UNIVERSITY OF NAIROBI. FACULTY OF HEALTH SCIENCES

DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

CLINICAL CHARACTERISTICS AND OUTCOMES OF COVID 19 PNEUMONIA PATIENTS ON HIGH FLOW OXYGEN DELIVERY SYSTEMS IN NAIROBI: A RETROSPECTIVE STUDY

BY

DERRICK NYAGA MUTIGA

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE.

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DECLARATION

I, Dr. Derrick N. Mutiga, declare that this is my original work and that to the best of my knowledge it has not been presented before for a degree or any other academic award at this or any other university.

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ABBREVIATIONS AND ACRONYMS

ACE2	-	Angiotensin converting enzyme 2
AKI	-	Acute kidney injury
ALT	-	Alanine transaminase
ARDS	-	Acute respiratory distress syndrome
AST	-	Aspartate transaminase
BGA	-	Blood gas analysis
CT	-	Computed tomography
COPD	-	Chronic obstructive pulmonary disease
CPAP	-	Continuous Positive Airway Pressure
CRP	-	C-Reactive protein
CVA	-	Cerebrovascular accident
DKA	-	Diabetic ketoacidosis
DM	-	Diabetes mellitus
DRC	-	Democratic republic of Congo
FiO2	-	Fraction of inspired oxygen
GGO	-	Ground glass opacification
HDU	-	High dependency unit
HFNC	-	High flow nasal cannula
HFOS	-	High flow oxygen systems

HIV	-	Human immunodeficiency virus
HRCT	-	High resolution computed tomography
IBW	-	Ideal body weight
ICU	-	Intensive care unit
JAK	-	Janus Kinase
LFT	-	Liver function tests
LMIC	-	Low middle income country
LOS	-	Length of stay
NIV	-	Non-invasive ventilation
PCT	-	Procalcitonin
PI	-	Principal Investigator
PO2/FIO2	-	Partial pressure of arterial oxygen to fraction of inspired oxygen ratio
qSOFA	-	Quick Sequential Organ Failure Assessment
RNA	-	Ribonucleic acid
ROX	-	Respiratory oxygenation index
RT-PCR	-	Reverse transcription polymerase chain reaction
SARS-CoV2	-	Severe acute respiratory syndrome coronavirus 2
SOFA	-	Sequential Organ Failure Assessment
SPSS	-	Statistical Package for Social Sciences
TMPRSS2	-	Type 2 Transmembrane serine protease
TB	-	Tuberculosis

UEC	-	Urea electrolytes creatinine
UGIB	-	Upper gastrointestinal bleeding
UN	-	United Nations
USA	-	United States of America
WBC	-	White blood count

ABSTRACT

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) is a novel virus that has caused a global pandemic leading to increased hospitalization and increased need for critical care and mechanical ventilation. As at 16th January 2023 more than 342,000 cases and more than 5,600 deaths were reported in Kenya. There is limited research and data on clinical characteristics and outcomes of patients with COVID-19 requiring mechanical ventilation and those on High Flow Nasal Cannula (HFNC).

Objectives: The broad objective was to describe the clinical characteristics and outcomes of critical COVID 19 pneumonia patients requiring high flow oxygen delivery system admitted in the critical care unit of Avenue hospital Parklands COVID isolation unit between 01 April 2020 and 01 April 2022

Materials and methods: This was a retrospective cohort study among SARS-CoV2 confirmed patients requiring high flow oxygen delivery systems. The study area was Avenue Hospital Parklands records department. Categorical data was summarized as frequencies and percentages while Continuous data was described as medians.

Results: A total of 131 patients' records were included in this study. Male patients were 66% and median age was 57 years. Hypertension (52%) and diabetes (44%) were the commonest co-morbidities. Key laboratory and chest imaging findings included reduced PO2/FIO2 ratio (100%), elevated C-reactive protein (99%), lymphopenia (75%), elevated D-dimers levels (74%), elevated aspartate transaminase (63%) and high CT severity scores (100%).The median duration from onset of symptoms and initiation of mechanical ventilation was 7 days. All patients received steroids and prophylactic low molecular weight heparin. Other medications used included remdesivir (61%), tocilizumab (57%) and baricitinib (44%). All patients were put on mechanical ventilation with majority being put on non-invasive ventilation (NIV) (81%). The median length of ICU stay was 6 days and longer stay was associated with increased complications arising from COVID-19 disease and some of the intervention used for treatment. The overall mortality of patients with critical COVID-19 pneumonia was 50%

Conclusion: Critical COVID-19 disease was more prevalent in male, older patients with associated pre-existing condition and mortality in critical COVID-19 disease was high (50%).

CHAPTER ONE: INTRODUCTION

SARS-Cov-2 was identified to cause pneumonia at the end of 2019, starting from China before spreading to cause a global pandemic. Reported cases globally are more than 662 million with deaths exceeding 6.7 million as at 16th January 2023 (1) In Kenya since the pandemic started we have had more than 342,000 cases and more than 5,600 deaths reported as at 11th January 2023(2). The first case being reported on March 13, 2020. SARS-CoV-2 causes COVID 19 pneumonia which has a range of clinical features:

- Asymptomatic-patients who test positive but have no symptoms of COVID-19(3)
- Mild COVID-19 illness- patients who have several symptoms of covid-19 but do not develop difficulty in breathing or abnormal imaging(3)
- Moderate COVID-19 illness-patients with evidence of a lower respiratory tract infection on examination and imaging but have oxygen saturation above 94% on room air(3)
- Severe COVID-19 illness- patients who are saturating below 94% on room air, pao2/fio2 ratio less than 300, respiratory rate more than 30/min or lung infiltrates more than 50% on imaging(3)
- Critical COVID-19 illness- patients with acute thrombosis, multiple organ dysfunction, sepsis/septic shock, and respiratory failure (3)(4)

COVID 19 pneumonia has led to increased cases of acute respiratory distress syndrome (ARDS), subsequently causing increased need for mechanical ventilation and ICU care(5). Studies showed that up to 29% of hospitalized patients developed ARDS(5) with ICU admissions ranging from 7-26% of those admitted(5–8). It is estimated that the overall case fatality rate is 2.3%(9)(3). In ICU the mortality and morbidity is increased with mortality ranging from 26%-48.2%(6,10–14). In Kenya Ombajo et.al demonstrated in her study a 43% mortality in patients admitted to the ICU(8). In resource limited settings the case fatality in admitted patients was higher with rates as high as 60.4%. This being attributed to comorbidities and scarcity of resources (14) as demonstrated by the African COVID 19 Critical Care Outcomes Study (ACCOS) (14). Several risk factors have been associated with more severe forms of disease including:

- Advancing age- case fatality increases with age with a rate of 8% and 15% in patients aged between 70-79 years and 80 years respectively(9)
- Comorbidities such as chronic obstructive pulmonary disease, diabetes, cardiovascular disease, hypertension, obesity and cancer(15)
- Laboratory abnormalities such as lymphopenia, low platelet counts, elevated inflammatory markers such as C-Reactive Protein(CRP), elevated liver enzymes and acute kidney injury(16)

SARS-CoV-2 is a new virus that has caused a global pandemic, there is a paucity of data in Africa and more so in Kenya especially for patients with critical disease and admitted in critical care units. Lack of local data may be detrimental both in the current pandemic and in future in case of similar pandemics.

We aim to document the clinical characteristics and outcomes of COVID 19 pneumonia patients admitted at the Avenue hospital Parklands critical care COVID 19 isolation unit requiring high flow oxygen delivery systems.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology

Reported cases globally are more than 662 million with deaths exceeding 6.7 million as of 16th January 2022(1). In Kenya since the pandemic started we have had more than 342,000 cases and more than 5600 deaths reported as of 11th January 2022(2). A review of several studies shows similar patient characteristics in the African setup compared to other regions like America and Asia with more males being affected and patients with severe and critical disease being older and having associated comorbidities such as hypertension and diabetes. There are conflicting results of patients with Human Immunodeficiency Virus (HIV)/COVID 19 pneumonia co-infection with some studies showing no differences between those with HIV and those without while other studies show increased mortality in people living with HIV (17–19).

COVID-19 pneumonia has been associated with higher ICU mortality(40%) compared to other viral pneumonias(22%)(10) although the mortality in patients with critical disease in Africa was

higher compared to the rest of the world and this was postulated to be due to scarcity of resources and inadequacy of critical care beds(14).

In a multicenter cohort study done in Kenya by Ombajo et.al at 6 hospitals between March and September 2020 a total of 787 patients with COVID 19 were analyzed. The median age of patients was 43 years. Patients older than 60 years, those with comorbidities such as cardiovascular disease, diabetes mellitus (DM), renal insufficiency and males were associated with severe/critical disease and increased mortality(8). Shah R et.al did a single centre retrospective cohort study in a tertiary facility in Kenya and found that patients with COVID-19 had a high incidence of comorbidities and more male were affected(20). Similar results were found by an observational study done in 11 ICUs in Libya by M. Elhadi et.al which showed that patients with critical COVID-19 pneumonia were older (>60years), male and had a pre-existing condition.

In a prospective observational cohort study done in New York by Cummings et.al between March 2 and April 28, a total of 1150 patients were admitted with confirmed COVID 19 disease. Of the total, 257 (22%) were critically ill and majority of the critically ill patients were older (above 62 years), had at least one comorbidity and were male(21). Similarly in a systematic review and meta-analysis of observational studies on ICU mortality of adults admitted with COVID 19 up to 31st march 2020 done by Armstrong et.al the mortality rate was found to be 41.6% among international studies(10), further demonstrating increased mortality in patients with critical COVID-19 and patients with pre-existing comorbidities.

In a case series report summarized by WU et.al in February 2020 in China among a total of 72,314 cases, 44,672(62%) had a positive viral nucleic acid test and 2087(5%) had critical disease with a case fatality rate of 49% among the critically ill.(9) Patients with preexisting medical conditions such as hypertension, diabetes, chronic respiratory diseases, cardiovascular disease and cancers and older patients had increased fatality rate.

Patients with COVID 19 pneumonia presenting with certain clinical characteristics such as older age, male sex, comorbidities, and certain laboratory parameters such as lymphopenia, elevated aminotransferases and elevated inflammatory markers have been demonstrated to have increased risk of developing severe and critical disease. Patient with critical disease secondary to COVID

19 pneumonia have increased risk of mortality and increased length of ICU stay compared to other viral pneumonias. This has been demonstrated in many studies worldwide, there are limited studies conducted on the characteristics and outcomes in critical COVID 19 pneumonia in Kenya and it is important to study this cohort of patients.

2.2 Clinical presentation and complications

COVID-19 disease can present without any symptoms, in a meta-analysis of 95 studies up to 40.5% of patients confirmed to have COVID-19 disease were asymptomatic(22). The spectrum of symptomatic infection ranged from mild to critical disease. A survey from the Chinese CDC demonstrated that presentation varied from mild disease(81%), severe disease(14%) and critical disease(5%)(23) with the common symptoms including: cough, fever, difficulty in breathing, muscle pains, headache, fevers, loss of taste and smell, vomiting, diarrhea, confusion and fatigue(24).

A case surveillance carried out by the Center for Disease Control and Prevention (CDC) among confirmed COVID-19 patients between January 22 and May 30, 2020 showed that the commonest symptoms included fever, cough and shortness of breath which affected up to 70% of the patients, muscle aches which affected 36% of patients, headaches which affected 34% of patients and loss of smell and taste which affected 8% of patients. A systematic review and meta-analysis done by Tong.et.al demonstrated that olfactory and gustatory dysfunction was higher with 52% and 43% of patients being affected respectively(25). Some of the patients with initially non-severe disease may progress over the course of one week and develop acute complications.

Acute complications of COVID 19 disease included respiratory complications such as ARDS with some studies showing that up to 20% of patients developed ARDS(26) and as high as 12-23% of the patients ended up requiring mechanical ventilation subsequently(15,27). Cardiac/cardiovascular complications included arrhythmias, myocardial injury, myocarditis, heart failure and shock possibly due to hypoxic injury and ischemic injury caused by microvascular dysfunction and small vessel vasculitis(28).

Thrombotic complications such as deep venous thrombosis and pulmonary embolism were noted

particularly in patients admitted in the ICU with some studies showing between 10-40% developing either(29). Similarly arterial thrombotic events such as acute stroke and limb gangrene were noted as a result of a hypercoagulable state due to the thromboinflammation caused by SARS-COV-2 virus(30).

Neurological complications such as encephalopathy was noted particularly in patients admitted to ICU, seizures, ataxia, motor and sensory deficits and movement disorders occurred though less frequently(31). Intense inflammatory response marked by persistent fever and elevated inflammatory markers was noted in some patients, rarely this could progress to a Kawasaki-like disease characterized by multiple organ dysfunction called Multisystemic inflammatory syndrome in adults(32).

Secondary infections from bacteria and fungi was seen. Bacterial co-infections was noted in 19% and bacterial superinfection seen in 20% of patients(32). Renal complications was noted in patients with COVID-19 disease, in a meta-analysis by Sheliaf et.al upto 17% of patients developed acute kidney injury with 5% of them progressing to requiring kidney replacement therapy(33)

2.3 Severity grading

The spectrum of symptomatic COVID-19 infection can range from mild to critical disease.

- Mild COVID-19 illness- patients who have several symptoms of covid-19 but do not develop difficulty in breathing or abnormal imaging(3)
- Moderate COVID-19 illness-patients with evidence of a lower respiratory tract infection on examination and imaging but have oxygen saturation above 94% on room air(3)
- Severe COVID-19 illness- patients who are saturating below 94% on room air, pao2/fio2 ratio less than 300, respiratory rate more than 30/min or lung infiltrates more than 50% on imaging(3)
- Critical COVID-19 illness- patients with acute thrombosis, multiple organ dysfunction, sepsis/septic shock, and respiratory failure (3)(4)

2.4 Risk factors for severe and critical disease

Several factors have been associated with severe and critical disease such as older age. Severe/critical COVID 19 has been reported in patients above 60 years of age(6,8,13,34) similarly mortality has been noted to increase with age with studies showing mortality of 8% and 15% in patients aged 70-79 and above 80 years respectively despite a case fatality rate of 2.3% for the whole population(9). Male patients were noted to develop more severe COVID 19 disease and had higher mortality compared to females(13).

Comorbidities such as hypertension, diabetes, obesity, malignancy, heart failure, chronic kidney disease have been associated with more severe forms of COVID 19 and higher mortalities(12–14). Physical inactivity, defined as people participating less than 150 minutes per week in physical activity was associated with higher rates of hospitalization, mechanical ventilation and death(39).

Lab parameters such as lymphopenia, thrombocytopenia, deranged liver functional tests, acute kidney injury, elevated d-dimers, elevated C-reactive Protein (CRP), elevated lactate dehydrogenase and elevated troponins were associated with worse outcomes in COVID 19 disease(16).

Viral factors such as high viral ribonucleic acid (RNA) levels in the respiratory specimen and detection of viral RNA in blood was associated with severe disease(40). Different SARS-CoV-2 variants were associated with varying risk of severe disease, with Delta variant being more transmissible and associated with higher risk of severe disease and hospitalization compared to other variants such as Omicron which was associated with milder disease(41). Genetic factors such as polymorphisms in genes encoding ABO blood group was associated with severity of COVID-19 with blood group type A being associated with increased risk for severe disease while type O was associated with lower risk for severe disease(42).

2.5 Laboratory features

Patients confirmed to have SARS-CoV-2 infection via a RT-PCR have associated laboratory findings which include: lymphopenia, thrombocytopenia, elevated inflammatory markers (CRP, ESR and ferritin) and elevated inflammatory cytokines (Interleukin-6 and tumor necrosis factor),

elevated lactate dehydrogenase, elevated D-dimers levels, elevated prothrombin time, elevated transaminases and deranged kidney function tests (elevated creatinine)(43)

Particular laboratory findings have been associated with worse outcomes and these include D-dimers>1000ng/ml, CRP>100mg/l, lymphocytes<800/microL, lactate dehydrogenase> 245units/L, ferritin>500mcg/L, troponins>2 times upper limit of normal and creatine phosphokinase>2 times upper limit of normal(43).

2.6 Radiological features

The commonest radiographic changes in COVID-19 pneumonia as demonstrated by CT chest included ground glass opacification (GGO) with or without consolidative abnormalities, a systematic review and meta-analysis performed by Cuiping et.al demonstrated that 83% of cases had bilateral GGO, 58% had GGO with mixed consolidation, 52% had pleural thickening, 48% had interlobar septal thickening and 46% had air bronchograms. Pleural effusion, pericardial effusion, bronchiectasis and lymphadenopathy were uncommon(44). These findings are similar to local data, a study done by Ombajo et.al demonstrated that the common radiological changes in severely ill patients included presence of GGO (72%)(8).

The CT involvement can be graded using a severity score. CT severity score is a score that assesses severity of lung involvement/injury by summing up the individual lobar involvement of the 5 lung lobes. The total sum can range from 0 (no involvement) to 25 (maximal involvement) when all 5 lobes show more than 75% involvement and it is categorized as scores less than 7 are mild, scores between 7-18 are moderate and scores greater than 18 are severe. It is an indicator of lung injury and studies demonstrated that patients with higher CT severity scores (score >18) had higher oxygen requirements including delivery by high flow nasal cannulas and mechanical ventilation and that higher scores were also associated with higher mortalities(45)

2.7 Treatment

The treatment for COVID-19 patients admitted to hospital can be both pharmacological and non-pharmacological. The Kenyan treatment guidelines recommend use of JAK 1 and 2 selective inhibitors such as baricitib in severe disease with progression and increasing inflammatory markers despite use of steroids or when steroid use is contraindicated. Remdesivir is also

recommended in severe COVID 19 disease but not critical disease and should be initiated within 10 days on onset of symptoms.

All patients admitted with severe/critical disease require to be initiated on corticosteroids, dexamethasone 6mg once a day for 10 days is the preferred drug and when unavailable prednisone 40mg or methylprednisolone 32mg once a day can be used as alternatives similarly venous thromboembolism prophylaxis is advocated for all patients admitted with COVID-19 disease and one can use low molecular heparin or unfractionated heparin. For patients with contraindications for use of heparin, mechanical thromboprophylaxis can be used(46).

Patients with severe/critical disease should undergo proning for a duration lasting between 12-16 hours as tolerated by the patient provided there are no contraindications(46). Prone ventilation refers to the delivery of mechanical ventilation with the patient lying in prone position. It alters the mechanics and physiology of gas exchange to result consistently in improved ventilation and may improve mortality in a select population of patients with severe ARDS(47).

As per the Kenyan treatment guidelines all patients with oxygen saturation below 94% should be initiated on oxygen theratpy with a target saturation of above 94%. HFNC is considered in patient requiring more than 90% of fractional inspired oxygen (FiO2) to maintain saturation above 90% and whose PO2/FiO2 ratio is more than 150mmHg. For patients requiring FiO2 higher than 80% on HFNC and their Respiratory Oxygenation Index (ROX) is more than 4 we prefer initiating them on Non-invasive ventilation (NIV) with pressures ranging between 10-15mgHg and maximum tidal volumes of 9ml/kg Ideal body weight (IBW).Patients who presents with PO2/FiO2 ratio less than 150mmHg and a ROX less than 3.8 should be intubated and ventilated using lung protective ventilation strategy for ARDS with emphasis on low tidal volumes of 4-6ml/kg, high Positive End Expiratory Pressure (PEEP) as per the ARDSNet ventilator strategy and avoiding high plateau pressure exceeding 30cmH2O(48)(49). Spontaneous/iatrogenic pneumothorax/pneumomediastinum have made acceptable PEEP to be no more than 12cmH2O in our practice.

There are no clear guidelines on the type and mode of ventilation to be used, some studies show favorable outcomes in patients who were initiated early on NIV and HFNC in terms of days free of respiratory support at 28 days and reduced incidences of intubation(50,51).

2.8 Outcomes

Mortality among ICU admitted COVID 19 patients ranged from 14% to 85.2% with reports showing mortality of 14%(8), 26%(13), 39%(21), 49%(9) and 60.4%(6).The mortality in patients with critical disease in Africa was higher compared to the rest of the world and this was postulated to be due to scarcity of resources and inadequacy of critical care beds(14).

A systematic review by Rees et.al showed length of ICU stay was 8 days across china and 7 days outside china(52) similarly Elhadi et.al showed that in Libya the median length of ICU stay was 7 days(6).

CONCEPTUAL FRAMEWORK FOR THE STUDY

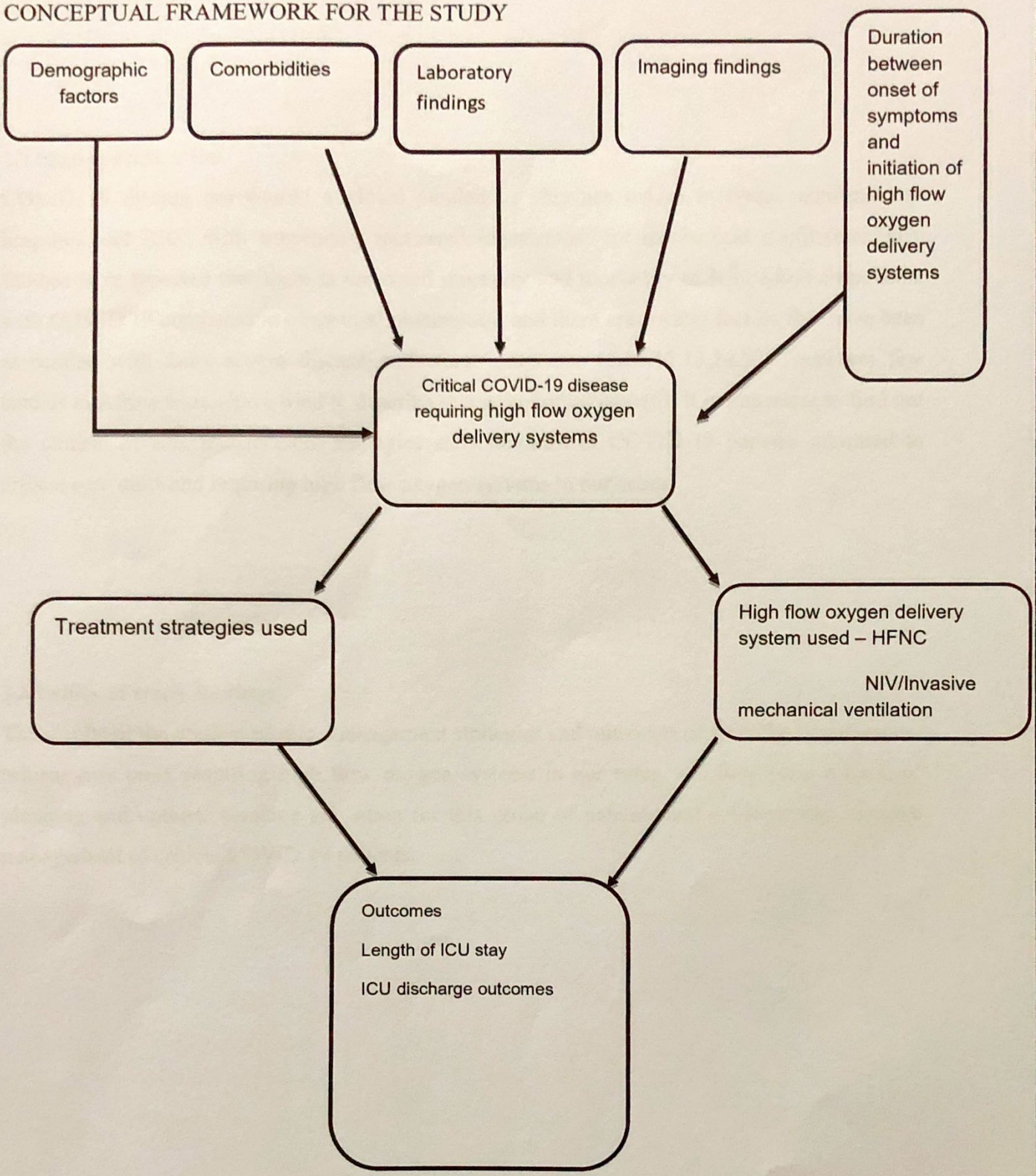


Figure 1 Conceptual framework: Clinical characteristics including: demographic characteristics, comorbidities, laboratory findings, imaging findings and duration between onset of symptoms and initiation of high flow oxygen delivery systems in patients with critical COVID-19 requiring high flow oxygen delivery systems and documented treatment strategies used, high flow oxygen delivery systems used and outcomes in the critical care unit

2.7 Study justification

COVID 19 disease has caused a global pandemic. This has led to increased admission to hospitals and ICU with subsequent increased requirement for mechanical ventilation(7)(6). Studies have reported that there is increased mortality and morbidity in ICU admitted patients with COVID 19 compared to other viral pneumonias and there are several factors that have been associated with more severe disease and worse outcomes (6,10,11,13,14,53).There are few studies in Africa which have tried to describe this group of patients(6). It is important to find out the clinical profile, management strategies and outcomes of COVID-19 patients admitted to critical care units and requiring high flow oxygen systems in our setup.

2.8 Utility of study findings

The results of the clinical profile, management strategies and outcomes of COVID-19 patients in critical care units requiring high flow oxygen systems in our setup will help form a basis of planning and optimal resource allocation for this group of patients and subsequently improve management of critical COVID 19 patients.

2.9 Study question

What are the clinical profile and outcomes of critically ill COVID 19 patients requiring high flow oxygen admitted at the Avenue Hospital Parklands COVID isolation unit between 01 April 2020 and 01 April 2022?

2.10 Study objectives

Broad objectives

1. To describe the clinical characteristics and outcomes of critical COVID 19 pneumonia patients requiring high flow oxygen admitted in the critical care unit of Avenue Hospital Parklands between 01 April 2020 and 01 April 2022.

Specific objectives

1. To document selected co-morbidities, laboratory findings and chest imaging results of patients with critical COVID-19 pneumonia requiring high flow oxygen on admission to critical care unit
2. To document the time interval between onset of symptoms and initiation of high flow oxygen
3. To describe treatment modalities given to patients with critical COVID-19 pneumonia requiring high flow oxygen
4. To describe the ICU discharge outcomes and length of ICU stay of patients with critical COVID-19 pneumonia requiring high flow oxygen

CHAPTER THREE: METHODOLOGY

3.1 Study Design

Retrospective cohort study

3.2 Study Site

Avenue Hospital Parklands

Avenue Hospital Parklands is a private hospital located in the Parklands area in Nairobi County, it has been key in COVID 19 care for both local and regional patients. The management of the COVID-19 patients in the hospital is in conformity to the National COVID-19 case management guidelines published by the Ministry of Health – Kenya.

Avenue Hospital Parklands is a 140-bed facility containing 7 ICU beds and 17 High Dependency Unit (HDU) beds and caters for both local patients and international patients from the neighboring countries. During the COVID-19 pandemic, a COVID unit was created that had a capacity of 17 critical care beds.

3.3 Study Population

Records of RT-PCR SARS-CoV2 confirmed patients with critical COVID-19 pneumonia requiring high flow oxygen admitted to Avenue Hospital Parklands isolation unit between 01 April 2020 and 01 April 2022

3.3.1 Case definition

The study case definition included:

- Patient with COVID 19 pneumonia confirmed by RT-PCR.
- Critical COVID-19 disease included those with respiratory failure, sepsis/septic shock, multiple organ dysfunction or acute thrombosis requiring high flow oxygen. High flow

oxygen included mechanical ventilation (both noninvasive ventilation and invasive ventilation) and oxygen delivery using high flow nasal cannula (HFNC)

- Selected documented co-morbidities included hypertension, diabetes mellitus, obesity, asthma, COPD, CKD and HIV and were defined as: documented pre-existing comorbidities of interest, records showing patients on treatment for comorbidities of interest or records showing patients meeting guidelines for diagnosis of comorbidities of interest.
- Selected documented laboratory results on admission to the critical care unit for patients with critical disease included PO2/FiO2 ratio, lymphocyte counts, platelet counts, C - reactive protein (CRP), D-dimers, creatinine, and aspartate aminotransferase.
- Selected documented computerized tomography (CT) scan findings on admission to the critical care unit included CT severity score of the patient. CT severity score is a score that assesses severity of lung involvement/injury by summing up the individual lobar involvement of the 5 lung lobes. The total sum can range from 0 (no involvement) to 25 (maximal involvement) when all 5 lobes show more than 75% involvement.
- Documented time interval between onset of symptoms and initiation of high flow oxygen in the critical care unit
- Documented treatment strategies used included standard of care COVID 19 medications: steroids (dexamethasone, prednisolone, or methylprednisolone), tocilizumab, baricitinib, remdesivir, low molecular weight enoxaparin and proning. Oxygen delivery systems used: high flow nasal cannula, noninvasive ventilation, and invasive ventilation.
- Documented outcomes from the critical care unit include dead or alive, duration of ICU stay and complications.

3.3.2 Inclusion Criteria

The cases included in the study met the following criteria:

- Age 18 years and above
- RT-PCR confirmed SARS-CoV2 infection.
- Admission to Avenue Hospital Parklands critical care isolation unit

- Critical COVID-19 disease requiring HFNC.
- Critical COVID-19 disease requiring mechanical ventilation (non-invasive and invasive)

3.3.3 Exclusion Criteria

Cases not meeting the inclusion criteria in the following were excluded from the study:

- RT-PCR confirmed SARS-CoV2 patients on mechanical ventilation and HFNC due to other causes other than COVID 19 pneumonia e.g., traumatic brain injury.

3.4 Sample Size Determination

COVID 19 patients hospitalized to Avenue Hospital Parklands between 01 April 2020 and 01 April 2022 made up the research population. The sample size was calculated using Fisher et al (1998). The 60-day death rate of 60.4 percent was used in the study, which comes from M. Elhadi et al: Epidemiology, prognosis, and utilization of intensive care unit resources for critically ill COVID-19 patients in Libya (6).

$$n = \frac{Z^2 p(1-p)}{d^2}$$

Where;

n=Desired sample size.

Z=95% Confidence level (1.96)

P=Proportion of the target population estimated to have characteristics being measured.

d=Degree of accuracy desired set at 0.05 margin of error

$$\frac{1.96^2 \times 0.604 \times (1 - 0.604)}{0.05^2} = 367$$

Factoring for finite population size

N= Population size

New sample size = $\frac{nN}{n+(N-1)}$

$$\frac{367 \times 165}{367 + (165 - 1)} = 114$$

The minimal number of our final sample size was **125** after allocating a 10% margin for errors in records and data collection, however we included all the records of the cases that met our inclusion criteria into the study.

3.5 Sampling Procedure

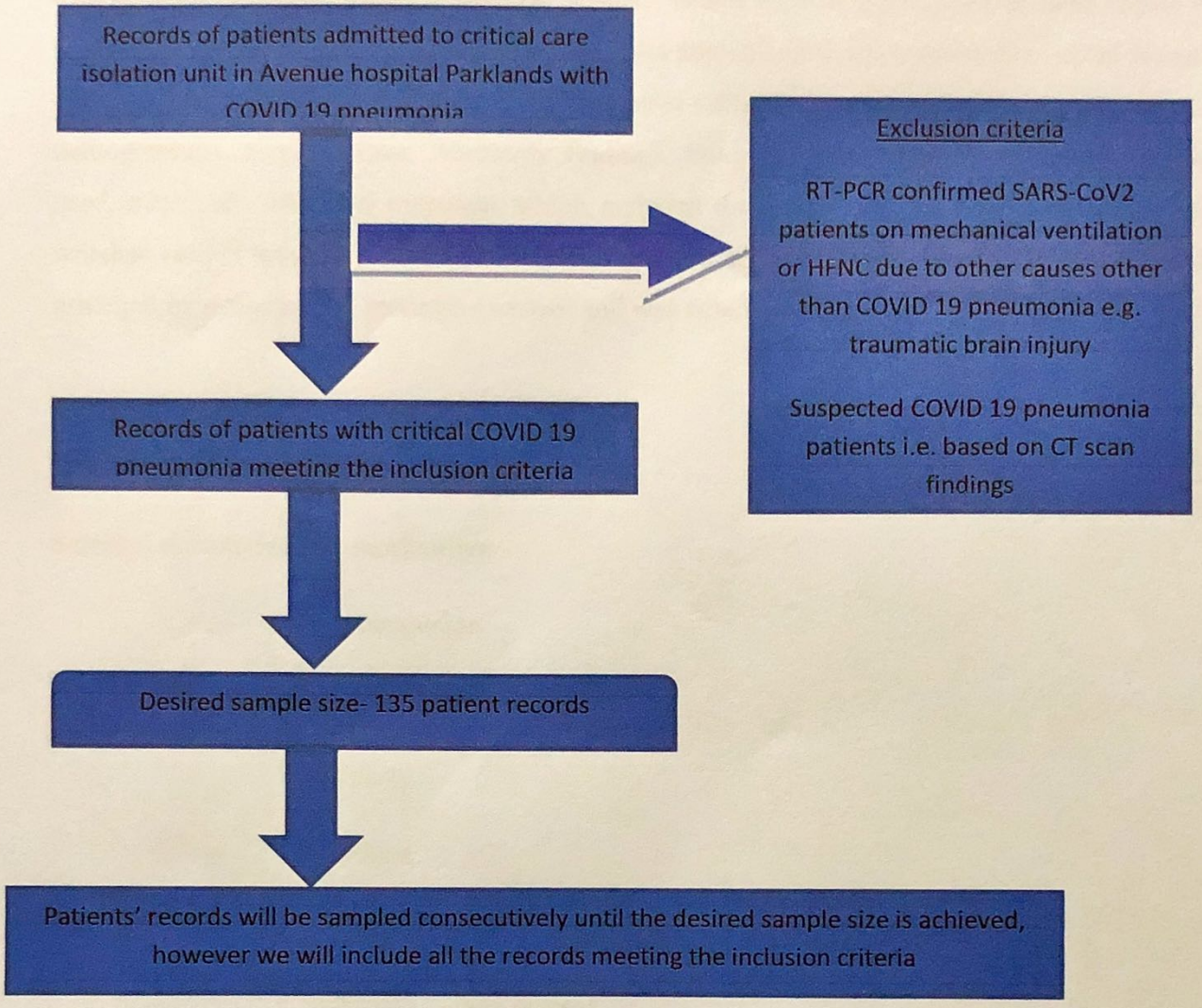


Figure 2 flowchart of sampling procedure

3.6 Recruitment

We identified and used medical records of patients meeting the inclusion criteria between 01 April 2020 and 01 April 2022 in Avenue hospital Parklands critical care isolation unit

3.7 Data Collection Procedures

The primary data was stored in Avenue hospital health records department as hard copies of patient records. Data was systematically identified and collected from patients' medical records that met the inclusion criteria using a detailed data collection tool. The tool captured patients' demographics, comorbidities, laboratory findings, imaging results, high flow oxygen system used, treatments used and outcomes which included duration of ICU stay, complications and whether patient was alive or dead on discharge from ICU. The tool was administered by the principal investigator and research assistant and was filled manually.

3.8 Study Variables

The study variables were:

Selected documented co-morbidities:

- Hypertension
- Diabetes mellitus
- Obesity
- Asthma
- COPD
- Chronic kidney disease
- Human immunodeficiency virus (HIV)

Selected documented laboratory findings:

- CRP (mg/ml)
- PO2/FIO2 ratio – Mild reduction (200-300)

  Moderate reduction (100-200)

  Severe reduction (<100)

- D-dimers (ng/ml) – Elevated (500-1000 ng/ml)

  Markedly elevated (> 1000ng/ml)

- Platelet counts (*10^9)
- lymphocytes count (*10^9)
- AST (u/l)
- Creatinine (umol/l)

Selected documented chest imaging results:

- CT severity score- Mild (< 7)

  Moderate (7-18)

  Severe (> 18)

Time interval between onset of symptoms and initiation of high flow oxygen delivery systems (days) – ≤6 days, 7-12 days, ≥13 days

Treatment modalities

- Standard of care COVID-19 medications- steroids, tocilizumab, remdesivir,baricitinib and low molecular weight heparin
- Proning
- High flow oxygen system
  - HFNC
  - NIV
  - Invasive ventilation

ICU discharge outcomes

- Alive or dead

- Length of ICU stay (days)
- Complications

3.9 Quality Assurance

A qualified nurse was the research assistant and helped identify and collect the required data. The Principal Investigator (PI) trained the research assistant on the inclusion criteria and required clinical information and how to fill the data collection forms for at least 1 week. The PI continued with supervision and training throughout the duration of the data collection process.

3.10 Ethical Consideration

Approval to conduct the study was sought from the Department of Clinical Medicine and Therapeutics, Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON ERC) and Avenue hospital Parklands management through the Hospital's Ethics and Research Committee (ERC)

Waiver of consent was sought from KNH/UON ERC

Data collection was done in the approved areas within Avenue hospital and patient records were not taken out of the hospital/approved areas of data collection.

The PI issued a unique study number that only the research assistant and PI recognized, therefore hospital unit numbers or patients' name were not used. All copies of the data collection forms were put under lock and key and were accessible only to the research assistant and PI. Softcopy data was stored in a computer with a password accessible only to the PI.

3.11 Data analysis and management

Data was extracted from the patients' records using the data extraction tool. The data was checked for completeness then entered, cleaned and analyzed using Statistical Package for Social Sciences (SPSS) version 26

Categorical data including gender, race and comorbidities was summarized as frequencies and percentages and presented as tables.

Continuous data such as age was analyzed using median and presented as a table, laboratory results and chest imaging results was analyzed as percentages and presented as tables.

The time interval between onset of symptoms and initiation of high flow oxygen systems was analyzed using median and presented as a table.

The treatment modalities used were analyzed as percentages and presented as tables.

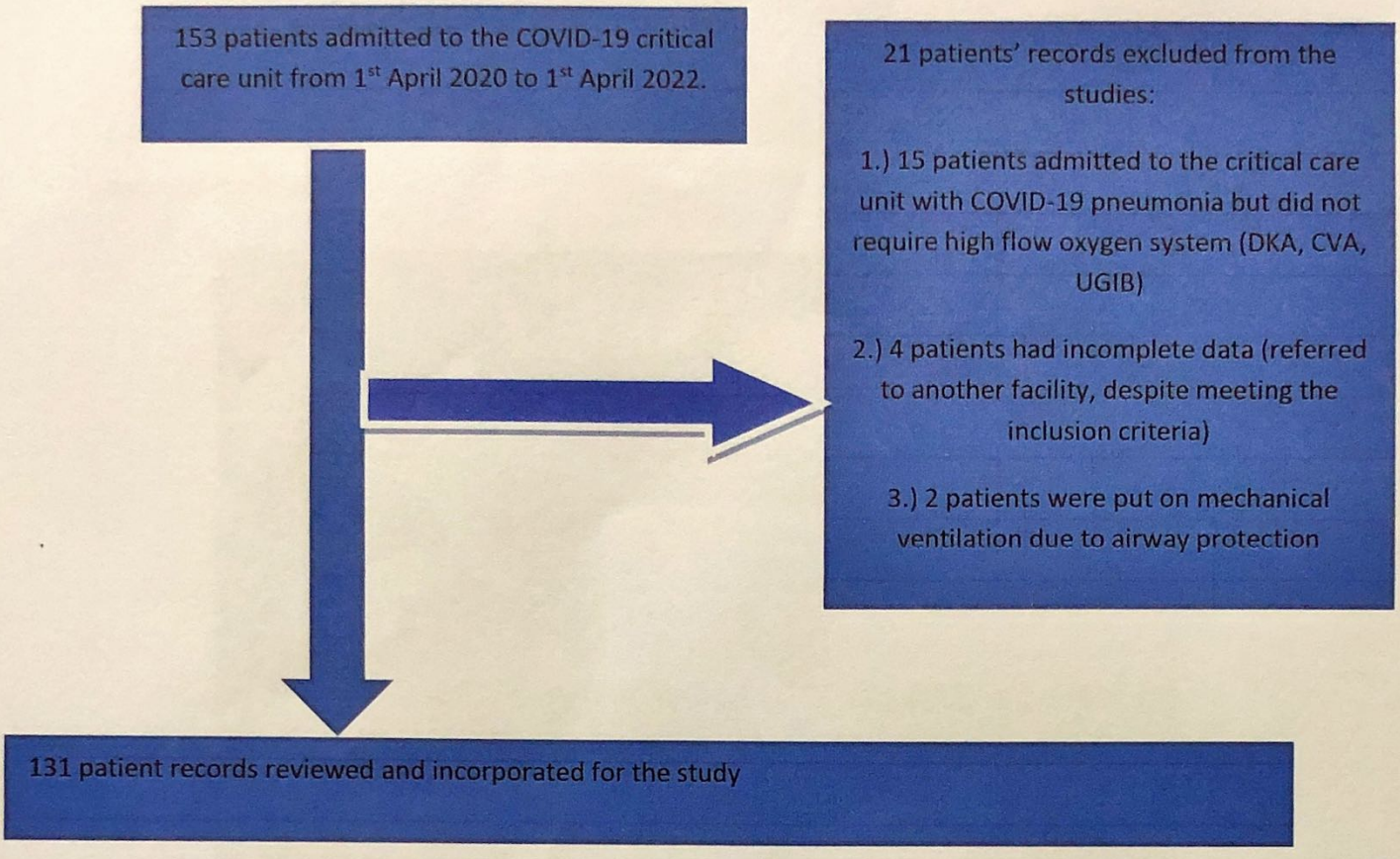
The ICU outcome was determined as death or discharge from the ICU and was presented as a percentage of the total studied participants. The length of ICU stay was presented as a median of the total length of ICU stay for the study participants.

CHAPTER FOUR: RESULTS

This retrospective study was undertaken between 01 April 2020 and 01 April 2022 and included records of patients admitted in Avenue hospital Parklands critical care isolation unit and diagnosed with COVID-19 pneumonia via RT-PCR and who required non-invasive or invasive mechanical ventilation.

A total of 153 records of patients were reviewed and of these 131 met the inclusion criteria while 21 were excluded as illustrated in figure 4 below.

Figure 3: A flow diagram of inclusion of records of patients with critical COVID-19 on mechanical ventilation admitted in Avenue hospital Parklana



4.1 Demographic Characteristics

Male patients accounted for 66% (87) of the study population. Most of the study population was African, accounting for 76% (100) the rest being Asian 24% (31).The median age of the patients was 57 years. Age was categorized as follows: 12% (16) were between 18-40 years, 40% (53) were between 40-60 years and 47% (62) were over 60 years old as illustrated in table 1 below.

Table 1: Demographics characteristics of patients admitted with critical COVID-19 in Avenue hospital Parklands

Demographic characteristic		**Total** N=131 (%)
Age Median (Min-Max)		**57 (27-95)**
Age	18-40	16(12%)
	40-60	53(40%)
	>=60	**62(47%)**
Sex	Male	**87(66%)**
	Female	44(34%)
Race	Black	**100(76%)**
	Asian	31(24%)

4.2 Co-morbidities

A total of 95 (73%) patients had a pre-existing condition, with the prevalence being as follows: hypertension and diabetes accounted for the bulk of the comorbidities at 52% (68) and 44% (57) respectively, obesity 13% (17), asthma 11% (14), CKD 7% (9), COPD 5% (6) and HIV 5% (6) as illustrated in table 2 below.

Table 2: Comorbidities of patients admitted with critical COVID-19 in Avenue hospital Parklands

Comorbidities	Total N=131 (%)
Any co-morbidity	**95 (73%)**
Hypertension	68(52%)
Diabetes mellitus	57(44%)
Obesity	17(13%)
Asthma	14(11%)
CKD	9(7%)
COPD	6(5%)
HIV	6(5%)

Comorbidities included were those documented in the patients' records/on treatment or patient meeting diagnostic criteria of a disease.

4.3 Laboratory and Chest Imaging Findings

Patients' laboratory results done on admission to the critical care unit were reviewed, all patients had a reduced PO2/FiO2 ratio with 53% (70) having a ratio below 100. Other laboratory abnormalities noted included: lymphopenia in 75% (98), elevated CRP in 99% (130), elevated AST in 63% (83) and elevated D-dimers in 74% (98). On chest CT imaging, majority of the patients had bilateral GGO (78%) and on the CT severity score was elevated in all patients with 85% (112) patients having score greater than or equal to 18 as illustrated in table 3 below.

Table 3: Laboratory findings and imaging findings of patients admitted with critical COVID-19 in Avenue hospital Parklands

Laboratory and Imaging findings		**Total** N=131 (%)
PO2/ FIO2 ratio	Severe (<100)	70(53%)
	Moderate (100-200)	53(40%)
	Mild (200-300)	8(6%)
CRP	Increased (> 5 mg/ml)	**130(99%)**
Lymphocyte	Reduced (<1.2*10^9)	**98(75%)**
D-dimers	Elevated (500-1000 ng/ml)	**15(11%)**
	Markedly Elevated (>1000ng/ml)	**83(63%)**
AST	Increased (>46 u/l)	**83(63%)**
Creatinine	Increased (>110 umol/l)	36(27%)
Platelets	Reduced (<150*10^9)	15(11%)
CT severity score	Moderate	19(15%)
	Severe (>18)	112(85%)

Laboratory findings on admission to the critical care unit were documented

4.4 Duration between onset of symptoms and initiation of HFOS

The duration between onset of symptoms and initiation of ventilation was reviewed and the median duration was 7 days. Patients were then distributed depending on the duration in days

between onset of symptoms and initiation of ventilation as follows: less than or equal to 6 days 28% (37), 7-12 days 67% (88) and greater than or equal to 13 days 5% (6) as demonstrated in table 4 below.

Table 4: Duration between onset of symptoms and initiation of mechanical ventilation in patients with critical COVID-19 admitted in Avenue hospital Parklands

Duration to initiation of ventilation (days)	**Total** N=131 (%)
Median duration (Min-Max)	**7 (3-21)**
≤6	37 (28%)
7-12	**88 (67%)**
≥13	6 (5%)

4.5 Treatment received

All patients reviewed received steroids with 57% (75) receiving methylprednisone and the rest receiving dexamethasone, 98% (129) of patients were on anticoagulation (prophylactic and some therapeutic) and the anticoagulation used was low molecular weight enoxaparin. Remdesivir was administered to 61% (80) patients, tocilizumab was administered to 57% (75) and baricitinib to 34 %(44) of the patients. None of the patients had prone positioning as demonstrated in table 5 below.

All patients included in the study were put on mechanical ventilation with majority 81% (106) put on non-invasive ventilation and the rest on invasive mechanical ventilation as demonstrated in table 6 below.

Table 5: Treatment administered to patients admitted with critical COVID-19 in Avenue hospital parklands

Treatment		Total N=131 (%)
Dexamethasone	Yes	56(43%)
Methylprednisolone	Yes	75(57%)
Prophylactic Low molecular weight heparin	Yes	114(87%)
Treatment dose low molecular weight heparin	Yes	16 (12%)
Remdesivir	Yes	80(61%)
Tocilizumab	Yes	75(57%)
Baricitinib	Yes	44(34%)
Proning	Yes	0

Documented treatment based on standard of care as per the Kenyan guidelines

Table 6: Critical COVID-19 Patients on mechanical ventilation admitted in Avenue hospital Parklands

Mechanical ventilation	**Total** N= 131 (%)
NIV	**106 (81%)**
Intubation	25 (19%)

4.6 Outcomes

The ICU discharge outcomes reviewed included discharge outcomes (dead or alive) and length of ICU stay. Of the patients admitted to the critical care unit 50 % (65) died as demonstrated in table 7 below and complications arising while in the critical care unit are demonstrated in table 8 below. The median length of ICU stay was 6 days, with majority of patients 55% (72) having a length of stay less than or equal to 6 days as demonstrated in table 9 below.

Table 7: Outcomes of patients admitted with critical COVID-19 in Avenue hospital Parklands

ICU discharge outcome	Frequency N=131	Percent (%)
Alive	66	50%
Dead	65	50%
Total	131	100%

Outcomes while in the critical care unit was documented

Table 8: Complications of patients admitted with critical COVID-19 in Avenue hospital Parklands

Complications	Frequency N=131	Percent (%)
AKI	39	30%
Venous thromboembolism	16	12%
Pneumothorax	10	8%
Post covid lung(fibrosis)	7	5%
Diabetes mellitus	5	4%

Complications documented while in the critical care unit

Table 9: Length of ICU stay in patients admitted with critical COVID-19 in Avenue hospital Parklands

Length of ICU stay (days)	Total
	N=131 (%)
Median Length of stay (Min-Max)	6 (2-40)
≤6	**72 (55%)**
7-12	40 (30%)
≥13	19 (15%)

Duration of stay in ICU was documented and represented as medians due to wide range in duration of stay

CHAPTER FIVE: DISCUSSION

This retrospective cohort single center study provides a summary of the clinical characteristics and outcomes of patients with critical COVID-19 pneumonia who required mechanical ventilation admitted between 1ST April 2020 to 1st April 2022 in Avenue hospital Parklands.

Patients presenting with critical COVID-19 disease were older (>60years), male and majority had a comorbidity (DM and hypertension being the most common). These are some of the risk factors which have been documented worldwide to be associated with severe/critical COVID-19

disease. More risky behavior such as smoking, alcohol use and lack of compliance with COVID-19 containment measures is thought to be the reasons why men are more affected by COVID-19 compared to women(54)(55) and the growing number of patients with non-communicable disease especially in the urban areas as demonstrated by the national strategic plan for the prevention and control of non-communicable diseases(56) could explain why hypertension and diabetes mellitus were the most common comorbidities. These findings are similar to the results of a prospective study done in multiple African countries (ACCCOS) assessing patients with COVID-19 pneumonia admitted in intensive care or high care units that found the mean age of patients was 56 years with majority of patients being male (60.4%)(14) and hypertension and diabetes mellitus being the most common comorbidities in patients with severe/critical COVID-19(27).

Laboratory results demonstrated that patients with critical COVID-19 had an inflammatory state due to elevated markers of inflammation such as CRP and D-dimers, features of ARDS and hypoxia due to reduced PO2/FiO2 ratio with multiple organ system involvement as demonstrated by elevated liver transaminases, elevated creatinine and reduced platelet and lymphocyte counts. COVID-19 causes an acute hyper-inflammatory state especially during the cytokine storm which can affect multiple organ systems and lead to increased CRP levels and elevated D-dimers (a fibrin degradation product) due to thrombotic complications and coagulopathies. These observations were similar to findings of smilowitz et.al and zhou et.al. where elevated CRP and D-dimers were noted in critical COVID-19 disease and were associated with increased mortality(57)(16).

All patients included in this study had a reduced PO2/FiO2 ratio. PO2/FIO2 ratio is a commonly used indicator of gas exchange impairment in critically ill patients and has been used in the definition of ARDS(58) especially in patients with lower respiratory tract infections on mechanical ventilation with positive end expiratory pressure. Santus.et.al demonstrated in his study that the patients with severe/critical COVID-19 had lower levels of PO2/FiO2 ratio and the severity of hypoxia as demonstrated by the PO2/FIO2 ratio is significantly associated with in hospital mortality(59)

Lymphopenia in COVID-19 patients is thought to be as a result of either bone marrow suppression, infection or destruction of the lymphocytes or a functional exhaustion of the

antiviral lymphocytes and has been demonstrated to predict disease severity in COVID-19, Zheng.et.al demonstrated that lymphopenia is a major laboratory finding in severe COVID-19 disease(60)

Majority of the patients had bilateral GGO on CT-chest with elevated CT-severity scores as a result of intense inflammatory response in the lungs. COVID-19 disease affects majorly the lungs, damage to the alveolar epithelial cells and endothelial cell with exudation of a proteinaceous fluid in the alveolar space produces diffuse alveolar damage with resultant features of ARDS and development of the ground glass opacification seen in CT-chest. This is similar to the findings by Saeed.et.al in his study that showed patients with higher CT severity scores (score >18) had higher oxygen requirements including delivery by high flow nasal cannulas and mechanical ventilation and that higher scores were also associated with higher mortalities(45).

The duration to initiation of mechanical ventilation in most of the patients presenting with critical COVID-19 coincided with the estimated duration of development of ARDS in COVID-19 pneumonia (7-12days). According to the Berlin definition of ARDS, ARDS develops within 1 week following a known clinical insult(61). Several studies conducted showed the development of ARDS in COVID-19 pneumonia was delayed with patients developing ARDS between 8-12 days with subsequent need for high flow oxygen delivery systems(62) and this is in-keeping with our findings.

Management of the patients with critical COVID-19 pneumonia was in line with the guidelines provided by the ministry of health of Kenya(46) whereby all patients included in this study were initiated on steroids and prophylactic doses of anticoagulation (low molecular weight heparin) while patients who had disease progression were added interleukin 6 inhibitors (tocilizumab) and JAK 1 and 2 selective inhibitors (baricitinib) where benefit has been demonstrated(63). Contrary to the guideline patient with critical COVID-19 received remdesivir which has not showed benefit in critical disease partly because some of the patients had been initiated on it before disease progression to critical illness or requirement of high flow oxygen.

The commonly used steroid was methylprednisone (75%), this was based on recent trials which had demonstrated that methylprednisone had been associated with better clinical outcomes (lower Ordinal scale for clinical improvement (OSCI)) and shorter hospital stay compared to

dexamethasone(64) while prophylactic doses of low molecular weight enoxaparin was used since no benefit had been demonstrated in using therapeutic doses in patients with critical COVID-19 disease without any venous thromboembolic event(65).

Majority of the patient were initiated on NIV compared to invasive mechanical ventilation in line with some studies which had demonstrated that Early NIV initiation in COVID-19 was associated with better outcomes compared to invasive ventilation as demonstrated by Daniel et.al (66) this is despite previous practices whereby management of ARDS included prompt invasive mechanical ventilation.

The median length of ICU stay was 6 days and the mortality in the patients admitted to the critical care isolation unit was 50%. A systematic review done by Rees et.al demonstrated that the length of stay (LOS) for patients in ICU across China was 8 days and outside China it was 7 days(52) while shorter ICU length of stay was associated with increase mortality. In this study longer ICU stay was associated with higher mortality, we noted that patients with longer ICU stay had complications such as AKI, pneumothorax and venous thromboembolism arising from COVID-19 or intervention given and these complications were significantly associated with increased mortality possibly explaining why longer ICU stay was associated with increased mortality. The mortality in developed regions was recorded to be 39% which is lower compared to mortality in most developing countries, however from a multicenter prospective observational cohort study performed in multiple African countries (ACCCOS trial) mortality was found to be 48.2% which was similar to our mortality, the higher mortality in developing countries could be as a result of insufficient critical care resources to take care of the patients in critical care units and inadequacy of critical care beds(14).

5.1 Study limitations

This was a single center study conducted in a private hospital in Nairobi with more resources compared to public treatment facilities in Kenya therefore these results may not be generalizable to public facilities.

5.2 Conclusions

In conclusion this study demonstrates that patients admitted to critical care isolation unit with Critical COVID-19 disease were older (>60 years), male and a majority had pre-existing conditions. Key laboratory and chest imaging findings included low PO2/FIO2 ratio, lymphopenia, elevated CRP, elevated D-dimers levels, elevated AST and high CT severity scores. Majority of patient with critical COVID-19 disease received steroids (mainly methylprednisone), prophylactic anticoagulation (low molecular weight heparin), remdesivir and tocilizumab though none of the patients were proned. The main modality of ventilation was NIV. The mortality in patients with critical COVID-19 was 50% and the median length of stay in ICU was 6 days.

5.3 Recommendations

Male patients above 60 years of age and patients with pre-existing conditions are more likely to develop critical COVID-19 disease, we therefore recommend that these patients on presentation with COVID-19 disease should be treated with a high index of suspicion of progression to critical disease. Further future studies can be done to compare the mortality between men and women.

Key laboratory findings that were associated with significantly higher mortality included lymphopenia (<1.2*10^9), markedly elevated D-dimers (>1000 ng/ml) and markedly reduced PO2/FIO2 ratio (<100). These laboratory tests should be performed to patients with COVID-19 disease on admission to critical care units.

Patients presenting with critical COVID-19 disease requiring high flow oxygen systems would benefit from initiation of Non-invasive ventilation. We recommend future studies in patients with critical COVID-19 disease especially on treatment modalities and ventilation strategies used in their management.

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Table 10: questionnaire

1) SOCIO-DEMOGRAPHIC CHARACTERISTICS

a. AGE (years)

b. WEIGHT (kgs)

c. OCCUPATION:

Unemployed ☐

Self employed ☐

Employed ☐

d. GENDER

Male ☐

Female ☐

e. RACE

Black ☐

Asian ☐

White ☐

2) CO-MORBIDITIES

a. Hypertension

YES ☐ NO ☐

b. Diabetes mellitus

YES ☐ NO ☐

c. Human Immunodeficiency Virus(HIV)

YES ☐ NO ☐

d. Obesity

YES ☐ NO ☐

e. Asthma

YES ☐ NO ☐

f. COPD

YES ☐ NO ☐

g. CKD

YES ☐ NO ☐

3) **TIME INTERVAL BETWEEN ONSET OF SYMPTOMS AND ADMISSION TO ICU**

a. Duration (days)

4) **INVESTIGATIONS**

a. Lymphocyte counts (10^9 L)

b. Platelets (10^9 L)

c. C-reactive protein(CRP) (mg/l)

d. Alananine aspartate(AST) (U/L)

e. D-dimers (ng/ml)

f. Creatinine (mg/dl)

g. PO2/FIO2 ratio

h. HRCT chest- CT Severity score

5) **MANAGEMENT**

a. Dexamethasone ☐

b. Methylprednisolone ☐

c. Low molecular weight heparin ☐

d. Remdesivir ☐

e. Baricitinib ☐

f. Tocilizumab ☐

6) **HIGH FLOW OXYGEN DELIVERY SYSTEMS AND SETTINGS INITIATED IN THE FIRST 24 HOURS OF ADMISSION IN THE ICU**

a. High flow nasal cannula ☐

b. Non-invasive mechanical ventilation ☐

c. Invasive mechanical ventilation ☐

7) **OUTCOMES**

a. ICU discharge outcomes

ALIVE ☐ DEAD ☐

b. Length of ICU stay (days)

APPENDICES