High-flow nasal oxygen in resource-constrained, non-intensive, high-care wards for COVID-19 acute hypoxaemic respiratory failure: Comparing outcomes of the first v. third waves at a tertiary centre in South Africa

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Background. High-flow nasal oxygen (HFNO) is an accepted treatment for severe COVID-19-related acute hypoxaemic respiratory failure (AHRF).
Objectives. To determine whether treatment outcomes at Groote Schuur Hospital, Cape Town, South Africa, during the third COVID-19 wave would be affected by increased institutional experience and capacity for HNFO and more restrictive admission criteria for respiratory high-care wards and intensive care units.
Methods. We included consecutive patients with COVID-19-related AHRF treated with HFNO during the first and third COVID-19 waves. The primary endpoint was comparison of HFNO failure (composite of the need for intubation or death while on HFNO) between waves.
Results. A total of 744 patients were included: 343 in the first COVID-19 wave and 401 in the third. Patients treated with HFNO in the first wave were older (median (interquartile range) age 53 (46 - 61) years v. 47 (40 - 56) years; $p<0.001$), and had higher prevalences of diabetes (46.9% v. 36.9%; $p=0.006$), hypertension (51.0% v. 35.2%; $p<0.001$), obesity (33.5% v. 26.2%; $p=0.029$) and HIV infection (12.5% v. 5.5%; $p<0.001$). The partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio at HFNO initiation and the ratio of oxygen saturation/FiO_2 to respiratory rate within 6 hours (ROX-6 score) after HFNO commencement were lower in the first wave compared with the third (median 57.9 (47.3 - 74.3) mmHg v. 64.3 (51.2 - 79.0) mmHg; $p=0.005$ and 3.19 (2.37 - 3.77) v. 3.43 (2.93 - 4.00); $p<0.001$, respectively). The likelihood of HFNO failure (57.1% v. 59.6%; $p=0.498$) and mortality (46.9% v. 52.1%; $p=0.159$) did not differ significantly between the first and third waves.
Conclusion. Despite differences in patient characteristics, circulating viral variant and institutional experience with HFNO, treatment outcomes were very similar in the first and third COVID-19 waves. We conclude that once AHRF is established in COVID-19 pneumonia, the comorbidity profile and HFNO provider experience do not appear to affect outcome.
Keywords. COVID-19, high-flow, oxygen.

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Study synopsis

What the study adds. This study adds to the body of evidence demonstrating the utility of high-flow nasal oxygen (HFNO) in avoiding invasive mechanical ventilation (IMV) in patients with severe COVID-19 hypoxaemic respiratory failure, and shows that this utility remained 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 favourable and consistent outcomes outside traditional critical care wards. It also confirms that the degree of gas exchange abnormality, and not pre-existing patient-related factors, circulating wave variant or provider experience, is the main predictor of HFNO failure.

At the end of 2019, the novel coronavirus SARS-CoV-2 resulted in an acute respiratory illness outbreak, later named COVID-19, in Wuhan, China.[1] The infection rapidly spread globally, and on 11 March 2020 the World Health Organization declared the outbreak a public health emergency of international concern.[2] Healthcare systems were overwhelmed globally, with associated high mortality rates.[3,4] The development and roll-out of COVID-19 vaccines resulted in a marked reduction in hospitalisation, severe disease and death.[5] Despite this, inequality in global vaccine distribution resulted in delays in country-wide vaccination in low- and middle-income countries (LMICs) such as South Africa (SA).[6] These countries were left vulnerable to recurrent infection waves, and as a result SA experienced a severe third wave of COVID-19 infections in the middle of 2021.[7,8]

Before roll-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 three waves of the pandemic in SA were characterised by severe constraints in access to mechanical ventilation in intensive care units (ICUs) to treat patients with acute hypoxaemic respiratory failure (AHRF).[11] One strategy that has been employed to manage 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] HFNO reduces anatomical dead space, work of breathing and respiratory rate, and increases positive end-expiratory pressure and compliance.[13] Prior to the pandemic, HFNO was used as a non-invasive alternative for the management of hypoxaemia in critically ill patients.[14] Its major benefits are its ease of use and superior tolerability compared with non-invasive ventilation and invasive mechanical ventilation (IMV).[14] Several observational studies suggested that if IMV became scarce, using HFNO was a feasible alternative to provide adequate oxygenation for these severely hypoxaemic patients, reducing the number needing IMV, increasing ventilator-free days and reducing the length of ICU stay.[15-20]

Groote Schuur Hospital (GSH), a tertiary referral hospital in Cape Town, SA, adopted the use of HFNO in non-ICU, high-care wards. This strategy increased the capacity to manage patients with AHRF secondary to COVID-19 outside an ICU, in anticipation that ICU ventilation capacity would quickly be overwhelmed.[21] An observational cohort study from GSH and Tygerberg Hospital showed that IMV could be avoided through the use of HFNO in up to 50% of patients with AHRF during the first COVID-19 wave.[16] This finding 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 HFNO, and immunisation roll-out might lead to differences between waves in respect of patient characteristics and the need for IMV.

Methods

Study design

We conducted a prospective observational study at GSH, which was approved by the Human Research Ethics Committee of the University of Cape Town Faculty of Health Sciences (ref. no. UCT HREC 295/2020). Informed consent was waived in acknowledgement of the fact that the intervention was being assessed within the routine clinical service. The study is reported in accordance with the STROBE guidelines for reporting cohort studies.[22]

Setting

GSH serves a population of ~4.5 million with a high prevalence of tuberculosis and HIV.[23] Waves of the pandemic were defined by the National Institute for Communicable Diseases as the period from when the COVID-19 weekly incidence was ≥30 cases per 100 000 persons until the weekly incidence fell to <30 cases per 100 000 persons.[24] The first case of COVID-19 in SA was identified on 5 March 2020 and, according to the above definition, the first wave spanned from 8 June 2020 to 23 August 2020, while the third wave spanned between 10 May and 19 September 2021.[24,25] In the present study, patients were included during the first wave between 7 May and 25 August 2020 (16 weeks) and during the third wave between 4 July and 4 September 2021 (9 weeks) (Fig. 1). There were 39 respiratory high-care beds available during 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), v. 59 beds and 50 machines available at the peak of the third wave.

Participants

Inclusion criteria were consecutive adult patients aged ≥18 years with AHRF and laboratory-confirmed COVID-19 pneumonia, i.e. detection of SARS-CoV-2 by real-time reverse transcription polymerase chain reaction on any respiratory sample who were treated with HFNO during hospitalisation. AHRF was defined as a respiratory rate ≥30 breaths per minute with oxygen saturation ≤92% despite inspired oxygen at 15 L/min via a reservoir bag, and/or partial pressure of arterial oxygen to FiO_2 (PaO_2/FiO_2) ratio <150. The decision to initiate HFNO was at the discretion of the treating clinical team, but HFNO was indicated in co-operative patients who were

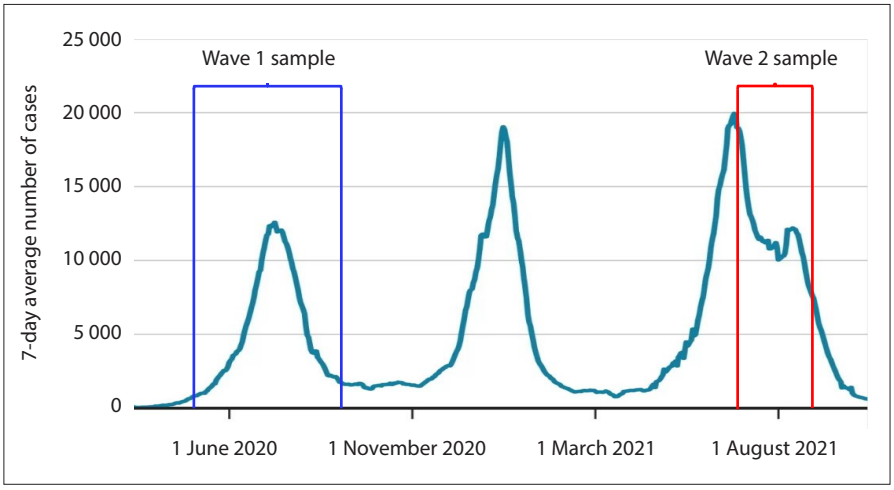

Fig. 1. Temporal relationship of the study sample (first wave v. third) to the national caseload.[25]

able to comply with awake prone positioning. Likewise, the decision on the timing of intubation and IMV was not protocolised but determined by the ICU team based on a composite assessment of respiratory effort, level of patient exhaustion, rising arterial partial pressure of carbon dioxide and altered mental state, rather than a single measure of oxygenation such as saturation or PaO_2. Awake proning 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 the RECOVERY trial released on 16 June 2020, all patients on HFNO received either dexamethasone 6 mg intravenously daily or prednisone 40 mg daily for 10 days.[26]

Viral variant

The ancestral variant of the COVID-19 virus in the first wave and the delta variant in the third wave were the predominant circulating viral variants during our sampling period.[27]

Sample size

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

Heated and humidified HFNO

Heated and humidified HFNO was exclusively provided in designated high-care medical wards outside the ICUs at GSH where patients were cohorted. HFNO was delivered either by an Airvo 2 system (Fisher & Paykel Healthcare, USA) or an Inspire O2FLO unit (Vincent Medical, Hong Kong, China). Flow was initiated at 50 - 60 L/min with FiO_2 0.8 - 1.0, titrated to aim for an oxygen saturation ≥92%.

Procedures

Demographic and clinical variables, and contemporaneous peripheral blood differential white blood cell counts and inflammatory biomarkers (D-dimers and C-reactive protein) if available, were recorded on commencement of HFNO. HFNO settings (FiO_2 and flow rate) along with heart rate, respiratory rate and peripheral oxygen saturation were recorded 6 hours after initiation of HFNO. Using these variables, we calculated the validated ROX score (ratio of oxygen saturation/FiO_2 to respiratory rate) at 6 hours (ROX-6).[28,29] For patients who were intubated before 6 hours, the variables at the time the decision was made that HFNO was failing were recorded. COVID-19 vaccination status was recorded, with 'full vaccination' defined as 2 weeks after a single dose of Johnson & Johnson's Janssen vaccine or 2 weeks after the second dose of the Pfizer-BioNTech.[30]

Outcomes

The primary endpoint was comparison of HFNO failure rates during the first and third waves of the pandemic at GSH. HFNO failure was defined as a composite of the need for intubation or death while on HFNO. Death on HFNO was a combination of unexpected deaths and patients who died on HFNO because they were not deemed candidates for IMV in the ICU. Secondary outcomes were overall predictors of HFNO failure and overall in-hospital mortality, and differences in outcomes associated with early v. late intubation. 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 interquartile ranges (IQRs). Non-parametric data were compared using Wilcoxon rank-sum tests. A CONSORT diagram reported the flow of patients in the study (Fig. 2). The crude cumulative proportion of HFNO failure 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 version 12.1 (StataCorp, USA). A p-value <0.05 was considered statistically significant.[31]

Results

Patient population

A total of 744 patients were included, 343 (46.1%) in the first wave and 401 (53.9%) in the third. The median (IQR) age was 50 (42 - 58) years, and 385/744 (51.7%) were male. 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'). Although similar numbers of patients were included in each wave, the institutional capacity to treat patients with HFNO was considerably higher in the third wave compared with the first, as reflected by the average number of patients included per week: 21/week in the first wave v. 45/week in the third. Patients treated with HFNO in the first wave were older (median 53 (46 - 61) years v. 47 (40 - 56) years; p<0.001), and had higher prevalences of diabetes (46.9% v. 36.9%; p=0.006), hypertension (51.0% v. 35.2%; p<0.001), obesity (33.5% v. 26.2%; p=0.029) and HIV infection (12.5% v. 5.5%; p<0.001). Patients in the first wave had worse oxygenation indicators prior to HFNO

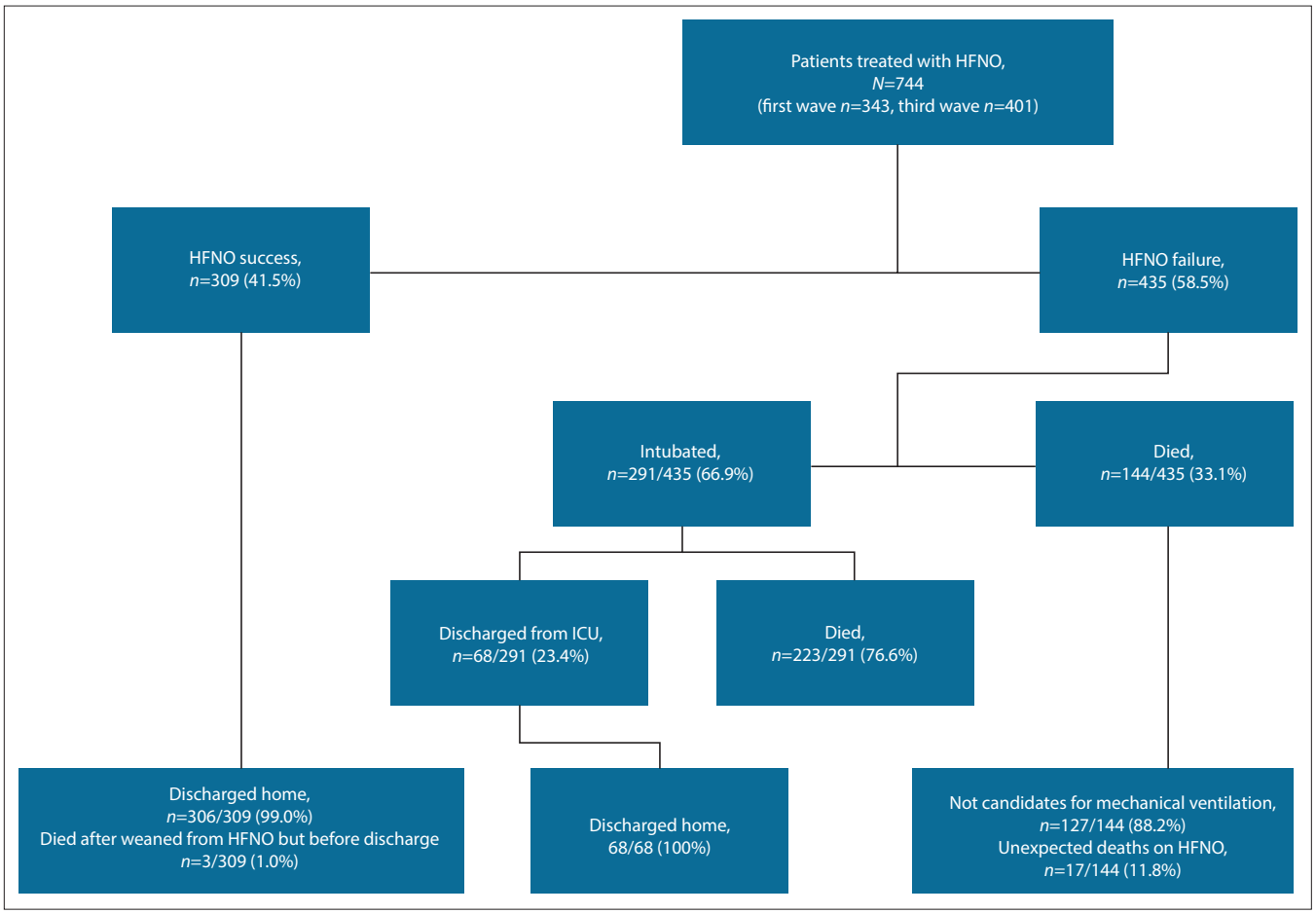

Fig. 2. CONSORT diagram. (HFNO = high-flow nasal oxygen; ICU = intensive care unit.)

initiation (PaO_2/FiO_2 57.9 v. 64.3 mmHg; p=0.005) and lower ROX-6 scores after initiation of HFNO (3.19 v. 3.43; p<0.001) (Table 1). As expected from the change in practice following the results from the RECOVERY trial,[26] patients in the third wave were more likely to have been treated with corticosteroids (100% v. 81.9%; p<0.001).

Primary outcome (first v. third wave)

HFNO failure did not differ between the first and third waves (57.1% v. 59.6%; p=0.498) (Table 1). Fig. 3 shows the proportions of patients with HFNO failure over time. There was no significant difference between the waves.

Secondary outcomes

Univariate predictors for HFNO failure were older age, obesity, not being treated with corticosteroids, lower PaO_2/FiO_2 ratio at the time of HFNO initiation, lower ROX-6 score 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 corticosteroids, lower PaO_2/FiO_2 at the time of initiating HFNO, and lower ROX-6 score on 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 (41.5%) were successfully weaned off HFNO (Fig. 2), and of these patients 306 (99.0%) were discharged (home or to a step-down facility). The proportion of patients who died on HFNO was 15.4% in the first wave v. 22.6% in the third wave (p=0.008). A total of 291 patients were intubated and received IMV, 143 patients in the first wave and 148 patients in the third wave (p=0.183). ICU mortality in patients requiring intubation was high: 223/291 (76.6%) died, with the rest all surviving to discharge (Fig. 2). Overall, in-hospital mortality did not differ significantly between the first and third waves (46.9% v. 52.1%; p=0.159).

Of the 291 patients requiring IMV, 155 (53.3%) were intubated within 48 hours of initiating HFNO (early failures): in-hospital mortality was 112/155 (72.3%) in this group. In-hospital mortality was 111/136 (81.6%) for patients intubated after 48 hours (late failures) (p=0.060).

Vaccination

No patients in the first-wave cohort were vaccinated. No patients in the third-wave cohort were fully vaccinated, with only 11 patients having received ≥1 dose of a COVID-19 vaccine. Of those who had started the vaccination process, 7/11 had received one of the two scheduled doses of the Pfizer-BioNTech vaccine, 1/11 presented within 1 week of the second dose of the Pfizer-BioNTech vaccine, and 3/11 presented within 1 week of having received the Johnson & Johnson vaccine.

Discussion

This study, which to our knowledge is the only comparison of outcomes between waves of patients with severe COVID-19 treated with HFNO

Table 1. Patient characteristics and outcomes across waves

Variable	Total (*N*=744), *n* (%)*	First wave (*n*=343), *n* (%)*	Third wave (*n*=401), *n* (%)*	*p*-value
Age (years), median (IQR)	50 (42 - 58)	53 (46 - 61)	47 (40 - 56)	<0.001
Sex male	385 (51.7)	174 (50.7)	211 (52.6)	0.607
Diabetes	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	316 (42.5)	175 (51.0)	141 (35.2)	<0.001
BMI (kg/m^2)				
≤25	79 (10.6)	48 (14.0)	31 (7.6)	0.006
25 - 30	365 (49.1)	146 (42.6)	219 (54.6)	0.001
30 - 35	220 (29.6)	115 (33.5)	105 (26.2)	0.029
≥35	80 (10.8)	34 (9.9)	46 (11.5)	0.494
HIV status				
Negative	519 (69.8)	238 (69.4)	281 (70.1)	0.839
Positive	65 (8.7)	43 (12.5)	22 (5.5)	<0.001
Unknown	160 (21.5)	62 (18.1)	98 (24.4)	0.035
CD4 count (if HIV positive) (cells/μL), median (IQR)	280 (138 - 416)	277 (130 - 423)	283 (201 - 370)	1.00
ART use (if HIV positive)	51/65 (78.5)	33/43 (76.7)	18/22 (81.8)	0.322
Duration of symptoms (days), median (IQR)	7 (6 - 11)	7 (5 - 10)	8 (6 - 14)	0.347
Corticosteroids as treatment	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 score, 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 (× 10^9/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-dimers (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 HFNO				
Success	309 (41.5)	147 (42.9)	162 (40.4)	0.498
Failure	435 (58.5)	196 (57.1)	239 (59.6)	0.498
Intubated	291 (39.1)	143 (41.7)	148 (36.9)	0.183
Died on HFNO	17 (2.3)	8 (2.3)	9 (2.2)	0.936
Palliated	127 (17.1)	45 (13.1)	82 (20.4)	0.008
In-hospital mortality	370 (49.7)	161 (46.9)	209 (52.1)	0.159

IQR = interquartile range; BMI = body mass index; ART = antiretroviral therapy; HFNO = high-flow nasal oxygen; PaO_2/FiO_2 = partial arterial oxygen pressure/fractional inspired oxygen; ROX-6 = ratio of oxygen saturation/FiO_2 to respiratory rate within 6 hours.
*Except where otherwise indicated.

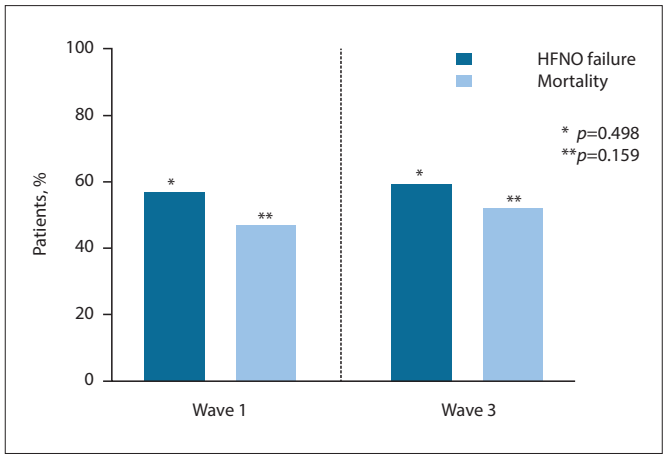

Fig. 3. Proportions of patients with unsuccessful outcome from initiation of HFNO. (HFNO = high-flow nasal oxygen.)

in SA, found no difference in HFNO success or mortality in patients treated in the first wave v. the third, despite several differences between the waves including viral variant, wave duration, corticosteroid use, HFNO bed capacity, clinician experience, patient risk factor profile, and baseline measures of oxygenation.

While the reasons for the differences in patient characteristics between waves is likely to be multifactorial, one explanation was the implementation of the Western Cape Critical Care Triage Tool in the third wave, which favoured selection of younger patients with fewer comorbidities associated with in-hospital mortality from COVID-19.[32,33] Another possible explanation relates to the vaccine roll-out in SA, which only began (starting with the elderly) on 17 May 2021, 7 days after what later proved to be the start of the third wave.[24,34] 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

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 (v. female)	744	1.07 (0.80 - 1.43)	0.644	-	-
Third wave (v. first wave)	744	1.11 (0.83 - 1.48)	0.498	-	-
HIV status (v. 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 ≥30 kg/m^2 v. 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 corticosteroids	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 1 × 10^9 increase)	505	0.82 (0.62 - 1.08)	0.158	-	-
C-reactive protein (v. <100 mg/L)	100			-	-
100 - 199	116	0.62 (0.36 - 1.08)	0.091	-	-
200 - 399	82	0.88 (0.48 - 1.61)	0.675	-	-
≥400	17	4.22 (0.91 - 19.50)	0.065	-	-
D-dimers (v. <1.5 mg/L)	461			-	-
1.5 - 5.0	85	1.67 (1.03 - 2.71)	0.037	1.88 (0.78 - 4.54)	0.159
>5	61	2.07 (1.16 - 3.70)	0.014	1.88 (0.78 - 4.54)	0.159

OR = odds ratio; CI = confidence interval; BMI = body mass index; PaO_2/FiO_2 = partial arterial oxygen pressure/fractional inspired oxygen; HFNO = high-flow nasal oxygen; ROX-6 = ratio of oxygen saturation/FiO_2 to respiratory rate within 6 hours.
*Best model fit obtained with inclusion of corticosteroid use, PaO_2/FiO_2 ratio before HFNO initiation and ROX-6.

that more rigorous triaging, necessitated by the increased caseload due to the more rapid epidemiological surge related to the increased transmissibility of the delta variant, skewed this demographic in the third wave.[35]

There are two possible explanations for the lack of observed differences between wave outcomes. Firstly, we speculate that the significantly younger third-wave cohort with fewer comorbidities balanced the expected increase in mortality associated with the higher caseload seen in the third wave.[7] Additionally, although HFNO provider experience and competence are likely to have 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 negative 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.[36]

The significant independent predictors of HFNO failure in our study were corticosteroid use, pre-HFNO PaO_2/FiO_2, and the ROX-6 score. This finding is in keeping with our previously published study[16] as well as the conclusions and recommendation of a systematic review by Attaway *et al.*[37] of the application of the ROX index in the COVID-19 setting. Patients with a ROX index ≥4.88 after 2, 6 and 12 hours of treatment were found to have a low risk of intubation, whereas a ROX index <3.85 at the same time points was associated with a high risk of failure. It is interesting that none of the other demographic variables or laboratory parameters were predictive of HFNO failure. This finding suggests that, while these other factors may be important in the development of severe acute respiratory distress syndrome from COVID-19 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 initiation (via the many putative mechanisms already described) that determines whether intubation or death will ultimately be avoided. The protective effects of corticosteroids on progression to AHRF and mortality in COVID-19 are well established, and the present study further reinforces that corticosteroid use reduces the incidence of HFNO failure.[26]

Our study found no significant difference in survival between patients intubated early or late. Timing of intubation in those failing HFNO remains an area of great interest. Guidelines from China, the UK and the USA recommend early intubation in critically ill COVID-19 patients.[38-40] The rationale for early intubation is the avoidance of 'crash' intubations and the potential prevention of patient self-inflicted lung injury associated with distressed spontaneous respiration.[41] In a prospective observational cohort study by Vera *et al.*,[42] late intubation (>48 hours after HFNO initiation) was associated with increased ICU mortality. This finding is in keeping with a systematic review and meta-analysis of non-randomised cohort studies by Papoutsi *et al.*[43] that 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. To our knowledge, no randomised controlled trials have been done to evaluate outcomes of early v. late intubation in patients

failing HFNO. Furthermore, no studies of the impact of timing of intubation on patients on HFNO in a non-intensive care ward-based environment are available to guide practice in resource-constrained settings employing this strategy of respiratory support.[44]

Study limitations

Our study had several limitations. First, it was a single-centre study in a tertiary academic hospital and therefore may not reflect the reality of the experience in other hospitals in SA or in LMICs with fewer resources. Second, patient management, particularly the decision to intubate, was at 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 ICU resources as the waves of the pandemic surged, triage criteria were adjusted, influencing patient selection for admission and resulting in significantly differing cohort demographics with the rise and fall of each wave. Furthermore, the sampling period was not of equal duration across each wave, which may have introduced selection bias; however, patients were included 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 limitations due to caseload and implementation of the Western Cape Critical Care Triage Tool, which means that inferences about differences in patient characteristics between waves being a result of triaging are strongly suggested but, in the absence of denominator data, unconfirmed.

Conclusion

Despite differences in overall caseload, baseline patient characteristics, viral variant and institutional experience with HFNO, we found no significant difference in treatment outcomes between the first and third COVID-19 waves. We conclude that once severe respiratory failure is established in COVID-19 pneumonia, comorbidities and HFNO provider experience make little difference to outcome.

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