University of Cape Town
Faculty of Health Sciences

High flow nasal oxygen versus mechanical ventilation as initial respiratory support in severe COVID-19 ARDS at Groote Schuur Hospital: a propensity score analysis

Minor dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medicine (MMed) in the Department of Medicine, Division of General Medicine

Dr Robert William van den Berg
MBChB (UCT), DA (SA), DipPEC (SA)
VDNROB002

Submitted: 09 November 2023

Principal Supervisor:
A/Prof Gregory Calligaro
BSc Hons, MBChB, Dip PEC (SA), MMed (Med), FCP (SA), Cert Pulm (SA)
Department of Medicine, Division of Pulmonology, Groote Schuur Hospital and University of Cape Town

Declaration

1. I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.
2. I have used the Vancouver convention for citation and referencing. Each contribution to, and quotation in, this minor dissertation from the work(s) of other people has been attributed and has been cited and referenced. Any section taken from an internet source has been referenced to that source.
3. This minor dissertation is my own work and is in my own words (except where I have attributed it to others).
4. I have not allowed and will not allow anyone to copy my work with the intention of passing it off as his or her own work.
5. I acknowledge that copying someone else's assignment or essay, or part of it, is wrong, and declare that this is my own work.

I, Robert van den Berg, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Date: 09 November 2023

Format

The contents of this minor dissertation are presented in the ‘publication-ready’ format.

Table of Contents

Authors and Acknowledgments

Robert van den Berg[1], Gordon Audley[1], Christel Arnold-Day[2], Richard N. Van Zyl-Smit[2,3,4,] Ivan Joubert[2], David A. Thomson[2], David L. Fredericks[2], Malcolm Miller[2], William L. Michell[2], Patrick L. Semple[2], Jenna L. Piercy[2], Lovemore Mapahla[1], Keertan Dheda[2,3,4,5] and Gregory L. Calligaro[2,3,4].

[1] Department of Medicine, University of Cape Town and Groote Schuur Hospital, 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] 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.

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

Acknowledgements:

We would like to acknowledge all staff who courageously and tirelessly cared for COVID-19 patients, your unwavering dedication saved lives. We dedicate this work to those patients who have passed on and to the survivors whose resilience have inspired many.

Abstract

OBJECTIVE: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic placed an unprecendented burden on global health care resources, and on intensive care unit (ICU) resources in particular. Due to ICU resource limitations, high-flow nasal oxygen (HFNO), a novel ventilation strategy, was implemented as an alternative to mechanical ventilation (MV) at Groote Schuur Hospital in Cape Town, South Africa, during the first COVID wave. Patients received MV if HFNO failed. The purpose of this study was to compare outcomes of this “HFNO first” strategy to a “MV first” strategy.

METHODS: This was a secondary analysis of two propsective cohort studies conducted during the COVID first wave at Groote Schuur Hospital. Propensity score matching was used to compare outcomes between HFNO as initial ventilation strategy and MV as first-line therapy. Eligible patients were adults (> 18 years) with severe respiratory failure and confirmed COVID-19 pneumonia. The primary endpoint was survival to hospital discharge and secondary analysis assessed duration of respiratory support.

RESULTS: After propensity score matching, 110 patients (55 in each group) were included in the final analysis. Survival to hospital discharge was significantly higher in patients treated with HFNO first compared to MV first; 31/55 (56%) versus 17/55 (31%), p=0.007. After adjustment for other covariates, the “HFNO first” group had a 71% increased chance of survival to hospital discharge when compared to the “MV first” group; OR=0.28, 95% CI [0.13 – 0.63], p=0.0018. There was a non-significant trend in patients treated with HFNO group requiring less time on respiratory support (p= 0.06).

CONCLUSION: This study supports the evidence for the use of HFNO as an initial ventilation strategy for patients with COVID-19-related acute respiratory distress syndrome (ARDS). Survival rates in the “HFNO first” cohort were significantly higher, even in those that subsequently required ventilation, compared to the “MV first” strategy. This study adds important evidence to the debate on the potential benefits and harms of HFNO as well as highlighting its advantages in a resource-constrained

setting. The efficacy and implementation of HFNO as an initial ventilation strategy require further investigation.

The “HFNO first” strategy employed at Groote Schuur Hospital in the first wave of the COVID-19 pandemic demonstrated a markedly higher survival rates. This suggests that HFNO is highly effective as an initial ventilation strategy in COVID-19 ARDS in a resource-limited setting.

Publication ready document

High flow nasal oxygen versus mechanical ventilation as initial respiratory support in severe COVID-19 ARDS at Groote Schuur Hospital: a propensity score analysis

Robert van den Berg[1], Gordon Audley[1], Christel Arnold-Day[2], Richard N. Van Zyl-Smit[2,4] Ivan Joubert[2], David A. Thomson[2], David L. Fredericks[2], Malcolm Miller[2], William L. Michell[2], Patrick L. Semple[2], Jenna L. Piercy[2], Lovemore Mapahla[1], Keertan Dheda[2,4,5] and Gregory L. Calligaro[2,4].

1 Department of Medicine, University of Cape Town and Groote Schuur Hospital, 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 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.

5 Faculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author:

Robert van den Berg
Division of General Medicine, Department of Medicine, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa
Tel: +27 725980735
E-mail: robert.w.vdberg@gmail.com

Word Count:

Abstract: 377
Main Text: 2530

STUDY SYNOPSIS:

What the study adds:

This study adds to the evidence base on the utility and timing of high flow nasal oxygen (HFNO) in severe COVID-19 respiratory failure, demonstrating a significant decrease in patient mortaily and mitigating the need for mechanical ventilation (MV) in those treated with a HFNO first ventilation strategy.

Implications of the study:

In resource-constrained settings, HFNO should be the first line ventilation strategy employed for patients with COVID-19 respiratory failure with improved survival and a trend toward fewer days requiring ventilatory support when compared to a MV first strategy.

INTRODUCTION

The SARS-CoV-2 pandemic placed an unprecedented burden on health care resources worldwide in general and on intensive care unit (ICU) capacity in particular[1]. This resulted in alternative strategies to invasive mechanical ventilation (MV) being considered for the management of acute hypoxaemic respiratory failure. One of the most widely used modalities that came into prominence was high-flow nasal oxygen (HFNO). HFNO is a cheaper alternative to MV that has been shown in our setting to avoid the need for intubation in about half of patients with COVID-related ARDS[2]. In comparison to MV, HFNO is better tolerated by patients, is less complex to deliver, requires far less supervision by trained providers[3,4], and can be used outside of the ICU[5] . During the first wave, Groote Schuur Hospital in Cape Town, South Africa, assumed a "HFNO first" strategy for the treatment of patients with acute hypoxaemic respiratory failure from COVID pneumonia, treating them in specially repurposed respiratory high-care wards run by non-ICU specialists, and only referring them for MV once they were deemed to have failed HFNO (and if they met triage criteria).

However, this practice was born of necessity rather than a solid evidence base, and some concerns remain. HFNO was never a therapy that was widely employed pre-COVID for patients with advanced hypoxaemic respiratory failure (especially those with PF ratios less than 200) and was never considered a substitute for MV. Previous work from our group showed that the mortality of HFNO failures in severe COVID pneumonia (those that were treated with HFNO first, and then went on to require MV) was exceptionally high (~75%)[2]. Whether this represent a sicker group of patients with irreversible respiratory failure (no matter which modality was employed), or whether the decision to use HFNO first was disadvantageous, is unclear. Prolonged HFNO

delaying invasive ventilation has been proposed to influence outcomes in subsequent MV by several mechanisms, largely due to worsening atelectasis from inadequate PEEP and reduced lung compliance resulting in smaller tidal volumes at high respiratory rates[6,7]. In addition, the negative inspiratory pressures generated by vigorous spontaneous respiration have also been suggested to worsen acute lung injury by a mechanism called patient self-induced lung injury (P-SILI)[8].

In the first wave, there was a cohort of patients who were still treated with MV *a priori* because they were intubated at a secondary level hospital where HFNO was unavailable, and then transferred to Groote Schuur Hospital. This practice changed to HFNO first at all centers as access to this modality was expanded in subsequent waves. However, this cohort of patients who were treated with mechanical ventilation from the outset represents a convenient group whose outcomes can be compared to patients treated with HFNO first using propensity score matching. Propensity score matching is a statistical technique that can be employed to compare two groups of patients when a randomised study design is not feasible or ethically viable and is a valuable tool for drawing causal inferences and informing decision-making in the absence of randomisation.

In this report, we enrolled patients with severe COVID pneumonia, and using propensity score matching to balance the baseline characteristics and confounding factors between the two groups, compared outcomes of a HFNO first vs MV first strategy. We hypothesised that a HNFO first strategy would result in a higher proportion of patients surviving to hospital discharge.

METHODS

Study design

This study was a secondary analysis of two prospective single-centre cohort studies conducted at Groote Schuur Hospital during the COVID first wave in the repurposed high care wards (where HFNO was provided) and the ICU, respectively. The first cohort enrolled sequential patients initiated on HFNO in repurposed acute respiratory wards, whereas the other cohort study enrolled patients transferred to the ICU for mechanical ventilation.Both studies were approved by the University of Cape Town Research Ethics Committee (UCT HREC 295/2020 and 396/2020).

Setting

The study was conducted at Groote Schuur Hospital (GSH), a public sector academic hospital servicing a population of ~2.5 million with high tuberculosis and HIV prevalence[9] in Cape Town, South Africa. Patients were enrolled from the 5th of April to the 31st of September 2020.

Patients

Eligible patients were consecutive adult patients (aged ≥18 years) with severe respiratory failure, and laboratory-confirmed COVID-19 pneumonia [detection of SARS-CoV2 by real-time polymerase chain reaction (RT-PCR) on any respiratory sample] who were either treated with HFNO during hospitalisation at Groote Schuur Hospital, or intubated for severe respiratory failure at a secondary hospital (where HFNO was unavailable) and transferred to Groote Schuur Hospital. 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 but was indicated in cooperative patients who were able to comply with awake proning. Patients who were deemed to be failing HFNO were intubated. Decisions on the timing of intubation and mechanical ventilation were also 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. Therapeutic interventions like anticoagulation were standardised across the respiratory wards and the ICUs and no other SARS-CoV-2 directed therapy was provided to any patient, either off-label or as part of a clinical trial.

HFNO

Heated and humidified HFNO was exclusively delivered within designated medical wards (non-ICU) at GSH where patients were cohorted. HFNO was delivered either by an Airvo™ 2 (Fisher & Paykel Healthcare, Irvine, California, USA) or Inspire™ O^2FLO (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%.

ICU care

As per the hospital response plan, admission to the COVID-10 ICU was only for intubated patients requiring MV. ICU care for patients diagnosed with COVID pneumonia in our study was protocolised and included a multidisciplinary team consisting of intensivists, pulmonologists, and critical care nurses. Proning was implemented whenever feasible. Inhaled nitric oxide and extracorporeal membrane oxygenation were not utilised for any patient during the study period.

Outcomes

The primary endpoint was the proportion of patients surviving to hospital discharge. Of secondary interest was the duration of respiratory support (HFNO or MV) in both groups; for patients treated with HFNO first who failed a non-invasive strategy and were subsequently intubated, this was the sum of the days on HFNO plus those receiving mechanical ventilation.

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 described using means and standard deviations if normally distributed or else medians and inter-quartile ranges were used. We tested for normality on continuous variables using Shapiro Wilk test. Students unpaired t tests or the non-parametric test, Wilcoxon rank-sum tests were used for categorical, normally and non-normally distributed continuous variables, respectively. A CONSORT diagram reported the flow of patients in the study (Figure 1). The propensity score was then estimated for each patient using baseline covariates[10]. Based on the available literature on risk factors associated with mortality in severe COVID-19, the following covariates were selected for propensity matching: age, sex, history of hypertension, history of diabetes, BMI, HIV status, creatinine and total lymphocyte count. Baseline measure of oxygenation were not included as all patients had bilateral radiologically confirmed infiltrates and were assessed as failing oxygen via a non-rebreather facemask, and blood gas data from peripheral hospitals prior to intubation was incomplete. To assess the balance of measured covariates between treatment groups, we used the standardised mean differences before and after PS weighting[11]; an absolute difference of 10% or greater was considered indicative of imbalance. Variables with more than 5% missing data

were not considered. Following 1:1 PS matching, logistic regression models were constructed to assess the effect of respiratory support strategy on outcome, incorporating cluster-robust variance to account for matched observations. Statistical analyses were performed using Stata (V.12.1, Stata Corp, College Station, Texas, USA)[12] and Rstudio (AGPL v3)[13]. All statistical test were done at 5% level of significance. The first and last authors had full access to the data and were responsible for the submission of the manuscript.

RESULTS

Patient population

Two hundred and seventy-six patients were treated during the study period with HFNO in one of the designated COVID-19 respiratory wards (non-ICU), whilst 60 were intubated at peripheral hospitals and transferred to Groote Schuur Hospital for MV in the ICU. In the MV group, 5/60 patients were excluded because they were ventilated for reasons other than ARDS (and the COVID diagnosis was incidental). In the analysis using propensity scoring, 110 patients were matched with a 1:1 ratio between treatment groups (figure 1). Overall, the mean (SD) age was 49 (11) years and 44/110 (47%) were males. Every patient was on via reservoir face mask at 15L/min prior to initiation of either HFNO or MV. The median (IQR) duration of symptoms prior to treatment with either modality was 7 (4-9) days. Comorbidities were highly prevalent: 44/110 (40%) of patients were diabetic, with median (IQR) Hba1c 10.7 (7.7-13.2); 57/110 (52%) were hypertensive, 59/110 (54%) were obese (body mass index≥30), and 12/110 (11%) were HIV positive. All other baseline characteristics of propensity matched patients are summarised in Table 1.

Arterial blood gas measurement was not performed routinely before commencement of HFNO, nor was there complete data on the P_aO2/FiO_2 of patients in the MV group prior to intubation. However, the median (IQR) $SpO2/FiO_2$ in patients in the first six hours after initiation of HFNO was 102 (97-108), whilst the median (IQR) P_aO2/FiO_2 for patients after initiation on MV was 120 (78-168). The $SpO2/FiO_2$ (SF) ratio has been shown to correlate well with the P_aO2/FiO_2 (PF) ratio and is a proven surrogate for the diagnosis of patients with ARDS, with a SF ratio of 235 corresponding to a PF ratio of 200[14-16]. Thus despite inconsistencies in measures to assess oxygenation in the study prior to initiation of either therapy, moderate-to-severe ARDS was present in all patients.

Outcomes

In the unadjusted analysis of the primary outcome, survival to hospital discharge was significantly higher in patients treated with HFNO first compared to MV first; 31/55 (56%) versus 17/55 (31%), p=0.007. After adjustment for other covariates, a HFNO first group had a 72% increased chance of survival to hospital discharge when compared to the MV first group: OR=0.28, 95% CI [0.13 – 0.63], p=0.0018. Mortality was 24/55 (43.6%) vs 38/55 (69%) (p<0.001) in the HFNO first group and MV first groups, respectively, with mortality for patients on MV being 58/100 (53%) overall. There was a non-significant trend in patients treated with HFNO group (even If subsequently intubated) requiring less time on respiratory support; 8 (4-15) versus 12 (6-27) days (IQR), p=0.06.

DISCUSSION

In this secondary analysis of an observational cohort study of patients treated with HFNO and MV for severe COVID-19 ARDS, we found that a HFNO first strategy increased the chances of survival to hospital discharge by 70%. This was despite half of patients failing this modality and requiring MV as salvage. Our study also confirmed the poor outcomes in our setting of MV (either provided *a priori* or following HFNO failure) of severe COVID pneumonia[17-19]. Lastly, although not statistically significant, there was a trend towards fewer days requiring respiratory support (either HFNO or MV) in patients treated with HFNO first, which has important implications for resource allocation in pandemic circumstances.

This study adds to the evidence base on the utility and timing of HFNO in severe COVID. The use of HFNO in patients with acute hypoxaemic respiratory failure before MV was a strategy during the COVID pandemic that arose out of necessity due to pressure on ICU resources but is not without controversy. Comparisons of studies are limited by the impracticality and unfeasibility of a randomised design to answer this question, the lack of standardised triggers for intubation, and differences in the patient characteristics and setting (respiratory ward versus ICU) in which patients receive HFNO. In the pre-COVID era at least, it was suggested that patients placed on HFNO in the ICU who ultimately required intubation had a higher mortality when intubation was delayed[20]. Several subsequent retrospective studies in COVID patients showed increased mortality in ventilated patients who received HFNO before MV compared to those who were treated with MV alone, and worse outcomes in patients who were eventually intubated after longer trials of HFNO[21,22]. These studies only included patients who had received MV, either after or without HFNO use, without considering

those in whom HFNO was successful (and in whom MV was thus not required). The significant incidence of HFNO success is a major finding from our study and is congruent with a systematic review and meta-analysis assessing the effectiveness of HFNO in treating COVID-19 pneumonia (in which our original report was included[2]) which confirmed success rates between 44-62% for HFNO therapy when used as a ventilation strategy in patients with severe COVID[23]. That almost half of patients with severe COVID can be treated without the need for an ICU-specific intervention like MV (possibly even in a ward setting), and the ease of implementation of this therapy compared to the complexities associated with MV, bear significant implications for resource-limited health settings such as South Africa during pandemic responses to respiratory viruses.

Although the mortality rate for patients who do not respond to HFNO therapy and subsequently require MV is notably high, it is crucial to recognise that the mortality rate for COVID patients necessitating MV is already considerably elevated[17-19]. HFNO demonstrates a benefit in mitigating the need for intubation in significant amount of cases. While acknowledging the challenges and complexities involved in treating severe COVID-19 cases, we believe that these data show that the implementation of HFNO is a valuable intervention to manage respiratory failure and to improve overall patient survival rates.

Several limitations of this study merit consideration. Firstly, our study was performed in a single centre and thus may not reflect the reality of the experience in other hospitals in South Africa. Secondly, whilst propensity score matching can reduce selection bias through balancing observed covariates between treated and control groups, it cannot completely eliminate it. Unmeasured or unknown confounders could

still have impacted treatment assignment and outcomes, leading to residual bias between groups. Several aspects of our intervention, like the triggers for intubation, were not protocolised, but this is also indicative of the “real world” nature of this study. Thirdly, absence of complete arterial blood gas values from peripheral hospitals did not allow us to use the PF ratio as a matching criterion; however, all patients had severe ARDS by conventional criteria, and the indication for escalation of respiratory support was clinically driven. Lastly, patients in the MV first group were intubated at peripheral hospitals, and the transport of these unstable patients to a tertiary ICU may have involved additional complications and additive risk that increased the mortality in this group.

CONCLUSIONS:

In this single-centre analysis of patient with COVID-19 associated respiratory failure, patient that were exposed to HFNO prior to intubation had 70% higher chance of survival to hospital discharge compared to patients intubated without receiving HFNO therapy. Our data suggests that HFNO be the first line ventilation strategy for patients with COVID-19 respiratory failure.

Ethics

This study was approved by the local Research Ethics Committees at the University of Cape Town (UCT HREC 242/2023).

Funding

None.

Author contributions

RVDB and GLC were involved in the conception and design of the study. RVDB, GA, CAD, JP and GLC were involved in study implementation and data collection. RVDB, LM and GLC did the data analysis. RVDB and GLC interpreted the data and wrote the initial draft. All authors contributed to writing and editing the manuscript.

Declaration of competing interests

None.

Acknowledgements

We would like to express our sincere gratitude to the patients and healthcare workers whose participation and dedication were integral to the completion of this study.

REFERENCES

1. Mendelson M, Booyens L, Boutall A, et al. The mechanics of setting up a COVID-19 response: Experiences of the COVID-19 epidemic from Groote Schuur Hospital, Cape Town, South Africa. *S Afr Med J* 2020; **110**(10): 968-72.
2. Calligaro GL, Lalla U, Audley G, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. *EClinicalMedicine* 2020; **28**: 100570.
3. Mauri T, Wang YM, Dalla Corte F, Corcione N, Spinelli E, Pesenti A. Nasal high flow: physiology, efficacy and safety in the acute care setting, a narrative review. *Open Access Emerg Med* 2019; **11**: 109-20.
4. Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care* 2015; **3**(1): 15.
5. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020.
6. Nunn KP, Blackstock MJ, Ellis R, Sheikh G, Morgan A, Rhodes JKJ. The Considerations and Controversies in Using High-Flow Nasal Oxygen with Self-Prone Positioning in SARS-CoV-2 COVID-19 Disease. *Case Reports in Critical Care* 2021; **2021**: 5541298.

7. Siempos II, Xourgia E, Ntaidou TK, et al. Effect of Early vs. Delayed or No Intubation on Clinical Outcomes of Patients With COVID-19: An Observational Study. *Frontiers in Medicine* 2020; **7**.
8. Artaud-Macari E, Girault C. High-flow nasal cannula oxygen therapy: P-SILI or not P-SILI? *ERJ Open Res* 2022; **8**(2).
9. van Zyl Smit RN, Pai M, Yew WW, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. *Eur Respir J* 2010; **35**(1): 27-33.
10. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; **46**(3): 399-424.
11. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in medicine* 2009; **28**(25): 3083-107.
12. StataCorp. Stata Statistical Software: Release 12.: College Station, TX: StataCorp LP.; 2011.
13. Appelhans T, Detsch F, Nauss T. remote: Empirical Orthogonal Teleconnections in R. *Journal of Statistical Software*\ 2015; **65\(**10\): 1-19\.
14. Jusi RL, Limpin E, Bayot R, Guia TD, Ayuyao F. Determination of critical threshold value of SPO2/FiO2 ratio in the diagnosis of acute lung injury. *European Respiratory Journal* 2012; **40**(Suppl 56): P2020.
15. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest* 2007; **132**(2): 410-7.
16. Sirohiya P, Vig S, Pandey K, et al. A Correlation Analysis of Peripheral Oxygen Saturation and Arterial Oxygen Saturation Among COVID-19 Patients. *Cureus* 2022; **14**(4): e24005.
17. Alhazzani W, Møller HM, Arabi Y, Loeb M. Surviving Sepsis Campaign:Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19), 2020.
18. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive care medicine* 2020; **46**(6): 1099-102.
19. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**(20): 2052-9.
20. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive care medicine* 2015; **41**(4): 623-32.
21. Nurok M, Friedman O, Driver M, et al. Mechanically Ventilated Patients With Coronavirus Disease 2019 Had a Higher Chance of In-Hospital Death If Treated With High-Flow Nasal Cannula Oxygen Before Intubation. *Anesthesia and analgesia* 2023; **136**(4): 692-8.

22. Vera M, Kattan E, Born P, et al. Intubation timing as determinant of outcome in patients with acute respiratory distress syndrome by SARS-CoV-2 infection. *J Crit Care* 2021; **65**: 164-9.

23. Shallik N, Bashir K, Elmoheen A, Iftikhar H, Zaki HA. High flow nasal oxygen (HFNO) in the treatment of COVID-19 infection of adult patients from – An emergency perspective: A systematic review and meta-analysis. 2023; **50**: 101238.

Appendices

1. Figure 1 CONSORT diagram
2. Table 1 Patient characteristics
3. Instructions for authors (Journal: African Journal of Thoracic and Critical Care Medicine (ISSN: 2617-0205))
4. Human Research Ethics Committee approvals
5. STROBE checklist
6. Contact Details

Figure 1. CONSORT diagram

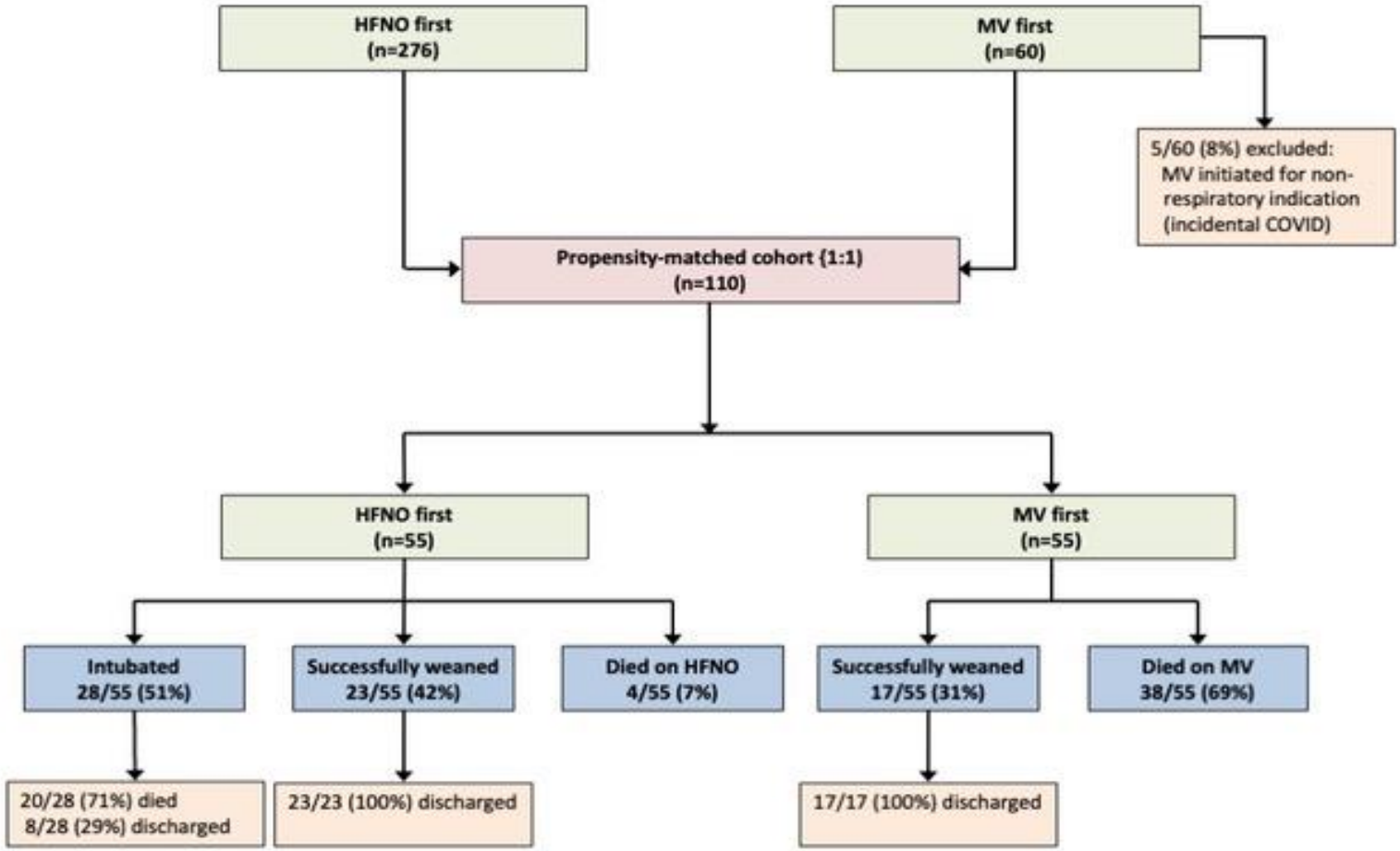

Table 1. Patient characteristics

	Total (n = 110)	HNFO first (n = 55)	MV first (n = 55)	P-value
Age (years)				
Mean (SD)	49 (11)	49 (11)	48 (12)	0.702
Sex				
Males, n (%)	47 (43)	23 (42)	24 (44)	0.847
Diabetes				
n (%)	44 (40)	22 (40)	148 (36.9)	1.000
HbA1c, median (IQR)	10.7 (7.7-13.2)	10.9 (7.2-13.0)	10.7 (7.7-13.2)	0.913
Hypertension				
n (%)	57 (52)	28 (51)	25 (45)	0.567
BMI class				
≤25 (normal weight), n (%)	79 (10.6)	48 (14)	31 (7.6)	0.006
25-30 (overweight), n (%)	365 (49.1)	146 (42.6)	219 (54.6)	0.001
30-35 (obese), n (%)	220 (29.6)	115 (33.5)	105 (26.2)	0.029
≥35 (morbidly obese), n (%)	80 (10.8)	34 (9.9)	46 (11.5)	0.494
HIV status				
Positive, n (%)	12 (11)	5 (9)	7 (13)	0.541
Duration of symptoms				
Days, median (IQR)	7 (4-9)	7 (6-9)	5 (3-8)	0.002
PaO_2/FiO_2 ratio at treatment initiation* mmHg, median (IQR)	62.2 (48.6-77.7)	57.9 (47.3-74.3)	64.3 (51.2-79)	0.005
Creatinine (µmol/L)				
Median (IQR)	68 (56-87)	70 (58-89)	66 (55-85)	0.031
Lymphocyte count ($x10^9$/L)				
Median (IQR)	1.19 (0.88-1.63)	1.23 (0.92-1.63)	1.16 (0.8-1.58)	0.141
C-reactive protein (mg/L)				
Median (IQR)	148 (85-236)	171 (106-267)	120 (75-180)	0.001
D-dimer (mg/L)				
Median (IQR)	0.59 (0.36-1.41)	0.69 (0.38-1.66)	0.53 (0.34-1.17)	0.003
Outcome				
Success n (%)	48 (43.6)	31 (56.3)	17 (31)	0.007
Failure n (%)	62 (56.3)	24 (43.6)	38 (69)	
Intubated n (%)	58 (53)	20 (36.6)	38(100)	
Demised on HFNC n (%)	4 (3.6)	4(7)		
Mortality				
Demised n (%)	62 (56.3)	24 (43.6)	38 (69)	<0.001

IQR = interquartile range; n = number: HIV = human immunodeficiency virus; BMI = body mass index; ART = antiretroviral therapy; HFNO = high-flow nasal oxygen; PaO_2/FiO_2 ratio = arterial oxygen partial pressure to fractional inspired oxygen ratio.

*P/F ratio in "HFNO first" group calculated using the equation SF+57+0.61*P/F derived from Bilan N, Dastranji A, Ghalehgolab Behbahani A. *Comparison of the spo2/fio2 ratio and the pao2/fio2 ratio in patients with acute lung injury or acute respiratory distress syndrome*. J Cardiovasc Thorac Res. 2015;7(1):28-31. doi: 10.15171/jcvtr.2014.06. Epub 2015 Mar 29. PMID: 25859313; PMCID: PMC4378672.

Appendix 1: Instructions for authors (Journal: African Journal of Thoracic and Critical Care Medicine (ISSN: 2617-0205))

Journal: *African Journal of Thoracic and Critical Care* Medicine (ISSN: 2617-0205)

Author Guidelines

Author Guidelines

First time authors, click here:Submission guidelines

To submit a manuscript, please proceed to the *AJTCCM* editorial platform website: https://samajournals.co.za/index.php/ajtccm/index

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: publishing@samedical.org).

Please note that the AJTCCM will consider papers that have been posted on Preprint servers.

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged.

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The AJTCCM therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

CONSORT Statement

All papers that describe clinical trials must adhere to the principles outlined in the CONSORT Statement which provides an evidence-based approach to improve the quality of reports of clinical trials. The CONSORT Flow Diagram showing the patients available for the study, those included, and the number at each stage of the study should also be included and the CONSORT Checklist completed and submitted with the manuscript.

Research with animals

When animals are used as subjects, institutional approval of the protocol is necessary and authors should include a statement in the Methods indicating that investigators complied with the relevant national or intetnational guidelines administered by the author's governmental regulatory body. When no formal ethics review process is available, authors must state that humane care was provided in animal experiments, in accordance with stated relevant guidelines.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

IMAGES/PHOTOGRAPHS

Acceptable file types

The image file should be submitted as a high resolution jpeg or tiff Important: Images embedded in a Word document are not acceptable.

Resolution

Images must have a minimum resolution of 300 dpi (dots per inch).

Screenshots and images from the internet

Screenshots and images from the internet are usually only 72 dpi – this is the average resolution that computer screens use – therefore images downloaded from the internet are almost always too small to use for print even though they might look fine on screen.

Author Quick check

If the actual size of the file is:

• less than 500 kb - not great for print
• 500kb - 1000 kb (1 mb) - better
• greater than 1000 kb (i mb) - ideal

The image sent has to be the original i.e. the very first image created.

If it was taken on a camera/cell phone, then that image has to be sent directly from the device's image gallery.

Not a screenshot of the image or via a secondary app (Word, Whatsapp) or uploaded to a website.

Cameras (cell phones) should be set to the highest possible image size

GRAPHS/FIGURES

Acceptable file types

All graphs and figures should be submitted as PDF files

Genetic nomenclature

AJTCCM is a medical journal covering all aspects of respiratory health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Each paper should have a clear rationale, logical study aims, sufficiently detailed methods, and well supported conclusions. It is advisable to clearly state the hypothesis or aim of the work in the introduction section. The discussion and abstract conclusions should be clearly stated and should be backed up by the data presented in the manuscript. The study outcomes or metrics used to inform the conclusions should be clearly stated and outlined.

Study synopsis: All studies submitted with an abstract should, in addition, have a study synopsis sub-section, with a maximum word count including sub-headings of 120 words.

The purpose is to crystalise the findings of the study and thus improve understanding and retention. The study synopsis should have 2 sub-headings: 'What the study adds' and 'Implications of the findings'.

The first sub-heading should tersely outline what new knowledge or additional information the study brings to the field. The second sub-heading should provide the implication of the findings to researchers, clinicians, policy makers, and other stakeholders and could allude to the broader implications of the work.

The study synopsis should not repeat verbatim what is already in the abstract but provides an additional opportunity to emphasise key findings of the study and the implications of the work.

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 – 25 references

*Structured abstract (please note the requirement for the **Study synopsis** outlined above)*

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
    - Do not include any references in the abstracts.

Click Here for an example of a good abstract.

Brief Reports

This may include case series or interesting basic science findings accompanying a case or several cases.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Contributors are encouraged to write to the Editor about possible papers to be considered for review, and where appropriate a review outline will be submitted to experts in the field for consideration before a full review is commissioned. It is expected that an author or authors have substantial experience and track record in the field that the review is about.

*Guideline word limit: 3 500 words (*unless an alternative word limit has been arranged with the Chief Editor)

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Review articles aimed at registrars (residents) and senior registrars in training and junior attending pulmonologists/consultants.

This will follow the typical format of a review article, with an unstructured abstract of ~150 words but the manuscript will be structured in question format with answers in mini-assay format.

Typically the questions could be clinical or basic science orientated under a thematic subject heading, e.g. asthma. The answer format to the questions posed in the review should typically take ~10 minutes to write out by hand.

The format is designed to be useful to trainees preparing for their respiratory medicine or pulmonology examinations.

There should be 10 multiple choice MCQ's at the end (5 choices to each question) with the answers provided in the correspondence section.

This type of review will typically be written by a group of trainees, ideally with co-authorship from varied geographical regions within a country or across multiple countries. Thus, collaboration across countries and continents is encouraged.

Guidelines, position statements and recommendation-type articles

Must preferably be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

- A structured abstract not exceeding 450 words *(please note the requirement for the **Study synopsis** outlined above)*
- Recommended sub-headings: Background and recommendations (a conclusion sub-heading is optional).
- Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents.
- References, appendices, figures and tables must be kept to a minimum.

Case Reports, Scientific Letters and Correspondence (Letters to the Editor)

As of 2022, case reports are to be submitted as a Scientific Letter.

These may include side effects of drugs and brief or negative research findings.

Guideline word limit: 850 words

- No abstract
- May include only one illustration or table
- A maximum of 6 references
- They should end with a conclusion of no more than 75 - 100 words.

Correspondence guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the AJTCCM or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Pick of the Pics

We invite colleagues to submit an image or picture of an interesting finding. This could be a clinical sign, pathology, bronchoscopic image, or any inetresting visual representation of respiratory medicine or critical care. It should be accompanied by a narrative of a max 150 words explaining the image.

Preceding the narrative, there should be an interesting question about the image, e.g. *what the underlying clinical sign or pathological feature is?*

The title should be submitted in a question-like format.

Technical specifications:

The narrative text, including the figure legend, must be in Microsoft Word document format.

When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each one should be identified and explained clearly in the legend.

Acceptable image file types

The image file should ideally be submitted as a high resolution TIFF. JPEGs are acceptable if the image was originally captured as a large JPEG file with minimal or no compression.

When uploading the image file, please be sure to upload the original source file. The system will convert the file to a quick-view PDF and the original source file will be available to the editors.

Please supply two versions of the image files. The first should include any scale bars, symbols, arrows, numbers or letters and the second, with those elements excluded.

Resolution

Images must have a minimum resolution of 300 dpi (dots per inch).

Consent

Any information in photographs that might identify a patient or hospital/facility should be removed or edited out of the image, as far as possible. Where necessary, patient information must be obtained.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.

- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *AJTCCM* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Author Agreement form [forthcoming]
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
    - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at AJTCCM.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Sponsored supplements

Contact admin@pulmonology.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (jpeg or pdf). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Copyright Notice

Material submitted for publication in the AJTCCM is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The AJTCCM does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy Statement

The *AJTCCM* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *AJTCCM* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Appendix 2: Human Research Ethics Committee approvals

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

10 August 2023

HREC REF: 242/2023

A/Prof G Calligaro
Division of Pulmonology
E-16 Respiratory Clinic, NGSH
Email: greg.calligaro@uct.ac.za
Student: Robert.w.vdberg@gmail.com

Dear A/Prof Calligaro

PROJECT TITLE: HIGH-FLOW NASAL OXYGEN VERSUS MECHANICAL VENTILATION AS INITIAL FORM OF RESPIRATORY SUPPORT IN SEVERE COVID-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME: A PROSPECTIVE OBSERVATIONAL STUDY-SUB-STUDY LINKED TO 295/2020 & R020/2021
(MASTERS CANDIDATE-DR ROBERT VAN DEN BERG)

Thank you for your response letter addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Robert Van Den Berg will also be involved in this study.

Please quote HREC REF 242/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/ref 242.2023

Appendix 3: STROBE checklist

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
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
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time

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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

Appendix 4: Contact Details

Dr Robert William van den Berg

Division of General Medicine, Department of Medicine
Groote Schuur Hospital
Observatory
Cape Town
7925, South Africa

Tel: +27 725980735
E-mail: robert.w.vdberg@gmail.com