University of Cape Town
Faculty of Health Sciences

High flow nasal oxygen in resource constrained, non-intensive care high care wards for COVID-19 acute hypoxaemic respiratory failure: comparing outcomes of first versus third waves

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

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Acknowledgements:

We would like to acknowledge with immense gratitude all those who, wave after wave, have given so much towards the care of our patients with severe COVID-19. We dedicate this article to all the patients who have passed on and to those who have left our hospital to return to friends and family.

Abstract:

Background: High flow nasal oxygen (HFNO) is an accepted treatment for severe COVID-19 related acute hypoxaemic respiratory failure (AHRF) especially where limited access to intensive care unit (ICU) resources exists, and approximately halves the need for invasive mechanical ventilation.

Objectives: To determine if treatment outcomes would be better in the third COVID wave (irrespective of differences in variant virulence; ancestral vs delta) due to increased institutional experience and capacity for HNFO and more restrictive admission criteria for respiratory high care wards and ICU dictated by the higher case load in the third wave.

Methods: We included consecutive patients with COVID-19-related AHRF treated with HFNO during the first (7 May to 25 August 2020) and third COVID waves (4 July to 4 September 2021) at Groote Schuur Hospital. The primary endpoint was comparison of HFNO failure between the first and third waves of the COVID-19 pandemic.

Findings: A total of 744 patients were included: 343 in the first, and 401 in the third COVID-wave. Patients treated with HFNO in the first wave had an older median (IQR) age (53 (46-61) vs 47 (40-56) years, p<0.001), and a higher prevalence of diabetes (46.9 vs. 36.9%, p=0.006), hypertension (51.0% vs 35.2%, p<0.001), obesity (33.5% vs 26.2%, p=0.029) and HIV infection (12.5% vs 5.5%, p<0.001). Median (IQR) arterial oxygen partial pressure to fraction inspired oxygen ratio (PaO2/FiO2) at HFNO initiation and the ratio of oxygen saturation/FiO2 to respiratory rate within 6 hours (ROX-6 score) after HFNO commencement were lower in the first wave compared with the third: 57.9 (47.3-74.3) vs 64.3 (51.2-79.0), p=0.005 and 3.19 (2.37-3.77) vs 3.43 (2.93-4.00), p<0.001, respectively. Despite these differences in comorbidities and baseline measures of oxygenation, the likelihood of HFNO failure (57.1% versus 59.6.1%, p=0.498) and mortality (52.1% vs 46.9%, p=0.159) did not differ between first and third waves the first and third COVID waves.

Conclusion: Despite differences in overall case load, baseline patient characteristics, virulence of the circulating wave variant and institutional experience with HFNO, treatment outcomes were very similar in the first and third COVID waves. We conclude that once severe respiratory failure is established in COVID pneumonia, comorbidities and HFNO provider experience make little difference to outcome.

Introduction:

At the end of 2019, the identification in Wuhan, China of a novel coronavirus SARS-CoV-2 rapidly lead to the spread of a global respiratory pandemic called COVID-19. The pandemic quickly overwhelmed global and South African hospitals, particularly critical care resources, where access to mechanical ventilation was limited. High flow nasal oxygen (HFNO) – a form of non-invasive respiratory support that provides of a constant fraction of inspired oxygen with adequate humidification – was proposed early during the first wave as a non-invasive alternative for the management of hypoxia in critically ill patients with acute COVID-19 hypoxic respiratory failure (AHRF) in anticipation that the need for intubation and invasive mechanical ventilation (IMV) would be reduced.

At Groote Schuur Hospital, a "HFNO-first" strategy was quickly adopted, where patients with severe AHRF due to COVID-19 were treated in dedicated non-ICU respiratory high care wards. Early data from our research group in collaboration with Tygerberg Hospital showed that IMV could be avoided in up to 50% of patients with severe COVID-19 AHRF when HFNO was employed.

This study, extending these early findings, aimed to evaluate and compare the outcomes of patient with severe AHRF due to COVID-19 treated with HFNO across the first and third waves of the pandemic at Groote Schuur Hospital, Cape Town, South Africa. We hypothesised that differences in viral variant, wave duration, HFNO bed capacity, corticosteroid use, institutional familiarity with this form of respiratory support and immunisation rollout may lead to differences between waves in patient characteristics and the need for intubation.

Publication ready document:

High flow nasal oxygen in resource constrained, non-intensive care high care wards for COVID-19 acute hypoxaemic respiratory failure: comparing outcomes of first versus third waves.

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Conclusion: Despite differences in overall case load, baseline patient characteristics, virulence of the circulating wave variant and institutional experience with HFNO, treatment outcomes were very similar in the first and third COVID waves. We conclude that once severe respiratory failure is established in COVID pneumonia, comorbidities and HFNO provider experience make little difference to outcome.

STUDY SYNOPSIS:

What the study adds:

This study adds to the body of evidence demonstrating that the utility of high flow nasal oxygen (HFNO) to prevent invasive mechanical ventilation (IMV) in patients with severe COVID-19 hypoxic respiratory failure remains consistent across different waves of the COVID-19 pandemic.

Implications of the study:

In resource-constrained settings, HFNO is a feasible non-invasive alternative to IMV and can be employed with consistent outcomes outside of traditional critical care wards. It also confirms that the degree of gas exchange abnormality, and not patient-related factors, circulating wave variant, or provider experience, is the main predictor for HFNO failure. It also confirms the role of corticosteroids in reducing the need to escalate respiratory support.

INTRODUCTION

At the end of 2019, a novel coronavirus SARS-CoV-2 resulted in an acute respiratory illness epidemic - COVID-19 - in Wuhan, China. [1] The disease rapidly spread globally and on 11 March 2020 the World Health Organization declared the outbreak a pandemic. [2] This rapidly overwhelmed health care systems globally, with associated high mortality rates. [3,4] The development and roll-out of COVID-19 vaccines has shown a marked reduction in cases of hospitalisation, severe disease and death. [5] Despite this, inequality in distribution of the vaccines resulted in delays in country-wide vaccination in lower and middle-income countries like South Africa. [6] These countries were left vulnerable by this vaccination delay and as a result experienced a severe third wave of the pandemic during the middle of 2021. [7,8]

Prior to the role out of the vaccines, 1 in 5 people with COVID-19 required hospitalisation. [9] In most cases the indication for hospitalisation was hypoxaemia requiring variable levels of supplemental oxygen therapy. [10] The first 3 waves of the pandemic in South Africa thus far has been characterised by severe constraints in treating patients with acute hypoxic respiratory failure (AHRF) with mechanical ventilation in intensive care units (ICU). [11] One strategy that has been employed to combat severe COVID-19 respiratory failure and hypoxaemia is high

flow nasal oxygen (HFNO). [12] HFNO is a device that delivers 30–60 L/min of heated and humidified air and oxygen blend at the desired fraction of inspired oxygen (FiO_2) via a wide-bore nasal interface. [13] This reduces anatomic dead space, work of breathing and respiratory rate, and increases positive end-expiratory pressure and compliance. [13] Prior to the pandemic, HFNO was being used as a non-invasive alternative for the management of hypoxia in critically ill patients. [14] Its major benefits are its ease of use and superior tolerability when compared to non-invasive ventilation and invasive mechanical ventilation (IMV). [14] Several observational studies suggested that if mechanical ventilation becomes scarce, using HFNO is a feasible alternative to provide adequate oxygenation for these severely hypoxic patients, reducing the number needing IMV, increasing ventilator free days and reducing length of ICU stay. [15–20]

Groote Schuur Hospital (GSH), a tertiary referral hospital in Cape Town, South Africa, adopted the use of HFNO in non-intensive care high care wards to increase the capacity to manage patients with acute hypoxic respiratory failure secondary to COVID-19 and in anticipation that ICU capacity would quickly be overwhelmed. [21] An observational cohort study from our research team at GSH in collaboration with nearby Tygerberg Hospital (TBH) found that intubation and ventilation could be avoided in up to 50% of patients with acute hypoxic respiratory failure during the first wave in the resource constrained South African health care setting. [16] This prompted GSH to expand this high-care HFNO service into subsequent waves of the pandemic.

We hypothesised that differences in viral variant, wave duration, HFNO bed capacity, corticosteroid use, institutional familiarity with this form of respiratory support and immunisation rollout may lead to differences between waves in patient characteristics and the need for intubation.

METHODS

Study design

We conducted a prospective observational study at GSH, Cape Town, South Africa. The study was approved by the local ethics committees at the University of Cape Town (UCT HREC 295), and informed consent was waived in acknowledgement that the intervention was being

assessed within the routine clinical service. The study is reported in accordance with the STROBE statement for cohort studies.[22]

Setting

GSH is a tertiary academic hospital that services a population of ~4.5 million with high tuberculosis and HIV prevalence. [23] The waves of the pandemic are defined by the National Institute of Communicable Diseases (NICD) as the period from when COVID-19 weekly incidence is equal to or greater than 30 cases per 100 000 persons until the weekly incidence equal or below 30 cases per 100 000 persons. [24] The first case of COVID-19 in South Africa was identified on the 11 March 2020 and, according to the above definition, the first wave spanned until the 23rd of August 2020, while the third wave spanned between the 10th of May and the 19th of September 2021. [24] In this study patients were enrolled from the first wave between the 7th of May and the 25th of August 2020 (16 weeks) and from the third wave between the 4th of July to the 4th of September 2021 (9 weeks) (Figure 1). There were 39 respiratory high care beds available in the first wave and 10-30 HFNO machines available to treat patients (the number of HFNO machines increased during the wave as the utility of this method of non-invasive respiratory support was increasingly recognised), vs 59 beds and 50 machines available during the peak of the third wave.

Participants

Eligible participants 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 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 but was indicated in cooperative patients who were able to comply with awake proning. 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 PaO_2. Prone position was encouraged at every clinical encounter and reinforced by nursing staff according to a shared

clinical protocol. Following the preliminary report of the efficacy of dexamethasone by RECOVERY, all patients on HFNO received either dexamethasone 6mg intravenously daily, or prednisone 40mg daily for 10 days.[25]

Sample Size

In the cohort study during the first wave by Calligaro et al. the HFNO failure rate in patients with severe COVID-19 hypoxic respiratory failure was 53%.[16] We calculated that a sample size of 319 patients in each wave would be required to detect a 10% difference between arms (OpenEpi, Version 3, open-source calculator).

Heated and humidified HFNO

Heated and humidified HFNO was exclusively provided within designated high-care medical wards (non-ICU) at GSH where patients were cohorted. HFNO was delivered either by a 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%.

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 (ratio of oxygen saturation/FiO2 to respiratory rate) at 6 hours (ROX-6).[26,27] For patients who were intubated before 6 hours, the variables at the time that the decision was made that HFNO was failing were recorded. COVID-19 vaccination status was recorded with 'full vaccination' defined as 2-weeks post single dose of Johnson & Johnson's Janssen vaccine or 2-weeks post the second dose of the Pfizer-BioNTech. [28]

Outcomes

The primary endpoint was comparison of HFNO failure between the first and third waves of the pandemic. HFNO failure was defined as composite of the need for intubation or death whilst on HFNO. Death on HFNO was a composite of unexpected deaths on HFNO and patients who

demised on HFNO as they were not deemed candidates for intubation and mechanical ventilation in ICU. Secondary outcomes were predictors of HFNO failure, overall in-hospital mortality, and difference in early versus late intubation on outcome. Early intubation was defined as occurring within 48 hours of initiation of HFNO; late intubation occurred thereafter.

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 2). The crude cumulative proportion of HFNO success for each wave was calculated. We analysed univariate and multivariate associations between need for intubation initiation using clinically important variables selected *a priori* for the model. Data were analysed using Stata (V. 12.1, StataCorp, College Station, Texas. USA). A p-value of <0.05 was considered statistically significant. [29,30] The first and last authors had full access to the data and were responsible for the submission of the manuscript.

RESULTS

Patient population

A total of 744 patients were enrolled. The median (IQR) age was 50 (42-58) years; 385/744 (51.7%) were males. Every patient was on at least a reservoir face mask at 15 L/min prior to initiation of HFNO (often, as became the practice, with the addition of nasal prong oxygen – so-called "double oxygen"). 346 (46%) patients were enrolled in the first wave and 401 (54%) in the third. Although similar numbers of patients were enrolled in each wave, the institutional capacity to treat patients with HFNO was considerably higher in the third compared to the first wave, as reflected by the average number of patients enrolled per week: 21/week in the first wave vs 45/week in the third wave. Differences between waves in the numbers of HFNO machines and respiratory high-care ward beds available have been detailed above. The third wave cohort was younger (47 vs 53, p<0.001), with a lower prevalence of hypertension (35% vs 51%, p<0.001), diabetes (37% vs 47%, p=0.006), HIV (5.5% vs 12.5%, p<0.001) and obesity (26.2% vs 33.5%, p=0.029). Patients in the third wave also had worse oxygenation prior to HFNO initiation (PaO_2/FiO2 64.3 vs 57.9, p=0.005) and higher ROX index at 6 hours post initiation of HFNO (3.43 vs 3.19, p<0.001) (Table 1). As expected from the change in

practice following RECOVERY, patients in the third wave were more likely to have been treated with corticosteroids (82% vs 100%, p<0.001). [25]

Primary outcome (first versus third wave)

HFNO failure did not differ between first and third wave (57.1% versus 59.6.1%, p=0.498). (Table 1). Figure 3 shows the proportion of patients with HFNO failure over time. There was no significant difference between waves.

Secondary outcomes

Univariate predictors for HFNO failure were older age, obesity, lower PF ratio, not being treated with steroids, lower PaO_2/FiO_2 ratio before HFNO initiation, lower ROX-6 after HFNO commencement, and higher D-dimer level (Table 2). The wave itself was not a predictor of poor outcome. On multivariate analysis of predictors of HFNO failure, not being on steroids, lower PaO_2/FiO_2 before HFNO and lower ROX-6 after HFNO were predictive. An increase in ROX-6 by one point was associated with a 59% relative reduction in the risk of HFNO failure.

Of all patients treated with HFNO, 309 (41%) patients were successfully weaned (Figure 2): 306/309 (99%) were discharged home. The proportion of patients who demised on HFNO was 13% in the first wave versus 20% in the third wave (p=0.008). ICU mortality of patients requiring intubation was high: 223/291 (77%) demised, with the rest all surviving to discharge (Figure 2). However, overall in-hospital mortality did not differ between first and third wave (46.9% versus 52.1%, p=0.159).

155/291 (53%) of the patients who were intubated within 48 hours of initiating HFNO (early): mortality was 112/155 (72%) in this group. Similarly, the in-hospital mortality was 111/136 (82%) for patients intubated after 48 hours (late failures) (p=0.060). Although the study was not powered to detect a difference between early and late failures, *post-hoc* analysis showed we still had 90% power to detect one.

Vaccination

No patients in either group were fully vaccinated, however 11 patients in the third wave had received a COVID-19 vaccine. Of those vaccinated, 7/11 had received one of the two scheduled doses of the Pfizer-BioNTech vaccine, 1/11 presented within one week of the second dose of

the Pfizer-BioNTech vaccine and 3/11 presented within one week of having received the Johnson & Johnson's Janssen vaccine.

DISCUSSION

This study, which to our knowledge is the only comparison of outcomes between waves of patients treated with HFNO with severe COVID-19 in South Africa, found no difference in HFNO success or mortality in patients treated in the first versus the third waves. This is despite several differences between waves including viral variant, wave duration, corticosteroid use, HFNO bed capacity, patient risk factor profile, and baseline measures of oxygenation.

Whilst the reasons for the difference in patient characteristics between waves is likely multifactorial, one explanation was the implementation of the Western Cape Triage Tool in the third wave, which favoured selection of younger patients with fewer comorbidities associated with in-hospital mortality from COVID-19.[31,32] Another possible explanation relates to the vaccine rollout in South Africa. Rollout of the vaccine to the general public (starting with the elderly) only began on 17th May 2021, 7 days after what later proved to be the start of the third wave. [24,33] This prioritisation of vaccinating the elderly may explain why the third wave cohort was younger - reflecting the protective effect of the vaccine against severe disease. However, it is more likely that rigorous triaging necessitated by the increased case load skewed this demographic in the third wave.

There are two possible explanations for the lack of observed difference between wave outcomes. Firstly, we speculate that the significantly younger and healthier third wave cohort balanced the expected increase in mortality associated with the more virulent delta variant and its corresponding higher case load.[7] Additionally, although HFNO provider experience and competence likely improved as the waves progressed, HFNO bed capacity in the third wave increased disproportionally to the number of doctors and nurses looking after these patients (in particular, the number of doctors available after-hours). The effect of reduced staffing ratios and senior oversight after hours on outcomes in critically ill patients is well described and this too may have had a deleterious effect that further balanced the inter-wave outcomes.[34]

The significant independent predictors of HFNO failure in our study were steroid use, pre-HFNO PaO_2/FiO_2, and the ROX-6 score. This is in keeping with the findings of an earlier study

from our research team at GSH in collaboration with nearby TBH as well as the conclusions and recommendation of a systematic review by Attaway et al of the application of the ROX index in the setting of COVID-19 that found patients with a ROX index ≥4.88 after 2, 6, and 12 hours of treatment had low risk of intubation, whereas a ROX index <3.85 at the same time points was associated with a high risk of failure. [16,35] It is interesting that none of the other demographic variables or laboratory parameters were predictive of the need for intubation. This suggests that - whilst these other factors may be important in the development of severe acute respiratory distress syndrome (ARDS) from COVID pneumonia - once this pathological process is firmly established, it is only whether or not HFNO is actually able to improve gas exchange and respiratory rate within a few hours of its institution (via the many putative mechanisms already described) that determines whether intubation will ultimately be avoided. The protective effects of steroids on the progression to respiratory failure and mortality are well known, and this study further reinforces that steroid use reduces the incidence of HFNO failure. [25]

Our study found no significant difference in patient survival in those intubated early (<48 hours) versus those intubated late (>48 hours). Although this was not a primary outcome, we were adequately statistically powered to answer this question. Timing of intubation in those failing HFNO remains an area of great interest. Guidelines from China, the United Kingdom and the United States of America recommend early intubation in critically ill COVID-19 patients. [36–38] The rationale for early intubation is the avoidance of "crash" intubations and the potential prevention of patient self-inflicted lung injury (PSILI) associated with distressed spontaneous respiration. [39] In a prospective observational cohort study by Vera et al, late intubation (defined as >48 hours after HFNO initiation) was associated with increased ICU mortality. This finding is in keeping with a systematic meta-analysis on non-randomised cohort studies by Papoutsi et al, which evaluated the impact of timing of intubation (within 24-hours of ICU admission or later) and found that timing had no significant effect on mortality and morbidity of critically ill patients with COVID-19. [40] To our knowledge, no randomised control trials have been done to look at outcomes of early versus late intubation in those failing HFNO. Furthermore, no studies of the impact of timing of intubation on patients failing HFNO in a non-intensive care ward-based environment are available to guide practice in resource constrained settings employing this strategy of respiratory support. [41] This highlights a need for further research in this area to better guide practice.

Limitations

Our study had several limitations. First, it is a single-centre cohort study in a tertiary academic hospital and thus may not reflect the reality of the experience in other hospitals in South Africa with less resources. Second, patient management, particularly the decision to intubate, was left to the discretion of the treating team and not fully protocolised. This approach may differ from other local and international institutions influencing the generalisability of the results. Additionally, with ever changing pressure on intensive and high care resources as the waves of the pandemic surged, triage criteria were adjusted influencing patient selection for admission resulting in significantly differing cohort demographics with the rise and fall of each wave. Additionally, the sampling period was not of equal duration across each wave which may have introduced selection bias; however, patients were enrolled at the peak of both waves. Another limitation is the lack of data on the number and characteristics of patients who were not able to access HFNO because of resource limitation due to case load and implementation of the Western Cape Triage Tool. This means that inferences about differences in patient characteristics between waves being a result of triaging is strongly suggested but in the absence of denominator data, unconfirmed.

Generalisability

Our results are only hypothesis generating but do provide contextual evidence that may guide decision making in forthcoming COVID-19 waves.

Conclusion

Overall, despite differences in overall case load, baseline patient characteristics, virulence of the circulating wave variant and institutional experience with HFNO, treatment outcomes were very similar in the first and third COVID waves. We conclude that once severe respiratory failure is established in COVID pneumonia, comorbidities and HFNO provider experience make little difference to outcome.

Ethics

This study was approved by the local Research Ethics Committees at the University of Cape Town (UCT HREC 295).

Funding

None.

Author contributions

GA, KD and GC were involved in the conception and design of the study. GA and GC were involved in study implementation and data collection. GA and GC did the data analysis. GA, KD and GC interpreted the data and provided important intellectual input. All authors contributed to writing and editing the manuscript.

Declaration of competing interests

None.

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We would like to acknowledge with immense gratitude all those who, wave after wave, have given so much towards the care of our patients with severe COVID-19. We dedicate this article to all the patients who have passed on and to those who have left our hospital to return to friends and family.

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Figure 1. Temporal relationship of study sample (first wave vs. third) to national case load [42]

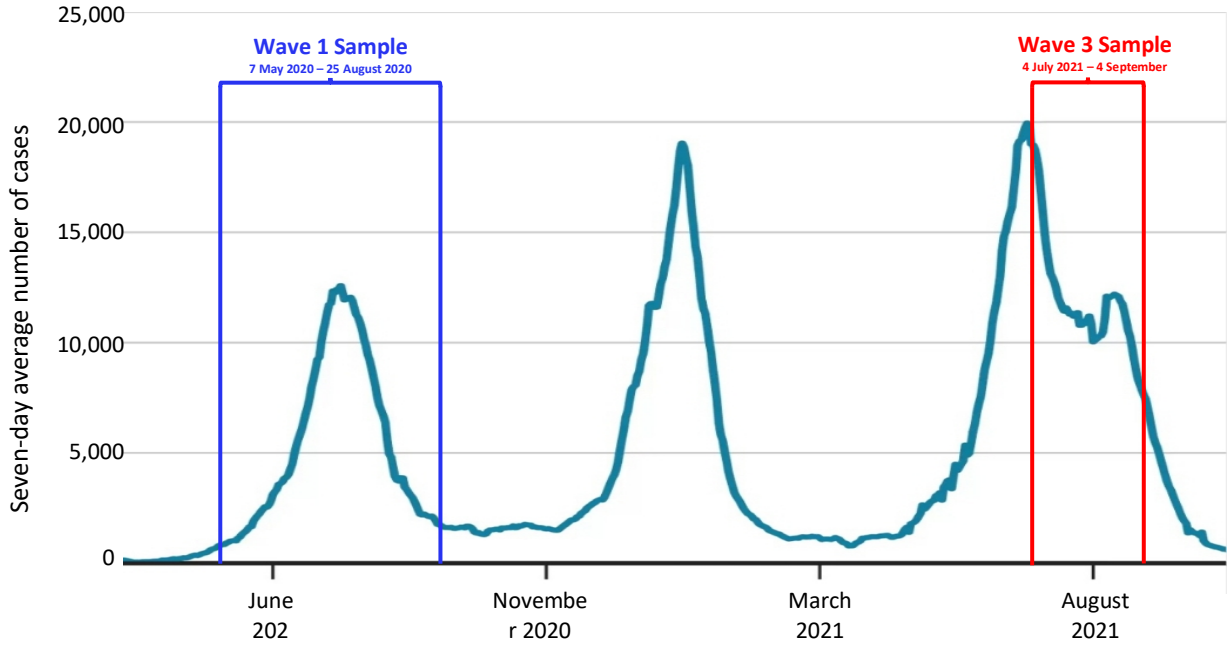

Figure 2. Consort diagram

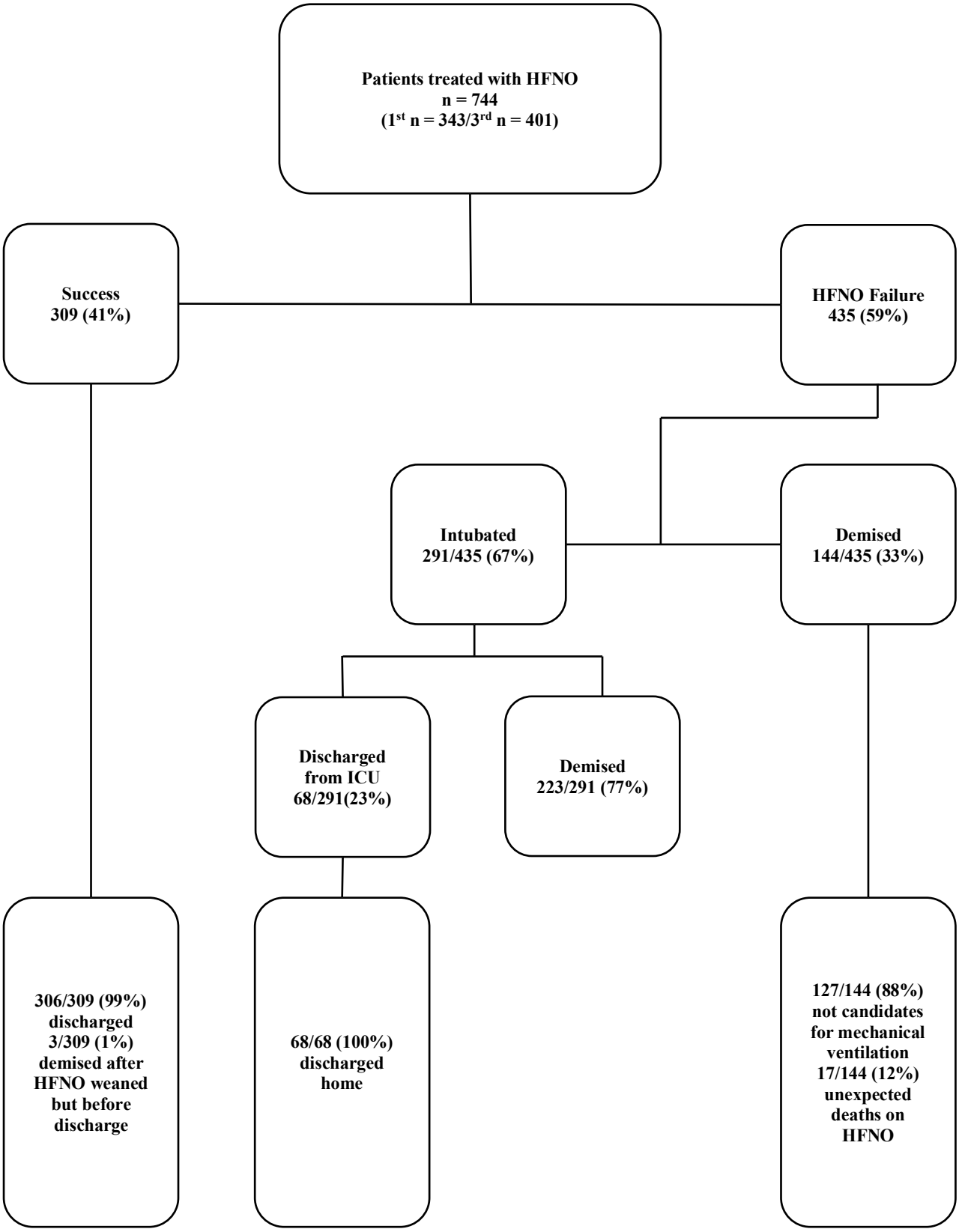

Figure 3. Proportion of patients with unsuccessful outcome from initiation of HFNO

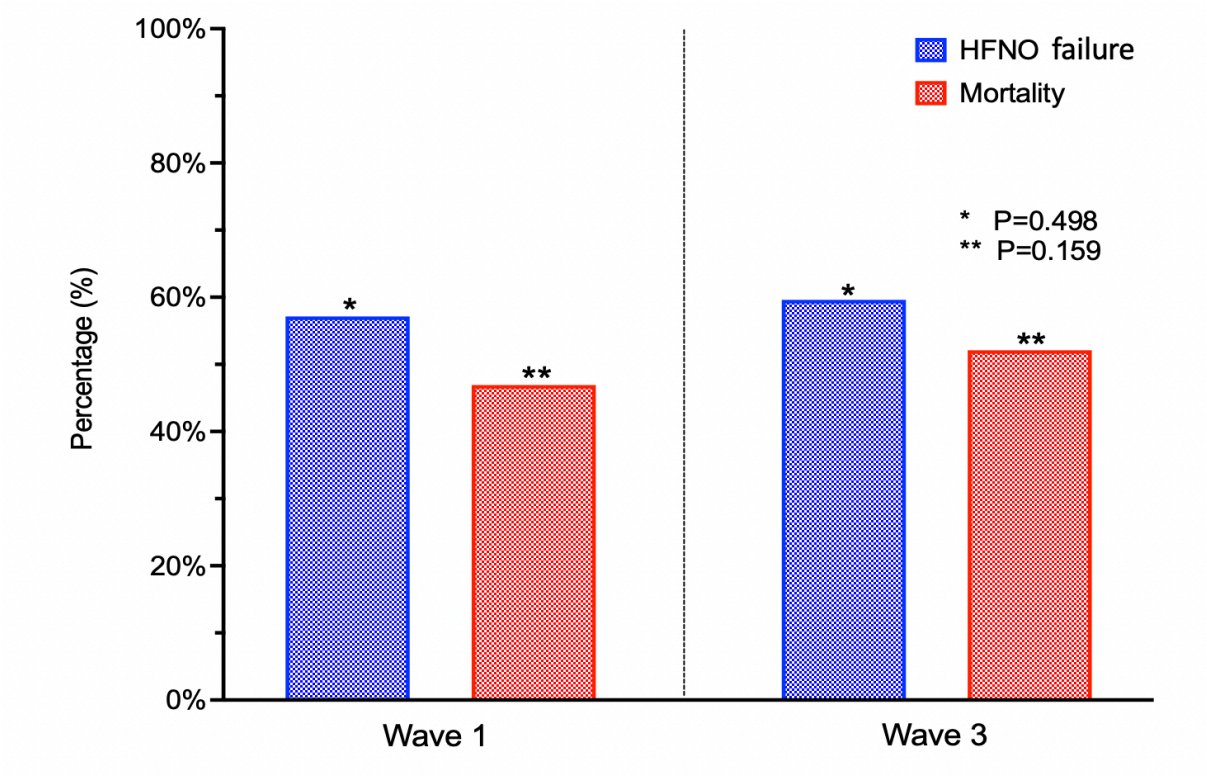

Table 1. Patient characteristics across waves

	Total (n = 744)	**First Wave (n = 343)**	**Third Wave (n = 401)**	**P-value**
Age (years)				
Median (IQR)	50 (42-58)	53 (46-61)	47 (40-56)	<0.001
Sex				
Males, n (%)	385 (51.7)	174 (50.7)	211 (52.6)	0.607
Diabetes				
n (%)	309 (41.5)	161 (46.9)	148 (36.9)	0.006
HbA1c, median (IQR)	9.45 (7.2-11.5)	9.8 (7.45-11.7)	8.5 (7-11.2)	0.165
Hypertension				
n (%)	316 (42.5)	175 (51)	141 (35.2)	<0.001
BMI class				
≤25, n (%)	79 (10.6)	48 (14)	31 (7.6)	0.006
25-30, n (%)	365 (49.1)	146 (42.6)	219 (54.6)	0.001
30-35, n (%)	220 (29.6)	115 (33.5)	105 (26.2)	0.029
≥35, n (%)	80 (10.8)	34 (9.9)	46 (11.5)	0.494
HIV status				
Negative, n (%)	519 (69.8)	238 (69.4)	281 (70.1)	0.839
Positive, n (%)	65 (8.7)	43 (12.5)	22 (5.5)	<0.001
Unknown, n (%)	160 (21.5)	62 (18.1)	98 (24.4)	0.035
CD4 count (if HIV +ve) (cells/m^3)				
Median (IQR)	280 (138-416)	277 (130-423)	283 (201-370)	1.00
ART use (vs. no ART if HIV +ve)				
n (%)	51 (78.5)	33 (76.7)	18 (81.8)	0.322
Duration of symptoms				
Days, median (IQR)	7 (6-11)	7 (5-10)	8 (6-14)	0.347
Steroids as treatment				
n (%)	682 (91.7)	281 (81.9)	401 (100)	<0.001
PaO_2/FiO_2 ratio at HFNO initiation				
mmHg, median (IQR)	62.2 (48.6-77.7)	57.9 (47.3-74.3)	64.3 (51.2-79)	0.005
ROX-6				
Median (IQR)	3.34 (2.65-3.92)	3.19 (2.37-3.77)	3.43 (2.93-4)	<0.001
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 on HFNC				
Success n (%)	309 (41.5)	147 (42.9)	162 (40.4)	0.498
Failure n (%)	436 (58.5)	196 (57.1)	239 (59.6)	0.498
Intubated n (%)	291 (39.1)	143 (41.7)	148 (36.9)	0.183
Demised on HFNC n (%)	17 (2.3)	8 (2.3)	9 (2.2)	0.936
Palliated n (%)	127 (17.1)	45 (13.1)	82 (20.4)	0.008
Mortality				
Demised n (%)	370 (49.7)	161 (46.9)	209 (52.1)	0.159

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.

Table 2. Predictors of HFNO failure

Variable	n	Estimated OR (95% CI)	P-value	Adjusted OR† (95% CI)	P-value
Age (per year increase)	744	1.02 (1.00-1.03)	0.008	1.02 (1.00-1.04)	0.074
Male (vs. females)	744	1.07 (0.80-1.43)	0.644		
Third wave (vs. first wave)	744	1.11 (0.83-1.48)	0.498		
HIV status (vs. negative)					
Positive	65	1.61 (0.96-2.71)	0.068		
Unknown	160	1.19 (0.67-2.13)	0.539		
Hypertension	316	1.23 (0.92-1.66)	0.164		
Diabetes	309	1.21 (0.90-1.63)	0.208		
Obesity (BMI ³30kg/m^2 vs. normal)	665	1.79 (1.12-2.86)	0.015	1.93 (0.87-4.29)	0.107
Duration of symptoms (per 1 day increase)	744	1.00 (0.96-1.03)	0.799		
Treatment with steroids	744	0.22 (0.10-0.45)	<0.001	0.24 (0.08-0.75)	0.014
PaO_2/FiO_2 ratio before HFNO initiation	479	0.98 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	0.050
ROX-6 score (per 1 point increase)	744	0.41 (0.34-0.50)	<0.001	0.52 (0.40-0.69)	<0.001
Lymphocyte count (per 1x10^9 increase)	505	0.82 (0.62-1.08)	0.158		
CRP (vs. <100mg/L)	100				
100-199	116	0.62 (0.36-1.08)	0.091		
200-399	82	0.88 (0.48-1.61)	0.675		
³400	17	4.22 (0.91-19.50)	0.065		
D-dimer (vs. <1.5mg/L)	461				
1.51-5.0	85	1.67 (1.03-2.71)	0.037	1.88 (0.78-4.54)	0.159
³5	61	2.07 (1.16-3.70)	0.014	1.88 (0.78-4.54)	0.159

Note: OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; CRP = C-reactive protein.
† Best model fit obtained with inclusion of steroid use, PaO_2/FiO_2 ratio before HFNO initation and ROX-6.

Appendices:

1. Instructions for authors (Journal: African Journal of Thoracic and Critical Care Medicine (ISSN: 2617-0205))
2. Human Research Ethics Committee approvals
3. Case Report Form
4. STROBE checklist
5. Contact Details

1-Instructions for Authors:

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).

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2-Human Research Ethics Committee approvals:

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 June 2020

HREC REF: 295/2020

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

Dear A/Prof Calligaro

PROJECT TITLE: HIGH-FLOW NASAL CANUULA (HFNC) FOR ACUTE HYPOXAEMIC RESPIRATORY FAILURE IN COVID-19 PNEUMONIA MASTERS CANDIDATE- DR GORDON AUDLEY -SUB-STUDY LINKED TO R023/2020; 213/2020; R021/2020

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 June 2021.

Please confirm that there will be data sharing with Prof Ntusi' s registry.

Please submit a progress form, using the standardised Annual Report Form 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 Gordon Audley will also be involved in this study.

Please quote the HREC REF 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

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS 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 2006), 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.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.07.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	14/7/2021

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you and many apologies for the incorrect email address

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	06/07/2021		
HREC REF Number	295/2020	Current Ethics Approval was granted until	30/06/2021
Protocol title	High-flow nasal cannula (HFNC) for acute hypoxaemic respiratory failure in covid-19 pneumonia masters candidate – Dr Gordon Audley – This is a sub-study linked to R023/2020, 213/2020, R021/2020		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	✓No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Greg Calligaro		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

3-Case Report Form

COVID-19 HFNC Case Report Form

Record ID	_____
Study Number	_____
1. PATIENT DETAILS	
Folder Number	_____
Name	_____
Surname	_____
Age (Years)	_____
Sex	◯ Male ◯ Female
Is the patient pregnant?	◯ Yes ◯ No
Specify gestational age (weeks)	_____ (weeks)
2. COMORBIDITIES	
What is the patient's BMI?	◯ Underweight ◯ Normal ◯ Overweight ◯ Obese ◯ Morbidly obese
Does the patient have a history of HPT?	◯ Yes ◯ No
Does the patient have a history of Diabetes?	◯ Yes ◯ No
What is the patient's HbA1c	_____
Does the patient have a history of COPD?	◯ Yes ◯ No
Specify the patient's MMRC Grade	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6

Does the patient have a history of CCF?	◯ Yes ◯ No

Xray disease severity	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6
Blood Gas Pre HFNC available	◯ Yes ◯ No
If blood gas available, specify pH	_____
pO2	_____
pCO2	_____
Bicarb	_____
Lactate	_____

4. HFNC

What was the Initiation Date?	_____
What was the Discontinuation Date?	_____
Duration (Days)	_____ (Days)
What was the outcome?	◯ Successfully weaned ◯ Intubated ◯ Died on HFNC ◯ Palliated
What is the Reason for HFNC failure?	◯ Exhaustion ◯ Rising CO2 ◯ Clinician assessment ◯ Unable to deliver HFNC ◯ Altered mental state ◯ Haemodynamic instability

5. THERAPEUTIC INTERVENTIONS ON HFNC

Was Anticoagulant used?	◯ Yes ◯ No
If yes, specify Anticoagulant	◯ None ◯ Prophylactic ◯ Therapeutic
Were Steroids used?	◯ Yes ◯ No

6. INTUBATED & VENTILATED

Was the patient intubated and ventilated?	◯ Yes ◯ No
Did the patient decline intubation?	◯ Yes ◯ No
What was the duration of ventilation? (Days)	_____ (Days)
What was the length of stay in ICU? (Days)	_____ (Days)
Any Acute Kidney Injury?	◯ Yes ◯ No
If AKI -? Dialysed?	◯ Yes ◯ No
Blood Gas Pre HFNC available	◯ Yes ◯ No
If blood gas available, specify pH	_____
pO2	_____
pCO2	_____
Bicarb	_____
Lactate	_____
Overall outcome	◯ Died ◯ Discharged ◯ Still admitted

7. DAILY REVIEW

	Patient condition prior to HFNC
HR (bpm)	_____
RR (bpm)	_____
SpO2 (%)	_____
Speech	◯ Undisturbed ◯ Broken sentences ◯ Words ◯ No speech
Cooperation	◯ Full cooperation ◯ Slow to cooperate ◯ Difficult to tolerate HFNC ◯ Agitated or unconscious
FiO2 (%)	_____
Flow Rate (l/min)	_____
HR (bpm)	_____
RR (bpm)	_____
SpO2 (%)	_____
Speech	◯ Undisturbed ◯ Broken sentences ◯ Words ◯ No speech
Cooperation	◯ Full cooperation ◯ Slow to cooperate ◯ Difficult to tolerate HFNC ◯ Agitated or unconscious
FiO2 (%)	_____
Flow Rate	_____
HR (bpm)	_____

4-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

5-Contact Information:

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