Mini Dissertation:

The effect of High Flow Nasal Cannula VS Continuous Positive Airway Pressure oxygen support in COVID-19 pneumonia in central South Africa

by

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"Submitted in partial fulfilment of the requirements in respect of the Master's Degree MMed (Cardiothoracic Surgery) in the Department of Cardiothoracic Surgery in the Faculty of Health Sciences at the University of the Free State."

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August 2023

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Acknowledgements

Immeasurable appreciation and gratitude is extended to my supervisor for the help and support that enabled this data to take the form of immense value.

Warmest thanks to Manie Hanekom whose guidance was invaluable in writing this mini dissertation.

Most importantly none of this would have been possible without the efforts of Drs Nkuna, Chigwada and Coetzee with whom I navigated a terrifying pandemic.

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Executive summary

Introduction: The sudden escalation of COVID-19 pneumonia proved to be a great challenge for an already taxed health system in Central South Africa. With minimal ICU beds and in resource limited hospitals, the use of non -invasive ventilation was soon identified as the attractive alternative. Thus, high flow nasal oxygen (HFNO) and continuous positive airway pressure (CPAP) were important forms of supplementary oxygen therapy for patients with COVID-19 pneumonia. Due to the limited data at the time on the pathophysiology of the disease with regards to the types of pneumonia as well as the concept of patient self-induced lung injury, it was difficult to formulate treatment guidelines as well as ventilation strategies. There existed no clear point for the escalation of management or for the prognostications of patients. In order to properly utilize resources and to ensure adequate treatment this study was conducted.

The aims of the study were to compare the outcomes of patients on HFNO to those receiving CPAP and to investigate the limitations of HFNO and CPAP therapy and modes of failure leading to death needs to be identified. The study also aimed to evaluate the practices in both high flow nasal oxygen and continuous positive airway pressure to explore the optimal point for escalation or failure.

Methods: This retrospective observational single centre study was conducted in a field hospital , House Idahlia in the Free State. A total of 146 adult patients with respiratory failure due to severe COVID-19 pneumonia were treated with either HFNO or CPAP as initial treatment. Respiratory failure due to severe COVID-19 pneumonia was defined as a respiratory rate of more than 30 breaths per minute, oxygen saturation of less than 93% despite oxygen flow of 15l/min via reservoir bag or an SpO2/FiO2 ratio of less than 150. Due to the severe lack of resources there was no access to radiology. Automated monitoring systems recorded observations and minimized the number of nursing staff required.

Demographics , infective markers, APACHE scores and length of stays were analyzed for all patients. Outcomes and survival related to the respiratory rate oxygenation (ROX) scores were analyzed and compared. The oxygen saturation, respiratory rate, flow rate, CPAP and respiratory swings were recorded in all patients who received CPAP. The respiratory swing was used as a surrogate for the transpulmonary pressure to assess the presence of patient self-induced lung injury These endpoints were used in a multivariate analysis to explore possible endpoints predicting death or discharge.

Results: The overall survival was 45,3%. Both groups were comparable with regards to demographics, baseline bloods and APACHE scores. All patients presented with severe respiratory failure as depicted with an SpO2/FiO2 ratio of less than 150. All patients with a ROX score > 3.85 survived. With a ROX score < 3.85 showing an overall mortality was 67,3%. A sustained respiratory rate >30 breaths/min,

respiratory swings >10 cmH_2O, CPAP >10 cmH_2O for more than 2-days and flow rates of more than 60 l/min were associated with increased mortality.

Conclusion: Non-invasive ventilation supplementary oxygen is a cost effective and reasonable strategy to manage patients with severe COVID- 19 pneumonia. Patients with sustained hyperventilation, high O_2-flows, and CPAP >10 cmH_2O combined with a sustained respiratory swing of >10 cmH_2O have poor outcomes on HFNO and CPAP. These patients must be considered for early intubation and mechanical ventilation to prevent further P-SILI, an important contributor to poor outcomes in COVID-19 pneumonia. One of the main limitations of this study was the relatively small study population and we recommend that further studies be conducted to further explore these findings.

List of Keywords

Continuous positive airway pressure

COVID-19

High flow nasal cannula

Hyperventilation

Indications for mechanical ventilation

Intensive care unit

Non-invasive positive pressure ventilation

Oxygen therapy

Patient self-induced lung injury

PPE

List of abbreviations

- ARDS- Acute respiratory distress syndrome
- CPAP- Continuous positive airway pressure
- H Type- High elastance type
- HFNO- High flow nasal oxygen
- ICU- Intensive care unit
- IDSA- Infectious Diseases Society of America
- L Type- Low elastance type
- mmHg- Millimetres of mercury
- PaO2- Partial pressure of oxygen in arterial blood
- PCR- Polymerase chain reaction
- PPE- Personal protective equipment
- P-SILI- Patient self-induced lung injury
- RR- Respiratory rate
- RNA- Ribonucleic acid
- SaO2- Arterial oxygen saturation
- SARS- Severe acute respiratory syndrome
- WHO- World Health Organisation

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Chapter 1 – Literature Review

1. INTRODUCTION

On January 30th, 2020, a novel SARS-2 corona virus (severe adult respiratory syndrome coronavirus-2) pneumonia outbreak from Hubei Province in Wuhan, China occurred. The World Health Organisation declared this a Public Health Emergency of International Concern. This disease that rapidly evolved into a global pandemic would later be named the corona disease of 2019 (COVID- 19). New information is constantly being discovered with the spread of the disease (Zu *et al.*, 2020). More than 200 countries have been affected by this virus with more than 10 million cases since July 2020 (Wiersanga *et al.*, 2020).

The novel SARS-2 corona virus has posed many new challenges from negatively affecting economies and education systems to challenging current respiratory distress and PPE (personal protective equipment) protocols. The guidelines for the respiratory illness are constantly evolving as we discover the unique pathophysiology of the virus. This combined with the poverty of resources has demanded a re-evaluation in our management of patients with invasive and non-invasive ventilation (Wiersanga *et al.*, 2020).

2. LITERATURE REVIEW

2.1 Background

COVID was first diagnosed in December 2019 in patients presenting with pneumonia in Wuhan, China. It was thought that this virus was initially hosted by bats and transmitted to humans by pangolins and other animals. It is enveloped, with a single strand ribonucleic acid and a solar corona- like appearance with surface spikes (Zu *et al.*, 2020). The rapid evolution of this respiratory virus into a pandemic is due to its ability to spread by droplets. Severe symptoms develop in approximately 5% of patients with COVID- 19 and in 20% of those hospitalized (often requiring ICU care); supplemental oxygen is required in more than 75% of those hospitalised (Wiersanga *et al*., 2020). Severe disease with complications is more likely to develop in those aged over 65, pregnant females and those with multiple comorbidities (Unhale *et al*., 2020).

Due to the heterogeneity of the pathophysiology of respiratory failure no specific treatment strategy exists for the treatment of severe pneumonia due to COVID-19. Many government in an attempt to curb the ferocious spread of the disease, employed, mandatory social distancing, quarantining, and wearing of masks.

2.2 Prevalence and Epidemiology

Since December 2019, more than 200 countries were seriously affected by this pandemic. It has affected health care systems, economies, and food production. The enormity of the pandemic has posed great challenges to developing countries: the already taxed health care systems are unable to manage with the added strain; unemployment has rocketed. Measures to prevent the spread of COVID- 19 are impossible to implement in densely populated rural communities. The current prevalence in South Africa as of 2 October 2020 is 679 716 positive cases with a mortality of 16 938. The Free State province accounts for 7.1% of these cases to date (https://www.nicd.ac.za/diseases-a-z-index/COVID-19/surveillance-reports/).

2.3 Clinical Presentation and Pathophysiology of COVID- 19 Pneumonia

There is much to still learn about the evolving COVID- 19 virus. A glance at the pathophysiology includes 3 phases of increasing severity of COVID 19 pneumonia namely:

- The asymptomatic stage
- the response of the upper airway and conducting airway
- finally there is hypoxia, ground glass infiltrates and progression to severe pneumonia

Stage 1: Asymptomatic stage

This stage represents infection and replication SARS-CoV2. Inoculation with the virus occurs via respiratory aerosols that bind to respiratory epithelium. This epithelium has a high expression of ACE-2 receptors which allows entry of the virus into the cell. During this stage,

the innate immune response is activated. The currently asymptomatic patient is highly infectious despite having a low viral load (Parasher *et al.,* 2021). RT PCR from nasal swabs can be used to diagnose patients in this stage (Mason *et al.*, 2020).

Stage 2: The Upper- airway and conducting- airway response

In this stage the virus then migrates to the upper respiratory tract via the conducting airways (Parasher *et al.,* 2021). Pulmonary inflammation and coagulopathy develop consecutively or overlap. The innate immune response is more marked, and due to the involvement of the upper airways symptoms can range from mild (80%) to severe in this stage (Mason *et al.,* 2020). Markers of severity and progression of disease include an elevated CRP, IL6 and D - Dimer (Polak *et al*., 2020). The immune response in this stage is often sufficient to contain spread of the infection and progression of disease in most patients (Parasher *et al.,* 2021).

Stage 3: Hypoxia, ground-glass infiltrates with progression to ARDS

Approximately 20% of infected progress to this stage and approximately 2% have fatal outcomes. This stage is characterised by disruption of the type II alveolar cells via the ACE-2 receptor. The virus replicates to produce more viral Nucleocapsids. These cells are typically peripheral and subpleural. This induces a cytokine storm with the release of interleukins (interleukin-1, interleukin -6, interleukin 8, interleukin 20, interleukin 12) as well as tumour-necrosis factor alpha among other chemokines. This attracts neutrophils and CD4 and CD8 cells that infiltrate the lung tissue. The diffuse damage of the Type II cells combined with fibrin rich hyaline membranes and giant multi-nucleated cells is specific to this stage. As host cells undergo apoptosis they release new virus particles that infect adjacent type 2 pneumocytes and process continues (Parasher *et al.,* 2021). This unremitting inflammation leads to ARDS with subsequent scarring and fibrosis (Mason *et al*., 2020).

Mortality is higher in the elderly as they have a diminished immune response and ability to repair epithelium. The incubation period for COVID – 19 is 5-14 days and patients may remain asymptomatic or experience mild to severe symptoms as listed in the table. The 'cytokine storm' discussed earlier is responsible for the complications seen with disease (Parasher *et al.,* 2021).

COVID – 19 pneumonia can range from mild to severe and is associated with hypoxemic respiratory failure. There still remains controversy as to whether its pathophysiology is similar to ARDS. What remains clear is that COVID -19 is a multi-system disease that micro and macrovascular involvement, endothelial injury, and inflammation with wide-spread thrombosis (Battaglini *et al*., 2021).

Three respiratory phenotypes of pneumonia requiring mechanical ventilation exist(Battaglini *et al*., 2021):

- Low elastance (L) type
- Intermediate phenotype : transition from type L to type H
- High elastance (H) type.

The L type is characterised with an almost normal lung weight. There is also high compliance with near normal gas volumes. The VQ ratio is low because of the loss of perfusion regulation and hypoxic vasoconstriction. There is very little recruitability due to very little non- aerated lung tissue. The H type is distinguished by the decrease in lung compliance. There is also increased pulmonary oedema and lung weight. There is impairment of gas exchange and a there is right to left shunting with a high VQ ratio due to the non- aerated lung being perfused by a large fraction of cardiac output. The high recruitability of non-aerated lung with PEEP is a feature of this phenotype (Polak *et al.*, 2020).

It is theorised that the underlying pathophysiology of the L-type pneumonia begins with the viral infections causing interstitial subpleural oedema. Hypoxaemia is caused by vasoplegia. This causes an increase in the minute ventilation, primarily by increasing the minute volume which causes a more negative intrathoracic pressure. The respiratory drive is increased by undetermined factors. The increase in minute ventilation causes hypocarbia (Gattinoni *et al*., 2019).

As COVID -19 pneumonia evolves the L-type may change to H -type. During the progression of disease there is increase in lung permeability due to inflammation. It remains unclear whether this progression is driven by the severity of disease or patient self-induced lung injury (Gattinoni *et al*., 2019).

Patient self-induced lung injury and its relationship to ventilation strategies in severe COVID-19 pneumonia is still controversial, however, Battaglini et al (2021) explained the pathophysiology and mechanism. They suggested 4 mechanisms for P-SILI : (1) an increase in lung stress/ strain, (2) inhomogeneous distribution of ventilation, (3) changes in lung perfusion, (4) patient-ventilator asynchronies during NIV.

The increase in stress/strain specifically alludes to the higher inspiratory pressures resulting in increased transpulmonary pressures that induce barotrauma. This is specifically worse in patients with diseased lung with heterogenous pressure and volume distribution. The heterogenous distribution of ventilation results in the pendelluft ventilation which increases the risk of P-SILI. The alteration in perfusion affects the trans-capillary and trans-alveolar gradients resulting in endothelial and epithelial cell damage and lung oedema. Asynchrony between the patient and the ventilator increases the transpulmonary gradient and worsens P-SILI (Battaglini *et al*., 2021).

2.4 Diagnosis

At the time of this study, the Infectious Diseases Society of America (IDSA) suggests nasal and mid turbinate swabs for SARS-CoV-2 RNA testing in symptomatic individuals suspected of having COVID -19 symptoms. It also recommends RNA testing for asymptomatic patients with known COVID-19 contact (Hanson *et al*., 2020).

While chest CT findings of COVID pneumonia support the diagnosis as shown in figure 1, RT PCR assay is necessary for confirmation. CT findings are non- specific and include multifocal bilateral ground glass opacification with patchy consolidation with a predilection for subpleural and posterior lobe distribution (Zu *et al*., 2020).

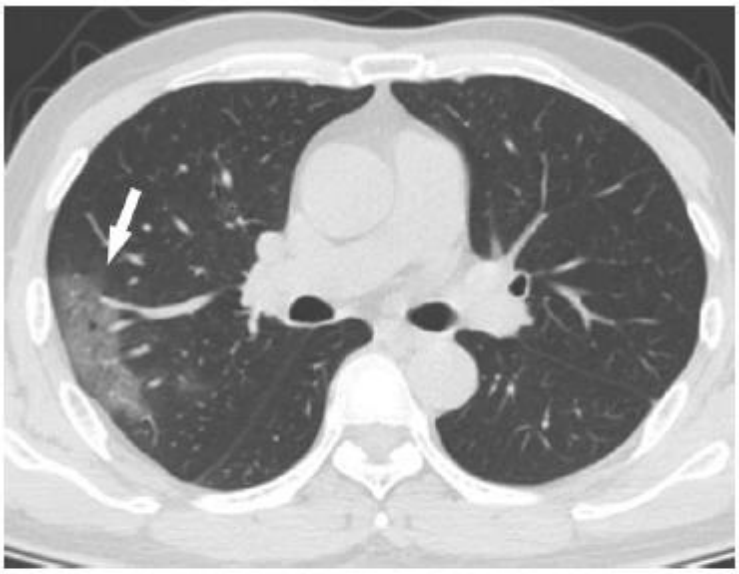

Fig. 1: CT findings of patchy ground glass pattern in a confirmed case of COVID-19 (Zu *et al*., 2020).

2.5 Current treatment practices

2.5.1 Prevention and quarantine:

This is the first step in managing the disease, at the time, and includes wearing of masks, social distancing, and self-isolation for those with positive PCR or symptoms (Nicola *et al*., 2020).

2.5.2 Supportive management:

The degree of supportive management required depends on the severity of disease, ability to self-isolate and need for hospitalisation. It was thought that asymptomatic patients can be managed with self-isolation at home on an out-patient basis (Nicola *et al*., 2020).

The WHO has defined supportive management for those with severe disease as follows: (Nicola *et al*., 2020)

1. Intravenous fluid administration
   - Judicious use of fluids should be use in these patients to prevent further complications and decompensation.
2. Oxygen therapy
   - Supplemental oxygen therapy should be administered immediately in patients with severe acute respiratory distress, hypoxaemia, or shock. Oxygen delivery end points are an SPO2 of ≥ 90% in adults and ≥ 94% in children.
   - Mechanical ventilation should be considered in patients with worsening hypoxia or increased work of breathing.
3. Corticosteroids
   - However the IDSA recommends its use. (Bhimraj *et al*., 2020)

Many other drugs including ARV's are still under investigation (Bhimraj *et al*., 2020).

It was initially recommended by the Surviving Sepsis Campaign that mechanically ventilated patients with COVID-19 be treated as those with ARDS in the ICU. The lung pathology of COVID-19 pneumonia often does not fulfil the Berlin criteria as there is normal compliance up to 50% of the time. The phenotype of COVID-19 pneumonia is often perplexing and diverse: patients may be silently hypoxaemic or overtly dyspnoeic; may or may not respond to NO (Nitric Oxide). They may have severe hyper/hypocapnia and have variable response to proning. The lack of consistent presentation has led to treatment being a challenging task (Gattinoni *et al*., 2019).

Non – invasive oxygen therapy including , conventional oxygen therapy, HFNO (high flow nasal oxygen , CPAP (continuous positive airway pressure) and NIV (non-invasive ventilation) are used in the treatment of COVID -19 pneumonia depending on its severity, prior to escalation to mechanical ventilation. Conventional oxygen therapy is not effective in patients with increased respiratory effort (Battaglini *et al.,* 2021). High flow oxygen delivered via nasal cannula (HFNC) has several advantages over conventional non- rebreather supplemental oxygen. Flows can be delivered more than 50l/min. This ensures that the increased oxygen requirements in patients with severe respiratory failure to be met more appropriately. It also can reduce oxygen dilution and respiratory dead space by washing out the CO2 from the conducting airways (Akoumianaki *et al*., 2021). It can also generate a degree of PEEP due to the expiratory resistance generated by the contours high flow (Akoumianaki *et al*., 2021). It does not however, prevent P-SILI (Battaglini *et al.,* 2021). The air can be humidified, and this facilitates clearance of secretions and decreases the development of bronchial hyper-response symptoms (Roca *et al*., 2020). High flow nasal oxygen prevents the entrainment of room air to ensure better and more accurate oxygen delivery and flow . There already exists a trend to use high flow nasal oxygen as part of the management of the patient severe COVID pneumonia with 2-64% of patients receiving high flow nasal oxygen. This is founded on the evidence existed before COVID-19 that high flow nasal oxygen reduces the need for mechanical ventilation in those suffering with acute respiratory distress syndrome (Akoumianaki *et al*., 2021).

Compared to conventional oxygen therapy, HFNC is associated with decreased risk for intubation and ICU admission, but not an increase in survival (Battaglini *et al.,* 2021). HFNC obviated the need for intubations and ventilations in 44-64% of patients in a review. It is currently the recommended therapy by the WHO, ANZIC and German Intensive Care Society for the treatment of COVID patients failing standard oxygen therapy (Whittle *et al*., 2020). The proposed algorithm for treatment is depicted in figure 2. While, HFNO may be useful in patients with low severity COVID- 19 pneumonia, it is not sufficient in those that have more severe pneumonia as it may increase the risk of P-SILI (Battaglini *et al.,* 2021).

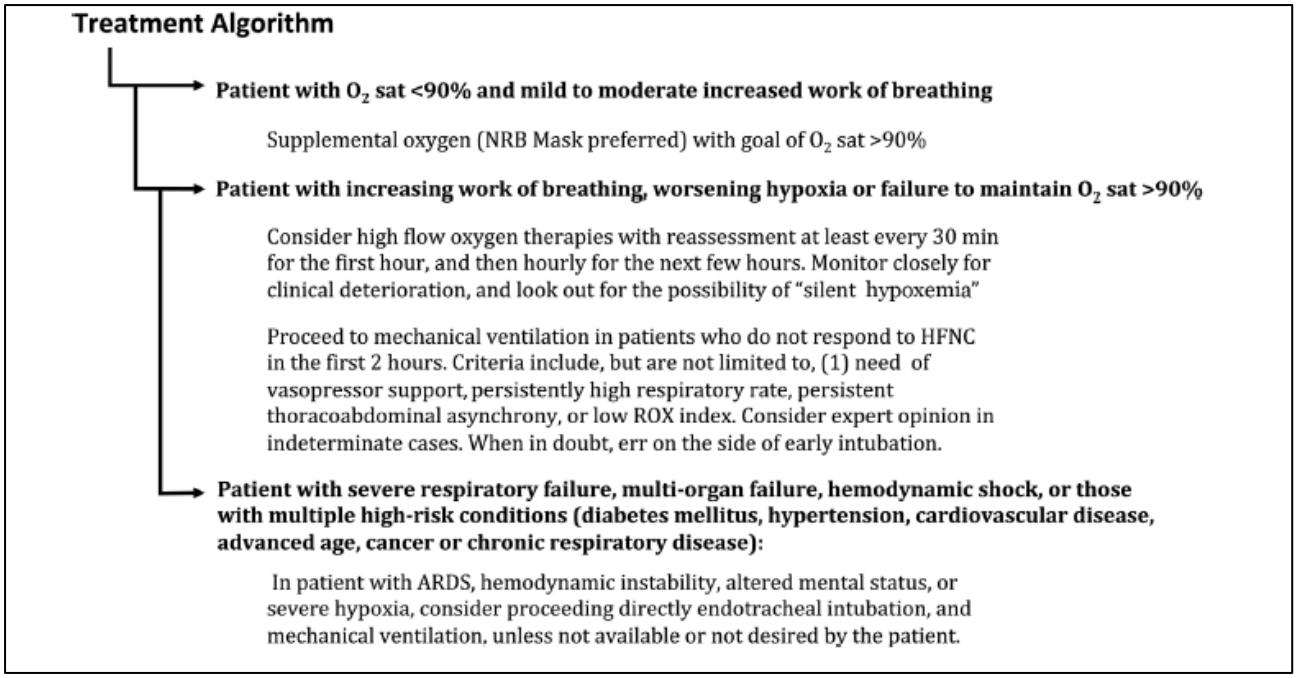

Fig 2: Proposed treatment algorithm for oxygen management in COVID-19 patients (Whittle *et al*., 2020).

Continuous positive airway pressure ventilation is a mode of non- invasive ventilation. It is spontaneous breathing via a mask with an expiratory valve that maintains positive end expiratory pressure. CPAP aids in ventilation by increasing the functional residual capacity. Adverse events from the use of CPAP include gastric insufflation, pressure sores from the mask and nosocomial pneumonia (Marino *et al*., 2014).

Initially, Non- invasive ventilation, including CPAP and BiPAP, was not favoured due to fears of barotrauma and aerosolization; emerging evidence now supports its use. Data from Italy and China show its benefit; in Italy, 50% of patients that used continuous positive airway pressure did not need invasive ventilation (Nicola *et al*., 2020). In another retrospective cohort, one third of patients with severe COVID-19 pneumonia treated with mask CPAP improved with the remainder dying. If applied within 7 days of admission, administration of CPAP lowers the risk of in-hospital death (Battaglini *et al*., 2021).

In patients on CPAP, the magnitude of inspiratory pleural pressure swings, measured via oesophageal catheter, may determine the transition from the L Type to the H type phenotype. Oesophageal pressure swings of 5-10 cmH2O are well tolerated. The risk of self- induced lung injury increases with swings >15cmH2O and intubation should be considered at this point (Gattinoni *et al*., 2020).

Awake proning allows more adequate ventilation of the dorsal dependent parts of the lung due to the change in the hydrostatic pressures. This allows more alveolar units to open. As a result, the end-expiratory volume may increase, ventilation distribution is more even, and pressures are more uniformly exerted on the lungs. The VQ ratio also improves and there is an increase in lung compliance (Akoumianaki *et al*., 2021). This results in an improvement in oxygenation and may also improve right heart failure. It also facilitates drainage of secretions

from dorsal lung regions (Raoof *et al.,* 2020). It was found that awake proning did not change the end point of intubation at 30 days in a multicentre COVID-19 RCT. In fact, a minority of patients were able to properly comply to the proning protocol (Akoumianaki *et al*., 2021).

All of COVID -19 treatments are novel and the only way to gauge success currently is the comparison of outcome in various units. In the SATICOVID trial, a prospective multicentre cohort study in Argentina, the mortality of patients ventilated in an ICU setting was 57% (1088 of 1909 patients) (Estenssoro *et al*., 2021).

A sub analysis of the HOPE COVID-19 registry by Bertaina et al (2021), showed that while more than half of the 20% (390) of patients treated with NIV survived without the need for intubation, it was important to identify the point of failure and prompt need for intubation . According to Akoumianaki et al (2021), 40% of all patients requiring mechanical ventilation for COVID-19 demised. In the study by Bellani et al (2021)showed there was a success rate of 65% in the group of patients treated outside the ICU setting with NIV.

One of the greatest concerns in the use of NIV is the delay in of intubation. Patients failing standard oxygen therapy or HFNC or CPAP require escalation to ICU for intubation (Nicola *et al*., 2020). Some studies proposed a worse outcome with NIV and HFNC , this is probably due to the delay in intubation . They also showed that patients with acute respiratory failure do not avoid mechanical ventilation regardless of NIV (high flow nasal cannula or continuous positive airway pressure). This is seen more often in those with severe hypoxaemia (Akoumianaki *et al.,* 2021) . However, some observational studies show that non-invasive ventilation does not in fact affect the time to admission to ICU, intubation, or survival: Grasselli et al (2021) reported early invasive ventilation was associated with a higher mortality at 60-days and Chandel et al (2021) observed that there was no statistically significant difference in hospital mortality in those receiving mechanical ventilation after failing non-invasive ventilation or those that initially received mechanical ventilation (Weerakoddy *et al*., 2021).

NIV does not ensure lung protective ventilation, patients with severe hypoxaemia display a high respiratory effort despite optimisation incur self- induced lung injury through an increase in tidal volumes which worsens pendelluft phenomenon and capillary leak and lung oedema. Another mechanism leading to failure on NIV is the insufficient unloading of the diaphragm causing fatigue and respiratory arrest due to persistence of increased respiratory efforts (Akoumianaki *et al*., 2021).

The question remains how to prevent P- SILI. HFNO should be used in those unable to maintain SaO2 >90% on Venturi face mask. This avoids the need for MV. With increased efforts , the patient should be escalated to CPAP. With failure of NIV , decreased mental status or haemodynamic status , the patient should be intubated. To prevent P-SILI with mechanical ventilation the tidal ventilation should be limited, PEEP should be applied, and the respiratory efforts should be reduced with adequate sedation and correction of metabolic derangements. High tidal volumes during NIV increase the risk of lung injury. Tidal volumes should be limited with NIV- it is often difficult to quantify and limit tidal volume on NIV. PEEP improves the heterogeneity in ventilation and decreases the pendelluft phenomenon. Using a higher PEEP

increases the end- expiratory lung volume, improving the curvature of the diaphragm , thus decreasing the risk of lung and muscular injury. Improvement of gas exchange with the use of PEEP can also decrease the respiratory drive. An increased respiratory drive worsens heterogenous ventilation, therefore patients should be adequately sedated and relaxed on mechanical ventilation (Battaglini *et al*., 2021).

Another great concern was the increased environmental contamination with the use of non-invasive ventilation compared to mechanical intubation. However, it was found that there is no difference in risk of exposure to health care workers with standard PPE, of aerosolised particles between spontaneous breathing, conventional oxygen therapy, high-flow nasal oxygen and NIV. The use of a facemask according to Nicola et al (2020) proved that this strategy completely suppressed particle dispersion during coughing in a patient on high flow nasal oxygen therapy . A further challenge with the use of non-invasive ventilation is the optimal placement in the hospital setting to ensure adequate monitoring of the patient to prevent a delay in escalation to intubation and mechanical ventilation. While these patients are critically ill, the intensive care unit is often reserved for those that are mechanically ventilated (Akoumianaki *et al*., 2021).

While there is a need for precise criteria to identify the point of NIV failure and the need for intubation, there exists little data to predict this point. Bertaina et al (2021) found that increased age, hypertension, and saturation on room air of <92% at presentation was associated with lymphopenia. The need for antibiotics were independently associated with the need for mechanical ventilation . Brusasco et al (2021) found that neither a PF ratio nor the lung weight were predictors of NIV failure. The magnitude of inspiratory efforts and expired tidal volumes on NIV predicted its failure and correlated to worsening lung injury and death (Akoumianaki *et al*., 2021).

Due to the challenge of assessing a patient's response to high flow nasal oxygen, the ROX-index (respiratory rate oxygen index) is used a prognostic score to evaluate these patients. It is calculated by the ratio of the SpO2/FiO2 to the respiratory rate. A score of more than 3.87 is a marker of good response (Akoumianaki *et al*., 2021).

Akoumianaki et al (2021) found that various intubation criteria were used for patients on NIV including persistent hypoxemia, lack of improvement on NIV, PF ratio <100mmHg, development of respiratory acidosis, evidence of accessory muscle usage, haemodynamic instability and altered mental status. They further showed evidence that PF ratio <150mmHG, expiratory tidal volume >9,5ml/kg PBW (predicted body weight) and HACOR (heart rate, acidosis, consciousness, oxygenation, respiratory rate) score >5 at the first hour of NIV showed a high probability of failure. An increase in oxygenation and a decrease in respiratory rate to <24 breaths per minute were predictors of NIV success. Ahmed et al (2022) supported this with the finding that patients with a higher respiratory rate on NIV failed, whilst an SF ratio >114 pre- CPAP or ≥180 at 30-120 minutes post initiation pointed to success. None of these are proven criteria for intubation.

2.6 Research problem

The SARS- CoV 2 pandemic has greatly taxed the already overburdened health system in South Africa. Due to lack of infrastructure, mechanical ventilation as a means for escalation is not possible in the vast majority. This poses a problem in the escalation of oxygen therapy in the severely ill. More research is required in modes of oxygen delivery like CPAP and HFNC to help alleviate the burden on ICU's and prevent progression to ventilation.

2.7 Aim

The aim of this study was to assess to effectiveness of different types of oxygen therapy, namely High Flow Nasal Cannula and Continuous Positive Airway Pressure, in the Central South African Population for the treatment of COVID-19, with regards to outcomes.

2.8 Objectives

1. To assess to difference in mortality in patients treated with HFNC or CPAP in the treatment of COVID pneumonia.
2. To assess the effect of associated comorbidities on the outcomes of the patients.
3. To explore the morbidity of HFNO or CPAP treatment in the management of COVID-19.
4. To evaluate the management practices used in each type of oxygen therapy to explore optimal escalation and weaning of therapy i.e., does the use of respiratory pressure 'swings' affect CPAP management.

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Chapter 2 – Publishable article

Note to examiner

The article has been edited according to the requirements of the SA Heart journal which also asks for the images and tables to not be embedded in the article. This however will make it more difficult for an examiner to review this manuscript as they would have to page up and down continuously. For ease for reading and examination of this manuscript the figures and tables have been embedded here in chapter 2, but will be submitted in accordance with the journal requirements to the journal.

Title

The effect of High Flow Nasal Cannula VS Continuous Positive Airway Pressure oxygen support in COVID-19 pneumonia in central South Africa

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Conflict of interest: none declared

Introduction: High flow nasal oxygen (HFNO) and continuous positive airway pressure (CPAP) are important forms of supplementary oxygen therapy for patients with COVID-19 pneumonia in resource-limited environments. The aims of this study were to compare the outcomes of patients on HFNO to those receiving CPAP and to investigate the limitations of HFNO and CPAP therapy and modes of failure leading to death in this setting.

Methods: 146 adult patients with severe respiratory failure due to COVID-19 pneumonia were treated with HFNO or CPAP. Outcomes and survival related to the respiratory rate oxygenation (ROX) scores were analyses and compared. The oxygen saturation, respiratory rate, flow rate, CPAP and respiratory swings were recorded in all patients who received CPAP.

Results: Overall mortality was 54,7%. All patients with a ROX score > 3.85 survived. Those with a ROX score <3,85 had a 67,3% mortality. A sustained respiratory rate >30 breaths/min, respiratory swings >10 cmH_2O, CPAP >10 cmH_2O for more than 2-days and flow rates of more than 60 l/min were associated with increased mortality.

Conclusion: Patients with sustained hyperventilation, high O_2-flows and CPAP >10 cmH_2O combined with a sustained respiratory swing of >10 cmH_2O have poor outcomes on HFNO and CPAP/BiPAP. These patients must be considered for early intubation and mechanical ventilation to prevent further P-SILI, an important contributor to poor outcomes in COVID-19 pneumonia.

Introduction

The lack of intensive care beds, suitably qualified personnel and mechanical ventilators present a unique challenge to resource-limited public health care systems.[1] This became especially evident during the COVID-19 pandemic in central South Africa.[2] In the Free State, the Department of Health only dedicated 9 beds, for the 2,917 million central South African population, for COVID-19 during the first wave between August and December 2020. This compelled us to develop a supplementary oxygenation program to meet the expected need within our resource limited environment. This undertaking would have to maximize the services and support facilities – thus a recreational hall in the nurses' home (House Idahlia) attached to Universitas Hospital was converted to a field hospital. In the protocol article by Smit et al. [3] they explained the rationale and technical developments undertaken for an open plan supplementary oxygen delivery system in a resource restricted environment such as Universitas Academic Hospital in Central South Africa.

The use of non-invasive supplementary oxygen programs has been previously described by Lalla et al.[4] and the successful use of HFNO specifically has been demonstrated in COVID-19 patients that did not require intensive care unit (ICU) care or intubation and mechanical ventilation.[5] The use of this strategy in a under-resourced environment during the current COVID-19 pandemic has been described by Calligaro et al.[6] showing that almost half of their patients could be weaned from HFNO without the need for mechanical ventilation. However, in these cohorts, there is very little data on predicting which patients would survive without mechanical ventilation and what were the limitations of non-invasive ventilation.

There still exists controversy over whether the pathophysiology of COVID -19 pneumonia is similar to that of ARDS, thus direct application of the principles of management of ARDS to COVID-19 pneumonia may be erroneous.[7] The theory of patient self-induced lung injury was described by Gattinoni et al.[8] and they proposed the significance of the different strategies for ventilation for the two phenotypes of COVID -19 pneumonia. The Type L pneumonia occurs during the early stage of COVID-19 and is characterized by low elastance and ventilation to perfusion (V/Q) ratio as well as a low lung weight and a low lung recruitability. It is proposed that the low V/Q ratio is due to pulmonary vasoplegia, but alternatively, this may also be explained by extensive intra-pulmonary thrombo-embolism" [9] In this phase d-dimers levels correlate with disease progression and computed tomography (CT) findings.[10] The next phase in COVID-19 pneumonia is dominated by severe hyperventilation and elevated swings in inspiratory- pressure; if the respiratory swings exceeds 15cmH20 this results in the patient self-induced lung injury (P-SILI).[8] Inflammation causes an increase in lung permeability which results in progressive lung edema as well as increased lung weight and dependent atelectasis. This is a very important transitional stage in the development of the type H-pneumonia, an acute respiratory distress syndrome (ARDS) like condition.[8] Battaglini et al.[7] also proposed an intermediate type as the disease progresses from Type L to Type H. Type H-pneumonia has the characteristic findings of a high pulmonary elastance, as well as increased right to left shunt. There is also an increase in lung weight and as well as increased lung recruitability.

The mechanism of P-SILI can be summarized into 4 parts: (1) increased lung stress/ strain, (2) inhomogeneous distribution of ventilation, (3) changes in lung perfusion, (4) patient ventilator asynchrony during NIV (Non- invasive positive pressure ventilation.[7]

The increased stress and strain specifically allude to the higher inspiratory pressures resulting in increased transpulmonary airway pressures that induce barotrauma. This is specifically worse in patients with diseased lung with heterogenous distribution of pressures and volume. The

heterogenous distribution of ventilation results in the pendelluft ventilation which increases the risk of P-SILI. The changes in perfusion alter the trans-capillary and trans-alveolar gradients resulting in endothelial and epithelial cell damage and lung oedema. Asynchrony between the patient and the ventilator also increases the transpulmonary gradient.[7]

This setting allows for speculation that by limiting the mechanical stress as a combination of respiratory rate and respiratory swings, P-SILI might be attenuated. Providing adequate O2 flow and enough PEEP to minimize inspiratory negative pressure might provide an early intermediate strategy between NIV (non-invasive ventilation) and MV (mechanical ventilation). Smit et al.[3] therefore proposed that a rational treatment program should include the early and phased approach including:

- An early reversal of hypoxemia
- Early and aggressive anti-coagulation protocol that is determined by D-dimers and other serology.
- Non-invasive options such as HFNO, CPAP and NIV are to be considered early in a patient who remains dyspneic or hyperventilates.
- It might be important to limit the time that the patient is exposed to hyperventilation with increased respiratory swings.

Battaglini et al.[7] also mentions the above rationale to prevent P-SILI in his 2021 publication.

These papers suggest that HFNO should be used in patients with COVID-19 pneumonia who are unable to maintain SaO2 >90% on Venturi face mask. This might avoid the need for MV if hyperventilation ceases. With increased respiratory efforts , the patient might benefit from CPAP. With failure of NIV , decreased mental status or haemodynamic status , the patient should be intubated. Tidal volumes should be limited with NIV, however, it is often difficult to quantify and limit tidal volume in these patients. PEEP improves the heterogeneity in ventilation, and decreases the pendelluft phenomenon. Using a higher PEEP increases the end- expiratory lung volume, improving the curvature of the diaphragm , thus decreasing the risk of lung and muscular injury. Improvement of gas exchange with the use of PEEP can also decrease the respiratory drive. An increased respiratory drive worsens heterogenous ventilation, therefore patients should be adequately sedated.[7]

Respiratory swings can be recorded either by esophageal pressure monitoring, or directly on the CPAP circuit. We postulated that high PEEP might reduce pleural pressure swings. This may limit P -SILI. Pressure swings of up to 5-10 cmH_2O are well tolerated according to Gattinoni et al.[8]

Importantly, a pulmonary pressure swing greater than 15 cmH_2O has been shown to produce mechanical trauma to the respiratory membrane, and therefore may necessitate endotracheal intubation as well sedation to prevent worsening P-SILI. If mechanical ventilation is required, low tidal volumes (6-7 ml/kg) and moderate PEEP of 8–10 cmH_2O is used. [7]

Type H pneumonia patients are treated as severe ARDS. Respiratory support might require higher PEEP, proning, mechanical ventilation and extracorporeal membrane oxygenation (ECMO). [8]

However, Akoumianaki et al.[11] warns about the limitation of NIV and argues that NIV does not ensure lung protective ventilation and that patients with severe hypoxaemia display a high respiratory effort despite optimisation. These patients may still incur self- induced lung injury through an increase in tidal volumes which worsens pendelluft phenomenon and capillary leak and lung oedema. Another mechanism leading to failure on NIV is the insufficient unloading of the diaphragm causing fatigue and respiratory arrest due to persistence of increased respiratory efforts.

The limitations of NIV approach are poorly described or defined in the literature as most programs allow transition to mechanical ventilation based on clinical assessment or clinician choice.[11]

As we had no access to mechanical ventilation the limitations of NIV could be assessed. Therefore, the aim of this study was to assess the use of HFNO and continuous positive airway pressure (CPAP) and secondly, to attempt to describe the limitations of non-invasive ventilation by analyzing the possible modes or indications of failure associated with mortalities during the COVID-19 pandemic in the Free State province. This could assist with the selection of patients for dedicated NIV programs in future pandemics.

MATERIALS AND METHODS

Study design

This was a retrospective observational study using a COVID – 19 registry of all patients admitted to the House Idhalia field hospital during the COVID- 19 pandemic (August 2020- February 2021). House Idhalia is located at Universitas Academic Hospital (UAH), the referral hospital of the Free State Province, South Africa. Ethical approval was obtained from the Health Science Research Ethics Committee of the University of the Free State (UFS-HSD2021/0357/3108-0001).

Unit Setting

An open plan supplementary oxygen facility was developed in the nurses' home community hall adjoined to Universitas Academic Hospital (UAH). The unit was equipped as a bed multiplier using multi-port mobile wall units, providing high flow oxygen capacity, vacuum, scavenging and electrical support for up to 4 beds or chairs in a mobile platform.[3] This system allowed for HFNO as well as CPAP support and could also support mechanical ventilators. Automated monitoring systems recorded observations, reducing the workload of the nursing staff. The unit provided 56 oxygen ports, and patients could be treated either as ambulatory (chairs) or in standard beds. The staff component included one part-time intensivist, 4 cardiothoracic surgery registrars, 2 internal medicine registrars, 4 medical officers, two visiting infective disease consultants, and a nurse ratio of 1:4 patients, 2 respiratory technologists and 2 physiotherapists. There was no radiology service.

Study population

Eligible participants were sequential adult patients above 18 years with severe respiratory failure and confirmed COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) admitted during the COVID -19 pandemic. Severe respiratory failure was defined as a respiratory rate >30 breaths per minute, oxygen saturation <93% despite oxygen at 15 l/min via reservoir bag or a SpO_2/FiO_2 ratio <150.[1]

HFNO was initiated at 50 l/min flow of 80% oxygen using the Fisher & Paykel Airvo™ 2 or CPAP initiated at 10 cmH2O and 80% oxygen with a flow rate of 70–80 l/minute using a Council for Scientific and Industrial Research (CSIR) CPAP circuit. ROX -scores were performed on all patients who received HFNO. The ROX score is a ratio of the oxygen saturation measured with pulse oximetry to the respiratory rate or inspired oxygen concentration in patients with severe respiratory failure to predict the success of HFNO. Patients who have failed HFNO as described below were put on CPAP upon admission. Patients referred on established CPAP were maintained on CPAP.

The aim of therapy was to ensure a patient was not in respiratory distress, with a breathing rate of <25 breaths/min, and oxygen saturation on pulse oximetry (SpO2) of >92%. Success was defined as successful stepwise de-escalation of supplementary oxygen therapy and discharge alive or to a step-

down facility on a 40% Venturi or air-entrainment oxygen mask with a normal respiratory rate (15/min) and oxygen saturation of >92%. CPAP patients were weaned to HFNO when breathing rate <25 breaths/min on a CPAP of 5 cmH2O with oxygen saturation >92%, followed by weaning to a facemask/rebreather as described above.

Patients who failed HFNO were escalated to CPAP if the respiratory rate remained >30/min or if the oxygen saturation remained <93% on 80% oxygen. Patients that received CPAP upon admission were maintained on this therapy. Direct pressure monitoring using a manometer (Medishield patient circuit manometer) was conducted on initiation of CPAP and when oxygen flow or PEEP settings were adjusted or if hyperventilation persisted (>30 breaths per minute). The oxygen flow and PEEP settings were increased incrementally in attempt to lower respiratory swings to <10 cmH20 and respiratory rate <25 breaths per minute. Oxygen flow was increased to a maximum of 80l/min and the PEEP to 20cm/H2O, if tolerated.

Demographics, risk factors, HIV status, white cell count (WCC), C-reactive protein (CRP), d-dimers, ferritin as well as comorbidities were recorded. An Apache score was performed to reflect multi-organ involvement upon admission. The SpO_2/FiO_2 ratio was recorded upon admission, as well as the length of stay. This data was collected from patient files as well as electronic records. All patients received dexamethasone and anti-coagulation as described in the World Health Organization (WHO) protocols (2); during the study period we did not have access to immune modulation treatment or anti-retrovirals Demographics and risk factors were compared using death as an endpoint for the whole patient group.

Respiratory rate oxygenation (ROX) -scores were performed on all patients on HFNO on admission and daily or with a change in clinical condition. The ROX score is the ratio of the SpO2 and the respiratory rate and is used to predict the risk of intubation in patients with respiratory failure. These patients were grouped into ROX-scores >4.88, between 3.85 and 4.88 and those with scores of <3.85. ROX-scores <3.85 are used as a theoretical indicator for the possible need of mechanical ventilation in a well-resourced environment.[(14)]

Using the endpoints of either death or survival the possible relationship between respiratory rate, oxygen saturation, flow rate, CPAP and the recorded respiratory swing was analyzed in an attempt to define the limitation of NIV. The respiratory swing or intrathoracic pressure difference between inspiration and expiration was directly recorded using a Medishield patient circuit manometer connected to the CO_2 sampling port on the heat moisture exchange filter in each patient's circuit, as previously described and shown in Figure 1. This was used as a surrogate for the trans-esophageal measure of transpulmonary gradient.

All patients under the age of 18 were excluded from the study as well as those who demised within 4 hours of admission. There was no access to any radiology services due to the restrictions imposed by the Dept of Radiology during the pandemic.

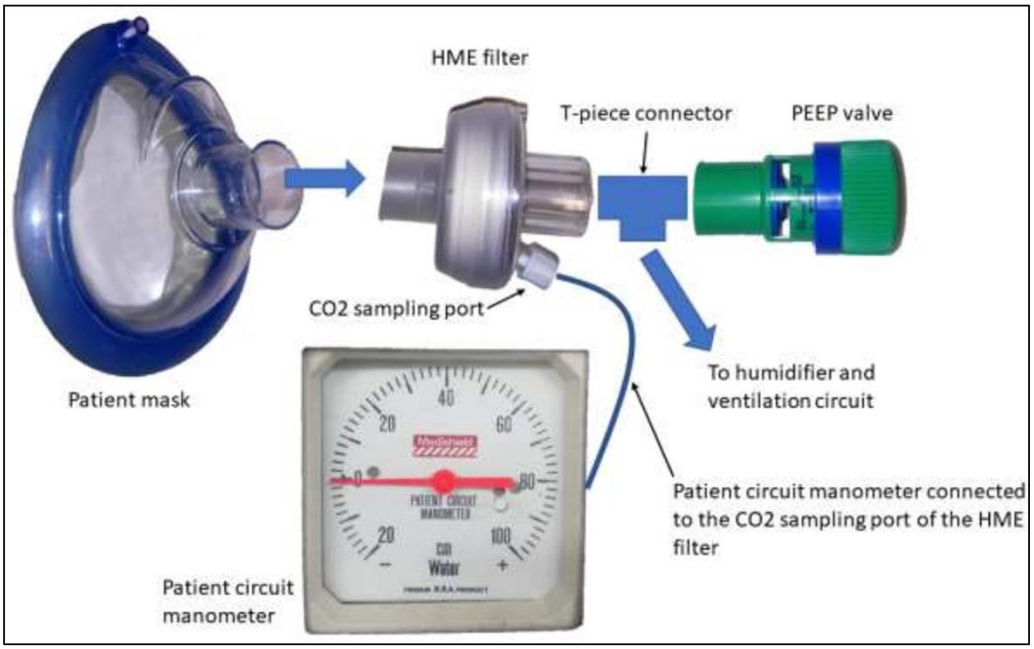

Figure 1. Connection diagram illustrating how the swings were measured.

RESULTS

The study included all of the 146 sequential patients that were admitted to the House Idhalia Supplemental Oxygen facility. The demographics and risk factors were compared between survivors and non-survivors in Table I. The groups were comparable regarding age, gender, risk factors, baseline blood results and Apache scores. Statistically significant risk factors for mortality were obesity, high blood glucose on admission, known DM, an elevated Pro-BNP on admission, ROX – index <3.85 on admission, the escalation to CPAP. The mortality of the study population was observed as 54.7%.

Table 1. Baseline characteristics of the study sample. Continuous variables were reported as median and interquartile range, categories were reported by counts and percentages.

	Survivors N = 66	**Deceased N = 80**	***P value**
Age (years)	58.0 (41.0; 68.0)°	64.0 (55.0; 71.0)°	0.0550
Men	28 (42.4)**	29 (36.3)**	0.4537
Women	38 (57.5)**	51 (63.75) **	
Black	49 (74.2)**	60 (75.0)**	0.9123
Coloured	10 (15.2)**	6 (7.5)**	0.1400
Indians	3 (4.5)**	5 (6.3)**	0.6357
White Caucasians	3 (4.5)**	9 (11.3)**	0.1380
Obese (BMI > 30 kg/m^2)	28 (42.4)**	47 (58.8)**	**0.0492**
Hypertension on admission	45 (68.2)**	59 (73.8)**	0.4583
Blood Glucose mmol/l	8.0 (6.6; 10.7)°	9.4 (7.6; 11.8)°	**0.0050**
HbA1c	6.4 (6.0; 8.1)°	6.7 (6.1; 8.4)°	0.2148
CRP	119.5 (66.0; 191.0)°	154.0 (87.0; 246.0)°	0.1127
Ferretin	942.0 (426.0; 1538)°	821.0 (387.0; 1781)°	0.3463
D dimer	0.9 (0.3; 4.2)°	1.1 (0.7; 3.2)°	0.1687
Pro BNP	323.0 (120.0; 1619)°	2130.0 (467.0; 5549)°	**0.0004**
AST	41.0 (29.0; 62.0)°	43.5 (31.5; 66.5)°	0.6691
Albumin	27.0 (22.0; 30.0)°	25.0 (23.0; 29.0)°	0.2001
White cell count	10.0 (7.5; 12.3)°	11.0 (8.3; 14.3)°	0.1127
Length of stay (days)	7.0 (6.0; 13.0)°	8.0 (5.0; 14.0)°	0.5984
ROX Index	3.9 (2.7; 4.7)°	3.0 (2.5; 3.5)°	**0.0112**
Resp rate on admission	32.0 (28.0; 36.0)°	35.0 (29.0; 38.0)°	0.3087
SaO2 on admission	85.0 (75.0; 90.0)°	82.0 (70.0; 88.0)°	0.6278
Escalation to CPAP	8 (12.1)**	35 (43.8)**	**<0.0001**
No escalation to CPAP	46 (69.7)**	16 (20.0)**	**<0.0001**
Known DM	14 (21.2)**	30 (37.5)**	**0.0333**

In Table 2 the outcomes were analyzed according to the ROX-scores obtained upon admission. No patient died with a ROX-score >4.88 or in the group between 3.85–4.88. No escalation to CPAP was required in these two groups.

The overall mortality of those with ROX-score <3.85 was 67.3%. A larger percentage of those that required escalation from HFNO to CPAP (85.7%) died compared to those that received CPAP from admission (64.7%). As described earlier, admission with a low ROX -score was predictive of mortality (P=0.0112).

Table 2. ROX scores related to treatment outcomes and survival.

ROX score <3,85	**n**	**Mortality**	**Survival**
HFNO without escalation	7	0	7 (100%)
HFNO with escalation to CPAP	28	24 (85.7% of 28)	4 (14.3% of 28)
HFNO total on admission	**35**	**24 (68.5% of 35)**	**11 (31.5% of 35)**
CPAP on admission	17	11 (64.7%)	6 (35.3%)

In Figures 2 and 3, the relationship between survivors and non-survivors were explored in those that received CPAP at some point during their admission using oxygen saturation, respiratory rate, flow rates, CPAP values and respiratory swing over time.

In the Figure 2 there is a clear divergence between survivors and non-survivors as early as day 2 in the flow rate required ($p < 0.001$), with the survivors having a flow rate of <60l/min by day 6. Similarly, by day 2 there is a clear divergence in the respiratory rate in survivors vs non survivors ($p < 0.001$): the persistance of a tachypnoe of more than 30 breaths per minute is observed in the non-survivor curve. While the Sp02 shows a divergence at day 2 ($p = 0.018$), the trend of the decreasing SaO2 in survivors can be explained by the weaning process in an attempt to discharge the patient.

In Figure 3 , there is a statistically significant relationship ($p<0.001$) observed between both an increased swing (cmH2O) and mortality as well as an increased PEEP (mmHg) and mortality.

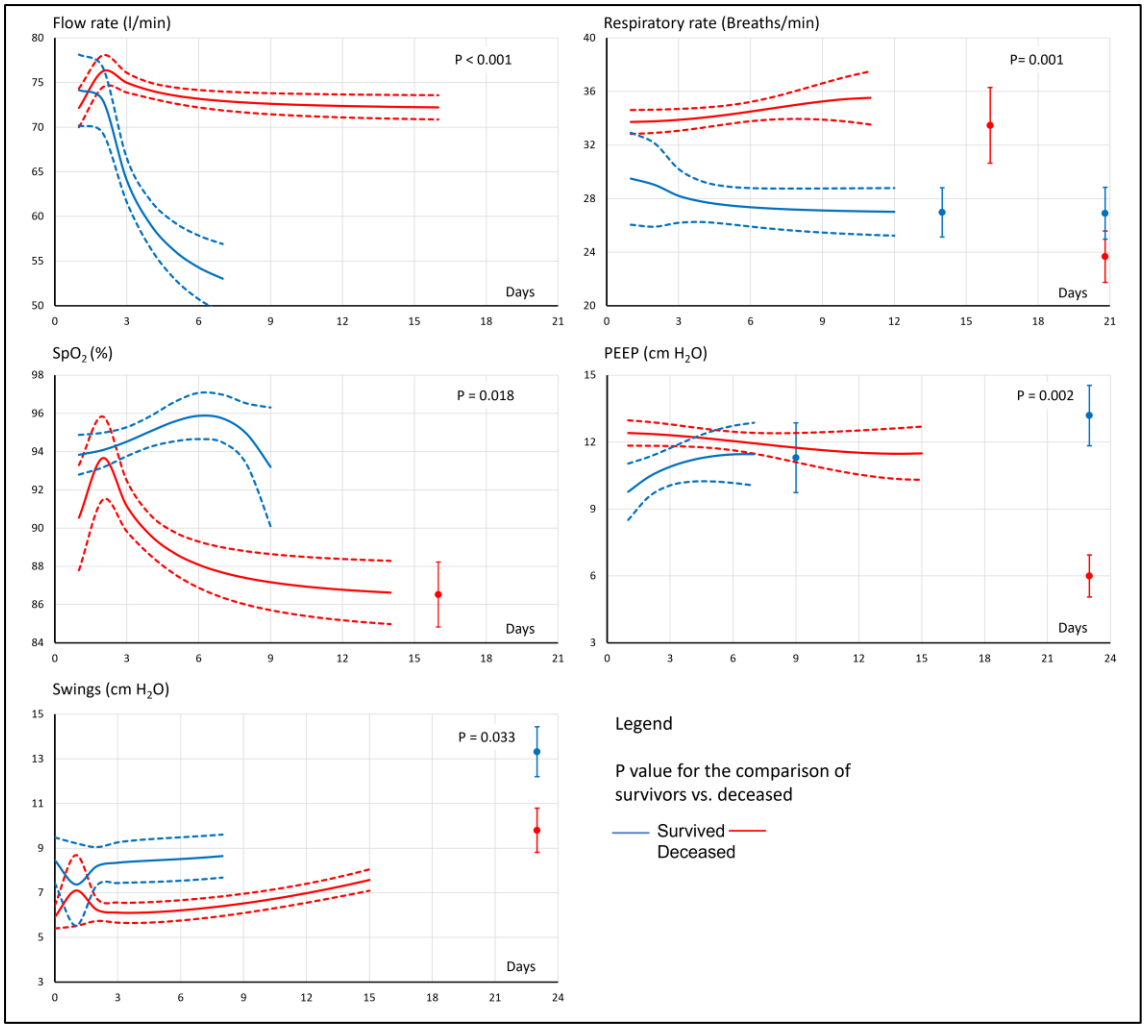

Figure 2. Relationship of survival and non-survival over time with regards to flow rate, respiratory rate, SpO2, PEEP and repiratory swings.

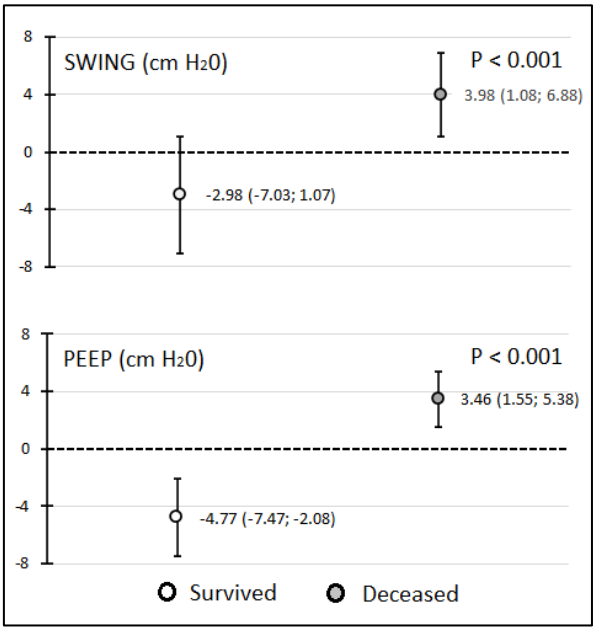

Figure 3. Relationship of mortality vs respiratory swings and PEEP.

DISCUSSION

Non-invasive supplementary oxygen programs probably constitute the only cost-effective or, at times, the only available alternative to ICU based mechanical ventilation in the treatment of COVID-19 pneumonia in resource-limited environments. In South Africa, Calligaro et al.[6] demonstrated the value of this approach in a recent publication.

In this study, confidence limits calculated show a divergence in outcomes and survival., The survivors required flow rates <60 l/min flow by day 2 ($p < 0.001$), CPAP levels <10 cmH_2O ($p<0.001$) and respiratory swings <10cmH2O ($p<0.001$) and a respiratory rates less than 30 breaths/minute. These findings may describe a flexion point identifying failure of NIV necessitating mechanical ventilatory support or ECMO.

It is important to note that all patients in this study were admitted with severe respiratory failure (defined as having failed oxygen rebreathing mask therapy, a respiratory rate >30 breaths/min, O_2 saturation <93% and had in fact SpO_2/FiO_2 ratios <100 in all patients) . Despite this, 45.3% of our patients survived in an open plan field hospital with a 4:1 ratio of nurses to patients, automated observations and no access to invasive ventilation or radiography.

All patients with ROX-scores >3.85 survived on either HFNO or CPAP and none of these patients failed HFNO or required escalation to CPAP. This suggests that a patient with a ROX-score of >3.85 may only require HFNO.[14]

The demographics in this study reflect international trends with age tending to increase mortality ($p=0.05$) as well as an increased risk for severe disease and mortality in patients with pre-exisiting conditions such as obesity ($p=0.04$) and diabetes ($p=0.03$).[15] Similarly an elevated pro-BNP was statistically significant for in-hospital death ($p=0.004$), this is in keeping with findings of Gao et al.[16] who found an elevated pro-BNP to be an independent predictor on in-hospital mortality in patients with severe COVID 19. An elevated random blood glucose at admission is also statisically signifcant as a risk factor for mortality ($p=0.005$). Patients with a low ROX- score were also at increased risk of mortality ($p=0.0112$) , this is clearly reflected in Table 2. Esclation to CPAP was associated with a higher mortality ($p=0.001$) , this reflects the progression of disease.

Respiratory rate oxygenation (ROX) -score less than 3.85, is an accepted value for initiation of mechanical ventilation after 12 hours on HFNO.[14] The failure rate of 68.5% in the HFNO patients with an admission ROX score <3.85 was thus not unexpectd. The survival rate on CPAP for patients with admision ROX score <3.85 was 35,3% and only 14.3% if CPAP was instituted after failing HFNO. During the COVID-19 pandemic, dismal results have also been recorded in populations with access to ICU based ventilator treatment, for example, an 88% mortality rate in a published New York series of 5700 patients early in the pandemic.[17] It is therefore not only important to evaluate the outcomes of supplementary oxygen therapy programs in the COVID-19 setting [5] but also attempt to define the limitations and patterns of failure using NIV.

In the context of the pathophysiology of the disease and the role of P-SILI in the development of Type H pneumonia as described by Gattinoni et al.[8] and Battaglini et al.[7] respiratory swings were recorded and an atttempt was made to integrate the findings of respiratory swing, required CPAP, respiratory rate and SpO2. Our results indicate that if the respiratory swing remains above 10cmH20, CPAP>10cmH2O, Respiratory rate >30/min and O2 sat <93% for more than two days, the patient mortality will increase significantly. These findings thus define the limits of NIV in this setting in our opinion and patients who do not show significant progress will require mechanical ventilation or ECMO support with sedation. It also supports a theory of P-SILI. It is unclear whether the increase in

respiratory swing and hyperventilation over time is a result of ongoing worsening of lung mechanics and P-SILI or if the increasing respiratory swing itself induces P-SILI. It is however quite clear when NIV fails using the parameemeters suggested.

CONCLUSION

We, therefore, conclude that in patients with a ROX-score of more than 3.85 upon admission HFNO probably will suffice. HFNO failed in 68.5% of patients with ROX score <3.85. In these patients it may be prudent to initiate CPAP treatment and increase the flow rate and CPAP if the respiratory swing and respiratory rate does not come down to 30 breaths /minuteand less than 10 cmH_2O. In patients in whom hyperventilation does not settle to less than 30 breaths per minute, with respiratory swings more than 10 cmH_2O and who require CPAP of more 10 cmH_2O for more than 2-days and flow rates of more than 60 l/min, our data suggests that non-invasive ventilation will be unsuccessful and mechanical ventilation and sedation might be required to prevent further P-SILI.

These findings might provide some guidance for future trials to better define limitations of non-invasive ventilation and identify patients for early intubation, sedation and mechanical ventilation. Early identification of patients with a significant potential for P-SILI might impact on outcomes of patients on mechanical ventilation and ECMO.

LIMITATIONS

Limitations include the lack of access to radiography and the small study population. Mechanical ventilation and ECMO as treatment options were not available during the study.

RECOMMENDATIONS

We recommend that the study be conducted in a large study population in the future if possible.

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List of Appendices

Appendix A - Letter of FINAL approval from Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

31-Jul-2023

Dear **Dr Shaaista Cassim**

Ethics Number: UFS-HSD2021/0357/3108-0001

Ethics Clearance: **The effect of High Flow Nasal Cannula VS Continuous Positive Airway Pressure oxygen support in COVID-19 pneumonia in central South Africa**

Principal Investigator: **Dr Shaaista Cassim**

Department: **Cardiothoracic Surgery Department (UFS Main Campus)**

Submission Page

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

- This is a retrospective sub-study of another approved study that recruited patients. This amendment is to correct a contradiction in the methods section increase the sample size to include all the patients recruited in the main study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

The Principal Investigator (PI) bears final responsibility for the RIMS application. In the event of any misconduct or improper activities perpetuated by a third party, the PI will be held vicariously liable. The HSREC will bear no responsibility or liability for any actions of a PI and/or third party or breach of confidentiality caused by the PI and/or third party.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Prof. A. Sherriff
Chairperson : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010096; FWA 00027947
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www.ufs.ac.za

Appendix B - Permission from DOH/NHLS

health
Department of Health
FREE STATE PROVINCE

01 July 2021

Dr S Cassim
Dept. of Cardiothoracic Surgery
UFS

Dear Dr S Cassim

Subject: The effect of High Flow Nasal Cannula VS Continuous Positive Airway Pressure oxygen support to Covid-19 pneumonia in Central South Africa.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- As part of the Recommendation access to KONTOS database must be given ICT Director Mr. B Ntombela of the Free State Department of Health so that he is also aware of the database.
- Participation in the study must be voluntary and a written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** scheelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Mr. MNG Mahlatsi
ACTING HEAD: HEALTH
Date: 5/07/2021

Head : Health
PO Box 227, Bloemfontein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfontein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail: khupemi@fshealth.gov.za/dhlobvup@fshealth.gov.za
www.fs.gov.za

Appendix C - Permission from HOD

PERMISSION LETTER FROM PRINCIPLE INVESTIGATOR OF MAIN COVID STUDY TITLED FREE STATE SUPPLEMENTAL OXYGENATION PROJECT FOR COVID-19 PATIENTS 2020 WITH HSREC NUMBER UFS-HSD2021/0161

I, Professor Francis Smit am the Head of Department for Cardiothoracic Surgery and principle investigator for the above mentioned project. I am granting permission to Dr Shaista Cassim to do her COVID 19 study as a sub-study of the above mentioned study for her MMED research project.

Yours faithfully

29/03/2021

Head of Department
Cardiothoracic Surgery

DATE

Appendix D - Copy of the FINAL research protocol as approved by the HSREC

The effect of High Flow Nasal Cannula VS Continuous Positive Airway Pressure oxygen support in COVID-19 pneumonia in central South Africa

by

Dr. Shaaista Cassim

MBChB (cum laude), University of Pretoria, 2015

MASTER OF MEDICINE IN CARDIOTHORACIC SURGERY

Department of Cardiothoracic surgery
College of Medicine

University of the Free State
Bloemfontein
Free State

Supervised by:
Prof. FE Smit (PhD)
Co-supervisor:
Mr M Hanekom

November 2020

Confidential

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List of abbreviations

- SARS- Severe acute respiratory syndrome
- ARDS- Acute respiratory distress syndrome
- PPE- Personal protective equipment
- WHO- World Health Organisation
- IDSA- Infectious Diseases Society of America
- L Type- Low elastance type
- H Type- High elastance type
- CPAP- Continuous positive airway pressure
- HFNC- High flow nasal cannula
- ICU- Intensive care unit
- RNA- Ribonucleic acid
- PCR- Polymerase chain reaction
- RR- Respiratory rate
- SaO2- Arterial oxygen saturation
- PaO2- Partial pressure of oxygen in arterial blood
- mmHg- Millimetres of mercury

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1. INTRODUCTION

On January 30th, 2020, a novel SARS-2 corona virus pneumonia outbreak from Hubei Province in Wuhan, China, was declared a Public Health Emergency of International Concern by the World Health Organisation. This disease that rapidly evolved into a global pandemic would later be named the corona disease 2019 (COVID- 19). New information is constantly being discovered with the spread of the disease (Zu *et al*, 2020). More than 200 countries have been affected by this virus with more than 10 million cases since July 2020 (Wiersanga *et al*, 2020).

The novel SARS-2 corona virus has posed many new challenges from negatively affecting economies and education systems to challenging current respiratory distress an PPE protocols. The guidelines for the respiratory illness are constantly evolving as we discover the unique pathophysiology of the virus. This combined with the poverty of resources has demanded a re-evaluation in our management of patients with invasive and non- invasive ventilation. (Wiersanga *et al*, 2020).

2. LITERATURE REVIEW

2.3 Background

COVID was first diagnosed in December 2019 in patients presenting with pneumonia in Wuhan, China. This virus is thought to initially be hosted by bats and transmitted to humans by pangolins and other wild animals. It is an enveloped, with a single strand ribonucleic acid and a solar corona- like appearance with surface spikes (Zu et al, 2020). The rapid evolution of this respiratory virus into a pandemic is due to its ability to spread by droplets. Severe symptoms develop in approximately 5 % of patients with COVID- 19 and in 20% of those hospitalized (often requiring ICU care); supplemental oxygen is required in more than 75% of those hospitalised. (Wiersanga et al, 2020). Severe disease with complications is more likely to develop in those aged over 65, pregnant females and those with multiple comorbidities. (Unhale et al, 2020). Since no vaccine or anti-viral treatment exists yet, management of COVID-19 includes supportive management and supplemental oxygen. Many governments, have, in an attempt to curb the ferocious spread of the disease, employed, mandatory social distancing, quarantining, and wearing of masks.

2.4 Prevalence and Epidemiology

Since December 2019, over 200 countries have been affected grievously by this pandemic. It has affected health care systems, economies, and food production. The enormity of the pandemic has posed great challenges to developing countries: the already taxed health care systems are unable to manage with the added strain; unemployment has rocketed. Measures to prevent the spread of COVID- 19 are impossible to implement in densely populated rural communities. The current prevalence in South Africa as of 2 October 2020 is 679 716 positive cases with a mortality of 16938. The Free State province accounts for 7.1% of these cases to date.(https://www.nicd.ac.za/diseases-a-z-index/COVID-19/surveillance-reports/).

According to the WHO the following represents the stage of the disease related to mortality. (Unhale et al, 2020)

Table 1: Severity related to mortality (Unhale *et al*., 2020)

Stage of severity	Rough percentage of people with COVID -19
Mild disease from which person can recover	>80%
Severe disease, causing dyspnoea and pneumonia	Around 14%
Critical disease, including septic shock, respiratory failure, and failure of >1 organ system	About 5%
Fatal disease	2%

2.3 Clinical Presentation and Pathophysiology of COVID- 19 Pneumonia

There are 3 main stages (stages 1 to 3) of increasing severity of COVID 19 pneumonia namely asymptomatic, Upper airway and conducting airway response and Hypoxia, ground glass infiltrates ad progression to ARDS stages.

Stage 1: Asymptomatic stage

This stage represents infection and replication SARS-CoV2. During this stage, the innate immune response is activated. RT PCR from nasal swabs can be used to diagnose patients in this stage. (Mason *et al.*, 2020)

Stage 2: Upper airway and conducting airway response.

Pulmonary inflammation and coagulopathy develop consecutively or overlap. The innate immune response is more marked, and symptoms can range from mild (80%) to severe in this stage. (Mason, 2020) Markers of severity and progression of disease include an elevated CRP, IL6 and D Dimer (Polak *et al*., 2020)

Stage 3: Hypoxia, ground glass infiltrates ad progression to ARDS

20% of infected progress to this stage and approximately 2% have fatal outcomes.

This stage is characterised by disruption of the type II alveolar cells. These cells are typically peripheral and subpleural. The diffuse damage of the Type II cells combined with fibrin rich hyaline membranes and giant multi-nucleated cells is specific to this stage. This leads to ARDS with subsequent scarring and fibrosis. (Mason *et al*, 2020)

Mortality is higher in the elderly as they have a diminished immune response and ability to repair epithelium.

COVID pneumonia can be classified into 3 stages of severity according to clinical manifestation (Table 2) (Polak et al, 2020). This assists in determining the level of care and mode of oxygen therapy.

Table 2: Clinical classification of severity of COVID pneumonia (Polak *et al*, 2020)

Clinical Severity and Findings
Mild
Mild clinical symptoms (fever <38°C [100.4°F], quelled without treatment, with or without cough, no dyspnea, no gasping, no chronic disease)
No imaging findings of pneumonia
Moderate
Fever, respiratory symptoms
Imaging findings of pneumonia
Severe*
Patient has any of the following:
Respiratory distress, RR ≥30 times a minute
SpO_2 ≥93% at rest
PaO_2/FiO_2 ≤300 mm Hg
Critical
Patient has any of the following:
Respiratory failure, needs mechanical assistance
Shock
"Extrapulmonary" organ failure, intensive care unit is needed

Two respiratory phenotypes of pneumonia requiring mechanical ventilation exist: Low elastance (L) type and high elastance (H) type.

The H type is characterised by decreased lung compliance with increased pulmonary oedema and lung weight. Gas exchange is impaired with a large fraction of cardiac output perfusing non aerated lung, leading to high right to left shunting with a high VQ ratio. High recruitability of non-aerated lung with PEEP is a feature of this phenotype. The L type is characterised by near normal lung weight and high compliance with almost normal gas volumes. The VQ ratio is low due to loss of perfusion regulation and hypoxic vasoconstriction. There is low recruitability due to very little non aerated lung tissue. (Polak *et al.*, 2020)

2.4 Diagnosis

The Infectious Diseases Society of America (IDSA) suggests nasal and mid turbinate swabs for SARS-CoV-2 RNA testing in symptomatic (table 3) individuals suspected of having COVID -19simptoms. It also recommends RNA testing for asymptomatic individuals with a known COVID-19 contact. (Hanson et al, 2020).

Table 3: Symptoms common in COVID- 19 mandating testing (Hanson *et al*., 2020).

Symptoms may appear 2–14 days after exposure to the virus People with these symptoms or combinations of symptoms may have coronavirus 2019	Respiratory symptoms alone • Cough • Shortness of breath or difficulty breathing Or at least 2 of these symptoms • Fever • Chills • Repeated shaking with chills • Muscle pain • Headache • Sore throat • New loss of taste or smell

While chest CT findings of COVID pneumonia support the diagnosis as shown in figure 1, RT PCR assay is necessary for confirmation. CT findings are non- specific and include multifocal bilateral ground glass opacification with patchy consolidation with a predilection for subpleural and posterior lobe distribution (Zu *et al*., 2020).

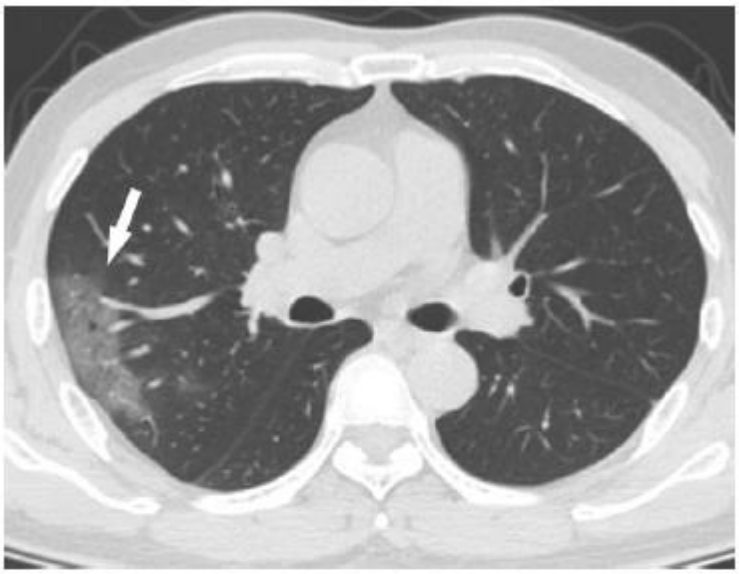

Fig. 1: CT findings of patchy ground glass pattern in a confirmed case of COVID-19. (Zu *et al,* 2020).

2.5 Current treatment practices

2.5.1 Prevention and quarantine:

This is the first step in managing the disease and includes wearing of masks, social distancing, and self-isolation for those with positive or symptoms (Nicola *et al,* 2020).

2.5.2 Supportive management:

The degree of supportive management required depends on the severity of disease, ability to self-isolate and need for hospitalisation. Asymptomatic patients can be managed with self-isolation at home on an out-patient basis (Nicola *et al*., 2020).

The WHO has defined supportive management for those with severe disease as follows: (Nicola *et al*., 2020)

4. Intravenous fluid administration
   - Judicious use of fluids should be use in these patients to prevent further complications and decompensation.
5. Oxygen therapy
   - Supplemental oxygen therapy should be administered immediately in patients with severe acute respiratory distress, hypoxaemia, or shock. Oxygen delivery end points are an SPO2 of ≥ 90% in adults and ≥ 94% in children.
   - Mechanical ventilation should be considered in patients with worsening hypoxia or increased work of breathing.
6. Corticosteroids
   - Nicola et al (2020) do not recommend the use of corticosteroids, however the IDSA (Bhimraj *et al*., 2020) does.

High flow oxygen delivered via nasal cannula (HFNC) has several advantages over conventional non- rebreather supplemental oxygen. Flows can be delivered more than 50l/min and can reduce oxygen dilution and respiratory dead space. It can also generate a degree of PEEP due to the expiratory resistance generated by the contours high flow. The air can be humidified, and this facilitates clearance of secretions and decreases the development of bronchial hyper-response symptoms (Roca *et al*., 2020).

Compared to conventional oxygen therapy, HFNC is associated with decreased risk for intubation and ICU admission. It is currently the recommended therapy by the WHO, ANZIC and German Intensive Care Society for the treatment of COVID patients failing standard oxygen therapy (Whittle et al, 2020). A proposed treatment algorithm is shown in figure 2.

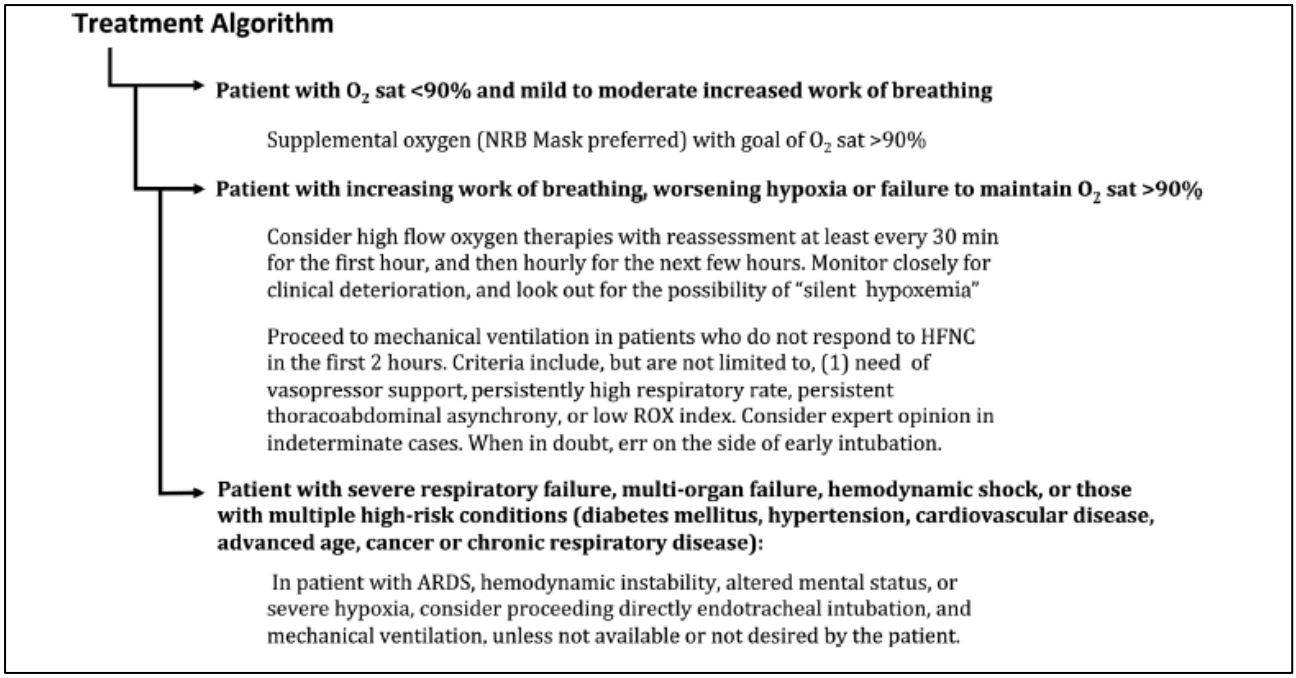

Fig 2: Proposed treatment algorithm for oxygen management in COVID-19 patients (Whittle *et al*., 2020).

Continuous positive airway pressure ventilation is a mode of non- invasive ventilation. It is spontaneous breathing via a mask with an expiratory valve that maintains positive end expiratory pressure. CPAP aids in ventilation by increasing the functional residual capacity. Adverse events from the use of CPAP include gastric insufflation, pressure sores from the mask and nosocomial pneumonia (Marino *et al*., 2014).

Initially, Non- invasive ventilation, including CPAP and BiPAP, was not favoured due to fears or barotrauma and aerosolization, emerging evidence now supports its use. Data from Italy and China show its benefit; in Italy, 50% of patients that used CPAP did not require invasive ventilation (Nicola *et al*., 2020).

In patients on CPAP, the magnitude of inspiratory pleural pressure swings, measured via oesophageal catheter, may determine the transition from the L Type to the H type phenotype. Oesophageal pressure swings of 5-10 cmH2O are well tolerated. The risk of lung injury increases with swings >15cmH2O and intubation should be considered at this point (Gattinoni *et al*., 2020).

Awake proning in both patients on HFNC and NIV reduces alveolar over distension in the non-dependant areas and improves ventilation perfusion mismatch. It allows for more homogenous ventilation and may facilitate drainage of secretions from dorsal lung regions. (Reroof *et al.,* 2020)

Patients failing standard oxygen therapy or HFNC or CPAP require escalation to ICU for intubation (Nicola *et al*., 2020).

The IDSA recommends corticosteroids as part of the medical management for COVID-19. Many other drugs including ARV's are still under investigation (Bhimraj *et al*., 2020).

2.6 Research problem

The SARS- CoV 2 pandemic has greatly taxed the already overburdened health system in South Africa. Due to lack of infrastructure, mechanical ventilation as a means for escalation is not possible in the vast majority. This poses a problem in the escalation of oxygen therapy in the severely ill. More research is required in modes of oxygen delivery like CPAP and HFNC to help alleviate the burden on ICU's and prevent progression to ventilation.

2.7 Aim

The aim of this study will be to assess to effectiveness of different types of oxygen therapy, namely High Flow Nasal Cannula and Continuous Positive Airway Pressure, in the Central South African Population for the treatment of COVID-19, with regards to outcomes.

2.8 Objectives

To assess to difference in mortality in patients randomised to HFNC vs CPAP in the treatment of COVID pneumonia.

To assess the effect of associated comorbidities on the outcomes of randomised patients

To explore the morbidity of each arm of treatment in the management of COVID-19

To evaluate the management practices used in each arm of oxygen therapy to explore optimal escalation and weaning of therapy i.e., does the use of respiratory pressure 'swings' affect CPAP management.

3. METHODOLOGY

3.1 Study Location

The research study will be conducted in the Department of Cardiothoracic Surgery, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa.

3.2 Study Design

This study will be a retrospective observational study that will include all patients that were admitted to our departmental supplemental oxygen unit as part of an umbrella research project. Patients admitted to House Idahlia were recruited as part of the main study with the title "Free State Supplemental Oxygen Project for COVID-19 patients" for which ethics approval (Ref no UFS-HSD2020/0507/3006) that has been approved in 2020.

3.3 Study Population

3.3.1 The number of subjects

The clinical information for approximately 100 patients that were admitted to our departmental supplemental oxygen unit (House Idahlia) (HSREC number UFS-HSD2020/0507/3006) that presented with COVID in 2020 will be obtained. Data will be sourced from the database of Cardiothoracic Surgery and patient files. Only patients older than 18 years will be included and data for the demographics age, sex, ethnic group diagnoses, pre-disposing factors, HIV status, pathogens, clinical outcomes, clinical treatment as well as long-term survival will be recorded for each patient.

3.3.2 In-and-Exclusion Criteria

3.3.2.1 Inclusion Criteria

- All patients, 18 years or older, with confirmed COVID pneumonia requiring escalation of oxygen therapy after failing (SO2< 90% or respiratory rate >30 breaths/min) none re-breather mask oxygen.

3.3.2.1 Exclusion Criteria

- Minors: patients less than 18 years of age.
- Patients that have already received HFNC or CPAP or invasive ventilation.

3.4 Study Layout

This study focusses on efficacy of oxygen therapy, namely HFNC and CPAP, in COVID- 19 pneumonia. Patients with confirmed COVID-19 pneumonia will be included in the study. These patients will otherwise receive medical treatment as per hospital protocol and according to any other trial/ study in which they may be enrolled.

Once a patient becomes hypoxaemic with an SO2< 90% on a conventional oxygen therapy or if the patient's work of breathing increases as noted with an elevated respiratory rate (RR) of more than 30 breaths per minute, the patient will be referred to the Idahlia Supplement Oxygen Unit.

A patient will then receive either HFNC or CPAP depending on the admission number. Those ending on an even number will receive HFNC and those on an odd number, CPAP. This is to prevent clinical bias in the allocation of methods of oxygen delivery. This is part of the main COVID study that has been approved by Freestate Department of Health and HSREC. The patients were randomized to one of two treatment regimens and was open label.

Those allocated on HFNC will be changed to CPAP in the event of: SO2< 90% or a RR>30/min.

Patients on CPAP similarly will be changed to HFNC in the event of: SO2< 90% or a RR>30/min.

Patients that remain hypoxaemic with an increased work of breathing (SO2< 90%, PaO2<55mmHG or a RR>30/min) on both CPAP (with atleast a CPAP of 10cmH2O) and HFNC will either be placed on BiPAP or ventilated invasively as per discretion of the critical care team.

The difference in inspiratory and expiratory pressure will further be monitored on patients on CPAP with a manometer attached to the respiratory circuit. The oxygen flow rates will be adjusted to maintain the difference to less than 10cmH2O.

This is summarised in figure 3:

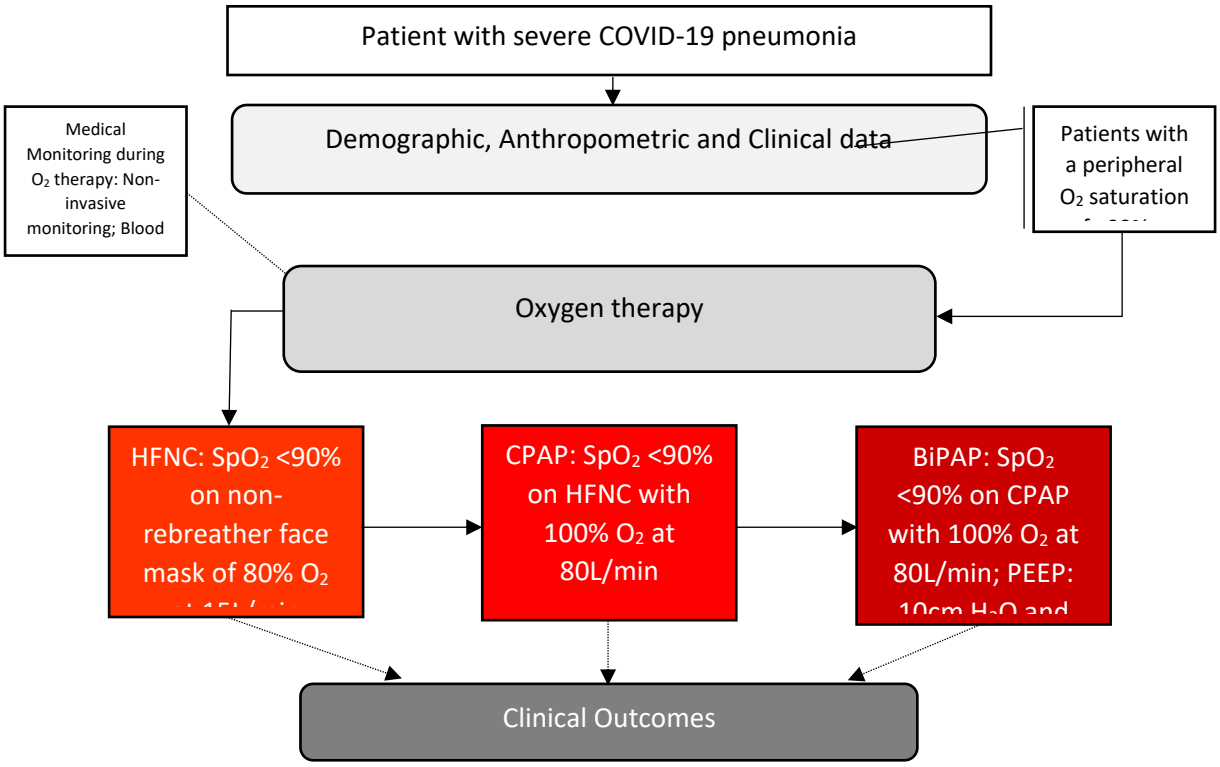

Figure 3. A summary of the conceptual framework and data collection of the study.

This study is a sub-study that forms part of an umbrella study titled "Free State Supplemental Oxygen Project for COVID-19 patients. All patients who met the inclusion criteria diagnosed with severe COVID-19 pneumonia were admitted to the supplemental oxygen unit. Patients were then linked to a Masimo® Rad-97 Monitor for continuous monitoring of blood pressure (BP); heart rate (HR); peripheral saturation (SpO_2); perfusion index (Pi) and plethysmography variability index (PVI). Patients also had an arterial blood gas (ABG) analysis on admission to the unit. Once a patient's peripheral saturation became less than 92% on room air, the patient received a standard oxygen therapy mask which supplies 40%-80% Oxygen at a flow rate of up to 15L/min.

If the patient's peripheral saturation subsequently continues to drop below 90% on a standard oxygen mask of 80% O_2, the intervention for the patient was escalated to high flow nasal cannula (HFNC) or a Continuous Positive Airway Pressure (CPAP) system.

If the patient's peripheral saturation continued to drop below 90% on HFNC and the patient required additional oxygen support or Intensive Care Unit admission the patient was started on a Continuous Positive Airway Pressure (CPAP) system.

If the patient became hypoxemic with finger probe saturation of ≤ 88% or PaO_2 ≤ 55 mmHg, despite a minimum of 80% supplemental oxygen with CPAP at 10 cmH_20, the patient was considered for intubated and ventilated should they meet the requirements for escalation.

All patients were continuously cared for by the attending medical personnel evaluated by the respiratory technicians to calculate their ROX indices as a guide to assist with escalation to a higher level of supplemental oxygen.

Patient's details on admission and daily notes were captured on an access-controlled database (KONTOS) to aid with a paper-free clinical care setup and allow access to patient's information outside of the unit without exposing an individual to contaminated documentation from within the unit.

Refer to **Error! Reference source not found.** for the complete layout.

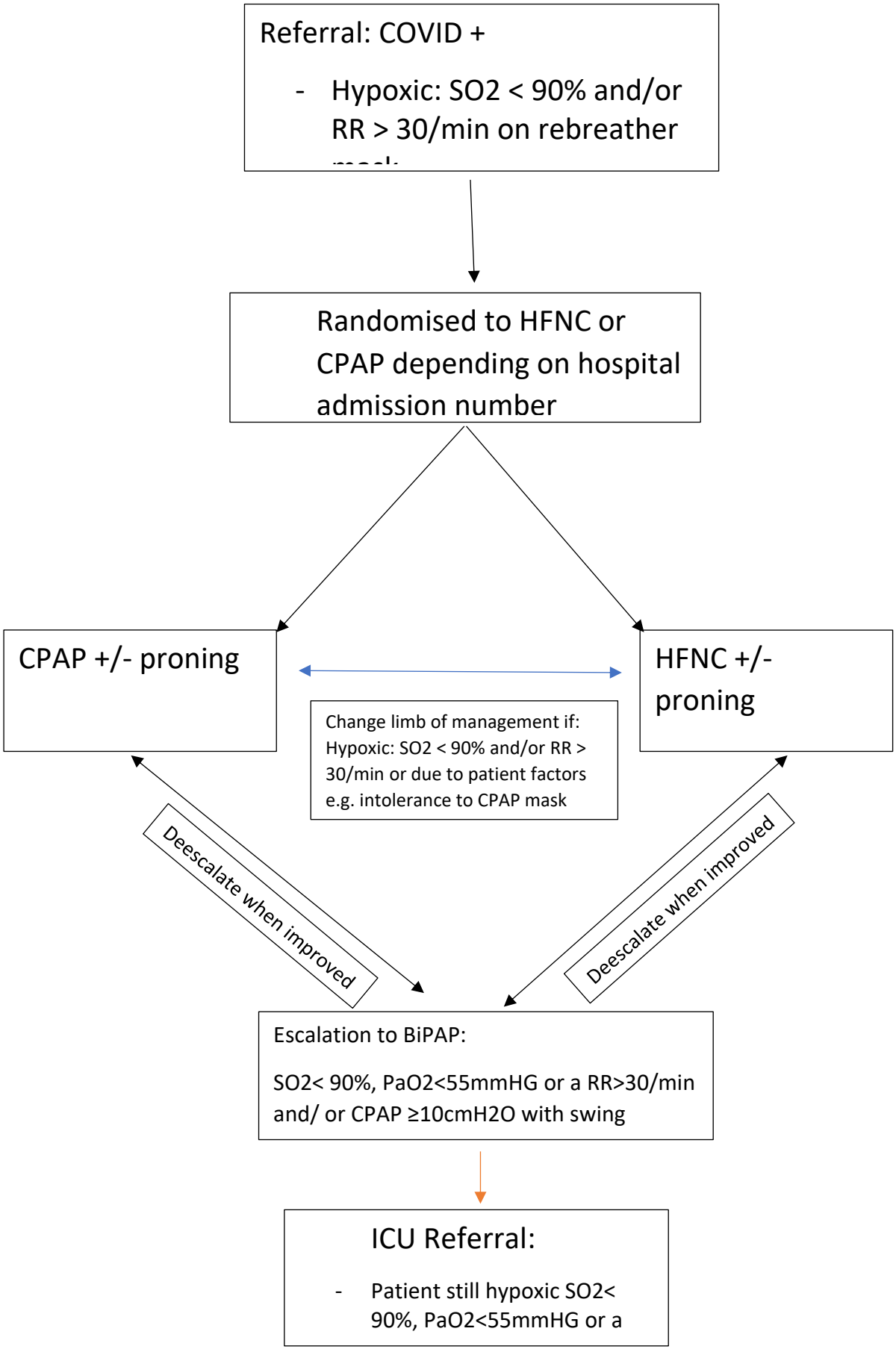

Figure 4: Algorithm for oxygen use

3.5 Research team

Project leader

Dr. Shaaista Cassim

Cardiothoracic surgery registrar

Department of cardiothoracic surgery

University of the Free State (UFS)

Supervisor

Prof Francis Smit

MMed Cardiothoracic Surgery

Head of Department of Cardiothoracic Surgery

University of the Free State (UFS)

Co-supervisor

Mr. HA Hanekom

MMedSc

Scientist: Cardiothoracic Surgery

University of the Free State

3.6 Withdrawal criteria & premature discontinuation of study

The study will be discontinued prematurely if the researcher or any of the study leaders feels that a patient's confidentiality might be breached or if any unethical procedures occur.

3.7 Project safety and Patient's safety

This study is deemed very safe with no risks to any patients as it will be a retrospective observational study that only analyses data of patients that have been captured.

3.8 Financial implications to the patient

There will be no financial implications to the patient.

3.9 Good Clinical Practice (GCP) / Quality Assurance

The researchers will adhere to the guidelines of the South African Good Clinical Practice principles.

3.10 Ethical aspects / clearance

The study will commence as soon as the ethical clearance from HSREC is obtained.

3.11 Special investigations

3.11.1 Demographical Data

- Age (years)
- Gender (male/female)
- Ethnicity (Caucasian/Black/Coloured/Indian)

3.12 Statistical analysis

The data will be captured electronically by the researcher onto the data sheet (Appendix F). The captured data will be analysed by a statistician utilizing appropriate statistical methods. Where applicable, continuous variables will be summarized descriptively, and frequencies will be subjected to a Chi2 or Fisher's exact test. The latter will be used should any of the cell counts be less than 5.

3.13 Confidentiality

Personal details of every patient participating in this study will be kept strictly confidential. At no time during the research may any of the patients' identification be made known to any other people other than the researchers. The data sheet will not contain the names or surnames of the patients, only the unique hospital number. The information in the datasheet will only be accessible to the researcher.

3.14 Contact details of the researchers

Department Cardiothoracic Surgery

- Principle investigator (PI)
    - Dr. Shaaista Cassim (MBChB)

- 0849786110
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- Co supervisor

  - Mr HA Hanekom (MMedSc)
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4. BUDGET

ITEM	AMOUNT
Publication fees	ZAR 5000 (depending on journal, fee estimated from publication in Cardiovascular Journal of Africa)
Statistician	ZAR 4000
Language editing	ZAR 4000
Total	**R 13 000**

The cost of the project above will be financed by the Department of Cardiothoracic Surgery.

5. TIMELINE

TASK	TIMEFRAME
Develop protocol	January - March 2021
Submission to HSREC Committee	March 2021
Modifications required by HSREC	April 2021
Approval by Department of Health	May 2021
Data gathering	May 2021-June 2021
Statistical analysis	July 2021
Publication of articles	August 2021

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[Cited 2 October 2020] available from: https://www.nicd.ac.za/diseases-a-z-index/COVID-19/surveillance-reports/

Appendix E - Forms for collecting data - e.g. questionnaire/data capture instrument(s)

Below is a screenshot of all the fields collected from the patients.

Patient UM Number	cpap on admin	HF on admin	cs to cpap	cs to hf	cpap bipap
hf bipap	no cs	icu	Swing Initiation	Swing escalation	cpap begin
end	age	race	gender	obese (Y/N)	hypertensive
ADMISSION GLUCOSE	CRP	Ferretin	D-dimer	pro-BNP	AST
Albumin	White cell count	length of stay	mortality (Y/N)	escalation to ICU	Aa
APACHE	ROX Index	RR	other	SaO2	co2

Appendix F - Instructions to authors of the named peer reviewed journal

SA HEART IS AN OFFICIAL JOURNAL OF THE SOUTH AFRICAN HEART ASSOCIATION AND APPEARS ON A QUARTERLY BASIS

Instructions for authors

SA Heart publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart may be reproduced without written permission. Permission may be sought from the Editor (Email: afd@sun.ac.za).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and the South African MRC ethics guidelines (http://www.sahealthinfo.org/ethics/index.htm). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.[10]

The following format should be used for references:

Articles
Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.)

Chapter in a book
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media
Norback JS, Llwellyn DC and Hardin JR (2001). Shoptalk 101. Integrating workplace communication into undergraduate engineering curricula [online]. Retrieved February 15, 2012: http://www.lionhrtpub.com/orms/orms-8-01/norback.html.

9. Articles are to be submitted by email. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.

Submission of manuscripts

Please submit the manuscript to the Editor (afd@sun.ac.za) and copy it to the Guest Editor (if applicable) and the secretary of the South African Heart Association (erika@saheart.org).

Appendix G - A summary report compiled in the Turnitin Plagiarism Search Engine (compulsory)

Chapter 1 – Literature review

chapter 1 13.08.23.docx

by Shaaista Cassim

Submission date: 13-Aug-2023 05:27PM (UTC+0200)
Submission ID: 2145144756
File name: chapter_1_13.08.23.docx (276.46K)
Word count: 3789
Character count: 20711

chapter 1 13.08.23.docx

ORIGINALITY REPORT

9%	5%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)

2%

★ www.researchgate.net

Internet Source

Exclude quotes	On	Exclude matches	< 8 words
Exclude bibliography	On		

Chapter 2 – Publishable article

Chapter 2 26.08.23.docx

by Shaaista Cassim

Submission date: 25-Aug-2023 06:25PM (UTC+0200)
Submission ID: 2151256542
File name: Chapter_2_26.08.23.docx (944.64K)
Word count: 3643
Character count: 20033

Chapter 2 26.08.23.docx

ORIGINALITY REPORT

6%	3%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Denise Battaglini, Chiara Robba, Lorenzo Ball, Pedro L. Silva, Fernanda F. Cruz, Paolo Pelosi, Patricia R.M. Rocco. "Noninvasive respiratory support and patient self-inflicted lung injury in COVID-19: a narrative review", British Journal of Anaesthesia, 2021 Publication	1%
2	www.thelancet.com Internet Source	1%
3	"Clinical Synopsis of COVID-19", Springer Science and Business Media LLC, 2020 Publication	1%
4	"Sunday, 31 August 2008", European Heart Journal, 09/02/2008 Publication	1%
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10	Vestbo, J.. "The value of mucus hypersecretion as a predictor of mortality and hospitalization. An 11-year register based follow-up study of a random population sample of 876 men", Respiratory Medicine, 198905 Publication	<1%
11	oro.open.ac.uk Internet Source	<1%
12	www.medrxiv.org Internet Source	<1%

Exclude quotes	On	Exclude matches	< 10 words
Exclude bibliography	On		

Appendix H - Proof of word count for Chapter 1 and Chapter 2 separately (including tables and figures but excluding references)