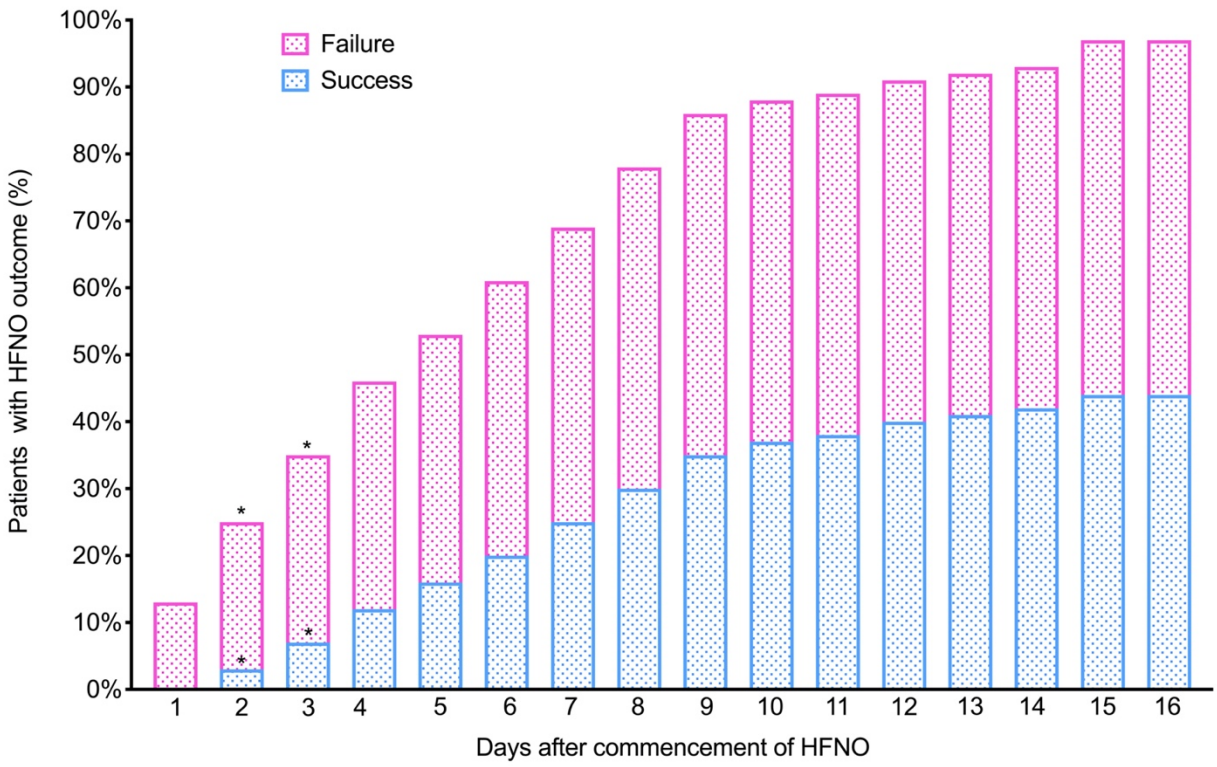


Figure 2. **Proportion of patients on HFNO reaching outcome per day of therapy.** The median (IQR) duration of HFNO was 6 (3-9) days in those successfully treated versus 2 (1-5) days in those who failed (p<0.001).
*P<0.05 when compared to proportion of previous day for same outcome (Pearson's χ^2 test).

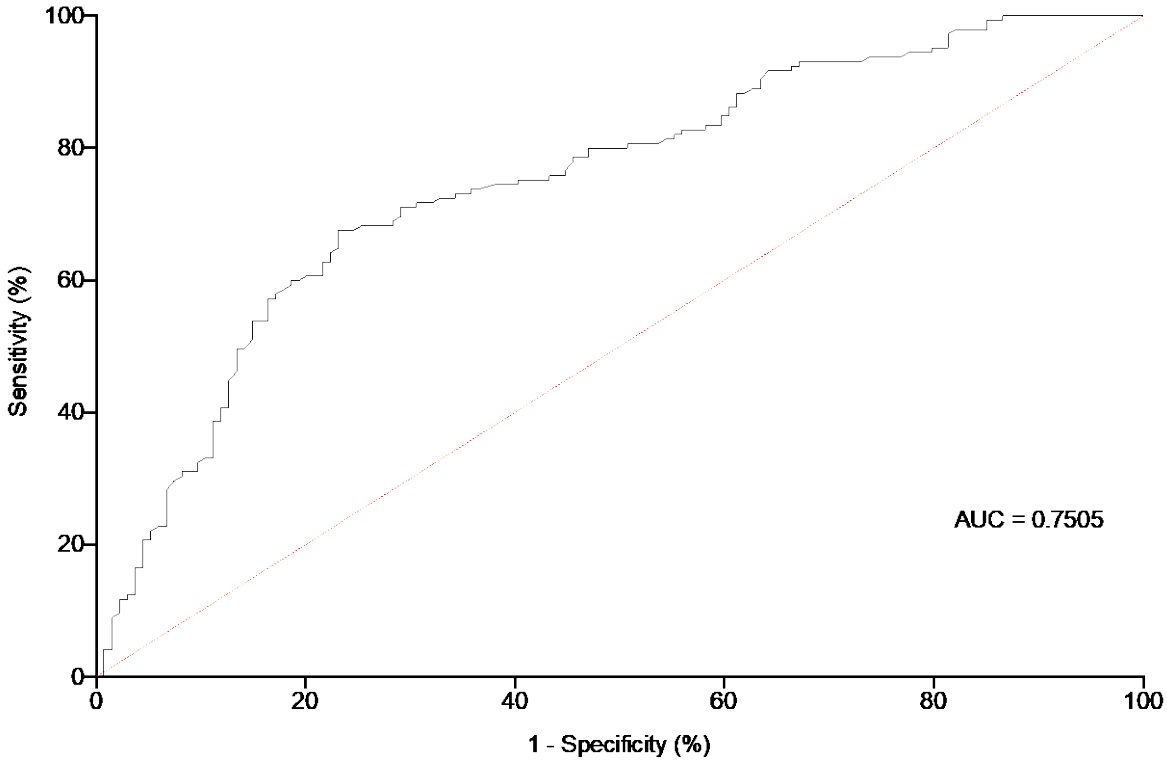
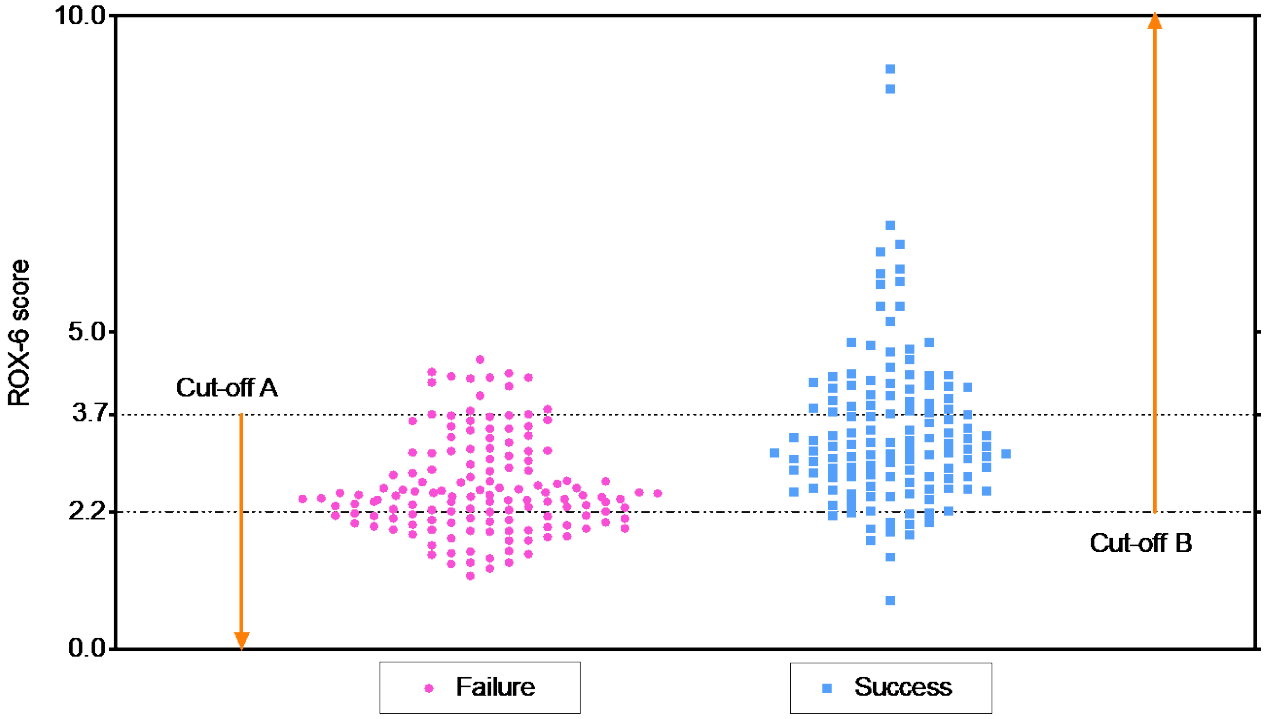


Figure 3A. **Receiver operating characteristic (ROC) curve for ROX-6 for predicting HFNO failure.** ROC was performed for ROX-6 (134 patients successfully treated with HFNO and 145 patients who failed HFNO). Area under the curve (AUC) for ROX-6 is 0.75 with $p<0.0001$.



Cut-point	Sensitivity	Specificity	PPV	NPV
3.7	90%	37%	56%	81%
2.7	68%	77%	72%	73%
2.2	33%	90%	74%	60%

Figure 3B. Scatter plot of ROX score (ratio of oxygen saturation/FiO2 to respiratory rate) at 6 hours (ROX-6) showing cut-offs maximising sensitivity and specificity.
PPV = positive predictive value; NPV = negative predictive value.
A ROX-6 below 3.7 (cut-off A, maximising sensitivity) was 90% sensitive (true positives) whilst ROX-6 above 2.2 (cut-off B, maximising specificity) was 90% specific (true negatives). The single cut-off that maximised sensitivity and specificity (Youden's index) was 2.7; the PPV and NPV at Youden's index was 72% and 73%, respectively.

Table 1. Patient characteristics

	Total (n=293)	Failure (n=156)	Success (n=137)	P-value
Age (years)				
Median (IQR)	52 (44-58)	53 (44-58)	50 (44-57)	0.187
Sex				
Males, n (%)	163 (56)	84 (54)	79 (58)	0.512
Diabetes				
Any diabetes, n (%)	158 (54)	82 (53)	76 (55)	0.697
Poorly controlled (HbA1c≥8%), n (%)	79 (27)	46 (29)	33 (24)	0.299
HbA1c, median (IQR)	9.3 (7.1-11.4)	9.6 (7.9-11.5)	8.75 (7-11.3)	0.259
Hypertension				
n (%)	131 (45)	72 (46)	59 (43)	0.562
BMI (kg/m^2)				
≤25, n (%)	31 (11)	13 (8)	18 (13)	0.182
25-30, n (%)	109 (37)	65 (42)	44 (32)	0.092
30-35, n (%)	94 (32)	55 (35)	39 (28)	0.214
≥35, n (%)	59 (20)	23 (15)	36 (26)	0.021
HIV status				
Negative, n (%)	211 (72)	116 (74)	95 (69)	0.340
Positive, n (%)	45 (15)	22 (14)	23 (17)	0.525
Unknown, n (%)	37 (13)	18 (12)	19 (4)	0.549
CD4 count (if HIV+ve) ($cells/m^3$)				
Median (IQR)	309 (146-441)	284 (145-388)	335 (267-455)	0.355
ART use (vs. no ART if HIV+ve)				
n (%)	36 (80)	19 (86)	17 (74)	0.230
Duration of symptoms prior to HFNO				
Days, median (IQR)	7 (4-9)	7 (5-9)	7 (4-8)	0.107
Modified SOFA score ††				
3-5	276 (95)	146 (94)	131 (96)	0.390
>5	14 (5)	9 (6)	5 (4)	0.390
Creatinine (μmol/L)				
Median (IQR)	80 (63-100)	81 (64-103)	77 (63-93)	0.261
PaO_2/FiO_2 ratio at HFNO initiation ††				
mmHg, median (IQR)	68 (54-92)	63 (51-83)	76 (58-102)	<0.001
Anticoagulation with LWMH*				
None, n (%)	2 (1)	1 (1)	1 (1)	1.000
Prophylactic, n (%)	10 (3)	3 (2)	7 (5)	0.198
Therapeutic, n (%)	281 (96)	152 (97)	129 (94)	0.237
Steroid treatment †				
n (%)	222 (76)	103 (66)	119 (88)	<0.001
ICU setting (vs. medical ward)				
n (%)	105 (36)	44 (28)	61 (45)	0.004
Lymphocyte count ($x10^9/L$) ††				
Median (IQR)	1.18 (0.89-1.58)	1.15 (0.92-1.57)	1.23 (0.83-1.62)	0.561
C-reactive protein (mg/L)††				
Median (IQR)	184 (11-310)	235 (142-344)	173 (105-274)	0.002
D-dimer (mg/L) ††				
Median (IQR)	0.83 (0.41-2.54)	1.03 (0.49-4.44)	0.56 (0.36-1.78)	0.002

Note: HFNO = high flow nasal cannula; ICU = intensive care unit; IQR = interquartile range; HIV = human immunodeficiency virus; ART = antiretroviral treatment; BMI = body mass index; SOFA = Sequential Organ Failure Assessment; PaO_2/FiO_2 = ration of arterial partial pressure of oxygen to inspired oxygen fraction; LMWH = low-molecular weight heparin; CRP = C-reactive protein.

* Prophylactic = 0.5mg/kg enoxaparin daily; therapeutic = 1mg/kg enoxaparin twice daily (dose adjusted for renal impairment where necessary)

† Dexamethasone 6mg or prednisone 40mg daily for 10 days

††n=290,250, 249, 197 and 240 for mSOFA, PaO_2/FiO_2 ratio at HFNO initiation, lymphocyte count, C-reactive protein and D-dimer results respectively.

Table 2. Oxygen requirement and respiratory parameters after 6 hours on HFNO

	Total (n=293)	**Failure (n=156)**	**Success (n=137)**	**P-value**
SpO_2 (%) Median (IQR)	90 (86-94)	89 (83-92)	91 (89-94)	<0.001
FiO_2 (%) Median (IQR)	90 (85-95)	90 (90-95)	90 (80-93)	<0.001
Respiratory rate (breaths/mins) Median (IQR)	37 (30-43)	40 (34-46)	32 (28-40)	<0.001
Heart rate (beats/mins) Median (IQR)	101 (90-108)	104 (92-110)	97 (88-105)	<0.001
SpO_2/FiO_2 ratio Median (IQR)	100 (93-107	98 (89-103)	104 (98-115)	<0.001
ROX index at 6 hours (ROX-6) Median (IQR)	2.78 (2.25-3.62)	2.41 (2.06-3.05)	3.26 (2.72-4.10)	<0.001
Modified ROX index at 6 hours (mROX-6) Median (IQR)	2.90 (2.16-3.74)	2.33 (1.92-3.12)	3.44 (2.67-4.20)	<0.001

Table 3. Predictors of HFNO failure

Variable	n	Estimated HR* (95% CI)	P-value	Adjusted HR† (95% CI)	P-value
Age (per year increase)	293	1.00 (0.99-1.02)	0.795		
Male (vs. females)	293	0.95 (0.70-1.29/)	0.749		
HIV status (vs. negative)					
Positive	45	0.75 (0.48-1.19)	0.224		
Hypertension	131	0.99 (0.73-1.34)	0.930		
Diabetes*					
Well-controlled (vs. no diabetes)	55	0.97 (0.63-1.50)	0.883	1.27 (0.81-2.00)	0.301
Poorly controlled (vs. no diabetes)	79	1.31 (0.93-1.88)	0.143	1.56 (1.06-2.28)	0.023
Obesity (BMI ≥30kg/m^2 vs. <30kg/m^2)	153	0.80 (0.58-1.09)	0.158		
mSOFA (per 1 point increase)	290	1.18 (1.04-1.36)	0.054		
Duration of symptoms (per 1 day increase)	293	1.02 (0.98-1.06)	0.313		
Treatment with steroids	221	0.31 (0.22-0.44)	0.001	0.25 (0.18-0.37)	<0.001
ICU setting (vs. medical ward)	105	0.68 (0.48-0.97)	0.032		
ROX-6 score (per 1 point increase)	279	0.46 (0.37-0.58)	<0.001	0.42 (0.33-0.53)	<0.001
mROX-6 score (per 1 point increase)	277	0.51 (0.42-0.61)	<0.001		
Lymphocyte count (per 1x10^9 increase)	249	1.19 (0.92-1.52)	0.181		
CRP (vs. <100mg/L)	38				
100-199	66	0.71 (0.38-1.30)	0.269		
200-299	50	0.88 0.46-1.70)	0.712		
300-399	31	1.14 (0.59-2.20)	0.701		
400-499	15	1.54 (0.70-3.38)	0.280		
≥500	7	2.99 (1.23-7.25)	0.015		
D-dimer (vs. <1.5mg/L)	150				
1.51-5.0	39	1.48 (0.93-2.36)	0.097		
≥5	42	1.99 (1.28-3.12)	0.002		

Note: HR = hazard ratio; CI = confidence interval; HIV = human immunodeficiency virus; mSOFA = Modified Sequential Organ Failure Assessment, ICU = intensive care unit; CRP = C-reactive protein.

* Well controlled = HbA1c≤8%; poorly-controlled = HbA1C>8%.

† ROX-6 used in adjusted model rather than mROX because of similar HR and diagnostic performance (see Figure S2, Supplementary Appendix) with fewer input variables than mROX-6.

‡ Best model fit obtained with inclusion of steroid use, diabetes (poorly-controlled vs. no diabetes), and ROX-6.

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:
The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study

Gregory L. Calligaro, Usha Lalla, Gordon Audley, Phindile Gina, Malcolm Miller, Marc Mendelson, Sipho Dlamini, Sean Wasserman, Graeme Meintjes, Jonathan Peter, Dion Levin, Joel Dave, Ntobeko Ntusi, Stuart Meier, Francesca Little, Desiree L. Moodley, Elizabeth H. Louw, Andre Nortje, Arifa Parker, Jantjie J. Taljjaard, Brian W. Allwood, Keertan Dheda and Coenraad F.N. Koegelenberg.

Corresponding author:

A/Professor Gregory Calligaro
Division of Pulmonology, Department of Medicine, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa
Tel: +27 21 404 4435 Fax: +27 21 404 7651
E-mail: greg.calligaro@uct.ac.za

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Multi-centre prospective observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	In a resource-constrained setting, HFNO for severe COVID-19 HRF is feasible even outside of the ICU and averts death or the need for mechanical ventilation in almost half of those who receive it.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	The utility of high-flow nasal oxygen (HFNO) for severe COVID-19 related hypoxaemic respiratory failure (HRF), particularly in settings with limited access to ICU resources, remains unclear.
Objectives	3	State specific objectives, including any prespecified hypotheses	8	The main aim of this study was to assess the impact of HFNO in avoiding mechanical ventilation in patients with severe respiratory failure secondary to COVID-19.
Methods				
Study design	4	Present key elements of study design early in the paper	8	We conducted a prospective multi-centre observational study within the public health system in Cape Town, South Africa.

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9	See "Setting".
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9	See "Participants".
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10	The primary endpoint was the proportion of patients with a successful outcome (weaned off HFNO).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at	N/A	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11	
		(*b*) Describe any methods used to examine subgroups and interactions		
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	11	No loss to follow-up
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12	CONSORT diagram
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram	24	Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	28	Table 1.
		(b) Indicate number of participants with missing data for each variable of interest	28	Footnote of Table 1.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	26	All patients in primary analysis have an outcome.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	13	"Primary outcome" in Results.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 and 30	See "Predictors of HFNO" section in Results, and Table 3.
		(*b*) Report category boundaries when continuous variables were categorized	28	Table 1.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15	
Discussion				
Key results	18	Summarise key results with reference to study objectives	15	First paragraph.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17	
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

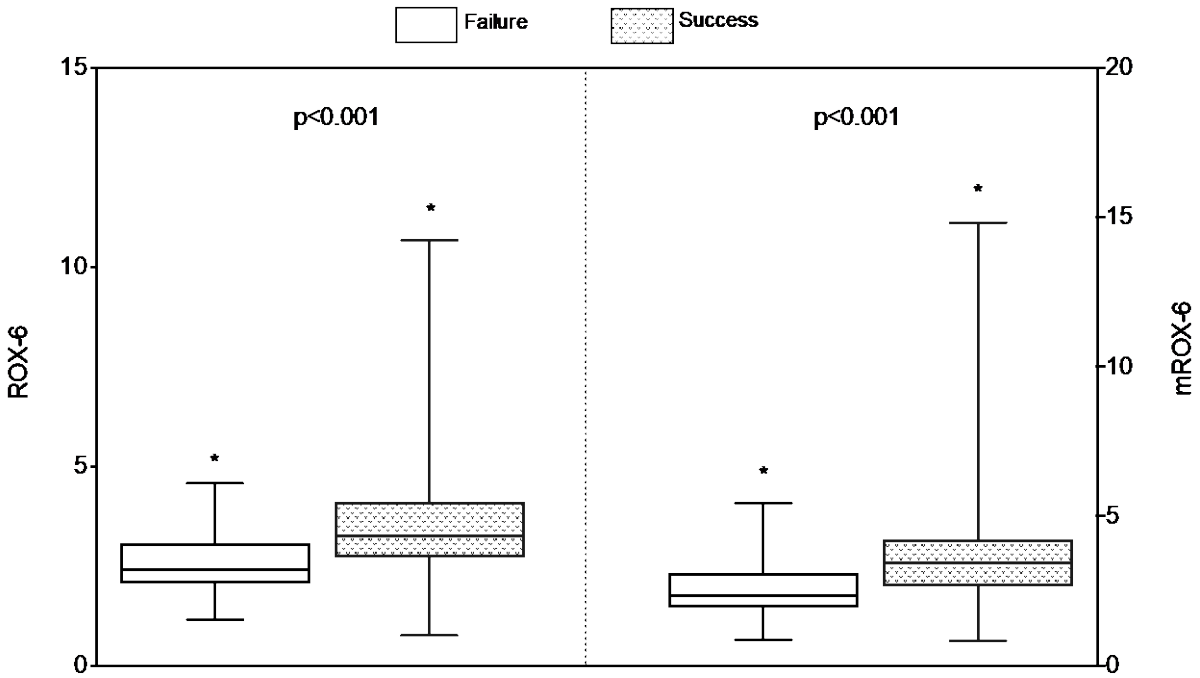


Figure S1. ROX score (ratio of oxygen saturation/FiO2 to respiratory rate) at 6 hours (ROX-6) and modified ROX score[20] (ROX score divided by heart rate) at 6 hours (mROX-6).
ROX-6 and mROX-6 were significantly lower among patients with HFNO failure vs. success: 2.41 (2.06-3.05) vs. 3.26 (2.72-4.10) for ROX-6 (p<0.001), and 2.33 (1.92-3.12) vs. 3.44 (2.67-4.20) for mROX-6 (p<0.001), respectively.