PREDICTORS OF TREATMENT OUTCOMES AMONG CRITICALLY ILL COVID-19 PATIENTS ON REMDESIVIR-BASED THERAPY AT WINDHOEK CENTRAL HOSPITAL

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ABSTRACT

Introduction: Corona virus disease, caused by the SARS-CoV-2 virus, was declared a pandemic by WHO in March 2020, with 575 million cases and 6.4 million deaths to date globally. Remdesivir, a broad-spectrum anti-viral, was one of the few treatment options available for the management of severe and critical COVID-19 cases. This study aimed to evaluate predictors of treatment outcomes among critically ill patients on remdesivir-based therapy at Windhoek Central Hospital.

Methods: A retrospective cohort study reviewed records of patients treated with remdesivir in the critical care unit at Windhoek Central Hospital from October 2020 to November 2021. Treatment success was defined as being medically stable enough to be discharged from the hospital within 14 days or being hospitalized but not requiring any supplemental oxygen nor receiving medical care related to COVID-19 at day 14. Data was analyzed using SPSS version 24 in which Bivariate and Multivariate regression analyses were performed.

Results: The proportion of males to females was the same (51.9% vs 48.1%). Most were <65 years old (84.8%), with median age being 53 years. Majority had undocumented vaccination status (91.1%). About 6.3% had a history of COVID-19. Some (63.3%) had co-morbidities with hypertension being the most recorded (74%), followed by diabetes (34%). Majority (86%) required mechanical ventilation at baseline. Hours before initiation of remdesivir was only recorded in 53 patients. Of those, remdesivir was initiated within 72 hours in 71.1% of the patients. Fifty-two percent of the patients were on remdesivir therapy for a duration of 6-10 days while 48% were on therapy for 5 days. Of the 79 records analyzed, there was a 21.5% treatment success rate. Some (34.2%) had complications with hyperglycemia being the most recorded (37%) followed by ARDS and anemia both at 33.3%. Bivariate analysis showed that complications are significantly associated with mortality (p=0.001).

Conclusion: Complications were significantly associated with death among critically ill COVID-19 patients on remdesivir-based therapy at Windhoek Central Hospital based on bivariate analysis, although this needs confirmation from multivariate analysis. Further research on laboratory and radiographic parameters as predictors of treatment outcomes is essential.

Key words: remdesivir, treatment outcomes, predictors, COVID-19 and critical.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

Azithro	Azithromycin
AKI	Acute Kidney Injury
ARF	Acute Renal Failure
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CCF	Congestive Cardiac Failure
CCL2	Chemokine (C-C motif) Ligand 2
CCSNA	Critical Care Society of Namibia
CD14	Cluster of Differentiation 14
COVID-19	Corona Virus Disease
COVID-ICU	Corona Virus Disease Intensive Care Unit
Colch	Colchicine
Ct	Cycle Threshold
CVDs	Cardiovascular Diseases
Dexa	Dexamethasone
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DVT	Deep Vein Thrombosis
ECMO	Extracorporeal Membrane Oxygenation

eGFR	Estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
HbAlc	Haemoglobin A1c
HFNC	High Flow Nasal Cannula
HIV	Human Immunodeficiency Virus
HTN	Hypertension
ICU	Intensive Care Unit
IQR	Interquartile range
IV	Intravenous
MoHSS	Ministry of Health and Social Services
NIH	National Institutes of Health
NIV	Non-invasive ventilation
PASC	Post Acute Sequelae of COVID-19
PCT	Procalcitonin
PO	Per Oral
RDV	Remdesivir
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous

SI	Selectivity Index
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
VTE	Venous Thromboembolism
WBC	White Blood Count
WCH	Windhoek Central Hospital
WHO	World Health Organisation

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DEDICATIONS

This thesis is dedicated to my babies, Maia, Meameno and Abi Sheikh. May you look at it one day when you are all grown and be encouraged in achieving your dreams.

To my younger sisters, Mina, Ndeshi, Maria and Lucy this is for you too. This should be a testimony that with God everything is possible. It should always remind you that you can do all things that you set your mind to, through Christ who strengthens you.

To all the health care workers at the previous COVID-ICU, this is for you. Your hard work and determination were evident in those patient records. The will to save every life possible was undeniable. Thank you so much for putting your own lives on the line to save others. You are the true unsung heroes and heroines of our times. God bless you so much!

To all the COVID-19 victims, this is for you too. The devil was amongst us, we fought hard and now we are on the other side of victory. Although not all of us. Glory be to God!

DECLARATION

I, Meameno Tulimevava Nghikembua, hereby declare that this study is a true reflection of my own research and that this work has not been submitted for a degree at any other educational institution.

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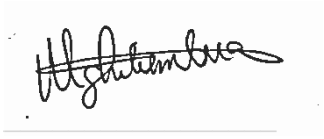

06 December 2023

Date

CHAPTER 1 INTRODUCTION

1.1 Background

Corona virus disease known as COVID-19, an infectious disease caused by the recently discovered SARS-CoV-2 virus, was a pandemic after a declaration by the WHO in March 2020 (1). The disease has ever since caused significant morbidity and mortality, with global burden estimated at 768 million cases and 6.9 million deaths (2). Due to inadequate public health care facilities and lack of medical resources, African countries, Namibia included have suffered greatly. The Centre of Disease Control and Prevention (CDC) then classified Namibia as a Level 4 COVID-19 zone (very high-risk destination) in May 2021 (3). At the time, the conditions for travelers visiting Namibia were: refrain from traveling to Namibia, and if travel was unavoidable, it was recommended to be fully vaccinated prior to departure (3). Despite being fully vaccinated, travelers may still be vulnerable to contracting and transmitting COVID-19 variants. To date, Namibia has reported 171 310 cases and 4 091 deaths (2). Of greater concern were the elderly (4–6) and those with underlying cardiovascular diseases, diabetes, renal disorders, and pulmonary conditions because they were likely to develop a more serious disease (4,7).

Remdesivir, a broad-spectrum anti-viral was considered highly active against coronaviruses (4). Remdesivir was the main option available for managing critically ill patients. Remdesivir gained recognition as a promising anti-viral medication in recent years, particularly for its ability to inhibit viral multiplication by inhibiting RNA polymerase, making it effective against RNA viruses (8). Viral replication has been observed to be what leads to most clinical manifestations of COVID-19. Anti-viral therapy works best in the initial replication phase before the disease progresses to hyper-inflammatory state (8), which may lead to further tissue damage and thrombosis.

For this reason, anti-viral therapy was recommended. Thus, the FDA approved the use of remdesivir in treating hospitalized patients, both adults and pediatrics aged 12 or more and weighing at least 40 kilograms, in October 2020, (9). Against this background, the Critical Care Society of Namibia (CCSNA) had included remdesivir in the COVID-19 treatment protocol, to be used within the first 72 hours of symptoms for 5 days, and no later than 10 days because anti-viral therapy has no effect after 10 days (10).

In April 2022, the use of remdesivir was extended to paediatric patients aged 28 days and weighing 3 kilograms or more and who are likely to progress to a severe disease, including hospital admission or fatality (11). Subsequently, the FDA repealed the emergency use authorization of remdesivir which had previously been granted for this paediatric patient population (11).

Various predictors of remdesivir treatment outcome have been described by using univariate analysis. They are thought to include age, fibrinogen, C-reactive protein and baseline estimated Glomerular filtration rate (12). Male gender has also been linked to severe COVID-19 infections and higher mortality (5,6).

1.2 Statement of the problem

Whilst remdesivir was the only approved treatment of hospitalized patients, conflicting reports emerged on its treatment outcomes across various patient populations (9). While some studies suggest that remdesivir accelerates rate of recovery in hospitalised COVID-19 patients others suggest that remdesivir has minimal effect or probably none on hospitalised patients. The WHO SOLIDARITY trial for example, showed little or no effect and in addition it noted consequences of poor treatment outcomes including overall mortality and increased duration of hospital stay, with most mortality findings

attributed to remdesivir and interferon (13). In Namibia, remdesivir was included in the protocol for use in critically ill patients, but data on the treatment outcomes in the Namibian population is not yet available.

While a few predictors of remdesivir treatment outcomes have been described from studies in different populations globally, more are yet to be elucidated and within the Namibian context such data does not exist yet.

This study investigated treatment outcomes for remdesivir-based therapy in critically ill patients at Windhoek Central Hospital. It also aimed to identify factors that predict treatment outcomes. Results from this study will then be used to inform treatment guidelines and protocols in these patients.

1.3 Objectives of the study

Overall aim

To investigate the treatment outcomes of remdesivir-based therapy among critically ill COVID-19 patients admitted to the Critical Care Unit of Windhoek Central Hospital

Specific objectives

i) To describe the demographic and clinical characteristics of critically ill COVID-19 patients on remdesivir-based therapy admitted to the Critical Care Unit of WCH.

ii) To estimate the treatment success rate (successful outcomes) and prevalence of other treatment outcomes (unsuccessful outcomes) of remdesivir-based therapy among critically ill COVID-19 patients admitted to the Critical Care Unit of WCH

iii) To identify predictors of treatment outcomes of remdesivir-based therapy among critically ill COVID-19 patients admitted to the Critical Care Unit of WCH

1.4 Significance of the study

Given that remdesivir was the mainstay treatment of COVID-19, the findings of this study were envisaged to inform the clinical case management, public health and policy strategies. Regarding the clinical benefits, the study evaluated the treatment outcomes to optimize case management and clinical outcomes in that patient population. Treatment success was defined as being medically stable enough to be discharged from the hospital within 14 days or being hospitalized but not requiring any supplemental oxygen nor receiving medical care related to COVID-19 on day 14.

The public health significance of the study pertained to reduced rate of transmission, reduced burden on health care facilities especially in resource-constraint settings such as Namibia and better appropriation of funds on treatments that are effective. The policy significance pertained to informing treatment guidelines, protocols, and policies in the management of critically ill COVID-19 patients in Namibia.

CHAPTER 2 LITERATURE REVIEW

2.1 Search strategy

Literature review was done by searching for articles using PubMed and Google Scholar. Only full text articles published between January 2020 to present and published in English were included in the review. Search key words were: remdesivir, treatment outcomes, predictors, COVID-19 and critical.

2.2 Conceptual framework

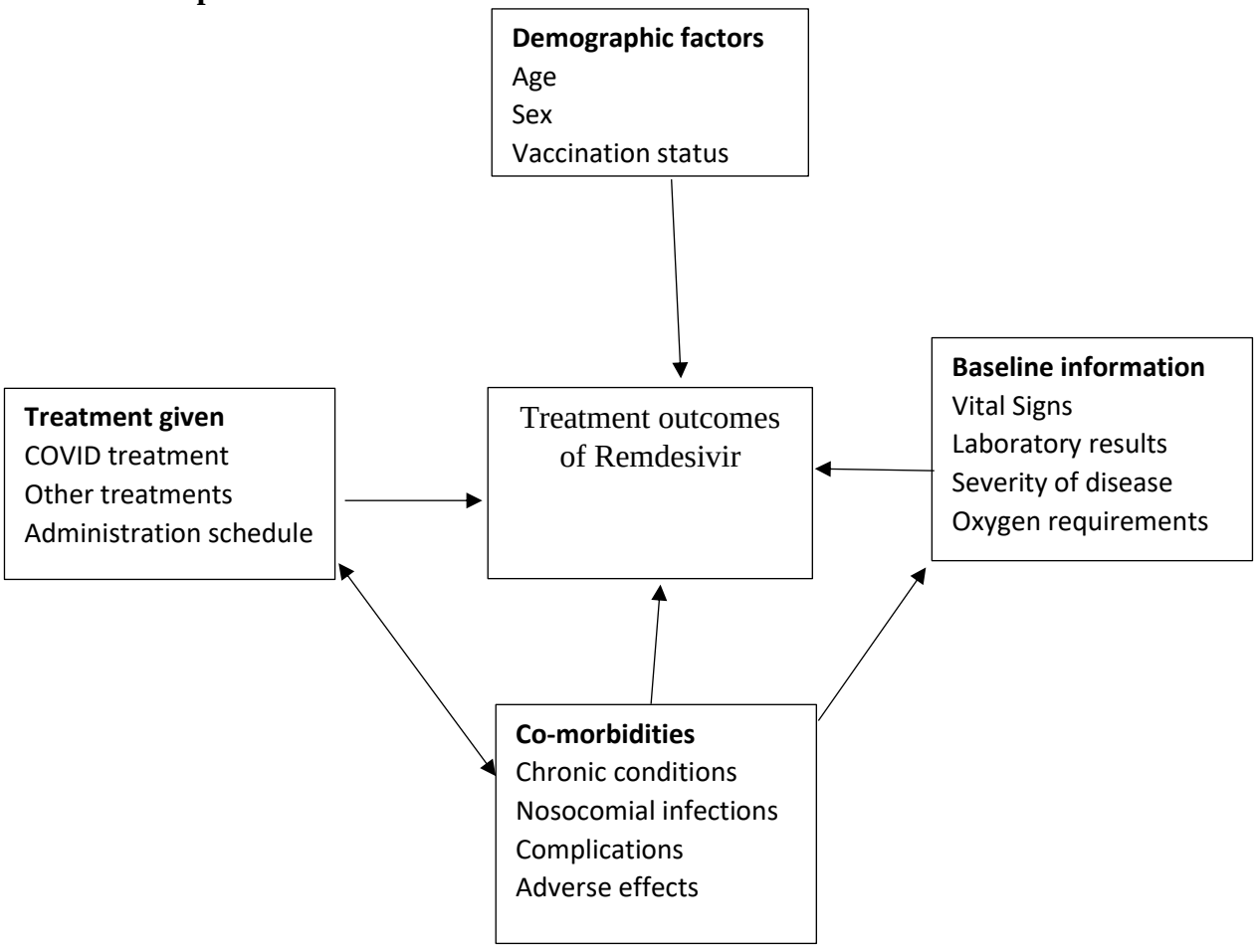

Figure 1: Conceptual framework on treatment outcomes of remdesivir-based therapy

A conceptual framework illustrates factors that may affect treatment outcomes of remdesivir. These may include patient demographic information, co-morbidities, oxygen requirements, baseline vital functions and other important laboratory results,

other medications received, complications developed, management of the complications and schedule of drug administration.

2.3 Initial efficacy in-vitro and in-vivo studies of remdesivir on COVID-19

SARS-Cov-2, SARS-Cov and MERS-Cov all belong to the Betacoronavirus family (14). At the time of the pandemic, there was no specific treatment for COVID-19. Due to high mortality rates, identifying medications that would yield good clinical outcomes was necessary. A timelier method to drug discovery was to test already available drugs used for similar viral infections. For instance, antiviral drugs such as ribavirin, interferon, lopinavir-ritonavir, and corticosteroids have been used to treat patients with SARS or MERS. Although effectiveness is a subject of debate, some had shown promise in treating these viral infections. Anti-viral effectiveness in COVID-19 was also evaluated for penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir and favipiravir (14).

Wang *et al* carried out an in vitro study employing standardized assays to evaluate the impact of various drugs on SARS-CoV-2. The study measured cytotoxicity, viral yield, and infection rates of SARS-CoV-2 in Vero E6 (14). Based on this study, remdesivir demonstrated effective inhibition of virus infection at a low concentration of micromoles and exhibited a high selectivity index (SI) (8). The findings of the study suggested high effectiveness for both remdesivir and chloroquine in curbing the spread of SARS-Cov-2. Since both drugs have been used safely in humans before, it was recommended to evaluate their efficacy in human patients with COVID-19 (14). Several other studies demonstrated that both remdesivir and chloroquine or hydroxychloroquine may be exceedingly efficacious in treating the SARS-CoV-2 virus (15–18)

Furthermore, there are in vivo studies that demonstrate the efficacy of remdesivir. These studies utilized animal models to gather pre-clinical data to determine the drug's efficacy in living organisms.

Williamson and others examined remdesivir efficacy in a rhesus macaque model infected with SARS-Cov-2. While the model does not fully capture severity of the disease experienced by some COVID-19 patients, the findings suggested that initiating remdesivir treatment early in patients can help prevent pneumonia onset (19). The study showed that administering remdesivir to rhesus macaques infected with SARS-CoV-2 led to a reduction in clinical illness and lung damage, utilizing dosages comparable to those given to humans (19). The initial impact of the treatment on clinical symptoms and viral replication was observed within 12 hours (19). The efficacy of direct-acting antivirals in treating acute viral respiratory infections typically diminishes when treatment is delayed (17). Therefore, for optimal treatment results, it is recommended to commence remdesivir therapy as soon as possible in individuals diagnosed with COVID-19 (19). Prior research has also demonstrated the efficacy of remdesivir against SARS-Cov and MERS-Cov in animal trials (20–22).

2.4 Outcomes of treatment with remdesivir including treatment success rates of remdesivir in clinical trials

Despite being seen as a potential option both in laboratory and animal studies, clinical trials on the safety and effectiveness of remdesivir in humans necessitated solid evidence from well-organized and sufficiently resourced studies.

The Adaptive COVID-19 Treatment Trial (ACTT-1) which began in February 2020, included sites from different parts of the world (23). According to the final report published in October 2020, by Beigel *et al.,* remdesivir was superior to the placebo in

shortening recovery time. The median recovery time was 10 days as compared with 15 days for patients on placebo (23). The patients on remdesivir were likely to have clinical improvement by day 15 compared to those on placebo. Mortality in the group on remdesivir was 6.7% by day 15 and 11.4% by day 29, while for those on placebo group was 11.9% by day 15 and 15.2% by day 29 (23).

A randomized, open-label trial determining the efficacy of 5 or 10 days of remdesivir compared with standard care by Spinner *et al*, revealed that, clinically, patients with moderate disease who received a 5-day course of remdesivir showed a statistically significant difference compared to those who received standard care (24). The 10-day course of remdesivir did not show this significance (24)

In the Goldman *et al* randomized, open-label phase 3 clinical trial, the efficacy of remdesivir for either 5 or 10 days in severe COVID-19 patients not requiring mechanical ventilation was investigated (25). No significant difference was observed between the two treatment durations. However, since there was no placebo control, the extent of the treatment's benefit could not be determined with certainty (25). However, the WHO SOLIDARITY trial interim report by Pan *et al* that examined remdesivir, lopinavir/ritonavir, interferon and hydroxychloroquine for their potential to treat hospitalized COVID-19 patients suggested that these drugs did not significantly improve patient outcomes, as measured by mortality rates, initiation of therapy, and duration of hospital stay. It was noted that most of the mortality findings were linked to remdesivir and interferon (13). A systematic review conducted by Qomara *et al*, which comprised of 15 studies that investigated the efficacy of favipiravir, remdesivir and lopinavir/ritonavir in treating COVID-19, concluded that remdesivir demonstrated promising benefits such as shortened time to recovery, reduced duration of hospitalization, and fewer adverse effects. However, the influence on reducing

mortality or the need for early mechanical ventilation remained unclear (26). The Solidarity trial included in this systematic review, specifically evaluated remdesivir-related mortality comparing 2743 patients treated with remdesivir to 2708 control patients treated with local standard of care. The study found that the group treated with remdesivir had 301 deaths, whereas the control group had 303 deaths. Additionally, the initiation of ventilation began among 295 subjects in the remdesivir-treated group and 284 subjects in the control group after randomization. Based on these results, remdesivir did not show any effect in reducing death or the need for ventilation (13). Another study included in the systematic review conducted by Kalil *et al*., examined the response of baricitinib and remdesivir in comparison to remdesivir and a placebo. The results demonstrated that baricitinib and remdesivir led to faster clinical improvement and shorter recovery time (7 days compared to 8 days) and lower 28-day mortality rate (5.1% compared to 7.8%) compared to remdesivir alone (27).

2.5 Treatment outcomes of remdesivir in hospitalized patients

2.5.1 Treatment Success

Literature has shown many successful outcomes with remdesivir use in patients with moderate to critical disease in different parts of the world. In the real world, remdesivir was found to decrease the risk of ICU admissions, increased likelihood of discharge at day 14 and 28 and a faster viral clearance (5). The findings of systematic reviews and meta-analyses indicate that remdesivir may offer some advantages to hospitalized COVID-19 patients (26,28).

A retrospective analysis by Gupte *et al* showed a clinical improvement or cure of 84%, with highest improvement seen in patients aged less than 60 and on oxygen at low flow (29). Garibaldi *et al* conducted a study in the United States, which was a multicenter

retrospective comparative study evaluating the effectiveness of remdesivir in the real world, which further supports this notion. The study showed that remdesivir patients had a significant likelihood to improve by day 28, specifically patients who were not on oxygen or were on low-flow oxygen. For overall mortality no substantial influence was observed, but patients on low-flow oxygen who received remdesivir had a less likelihood to die than those who did not receive the treatment. These findings support remdesivir use in patients who are not on or are on low-flow oxygen and suggest that routine use of the drug in more severely ill patients may not be beneficial (30). A retrospective cohort study by Chokkalingam *et al*, of 24 856 COVID-19 patients and 24 856 matched control patients revealed that treatment with remdesivir showed a substantial 17% lower likelihood of mortality (31). Another study by Tran et al in Vietnam revealed that, 92.3% of the patients got discharged and sent home (32).

In the trial conducted by Goldman *et al*, it was discovered that no substantial difference exists in the outcomes of severe COVID-19 patients not requiring mechanical ventilation, between those receiving remdesivir for 5 days or 10 days. However, without a control group, the extent of the benefit could not be determined with certainty (25). Upon adjustment for baseline characteristics, the assessed multiple endpoints including mortality from any cause proved to be comparable. However, these findings may not be generalized to patients on mechanical ventilation (25). This study implies that in settings with limited resources, scarce supplies may be conserved through the implementation of shorter treatment durations (25).

2.5.2 Other treatment outcomes

The Vietnamese study by Trans *et al* revealed that some patients (1.9%) condition deteriorated and were transferred to a referral hospital, while some (5.8%) demised (32). Furthermore, 55.2% tested negative for RT-PCR, and 37.1% tested positive with Ct values greater than 30 at discharge or transfer (32).

In terms of mortality, some research has suggested that remdesivir has no discernible effect on the likelihood of death overall, which leaves the role of remdesivir in reducing mortality still uncertain (26,28,30).

2.6 Predictors of remdesivir treatment outcomes

The treatment outcome of remdesivir is influenced by several factors, which have been uncovered from literature. The factors believed to be involved are discussed below.

2.6.1 Age

Older age, (65 years and older) has been linked to poorer outcomes (33,34). Older patients have a higher likelihood of severe disease, increased risk of death (35) and prolonged hospital stay (5,6). Factors such as immune dysfunction and multiple co-morbidities, which are common in older individuals, may add onto the poor outcomes in this specific patient group (36). Age is considered a risk factor for disease severity (37). Compared to older patients, younger patients have a lower likelihood to develop a severe disease (38). In older individuals, the virus is more likely to replicate at a rapid pace due to a slower response to viral alert signals and immune responses, as well as a decrease in specific immune cells (39). The elderly population's alterations in the structure of the lung and muscle wasting can result in decreased physiological function, reduced lung capacity, and diminished airway clearance (40). Finally,

research has shown that children are more likely to exhibit cross immune protection from other coronaviruses or nonspecific protection from other respiratory viruses, compared to individuals in older age groups (38). From the African context, two studies from Ethiopia indicated that older age is associated with poor treatment outcomes (41) and disease severity (42)

2.6.2 Sex

The male gender has been linked to higher likelihood of severe infections and higher mortality rates (43). Immune response disparities and influence of sex hormones which are characteristic of men and women, could provide an explanation for the variation in the severity of diseases and clinical outcomes that exist between the sexes (43,44). For instance, a study by Ali *et al* in Iraq, revealed that males have a 1.8 chance to develop a more serious disease than females (37). This probability could be ascribed to variations in innate and adaptive immune responses between males and females, such as the influence of sex-specific inflammatory responses resulting from X chromosome, which contain immune-related genes (45). Some studies postulated that males possess more ACE-2 receptors (46) which facilitate the movement of SARS-CoV-2 into cells. The replication of the virus takes place in the upper respiratory tract, which is the area where ACE-2, is most abundant and in addition, the viral load at this site was shown to be positively linked to disease severity (47–49).

2.6.3 Early intervention

Literature indicates that, administering remdesivir early on may prove to be more beneficial in viral load reduction and improving outcomes (50–52). This is partly because early intervention with anti-viral therapy has also been shown to decrease disease progression (13,26). For this reason, the Critical Care Society of Namibia

(CCSNA) had included remdesivir in the COVID-19 treatment protocol, to be used within the first 72 hours of symptoms (10). In a study conducted by Chokkalingam *et al*., the median number of days from admission to the initiation of remdesivir was 1 day (31). The study revealed that the initiation was linked to a statistically significant 17% decrease in mortality (31)

2.6.4 Co-morbidities

Co-morbidities which are long term health conditions that co-exist with a certain ailment in question, in this case COVID-19 (53) have been recognized to have an impact on outcomes since the beginning of COVID-19 (7). The health outcomes are influenced by these distinct pathological mechanisms that are not present in all patients, and they operate in the three phases of the disease (7). Certain comorbidities may worsen the pathological processes or decrease the patient's ability to withstand tissue damage.

In addition, comorbidities affect clinical decisions made by clinicians to provide the necessary care. Research using models has determined that globally, 1.7 billion individuals have at least one comorbidity that increases their risk of experiencing severe COVID-19 (54).

Initially COVID-19 was illustrated as a two-phase disease (55), using the ISARIC Clinical Characterization Protocol (56). Death can result from two distinct pathways: the initial viral illness where there is viral replication and the subsequent inflammatory lung injury phase, both of which can be fatal (57–59). The differences between the two phases were evidenced by the RECOVERY trial results for dexamethasone (60). The findings of this study revealed a positive outcome overall, yet a predefined subgroup analysis indicated that patients who needed invasive ventilation experienced a greater

reduction in mortality, while a tendency reflecting harm was observed among patients not requiring oxygen at the time of randomization. Similarly, the influence of dexamethasone varied between patients with and without hypoxia, and the same may apply to the impact of some comorbidities in the two different phases of the disease.

While most individuals with SARS-CoV-2 recover completely, a few people continue to experience persistent symptoms, resulting in COVID-19 being described as a three-phase disease. The WHO defined it as post-acute sequelae of COVID-19 (PASC) or post-COVID condition or long COVID (61)

Co-morbidities that affect the initial viral replication

The ISARIC4C study, through the use of a globally harmonized protocol (56), showed that majority of the patients had one comorbidity at the minimum, in addition they had a higher likelihood of death (62). Previous reports from the Chinese mainland have indicated similar results for a smaller number of comorbidities, but the samples used were relatively small, limiting the reliability of these findings (63). In a larger study of the general population in England, data from primary care was used to assess the prevalence of 15 comorbidity categories, along with body mass index (BMI). Among these comorbidities, hypertension was the most prevalent, affecting 34.3% of the cohort, followed by asthma at 15.9% and diabetes at 9.9%. After adjusting for age and sex, all comorbidity groups were found to be at increased risk of dying. Among these groups, organ-transplant recipients and individuals with chronic kidney disease faced the greatest risk (64).

Immunosuppression has been identified as a potential contributor to resistance. This includes neutropenia, organ transplant, immunosuppressive therapy especially rituximab, HIV and Cytomegalovirus (7). Although the likelihood of dying from

COVID-19 is particularly high for organ-transplant recipients, an examination of a substantial US COVID-19 database revealed that receiving immunosuppressive therapy prior to hospitalization, regardless of the reason for admission (including organ transplant), was not linked to this likelihood (65).

In contrast, rituximab was associated with increased mortality when individual drug classes were evaluated. Among the 422 patients with COVID-19 treated with anti-CD20 therapy for underlying auto-inflammatory diseases, death was observed more in those who had received the drug within the past 6 months, and more of the individuals received their last dose 3 months before (66).

Concerning HIV, death was observed more in patients with COVID-19 who had HIV in comparison to individuals without (67). A CD4 count of less than 350 cells per microliter was linked independently to disease severity, in COVID-19 patients in the hospital with co-morbid HIV (68). A relationship between the ratio of CD4:CD8 and T cell activation in response to COVID-19 was found to be positive for individuals with HIV who had been on treatment for over two years, had undetectable viral load, and had CD4 counts ranging from 130 to 1,360 cells per microliter (69). Consequently, despite achieving viral suppression and displaying immune reconstitution, individuals with HIV may still possess subtle deficiencies that impair their T cell responses. The consequences of immunosuppressive treatments and HIV-related T cell weakening on SARS-COV-2 development suggest that immune responses are vital for fighting against COVID-19. This is in line with findings from studies on human immunology related to respiratory syncytial virus (70).

Cytomegalovirus (CMV) reactivation can happen in situations where the immune system is suppressed such as critical illness. This reactivation can result in

complications like pneumonitis, but it's important to note that having a latent infection can also lead to changes in the immune system and potentially contribute to immunosenescence (71). CMV reactivation has been observed in severe COVID-19 (72,73) although latent CMV infection has been demonstrated to increase chances of contracting COVID-19 and the severity of the disease (74).

Co-morbidities effects on inflammatory lung injury

Comorbidities have a negative impact on hypoxia which occurs after inflammatory lung injury. Some underlying conditions may drive the disease process such as obesity and some may reduce tolerance to injury such as chronic lung disease. Mendelian randomization is a tool that can be used to test the hypothesis that comorbidities cause serious or fatal outcomes for SARS-COV-2 (7). In Mendelian randomization studies, obesity has consistently been linked to heightened likelihood for critical COVID-19 (75).

A Swedish study showed that T2DM continued to serve as a risk factor for admission to hospital and ICU in COVID-19 patients following considering age and other co-morbidities (76). The study however did not find T1DM to be a standalone risk factor, but poor glycemic control in individuals with T1DM was linked to these outcomes. It also found that BMI was one of the undisputed predictors of poor outcomes in COVID-19 patients with co-morbid T2DM. In a cohort of T2DM individuals with COVID-19 in the US, it was observed that poor glycemic control, as indicated by HbA1c, was linked to an increased risk of admission to hospital and ICU, and the need for invasive mechanical ventilation or ECMO (77).

Using Mendelian-randomization methods, researchers have aimed to distinguish between associations and causations for severity of COVID-19, given the connection

between T2DM, glycemic control, and obesity. While T2DM has not been definitively linked to negative outcomes in COVID-19 through causal analysis, obesity, a closely related trait, has consistently demonstrated such an association (78,79).

Co-morbidities that affect post-acute sequelae

Evidence is emerging that individuals with underlying conditions are prone to developing PASC more than individuals without (80). A study revealed that the rampancy of PASC varied from 2.8% to 5.5% in individuals with underlying conditions, whereas it was only 1.8% in individuals without any underlying conditions (81). Individuals with multiple underlying conditions face a higher likelihood of experiencing persistent symptoms at 12 weeks after acute infection, as compared to those without. In a study that considered baseline symptom burden and employed appropriate comparison groups, the majority of the 80 comorbidities listed were found to be linked with persistent symptoms at 12 weeks (82), encompassing both physical comorbidities, pulmonary conditions, and mental health issues, including anxiety.

Recent evidence suggests that vaccination may not be as effective at preventing PASC as it is in preventing severe acute disease. Vaccination was found to decrease PASC likelihood by 15% only following a breakthrough infection and effectiveness was slightly decreased in the group of individuals with immunosuppression, which was the only comorbidity group that was assessed ((83).

2.6.5 Complications

While undergoing prolonged invasive ventilation, patients are at an increasing risk of experiencing complications related to organ support and extended critical illness. Complications encompass a range of issues such as neuropathy and myopathy (84), super infections such as ventilator-associated pneumonia, and delirium. The issues

mentioned are not exclusive to COVID-19 patients, but they serve as a crucial means through which complications can lead to a significant rise in mortality by diminishing the body's capacity to withstand injury (7). A study by Tian *et al* intending to uncover shared clinical and laboratory characteristics among 14 deceased COVID-19 patients revealed that severe complications, such as ARDS, heart and respiratory failure, septic shock, and multiple organ failures, were the primary causes of patient death while one case died from gastrointestinal bleeding (85).

2.6.6 Laboratory Parameters

Biological markers may be employed to evaluate COVID-19 severity and track its clinical progression. Compared to non-severe cases, severe cases are typically associated with an elevation in most biological markers (37). In a study by Ali *et al*, it was observed that the biological parameters, such as WBC, granulocytes, ESR, Ferritin, C-reactive protein, and D-Dimer, exhibited a significant increase in relation to the severity of the disease. On the other hand, lymphocytes and SpO2 displayed the opposite trend. A relationship between a higher count of red blood cells (RBCs) and the severity of COVID-19 was found, particularly pronounced in women (37).

Tomasiuk *et al* created a model to predict the outcome of COVID-19 treatment using a set of specific parameters, including C-reactive protein, procalcitonin, fibrinogen, D-dimers, immature granulocytes, and interleukin-6 (86). The study sample consisted of survivors and demised individuals and assessed the differences in the parameters studied between the study subjects. The findings of their study indicated a significant disparity between subjects in all the parameters that were assessed. As a result, a mathematical model that allows for the prediction of hospitalization outcome, employing laboratory parameters with a 97% precision in predicting the outcomes was

developed (86). The outcomes of this study suggested that the correlation between survivability and the specific levels of the parameters may be utilized as an effective diagnostic tool in a hospital setting (86)

A scoping review of laboratory parameters and treatment outcomes, conducted by Zhu *et al* found that blood urea nitrogen was reported mostly as a predictor of death (91%), while the neutrophil-to-lymphocyte ratio was the most frequent significant parameter in predicting severity (87). This review examined the development of laboratory values over time and assessed the unique usefulness of various markers in predicting clinical outcomes for COVID-19 (87). The collected data may be utilized in future research to conduct targeted quantitative meta-analyses examining the relationships between laboratory values and clinical outcomes, such as mortality and disease severity.

2.6.7 Oxygen requirements

A prospective cohort study by Bao Z *et al* on COVID-19 treatment outcomes specifically examined the role of pulmonary function indicators in predicting outcomes. The researchers found that certain indicators, including the oxygenation index and partial arterial oxygen pressure at admission, were significantly linked to the length of hospitalization and viral clearance (88). Poor lung function may prolong the duration of recovery (88). Remdesivir has been shown to be beneficial in patients on low flow oxygen or no oxygen as evidenced by the study by Garibaldi *et al* (30) . On the contrary, remdesivir was observed to increase the likelihood of death in patients on mechanical ventilation or ECMO as demonstrated by the Solidarity trial (13).

2.6.8 Vaccination status

Vaccination effectiveness has been proven in combating a severe COVID-19 disease, however, studies of the effects of vaccination on remdesivir treatment outcomes are not available. A retrospective cross-sectional study by Alsaffah and others in Saudi Arabia in 2021 assessing COVID-19 vaccines efficacy in enhancing the outcomes of patients hospitalized by comparing vaccinated and non-vaccinated groups found that mortality rates were significantly lower among the vaccinated group (35). Odds of admission to ICU and endotracheal intubation were also lower for the vaccinated group, although there was no statistical significance. The study also revealed significant correlation between the rate of death (irrespective of being vaccinated or not) and presence of chronic kidney disease or history of renal transplant in individuals aged 65 years or above. This study discovered substantial decrease in death and less complications for those vaccinated, despite the majority of admitted patients having only received one vaccine dose (35). Moreover, it was noted that elderly individuals, patients with chronic kidney disease, and renal transplant patients displayed suboptimal responses to the vaccines, resulting in less favorable outcomes when compared to other patients (35).

A retrospective study by Alkhafadji *et al*, which involved 624 COVID-19 patients hospitalized at two Saudi Arabian hospitals between April and July 2021, assessed the influence of vaccination on disease outcome. Severity and outcome of COVID-19 disease were compared based on three groups of vaccination status. Additionally, within the vaccinated group, the study investigated the influence of different vaccine types on severity and disease outcome.

A majority of hospitalized patients, amounting to three quarters, were found to be

unvaccinated (89). Lack of vaccination was found to be strongly linked to severe illness, while full vaccination was linked to a significantly milder disease. Additionally, lack of vaccination was found to be an independent predictor of longer hospital stays, admission to ICU, need for mechanical ventilation, and fatal outcomes. As expected, the fully vaccinated group had a much-reduced likelihood of ICU admission. Non-vaccinated patients with underlying conditions had worse severity and outcome of COVID-19 infection. Both Pfizer and AstraZeneca vaccine types had similar effectiveness against the poor outcomes of COVID-19 disease (89). Based on their findings, COVID-19 vaccination has been proven to decrease hospitalization rates, lessen symptoms severity, and enhance overall outcomes, particularly in patients at greater risk (89).

When it comes to long COVID, it has been shown that vaccination is less protective (7). A comprehensive study released in 2022 indicated that vaccination decreased the likelihood of PASC by 15% only following a breakthrough infection and the effectiveness of the vaccine was slightly reduced in subjects with comorbidities, specifically those with immunosuppression ((83).

This observation aligns with the findings of a systematic review conducted by Byambasuren et al, during which 1645 articles were thoroughly examined (90)Twelve studies reported data on vaccination before infection and 10 showed a substantial decrease in the occurrence of long covid (90). However, the diversity among the studies made it impossible to perform a meaningful meta-analysis. The studies did not account for possible confounding factors. Based on these findings, it was suggested that COVID-19 vaccines may provide some benefits for long COVID-19 (90).

2.6.9 Drug Regimens

Various drugs and drug regimens have been used for treating COVID-19 since the beginning of the pandemic. However, the influence of these drugs or combinations thereof, on ultimate treatment outcomes remains unclear. In a study to assess the impact of various treatment regimens on the outcomes of COVID-19 patients by Asadi and colleagues, it was discovered that there was no significant relationship between drug regimens and death or the need for a ventilator (91)

2.7 Gaps in literature

While a few predictors of remdesivir treatment outcomes have been described from studies in different populations globally, more are yet to be determined especially in the African context.

Specifically, there is no data from literature now indicating the effect of vaccination on the treatment outcomes of remdesivir. To shed more light on vaccines effects on remdesivir treatment outcomes, more robust comparative observational studies and trials are necessary.

2. 8 Summary

To summarize, the chapter appraised literature on the treatment outcomes and predictors of remdesivir in adults and paediatric patients. It was imperative that in vitro studies, in vivo studies in animals and clinical trials were done that warranted approval by the FDA. However, there is conflicting evidence on the treatment outcomes of remdesivir across different populations of COVID-19 patients, with some studies suggesting that remdesivir accelerates rate of recovery in hospitalised COVID-19

patients while some suggesting that remdesivir has minimal effect on hospitalized COVID-19 patients.

A few predictors of remdesivir treatment outcomes have been described from studies in different populations globally, however more are yet to be determined especially within the African context. Specifically, the effects of vaccination on remdesivir treatment outcomes are not studied.

CHAPTER 3 RESEARCH METHODS

3.1 Introduction

This chapter will describe the methods used to achieve the objectives. The chapter will detail the research design, the population, the sample size, data collection tool, data analysis and ethical considerations applied in this study.

3.2 Study design

To achieve the objectives of this study, a retrospective cohort design was adopted due to the availability of retrospective patient clinical records. The study cohort included critically ill patients who were on remdesivir-based therapy from October 2020 to November 2021.

3.3 Study setting

The study was conducted at Windhoek Central hospital Critical Care Unit which was created specifically for COVID-19 patients. WCH is a public referral hospital in Namibia, which was managing patients with severe forms of COVID-19.

3.4 Study population

The target population of the study was all clinical records of critically ill Covid-19 patients treated with remdesivir from October 2020 to November 2021 at WCH critical care unit. The accessible population was records that were available during the two-month study period, December 2022 to January 2023.

3.5 Inclusion criteria

Only clinical records of confirmed COVID-19 patients admitted at the WCH Critical Care Unit, treated with remdesivir for at least 5 days, were included in the study. Based on this, the following exclusion criteria was applied.

3.6 Exclusion criteria

The study excluded clinical records that lacked data on treatment outcomes.

3.7 Sample size

This study included all accessible clinical records of critical cases treated with remdesivir at the critical care unit of WCH between October 2020 to November 2021, who met the inclusion criteria. For security reasons, remdesivir was handled as a Controlled Substance (Schedule 4), therefore it was administered using a register. Based on a prior assessment of this register, this population was found to be roughly 110 patients.

3.8 Sampling

The list of patients who were on remdesivir between October 2020 to November 2021, as extracted from the register was used to draw out patient records. All accessible clinical records were included. Once the record was located, it was reviewed for critical data before abstraction and excluded if treatment outcome was missing.

3.9 Data Collection Tool

A tool for abstraction of data was designed. The tool was used to collect data on variables pertaining to the patient's socio-demographic, clinical, medication laboratory and medication characteristics, including treatment outcomes. The details

of the variables are documented in the data collection tool in Annexure 1. The instrument was piloted with 5-patient records and face-validated prior to data collection.

3.10 Piloting of Data Collection Tool

As a validation procedure, the data collection tool was piloted. Five patient records were selected and used to abstract data.

3.11 Data collection procedure

The researcher (MN) collected the data after receiving permission from the Ministry of Health and Social Services and the hospital management. Data on patient, clinical and medication variables were abstracted from records of patients treated with remdesivir between October 2020 to November 2021 from the critical care unit at WCH over a study period of two months.

3.12 Record review and Data extraction

The patient records were reviewed to extract variables that were critical to the study. The data from the patient records was entered into a physical data collection tool, which was then transcribed into an excel data collection tool.

3.13 Validity and reliability

To guarantee validity, the tool used for data collection was piloted and modified from existing, validated tools that had been utilized in studies with objectives similar to this study. The research findings were analyzed using appropriate statistical methods for quantitative research. To ensure reliability, the study employed valid and appropriate strategies and techniques relevant to the research.

3.14 Treatment Outcomes: Definitions

- The treatment outcome measures were clinical status on day 14, assessed on a 7-point ordinal scale (23,24), consisting of the following categories: 1. death; 2. hospitalized, receiving invasive mechanical ventilation; 3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4. hospitalized, requiring low-flow supplemental oxygen; 5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related to Covid-19); 6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care related to COVID-19 and 7. Discharged secondary to being medically stable within 14 days.
- Treatment success was defined as being medically stable enough to be discharged from the hospital within 14 days or being hospitalized but not requiring any supplemental oxygen nor receiving medical care related to COVID-19 at day 14: that is categories 6 and 7, of the ordinal scale above.
- Unsuccessful treatment was defined by categories 1 to 5 of the seven-point ordinal scale above.

3.15 Data analysis

Data was entered into excel for management and exported to SPSS. IBM SPSS Statistics Version 27.0.1 (IBM Corporation, 1 Orchard Rd, Armonk, NY 10504, USA) was used for quantitative analysis.

The characteristics of the patients were described quantitatively as follows. The mean, median and range were calculated for continuous variables and proportions for categorical variables.

The patients were grouped according to the outcomes: successful and unsuccessful treatment. The proportions of patients falling in either outcome group were calculated. The proportions of patients in each dependent variable were calculated for each independent variable.

The patients were also grouped according to mortality: ("alive" and "died") and the proportions of patients falling in each dependent variable were calculated for each independent variable.

Next, to find out if independent variables were significantly associated with the dependent variables (treatment success and mortality), bivariate analysis using Pearson's Chi Square or Fisher's exact test was done.

Multivariate binomial logistic regression analysis was used to identify the predictors of treatment success. The independent variables whose relationship with the outcome variable was measured at a *p*-value ≤ 0.250 using Pearson's Chi Square Test or Fisher's Exact Test, were considered eligible for inclusion in the multivariate analysis. To prevent over-fitting, the model, a 2-predictor model based on an event per variable of 10 was used. The level of statistical significance was set at a *p*-value <0.05. Since only one variable (complications) was significantly associated with mortality in the bivariate analysis using Pearson's Chi Square, a multivariate binomial logistic regression was not done.

Objective	Dependent variable (outcome)	Independent variable (predictor)	Measure/Outcome
1. To estimate the treatment success rate of remdesivir-based therapy in critically ill COVID-19 patients at WCH	Treatment success rate by day 14	• Socio-demographic • Baseline labs • Baseline clinical • Co-morbidities • Regimen	% treatment success by day 14
2. To estimate the prevalence of other treatment outcomes of remdesivir-based therapy in critically ill COVID-19 patients at WCH.	Death Complications Hospitalization	• Socio-demographic • Baseline labs • Baseline clinical • Co-morbidities • Regimen	Proportion of successful treatment outcomes vs unsuccessful treatment outcomes
3. To identify the predictors of treatment outcomes of remdesivir-based therapy in the management of critically ill COVID-19 patients at WCH.	Clinical Sociodemographic	• Socio-demographic • Baseline labs • Baseline clinical • Co-morbidities • Regimen	Adjusted odd ratios for the covariates

3.16 Dissemination of results

A copy of the publication/or thesis will be made available to the MoHSS, and the results of the study will be presented at a local conference in Namibia. For a wider audience, the findings in the form of an abstract or manuscript will also be published in a peer reviewed journal.

3.17 Research Ethics

The following ethical considerations were met when conducting the study:

Ethical clearance: Ethical clearance certificate was obtained from the University of Namibia Decentralized Ethics Committee (DEC).

Informed Consent: Permission from the hospital was obtained. No patients consent required since it is a retrospective study. Records of eligible patients were included in the analysis.

Beneficence and risks: This study utilized secondary data and thus there were no risks involved.

Respect for anonymity and confidentiality: Patient identity was kept anonymous and personal information regarding patient outcomes was kept confidential. The data obtained from the study was kept under lock and key, and password protected on the computer. There were no patient identifiers.

Respect for privacy: The files that contain patient information was handled by the researcher and this information was kept confidential in order to respect the privacy of patients.

CHAPTER 4 RESULTS

4.1 Introduction

This chapter presents the research findings obtained by examining the data collected. The quantitative outcomes are displayed using a mix of descriptive, inferential, and analytical styles, which align with the study's objectives. The demographic characteristics of the records are explained through measures such as frequencies, proportions, and means, as appropriate. Pearson's Chi Square, Fisher's Exact test, and multivariate binomial logistic regression analysis were used to assess the associations of independent variables on the dependent variable, treatment success and mortality. Variables with missing values were treated using pairwise deletion.

4.2 Demographic Characteristics

Out of the 105 records at WCH Critical Care Unit from October 2020 to November 2021, 79 of them were analysed. Due to the absence of crucial information, particularly the treatment outcomes, the analysis of the 26 records was not possible (Figure 2)

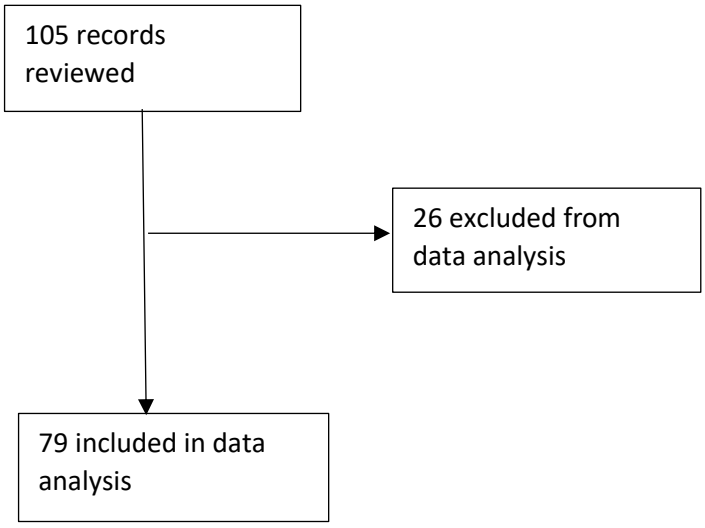

Figure 2: Flow chart for number of records included in the study analysis

Table 1: Age and sex distribution through measures of central tendencies

Measures of central tendency			Age groups		Sex	
Mean±SD		49.78 ±14.67	<65 years	67(84.8%)	Male	41(51.9%)
Mode		38	≥65 years	12(15.2%)	Female	38(48.1%)
Minimum		18	Total	79	Total	79
Maximum		85				
Median		53				
Interquartile range		23				
Percentiles						
	25	38				
	50	52				
	75	61				
Kolmogrov-Smirminov test		<0.001*				

*Kolmogrov-Smirminov test significance at $p<0.05$

Table 1 above presents findings on the age and sex variables in the COVID-19 cases. In this study, the proportion of males to females was the same (51.9% to 48.1%) respectively. The median age was 53 and the interquartile range was 23. Patients less than 65 years old made up most of the population with 84.8%, while elder patients above 65 made up 15.2% of the population. The Kolmogrov-Smirminov test yielded a p-value of <0.001, showing that the data was not symmetric. It had a little leftward tilt, implying that younger respondents made up a slightly larger proportion of the total.

Table 2: Clinical characteristics of patients

Variable	Frequency (%)
Vaccination Status	
Not Vaccinated	7(8.9)
Not known	72(91.1)
Total	79(100)
Mechanical ventilation	
Yes	68(86)
No	11(14)
Total	79 (100.0)
History of COVID-19	
Yes	5(6.3)
No	28(35.4)
Not known	46(58.2)
Total	79(100.0)
Co-morbidities	
Yes	50(63.3)
No	29(36.7)
Total	79(100)
Regimen	
RDV	1(1.3)
RDV+Azithro	2(2.5)
RDV+Azithro+Colch	1(1.3)
RDV+Colch	1(1.3)
RDV+Dexa	17(21.5)
RDV+Dexa+Azithro	8(10.1)
RDV+Dexa+Azithro+Colch	28(35.4)
RDV+Dexa+Colch	21(26.6)
Total	79(100)
Hours before initiation of Remdesivir	
Treatment initiated within 72 hours	38(71.7)
Treatment initiated after 72 hours	15(28.3)
Total	53(100)
Duration of Remdesivir therapy	
5 days	38(48.1)
6-10 days	41(51.9)
Total	79(100.0)
Complications	
Yes	27(34.2)
No	52(65.8)
Total	79(100)

Table 2 above presents clinical characteristics of the patients. Of the 79 patients whose clinical records were analysed, none were vaccinated, most of the patients' vaccination status was unknown because they were not documented while few patients confirmed

that they were not vaccinated. There were a few re-treatment cases with a history of COVID-19, some had no history while more than half had an unknown history of COVID-19.

Most of the patients required mechanical ventilation (invasive or non-invasive) at baseline (admission), while few were not but required other types of oxygen therapy at baseline mostly low flow oxygen. More than half of the patients had co-morbidities. The specific co-morbidities are illustrated in Figure 3.

The remdesivir-based regimens that the patients were on as part of the COVID-19 protocol are shown in Table 2. Most of the patients were on a combination of remdesivir + dexamethasone + azithromycin + colchicine. Remdesivir was administered within 72 hours of onset of symptoms in a greater proportion of patients, a considerable number received after 72 hours of onset of symptoms, as shown in Table 2, while some (26 records) did not have a clear indication on when remdesivir dosing was initiated with respect to onset of symptoms due to lack of treatment schedule. As a result, only 53 records are indicated for analysis under hours before initiation of remdesivir. Regarding the duration of remdesivir therapy, most were on therapy for 6-10 days, with a small proportion having been on therapy for 5 days.

Slightly more than a quarter of the patients were reported to have complications. The specific complications are illustrated in Figure 4. No laboratory measurements or radiographic results (Chest X-ray) were examined due to significant missing data.

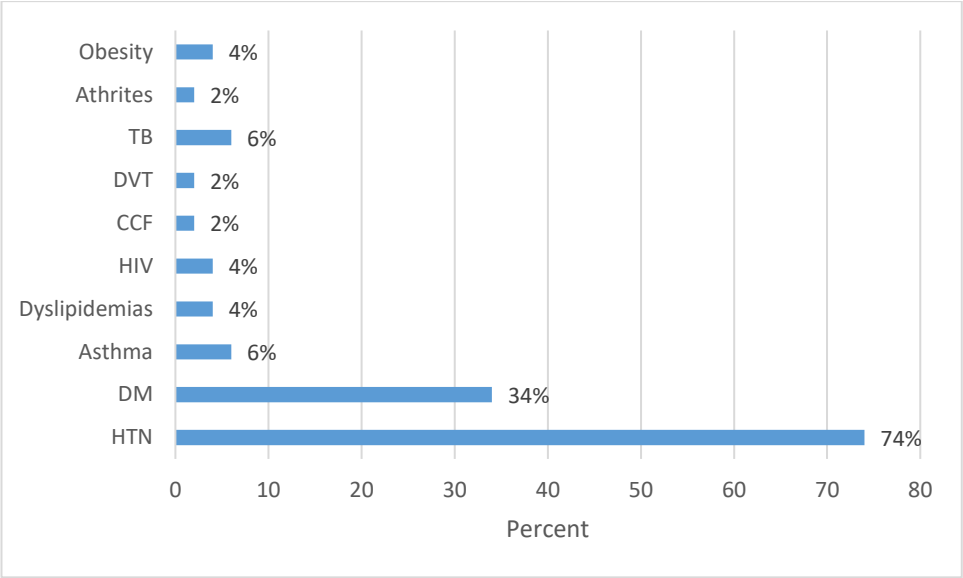

Figure 3: Co-morbidities among study patients

Hypertension was the most recorded co-morbidity, followed by diabetes.

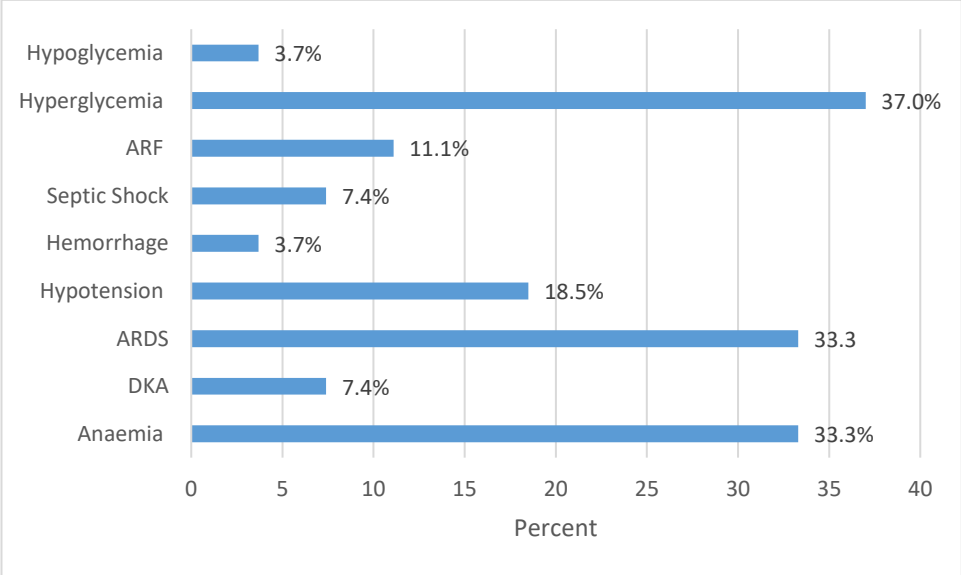

Figure 4: Complications among study patients

Hyperglycemia was the most recorded complication, followed by ARDS and anaemia

4.3 Treatment success among study patients

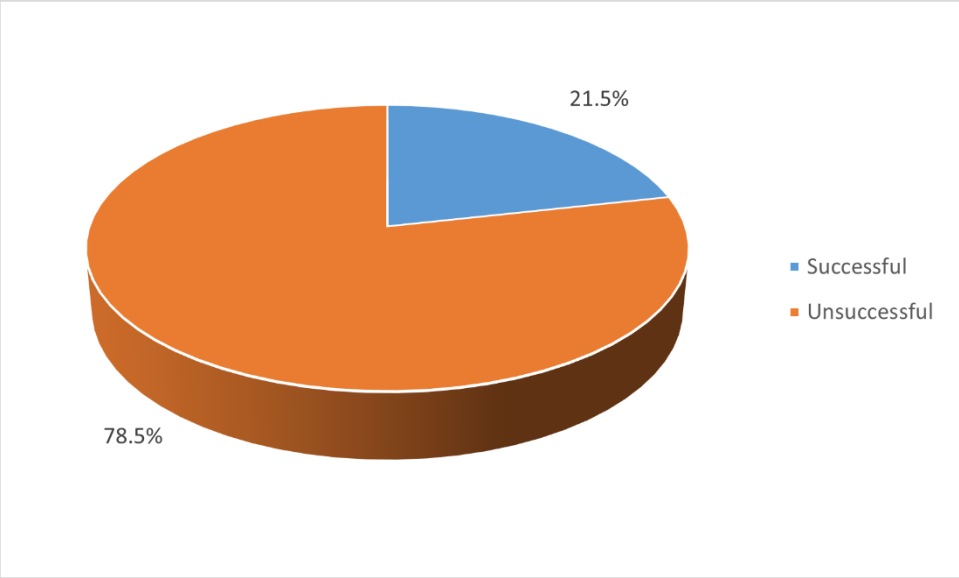

Figure 5: Treatment success rate

Only 21.5 % of the patients in the current study had successful outcomes. Patients who were discharged home and those who remained in hospital but not on oxygen nor on COVID-19 medical care were considered to have successful treatment outcomes. Most of the patients (78.5%) did not respond favourably to treatment.

4.4 Treatment outcomes among study patients

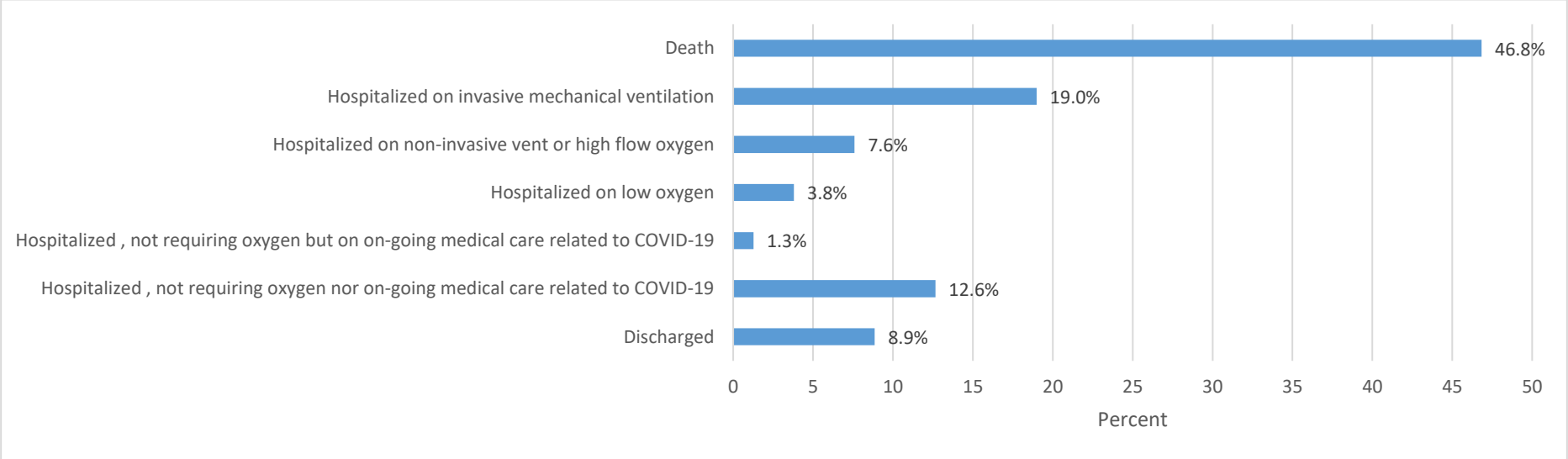

Figure 6:Treatment outcomes

Death was the most common outcome accounting for 46.8% of patients. The second most common outcome in 19% of the patients comprised patients who were hospitalised and needed invasive mechanical ventilation. Some patients (12.6%) were hospitalized even though they neither required oxygen nor on-going medical care related to COVID-19 due to non-COVID-19 medical conditions. Nine percent of the patients were discharged from hospital after recovery from COVID-19

4.5 Association of patient characteristics with treatment success

Table 3: Bivariate analysis of demographic variables and treatment success

	Successful		Not Successful		
	n	%	n	%	P
Sex					0.786
Male	8	47.1	33	53.2	
Female	9	52.9	29	46.8	
Age					0.714
< 65	14	82.4	53	85.5	
≥65	3	17.6	9	14.5	

Fisher's exact test with $p < 0.25$

Fisher's Exact Test was used to determine if there was an association between sex and treatment success. Similarly, it was used to determine if there is an association between age and treatment success. Results from this Fisher's exact test revealed that neither sex ($p= 0.786$) nor age ($p= 0.714$) was statistically significantly associated with treatment success

Table 4: Bivariate analysis of clinical characteristics and treatment success

	Successful		Unsuccessful		
	N	%	n	%	p
Hours before initiation of RDV					0.124
Within 72 Hours	5	50.0	33	76.7	
After 72 Hours	5	50.0	10	23.3	
Duration of RDV therapy					0.172
5 days	11	64.7	27	43.5	
6 - 10 days	6	35.3	35	56.5	
Regimen					0.147
RDV	0	0.0	1	1.6	
RDV+Dexa	6	35.3	11	17.7	
RDV+Dexa+Azithro	0	0.0	8	12.9	
RDV+Dexa+Azithro+Colch	4	23.5	24	38.7	
RDV+Dexa+Colch	5	29.4	16	25.8	
RDV+Colch	1	5.9	0	0.0	
RDV+Azithro	1	5.9	1	1.6	
RDV+Azithro+Colch	0	0.0	1	1.6	
History of Covid Treatment					1.000
Yes	1	20.0	4	14.3	
No	4	80.0	24	85.7	
Mechanical ventilation					0.226
Yes	12	75.0	54	88.5	
No	4	25.0	7	11.5	
Co-morbidities					0.577
Yes	12	70.6	38	61.3	
No	5	29.4	24	38.7	
Complications					0.150
Yes	3	17.6	24	38.7	
No	14	82.4	38	61.3	

Fisher's exact test at $p < 0.25$

Fisher's Exact Test was used to determine if there is an association between the different clinical characteristics with treatment success. With Fisher's exact test significance set at $p < 0.25$, four variables were eligible for inclusion in the multivariate analysis. These factors were: Hours before initiation of RDV ($p= 0.124$), Duration of RDV therapy ($p= 0.172$), Regimen ($p= 0.147$) and Complications ($p= 0.150$). These variables were then moved to a 2-predictor multivariate binomial logistic regression.

Table 5: Bivariate analysis of clinical characteristics and treatment success

	B	S.E.	Wald	Df	p	OR(95%5CI)	AOR(95%5CI)
Hours before initiation of RDV							
Within 72 Hours	-1.194	0.728	2.688	1	0.101	0.303(0.073, 1.263)	0.316(0.074, 1.356)
After 72 Hours	-	-	-	-	-	-	-
Complications							
Yes	-1.081	0.688	2.471	1	0.116	0.339(0.088, 1.306)	0.331(0.061, 1.800)
No	-	-	-	-	-	-	-

$p < 0.05$

B= beta

SE= Standard error

Wald= Wald Chi-Squared Test

Df= Degree of freedom

OR= Odd ratio

aOR= adjusted odd ratio

A binomial logistic regression was performed to determine the effects of hours before initiation of RDV and complications on treatment success. A logistic regression model was statistically insignificant, $x^2=2$, $p>0.05$. The model explained 13.2% of the variance in treatment success and correctly explained 67.1% of the cases. Sensitivity was 0.0%, specificity 100.0%, positive predictive value was 0.0% and negative predictive value was 81.1%. There was no statistically significant association between the two variables with treatment success.

Table 6: Multivariate Binomial Logistic Regression of clinical characteristics by treatment success (2-predictor)

	B	S.E.	Wald	Df	P	OR(95%5CI)	AOR(95%5CI)
Hours before initiation of RDV							
Within 72 Hours	-1.194	0.728	2.688	1	0.101	0.303(0.73, 1.263)	0.311(0.74, 1.310)
After 72 Hours	-	-	-	-	-	-	-
Duration of RDV Treatment							
5 days	0.866	.568	2.319	1	0.128	2.377(0.780, 7.242)	1.211(0.291, 5.047)
6 - 10 days	-	-	-	-	-	-	-

P< 0.05

A binomial logistic regression was performed to determine the effects of hours before initiation of RDV and duration of RDV treatment on treatment success. A logistic regression model was statistically insignificant, $x^2=2$, $p>0.05$. The model explained 8.1% of the variance in treatment success and correctly explained 67.1% of the cases. Sensitivity was 0.0%, specificity 100.0%, positive predictive value was 0.0% and negative predictive value was 81.1%.

Table 7: Multivariate Binomial Logistic Regression of clinical characteristics by treatment success (2-predictor)

	B	S.E.	Wald	Df	p	OR(95%5CI)	AOR(95%5CI)
Hours before initiation of RDV							
Within 72 Hours	-1.194	0.728	2.688	1	0.101	0.303(0.766, 13.988)	0.452(0.096, 2.119)
After 72 Hours	-	-	-	-	-	-	-
Regimen							
RDV	-19.411	40192.970	0.000	1	1.000	0.000	
RDV+Dexa	1.186	0.741	2.559	1	0.110	3.273(0.766, 13.988)	
RDV+Dexa+Azithro	-19.411	14210.361	0.000	1	0.999	0.000	
RDV+Azithro+Colch	-19.411	40192.970	0.000	1	1.000	0.000	
RDV+Dexa+Colch	0.629	0.744	0.713	1	0.398	1.875(0.436, 8.066)	1.992(0.278, 9.126)
RDV+Colch	22.995	40192.969	0.000	1	1.000	-	
RDV+Azithro	1.792	1.514	1.401	1	0.237	6.000(0.309, 116.606)	-
RDV+Dexa+Azithro+Colch	-	-	-	-	-	-	-

$p < 0.05$

A binomial logistic regression was performed to determine the effects of hours before initiation of RDV and regimen on treatment success. A logistic regression model was statistically insignificant, $x^2=2$, $p>0.05$. The model explained 19.7% of the variance in treatment success and correctly explained 67.1% of the cases. Sensitivity was 0.0%, specificity 100.0%, positive predictive value was 0.0% and negative predictive value was 76.7%.

Table 8: Univariate Binomial Logistic Regression of number of co-morbidities by treatment success

	B	S.E.	Wald	Df	p	OR(95%CI)
Number of co-morbidities	0.224	0.318	0.496	1	0.481	1.251(0.671, 2.323

A simple binomial logistic regression was done to determine the effects of number of co-morbidities on treatment success. The logistic regression model was insignificant, p>0.05. The model explained 1% of the variance in treatment success and correctly explained 100.0% of the cases. Sensitivity was 100.0%, specificity 0.0%, positive predictive value was 63.3% and negative predictive value was 0.0%.

Table 9: Univariate Binomial Logistic Regression of number of complications by treatment success

	B	S.E.	Wald	Df	p	OR(95%CI)
Number of complications	-0.102	0.323	0.100	1	0.752	0.903(0.480, 1.700)

Another simple binomial logistic regression was performed to determine the effects of number of patient complications on treatment success. The logistic regression model was insignificant, p>0.05. The model explained 0.2% of the variance in treatment success and correctly explained 100.0% of the cases. Sensitivity was 0.0%, specificity 100.0%, positive predictive value was 0.0% and negative predictive value was 65.8%.

4.6 Association of patient demographic and clinical characteristics with mortality

Table 10: Bivariate analysis of demographics by mortality

	Alive		Died		
	n	%	n	%	p
Sex					0.558
Male	20	47.6	21	56.8	
Female	22	52.4	16	43.2%	
Age					0.940
<65	35	83.3	32	86.5	
≥65	7	16.7	5	13.5	

Pearson Chi square at p< 0.25

A Pearson Chi-square test was done to determine the relationship between the demographic characteristics and mortality. Neither sex (p= 0.558) nor age (p=0.940) was statistically significantly associated with mortality.

Table 11: Bivariate analysis of Clinical Characteristics by Mortality

	Alive		Died		
	N	%	n	%	P
Hours before initiation of RDV					0.738
Within 72 Hours	15	65.2	23	76.7	
After 72 Hours	8	34.8	7	23.3	
Duration of RDV Treatment					0.893
5 days	21	50.0	17	45.9	
6 - 10 days	21	50.0	20	54.1	
Regimen					0.686
RDV	0	0.0	1	2.7	
RDV+Dexa	11	26.2	6	16.2	
RDV+Dexa+Azithro	3	7.1	5	13.5	
RDV+Dexa+Azithro+Colch	16	38.1	12	32.4	
RDV+Dexa+Colch	9	21.4	12	32.4	
RDV+Colch	1	2.4	0	0.0	
RDV+Azithro	1	2.4	1	2.7	
RDV+Azithro+Colch	1	2.4	0	0.0	
History of Covid Treatment					1.000*
Yes	3	16.7	2	13.3	
No	15	83.3	13	86.7	
Mechanical ventilation					0.675
Yes	34	82.9	32	88.9	
No	7	17.1	4	11.1	
Co-morbidities					0.613
Yes	25	59.5	25	67.6	
No	17	40.5	12	32.4	
Complications					0.001
Yes	7	16.7	20	54.1	
No	35	83.3	17	45.9	

*Fisher's Exact Test, p set at <0.05; All others were Pearson's Chi square, p <0.05

A Pearson chi-square test was performed to determine the association between clinical characteristics (except History of COVID-19) and mortality. For History of COVID-19, a Fisher's Exact Test was performed. Only one variable, complications was statistically significantly associated with mortality p=0.001

Since complications were the only significant variable, a multivariate binomial logistic regression could not be done, and a univariate binomial logistic regression would yield more or less the same p-value obtained from this Pearson chi-square test. It was therefore not necessary to proceed with the univariate binomial logistic regression.

4.7 Conclusion

This chapter presented the statistical results from the data collected. The following chapter discusses the implications of these results.

CHAPTER 5 DISCUSSION

5.1 Introduction

This chapter will focus on placing the findings of the current study in context of other published literature and will highlight the implication of these findings.

5.2 Demographic data and clinical characteristics

This retrospective cohort study evaluated the treatment outcomes of remdesivir-based therapy in critical COVID-19 cases at WCH, estimate the treatment success rate of remdesivir-based therapy, and identify factors that may predict treatment outcomes.

The median age of patients was 53 and ranged between 38-60 years. The finding is comparable to the one found by a study led by Burhan *et al.* in patients with moderate to critical illness in Indonesia, whose median age was 55 years (4). Elderly patients (≥ 65 years) accounted for 15.2 % of the patients, which is similar to a study by Luo *et al* in which they made up 12.6% of the patients (33). Prior research has indicated a greater likelihood of experiencing severe illness, increased risk of death, and extended hospital stays among elderly individuals infected with COVID-19 (5,6). The median age for the two studies were 60 (5) and 49 to 70.5 for the meta-analysis (6). These poor results could be ascribed to age-related aspects such as immunosenescence and the presence of various co-morbidities, which are prevalent in elderly patients (36). However, in the current study, both age and co-morbidities were not significantly associated with treatment outcomes. This could be ascribed to the small sample size in this study.

Age was found to be a risk factor of severe symptoms (37). Compared to older patients, younger patients have a lower likelihood of developing severe symptoms (38) because in older individuals, the virus often replicates at a higher rate since viral alert signals and immune

responses are slower to occur, along with a reduction in specific immune cells (39). As people age, changes in lung structure and muscle wasting can have an impact on physiological function, resulting in decreased lung capacity and impaired airway clearance. (40). Further, research has demonstrated that cross immune protection from other coronaviruses or nonspecific protection from other respiratory viruses occurs more frequently in children than in other age groups (38).

From the African context although not from a population of critically ill patients, a study performed in Nigeria reported that the mean age of patients was 40.1years (92) while a study undertaken in Ethiopia had a majority of patients over 54 years with a mean of 39 years (41). Another study carried out in Ethiopia had a median age of 45 years and it showed that age groups above 40 years were more likely to have severe disease compared with those less than 40 years of age (42). It also found out that those more than 60 years had a higher likelihood of dying in comparison to individuals less than 40 years (42).

Regarding sex, the proportions of males to females were the same 51.9% versus 48.1%. This finding contrasts the findings from multiple studies where most patients involved were predominantly males (41,42,85,92–95) and another one by Ali *et al* in Iraq which found that males have a 1.8 times higher likelihood of developing a more serious condition compared to females (37). Although literature indicates that being male is associated with severe infections and higher chances of death (5,6,43) due to heightened susceptibility to the disease, variations in the innate and adaptive immunological responses of males and females (45) and a greater abundance of ACE2 in males than in females (46), that was not the observation in the current study. The observation could be attributed to the small sample size of the study.

The current study found that of the 53 records in which the timing of initiation of remdesivir could be determined, 71.1% were initiated on remdesivir within 72 hours of onset of symptoms.

Early intervention with anti-viral therapy has been shown to decrease disease progression (23,24) because anti-viral therapy is most active in the initial stages of the disease before it progresses to hyper-inflammatory state (8). Other research indicates that initiating remdesivir at an early stage is generally more successful in lowering viral loads and improving clinical results (50–52). In this study however, 76.7% of the patients who received remdesivir within 72 hours of symptom onset had an unsuccessful treatment outcome. A study by Chokkalingam *et al*., found the median duration from admission to the initiation of remdesivir to be 1 day (24 hours) (31). In their study, it was found that starting remdesivir treatment at the beginning (index) was linked to a statistically significant 17% decrease in inpatient mortality (31). In terms of mortality for this study, 76.7% of those who received remdesivir within 72 hours of onset of symptoms died.

Almost all the patients in this study (86%) needed mechanical ventilation at baseline/admission (both invasive and non-invasive). The rest needed other forms of oxygen therapy, mostly low flow oxygen. Multivariate analysis from the Garibaldi *et al* study revealed that low-flow oxygen or no oxygen at admission is linked with reduced time to clinical improvement (23). In the current study, 88.5% of the patients with unsuccessful treatment outcomes needed mechanical ventilation. In terms of mortality in this study, 88.9% of the patients who died were on mechanical ventilation. From literature, remdesivir was found to be most effective in patients who do not require mechanical ventilation (96). Results from the final report of the Solidarity trial by Henao-Restrepo *et al*., indicated that among the patients who were already on ventilation, 151 out of 359 given remdesivir died, which is equivalent to 42.1% of the total while 134 out of 347 patients in the control group died, representing 38.6% of the total. For the patients who were not on ventilation but were on oxygen, 14.6% of those given remdesivir died, while 16.3% of the control subjects died (97)

Slightly more than half of the patients (51.9%) in the current study were on remdesivir therapy for 6-10 days whereas rest were on treatment for 5 days. Among those with a successful treatment outcome, 64.7% were on remdesivir for 5 days whilst among those with an unsuccessful outcome, 56.5% were on remdesivir for 6-10 days. This implies that for this study, treatment with remdesivir for 5 days yielded better outcomes than treatment for 6-10 days, although no significant difference was observed when entered into the multivariate binomial logistic regression. According to Goldman *et al*., it was observed that more patients in the 5 day group showed better clinical improvement than those in the 10-day group (25) although there was no significant difference between remdesivir given for 5-days and 10 days in patients with severe COVID-19 not requiring mechanical ventilation. The authors noted that their results could not be generalized to patients in the current study (25).

The studied patients' vaccination status was largely unknown (91.1%) because it was undocumented. Only 8.9% of the patients were not vaccinated based on documentation of vaccination status in the clinical records. Consequently, the current study could not evaluate the impact of vaccination on treatment outcomes of remdesivir-based therapy. Some studies have demonstrated that vaccination reduces need for hospitalization as patients who required ICU admission were un-vaccinated (35,89). Vaccination also reduces severity of COVID-19 and need for mechanical ventilation including endotracheal intubation (35,89). Vaccination has also been shown to improve treatment outcomes, especially in high-risk patient groups (35,89). Unvaccinated patients with co-morbidities had worse severity and treatment outcomes (89). The mortality rate was considerably lower among the vaccinated as opposed to the unvaccinated (35,89).

In this study, most patients had co-morbidities. From the patients with unsuccessful treatment outcomes, 61.3% had co-morbidities. A study from Vietnam showed that co-morbidities were significantly associated with outcomes of patients with COVID-19 (32). Their results showed

that patients without co-morbidities had a significant chance of having a successful treatment in comparison to those with co-morbidities (32). Another study by Idris *et al.,* from Nigeria found out that patients with co-morbidities had severe presentations and fatal poorer outcomes (92). In their study, patients with co-morbidities had a prolonged mean duration of symptoms compared to those without co-morbidities. Multivariate logistic regression showed that the odds of clinical recovery were lower in patients with hypertension, diabetes and HIV when compared to those with none (92).In this study comorbidities were not significantly associated with treatment outcomes.

In this study hypertension was the most recorded comorbidity, reported in 74% of the patients with co-morbidities, followed by DM reported in 34%, similar to results from studies from Ethiopia and Nigeria (42,92) However, none of these factors were found to be significantly linked to outcomes in this study, unlike in the Nigerian study (92).

In this study, the number of co-morbidities was not statistically significantly associated with treatment outcomes, when it was entered into a univariate binomial logistic regression. In contrast to findings from a substantial UK study of hospitalized COVID-19 patients, which revealed that crude mortality rates among those with multimorbidity were over twice as high as those without multimorbidity (37.2% vs 17.3%), even after accounting for demographic variables (98). Another study from Scotland also identified presence of multiple health conditions as an undisputed risk factor of in-hospital death (99)

Regarding complications, 34.2% of patients were reported to have complications. The most recorded complications were hyperglycemia, followed by ARDS and anemia, as shown in Figure 4. Findings from a comprehensive meta-analysis conducted by Potere *et al* on acute complications and mortality among hospitalized COVID-19 patients across 44 peer-reviewed studies, which involved a total of 14,866 patients from diverse settings revealed that on

average, 14% of the patients in that study developed ARDS, 15% experienced acute cardiac injury, 15% had venous thromboembolism, 6% had acute kidney injury, and 1-41% had coagulopathy. Additionally, 3% of the patients suffered from shock (100). Their research revealed that overall mortality for patients in ICU was 34%, 83% for patients requiring invasive ventilation, and 75% for patients who experienced ARDS. In the current study complications were found to have significant association with mortality (p=0.001) based on bivariate analysis.

Most of the patients (35.4%) were on a regimen consisting of Remdesivir+ Dexamethasone + Azithromycin + Colchicine as part of the COVID-19 regimen protocol, as set out in the COVID-19 Protocol version 1.0 by the Critical Care Society of Namibia (10), shown in Table 1. Multivariate binomial logistic regression found no significant association with treatment outcome and mortality in this study. A meta-analysis involving 1,703 critically ill patients, including the RECOVERY trial with some patients on mechanical ventilation, demonstrated that dexamethasone was effective in reducing mortality among critically ill patients with COVID-19 (101). Subsequent research on immunomodulator therapy found out that co-administration of an additional immunomodulator along with dexamethasone is superior to dexamethasone alone for patients who need mechanical ventilation or ECMO. In particular, a study involving tocilizumab has demonstrated improved overall survival rates for individuals with hypoxemia and systemic inflammation (102) and critically ill patients who require organ support (103). The Critical Care Society of Namibia has recommended the consideration of tocilizumab if no response to steroids (10). Only two of the patients in the current study were on tocilizumab in addition to dexamethasone. In a controlled trial, colchicine failed to show any advantage in terms of treatment outcomes including death at 28-days (104). Regarding the use of azithromycin, a study by Asadi et al, revealed that a combination of azithromycin with hydroxychloroquine had no substantial impact on admission to hospital, death, or use of ventilator (91)

5.2 Treatment success rate

For this study the treatment success rate of remdesivir-based therapy in critically ill patients was found to be 21.5%. An observational study led by Docherty et al. in the UK, involving 20,133 hospitalized patients and utilizing the ISARIC WHO Clinical Characterization Protocol, uncovered that a substantial proportion of patients, amounting to 41% (8,199 out of 20,133), were discharged alive. Seventeen percent of the 18,183 patients (3,001) needed admission either to high dependency unit or intensive care, and of those, 28% (826) were discharged. Among those on mechanical ventilation (1,658), 17% (276) were discharged alive (62). This rate of success for patients receiving mechanical ventilation is somewhat similar to the success rate observed in the current study.

The study conducted by Tran *et al*. in Vietnam discovered that an overwhelming majority of the patients, amounting to 92.3%, were successfully discharged from the hospital (32). Their research demonstrated strong effectiveness and progress. The authors reported that the percentage of patients with "very good" and "good" outcomes was 43.2% on day 3 and 70% on the discharge/transfer day (32). Notably, 55.2% of the patients had negative RT-PCR results on the day of discharge (32). Although the RT-PCR was not conducted on the day of discharge in the current study, the results are still informative. In a study conducted by Oda Yutaka during the third wave of COVID-19, it was found that out of the 587 patients treated at a specialized hospital, 496 (85%) recovered from their respiratory condition (95).

5.3 Other treatment outcomes

Death was the most common outcome accounting for 46.8% of patients. The second most common outcome in 19% of the patients comprised patients who were hospitalised and needed invasive mechanical ventilation.

This mortality rate is comparable to results from a study by Mikiewicz *et al*., in Polish patients requiring hospitalization in the ICU. The results of their research revealed that the mortality rate in the ICU was 44.4% (48/108), mortality after 30 days and 90 days was 50.0% (54/108), and 57.9% (62/108), respectively. They observed that the mortality rate at 90 days was higher for patients who were older (94). In the current study age was however not associated with mortality.

Based on the research by Tran *et al*, it was observed that 1.9% of the patients experienced a more severe illness and were transferred to a hospital with higher levels of care. Additionally, 5.8% of the patients died. Approximately 37.1% of the patients tested positive for RT-PCR with Ct values over 30 on the day of transfer (32).

According to the study by Docherty et al, 26% (5165/20133) of the participants died, while 34% (6769/20133) were still receiving care as of the reporting date. Additionally, 17% (3001/18183) required admission to high dependency or intensive care units and 32% (958/3001) of those died while 41% (1217/3001) continued to receive care at the reporting date. Furthermore, among those who received mechanical ventilation, 37% (618/1658) died, while 46% (764/1658) remained in the hospital (62). A study by Oda Yutaka and colleagues uncovered that the respiratory condition of 81 patients deteriorated; where 51 were transferred to tertiary hospitals and 30 died (95).

5.4 Predictors of treatment outcomes

A bivariate analysis of clinical characteristics and treatment outcome set at p value < 0.25 showed that four variables were eligible for inclusion in the multivariate analysis with treatment success (Table 4). However, none of them were statistically significant when entered into a multivariate binomial regression.

For timing of remdesivir administration, the finding of this study aligns with the findings by Wang and others, in a trial examining the influence of the timing of remdesivir administration on outcomes of severe disease. The trial included subjects who were administered remdesivir either within or after 10 days of onset of symptoms. Although no significance was established, an association was found between remdesivir administered within 10 days from symptom onset and a shorter time to improvement, as well as a lower mortality at 28-days (105). In contrast a study by Hussain *et al* indicates significance between timing of remdesivir relative to onset of symptoms and treatment outcomes. The findings indicated that initiating remdesivir treatment within the first 7 days of onset of symptoms led to a higher proportion of patients recovering by Day 14, decreased need for admission to ICU and mechanical ventilation, and reduced death rates by Day 28 (50). The findings obtained in the current study however may not reflect the reality because only 53 records had an indication on the timing when remdesivir was initiated, 26 records did not have an indication on the timing because the administration schedule was missing.

The findings of the current study with regards to the duration of remdesivir therapy are comparable to those of the Goldman et al study, which demonstrated no statistically significant difference in duration of treatment (5 vs 10 days) (25). Although patients from the Goldman study had a severe disease, they did not require mechanical ventilation, unlike patients in this study. Therefore, results from their study may not be generalized to patients in this study.

Another variable that was included in the regression analysis although no statistical significance was the regimen. Although the effects of several drugs on COVID-19 patients have been studied, the effect on outcome is not yet clear (91). The findings of a study conducted by Asadi on hospitalized patients in Iran indicated that the drug regimens did not have any discernible effect on the rate of death and utilization of ventilators. Nevertheless, it was apparent that the death rate was lower in the remdesivir group in comparison to other study groups (91).

A study carried out in the United States by Garibaldi *et al* examining the difference in time to recovery between remdesivir and remdesivir combined with corticosteroids indicated that the death rate in the remdesivir group was lower, although this difference was not significant (31). The Asadi study also showed that patients on interferons or a combination of interferons and lopinavir/ritonavir were 1.92 times likely to be admitted to ICU compared to those on hydroxychloroquine or hydroxychloroquine with azithromycin (91). Also, the study showed that patients on interferons or combinations of interferons with lopinavir/ritonavir had an extended length of stay in ICU (91).

A meta-analysis by Ye and colleagues on the use of corticosteroids in COVID-19 indicated that corticosteroids were the only treatment found to be effective in decreasing the number of days in hospital(106). A study by Lagier *et al* on 3737 subjects in France, published that the average length of hospitalization in ICU was shorter for patients receiving hydroxychloroquine and azithromycin compared to those on other regimens (107). In Iran Vahedi *et al* found out that the use of antivirals did not have an impact on recovery and instead extended the length of being in hospital in a study comparing two drug regimens (108). In addition, two studies from the US showed that hydroxychloroquine did not have influence on death (109,110). A study by Arshada *et al* found that patients who were hospitalized and treated with

hydroxychloroquine, alone or with azithromycin, experienced a substantial decrease in mortality by 71% (111).

Of all the variables examined in this study, complications were found to be statistically significantly associated with mortality using bivariate analysis (Table 7), implying that there is some association between complications and mortality. In the studied patients slightly more than half of the patients who died had complications and majority of the patients who survived had no complications. Although possibly associated, this association could not be confirmed using a multivariate analysis because complications were the only variable with a $p < 0.25$ to be included in a multivariate model. Therefore, this study cannot with certainty conclude that complications are predictors of mortality among critically ill patients on remdesivir-based therapy at WCH. Nonetheless, it is an important observation that requires further confirmation using multivariate analysis and a bigger sample size because of the high mortality rate (46.8%) observed in this study.

This is consistent with results from a study by Tian *et al* analyzing factors causing mortality in COVID-19 patients which revealed that, patient death was attributed to major complications such as ARDS, heart failure, respiratory failure, septic shock, and multiple organ failures while one case died of gastrointestinal bleeding (85). Some of these complications such as ARDS were observed in patients in the current study and probably contributed to the unsuccessful treatment outcomes observed. A study by Idris et al done in Northwestern Nigeria revealed that, patients with co-morbidities were likely to develop complications ranging from ARDS and acute kidney injury, required oxygen therapy and died compared to those without comorbidities (92).

A study conducted by Bode *et al* assessed the clinical outcomes of COVID-19 patients with or without diabetes or with acutely uncontrolled hyperglycemia across 88 hospitals in the US. The

results revealed that diabetes or uncontrolled hyperglycemia were frequent observations and they led to an extended length of stay in hospital and exhibited a significantly higher death rate in comparison to those without. The mortality rate was particularly elevated among patients with uncontrolled hyperglycemia (112)

A cohort study by Zhang *et al* across multiple centers in Wuhan, involving 312 patients, investigated the relationship between impaired fasting glucose and diabetes with the risk of complications and mortality. The results indicated that individuals with impaired fasting glucose (IFG) and diabetes were at a higher risk of developing ARDS, AKI, and septic shock compared to those with normal fasting glucose (NFG). Patients with IFG and diabetes had a greater risk of developing primary composite events including receiving mechanical ventilation and death, compared to patients with NFG but similar admission rates to ICU. Patients with IFG and diabetes had a higher probability of experiencing primary composite events, such as requiring mechanical ventilation or death, in contrast to those with NFG but all had similar ICU admission rates. Diabetes was found to be a strong indicator of primary endpoints, but IFG was not statistically significant however both IFG and diabetes showed a higher likelihood of death among COVID-19 patients. There was a 31% increased risk of mortality for every standard deviation increase in fasting glucose levels (113)

Another retrospective study by Wang and colleagues on 605 patients, discovered that a fasting blood glucose of 7.0 mmol/l or more upon admission serves as an undisputed predictor for death at 28 days in individuals with COVID-19 and no prior history of diabetes (114). One more study by Yang and others in 120 subjects in Wuhan reached the same conclusion. The study found that Fasting Blood Glucose (FBG) 7mmol/L or more was the only undisputed predictor for 21 deaths. Blood glucose served as an indicator of 25 multi-organ injury and is an earlier predictor for poor outcomes and death in COVID-19 patients (115)

A cohort study by Garcia-Vidal *et al* exploring the incidence, epidemiology, and clinical outcomes of superinfections in 989 hospitalized patients with COVID-19 in Spain revealed that patients with hospital-acquired superinfections had a significantly extended length of hospitalization with higher mortality rates compared to those without complications (116). They have found that co-infections involving bacteria, fungi, and viruses are relatively rare in hospitalized patients. However, when these infections do occur, they can lead to severe illness and poorer outcomes (116)

Anemia was another complication observed in this study. Anemia of inflammation has been described in patients with COVID-19, given the inflammatory processes involved in COVID-19 (117). An observational study by Bergamaschi and others intended to determine the prevalence and significance of anemia in hospitalized patients. The study found that the prevalence of anemia was 61% among 206 COVID-19 patients, which was higher compared to 45% for the control group consisting of 71 patients with symptoms suggestive of COVID-19 but tested negative. The study findings demonstrated that COVID-19 positive patients had a higher mortality rate compared to non-positive patients. Additionally, the results showed that females had a lower level of hemoglobin than males, and a higher prevalence of moderate to severe anemia(117). The relationship between hemoglobin and survival was not established, but rather, survival was impacted by factors such as red cell distribution width, age, lactate dehydrogenase level, and the ratio of arterial partial pressure oxygen to inspired oxygen fraction (117). Lack of laboratory parameters in the current study prevented analysis from being done. Due to the small sample size of the current study, analysis on specific complications against treatment outcomes was not done.

CHAPTER 6 CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

6.1 Introduction

Chapter 5 discussed the findings of the current study in comparison to other research studies. Chapter 6 will present the conclusion as well as recommendations. In this chapter, limitations of the study will also be highlighted.

The aim of this study was to investigate the treatment outcomes of remdesivir in the treatment of COVID-19 patients in critical care at Windhoek Central Hospital. This was achieved through the following specific objectives:

1. To describe the demographic and clinical characteristics of critically ill COVID-19 patients on remdesivir-based therapy admitted to the Critical Care Unit of WCH.
2. To estimate the treatment success rate (successful outcomes) and prevalence of other treatment outcomes (unsuccessful outcomes) of remdesivir-based therapy among critically ill COVID-19 patients admitted to the Critical Care Unit of WCH
3. To identify predictors of treatment outcomes of remdesivir-based therapy among critically ill COVID-19 patients admitted to the Critical Care Unit of WCH

The treatment success rate of remdesivir-based therapy among the study subjects at WCH was low because only 21.5 % of the cases in this study had successful outcomes. As per our definition, these include patients who were discharged home and those who were hospitalized not requiring any supplemental oxygen nor on COVID-19 medical care and transferred to a lower-level facility. This low level of success rate could be attributed to the fact that our patients were all critically ill patients with majority requiring mechanical ventilation at baseline. Remdesivir has been demonstrated not to be beneficial in critically ill patients receiving mechanical ventilation as suggested by results from a study by Garibaldi et al that

routine use of remdesivir in more severely ill patients such as patients in this study may not be of benefit (30).

The treatment outcomes for this study were mainly unsuccessful. Death was the most common outcome accounting for 46.8% of patients. The second most common outcome in 19% of the patients comprised patients who were hospitalised and needed invasive mechanical ventilation. The high mortality rate could probably be attributed to the fact that the patients had a critical disease, as demonstrated by previous research that COVID-19 severity of disease at admission was associated significantly with mortality and is a strong predictor of treatment outcomes, such as death (4,118–120). Critical patients with COVID-19 have an inherent risk of death which may be confounded by factors such as complications and these probably masked the effects of remdesivir on survival.

Factors associated with treatment outcomes were assessed using bivariate analysis and multivariate binomial logistic regression. Although various factors were described from literature that can predict treatment outcomes of remdesivir, from this study only complications were found to be statistically significantly associated with mortality. Other factors such as hours before initiation of remdesivir, duration of remdesivir therapy and regime were not statistically significant in the multivariate binomial logistic regression. Laboratory parameters and radiographic data were not analysed as predictors of unsuccessful treatment outcomes, therefore a detailed study to include them can be performed in the future.

6.2 Study Limitations

Several limitations were encountered in this study which may have affected the findings.

1. This study was a single site study and a hospital-based study; therefore, the findings may not be generalized to other facilities and settings.
2. The study sample was small since it was limited to critically ill patients. The results cannot be generalized to other patient populations.
3. As a result of the retrospective nature of the study, some records were missing while some had missing information particularly the treatment outcomes which led them not to be included in the study.
4. Laboratory results were largely not available; hence they were not included in the data analysis
5. Radiographic results were also not available hence they were also not included in the analysis.
6. Lack of a control or standard of care group prevented this study from establishing a causal relationship between remdesivir and treatment outcomes observed.

6.3 Recommendations

6.3.1 Introduction

Several recommendations can be made from this study. These are made to improve the treatment outcomes of critically ill COVID-19 patients and for possible future research.

6.3.2 Recommendations to improve treatment outcomes of critically ill COVID-19 patients.

1. Since there was no difference in terms of treatment outcomes between giving remdesivir for 5 days and 10 days in this study, for resource-limited countries such as Namibia, this study suggests that remdesivir be administered for 5 days only.
2. Remdesivir initiation should not be limited to the first 72 hours of admission as recommended by the Critical Care Society of Namibia in the COVID-19 treatment protocol. It may be initiated within 10 days of onset of clinical presentations.
3. As per the recommendations in the COVID-19 treatment guidelines by the NIH last updated 21 July 2023, all hospitalized patients who require mechanical ventilation and ECMO should receive dexamethasone together with a second immunomodulator: PO baricitinib or IV tocilizumab. Dexamethasone is not recommended in patients who do not require oxygen supplementation.
4. As per the recommendations in the COVID-19 treatment guidelines by the NIH last updated 21 July 2023, remdesivir should not be used in hospitalised patients requiring mechanical ventilation or ECMO, such as patients in this study.
5. As per the recommendations in the COVID-19 treatment guidelines by the NIH last updated 21 July 2023, remdesivir is also not recommended in hospitalized patients requiring HFNC or NIV expect patients who are immunocompromised, patients with on-going viral replication such as those with low Ct value or patients who are less than 10 days from onset of symptoms.
6. Clinicians should be wary of conventional ICU complications and try to minimize them, given that they are possible predictors of mortality in critically ill patients. These complications include, ARDS, hyperglycaemia, AKI, nosocomial infections such as

hospital acquired pneumonia, catheter-related blood stream infections and even prolonged delirium and/or encephalopathy.

6.3.3 Recommendations to improve future research.

1. Proper documentation of patient records so that all the information necessary for any data collection is available.
2. Further research is needed on laboratory and radiographic parameters as predictors of remdesivir treatment outcomes.
3. A study comparing patients who were on remdesivir and those who were not on remdesivir may be necessary to establish causal relationship of remdesivir to treatment outcomes.
4. Future well-designed and adequately powered studies to investigate effectiveness and safety of remdesivir in the Namibian population.
5. Future research should employ a larger population with a broader spectrum of patient populations to determine the treatment outcomes of remdesivir in these populations.
6. Study employing multivariate analysis between complications and mortality to confirm the association between the two.
7. Study examining the impact of vaccination on COVID-19 treatment outcomes in Namibia.

6.4 Summary

This chapter presented the conclusions, limitations, and recommendations to the MoHSS. The study objectives were all achieved.

6.5 Conclusion of the study

The treatment success rate of remdesivir-based therapy among critically ill COVID-19 patients at WCH was low. This was depicted by the high mortality. Complications were statistically significantly associated with mortality among critically ill patients on remdesivir-based therapy at Windhoek Central Hospital, based on a bivariate analysis, although the association needs further confirmation using multivariate analysis. Further research on laboratory and radiographic parameters as predictors of treatment outcomes is essential

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APPENDICES

ANNEX 1: University of Namibia Ethics Clearance Certificate

SCHOOL OF PHARMACY
University of Namibia, Private Bag 13301, Windhoek, Namibia
Florence Nightingale Street, Windhoek North
URL.: http//www.unam.edu.na

UNAM
UNIVERSITY OF NAMIBIA

DECENTRAILZED ETHICS COMMITTEE (DEC)
Tel: +264 (0) 61 206 5055, Mobile: +264 (0) 816018028
Enquiries: Dr. Francis Kalemeera, Email: fkalemeera@unam.na

18 August 2021

TO: Ms. Meameno Nghikembwa
Student number 201634097

FROM: Dr. Francis Kalemeera
Chair: School of Pharmacy DEC

DATE: 16-November-2021

SUBJECT: **ETHICAL APPROVAL OF RESEARCH STUDY "EFFECTIVENESS OF REMDESIVIR IN THE TREATMENT OF COVID-19 PATIENTS IN CRITICAL CARE AT WINDHOEK CENTRAL HOSPITAL"**

The following matter was discussed at the School of Pharmacy Decentralized Ethics Committee, and the following were recommended.

ETHICAL APPROVAL OF MASTERS IN PHARMACY (CLINICAL PHARMACY).

(1) Reference is made to your application for ethical approval of the above-mentioned study
(2) The proposal and table of corrections have been evaluated and found to have merit.
(3) Kindly be informed that DEC has recommended ethical approval to be granted the University of Namibia Ethics committee to conduct the study.

DEC RESOLUTION: FHSVM/SoP/DEC/11/21/2

DECISION: The School DEC APPROVED research project.

Yours Sincerely,

Dr. Francis Kalemeera

ANNEX 2: University of Namibia Research Permission Letter

CENTRE FOR RESEARCH SERVICES
Office of the Pro-Vice Chancellor: Research, Innovation & Development
University of Namibia, Private Bag 13301, Windhoek, Namibia
340 Mandume Ndemufayo Avenue, Pioneers Park, Office F223 - Fblock, Second Floor
☎ +264 61 206 4673; E-mail:kmbulu@unam.na; URL.: http//www.unam.edu.na

UNAM
UNIVERSITY OF NAMIBIA

RESEARCH PERMISSION LETTER

Date: 19/11/2021

Student Name: Meameno Nghikembwa

Student Number: 201634097

Programme: MASTERS IN PHARMACY (Clinical Pharmacy

Approved Research Title: Effectiveness of Remdesivir in The Treatment of Covid-19 Patients in Critical Care at Windhoek Central Hospital.

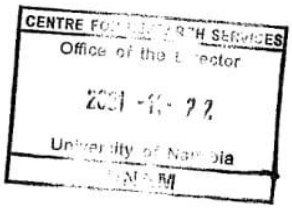
TO WHOM IT MAY CONCERN

I hereby confirm that the above mentioned student is registered at the University of Namibia for the programme indicated. The proposed study met all the requirements as stipulated in the University guidelines and has been approved by the relevant committees.

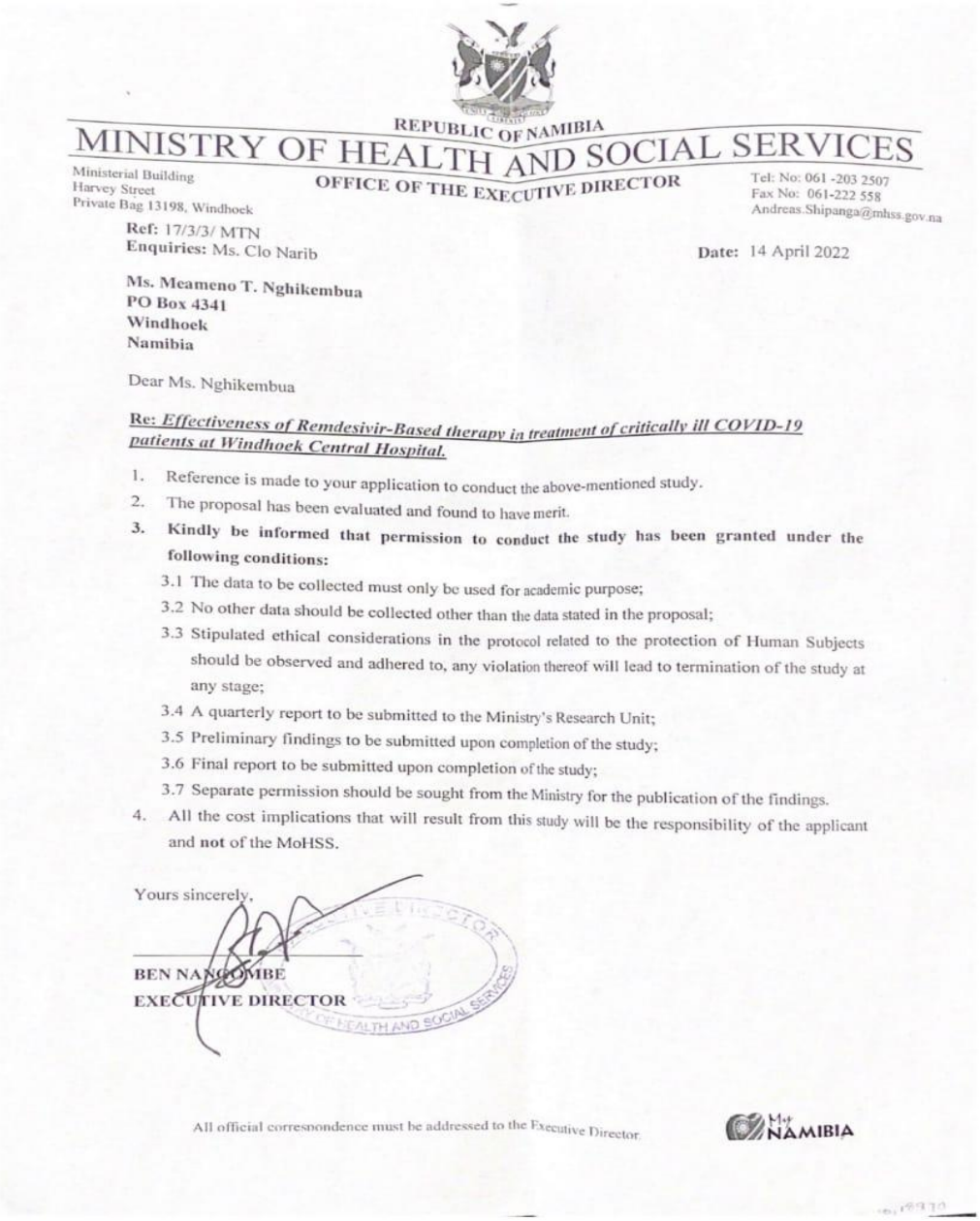
The proposal adheres to ethical principles as per attached Ethical Clearance Certificate. Permission is hereby granted to carry out the research as described in the approved proposal.

Best Regards

Dr. AEE Shikongo
Head: Postgraduate Support Services
Tel: +264 61 206 3129
E-mail: aeshikongo@unam.na



ANNEX 3: Ministry of Health and Social Services Approval Letter



REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

OFFICE OF THE EXECUTIVE DIRECTOR

Ministerial Building
Harvey Street
Private Bag 13198, Windhoek

Tel: No: 061 -203 2507
Fax No: 061-222 558
Andreas.Shipanga@mhss.gov.na

Ref: 17/3/3/ MTN
Enquiries: Ms. Clo Narib

Date: 14 April 2022

Ms. Meameno T. Nghikembua
PO Box 4341
Windhoek
Namibia

Dear Ms. Nghikembua

Re: *Effectiveness of Remdesivir-Based therapy in treatment of critically ill COVID-19 patients at Windhoek Central Hospital.*

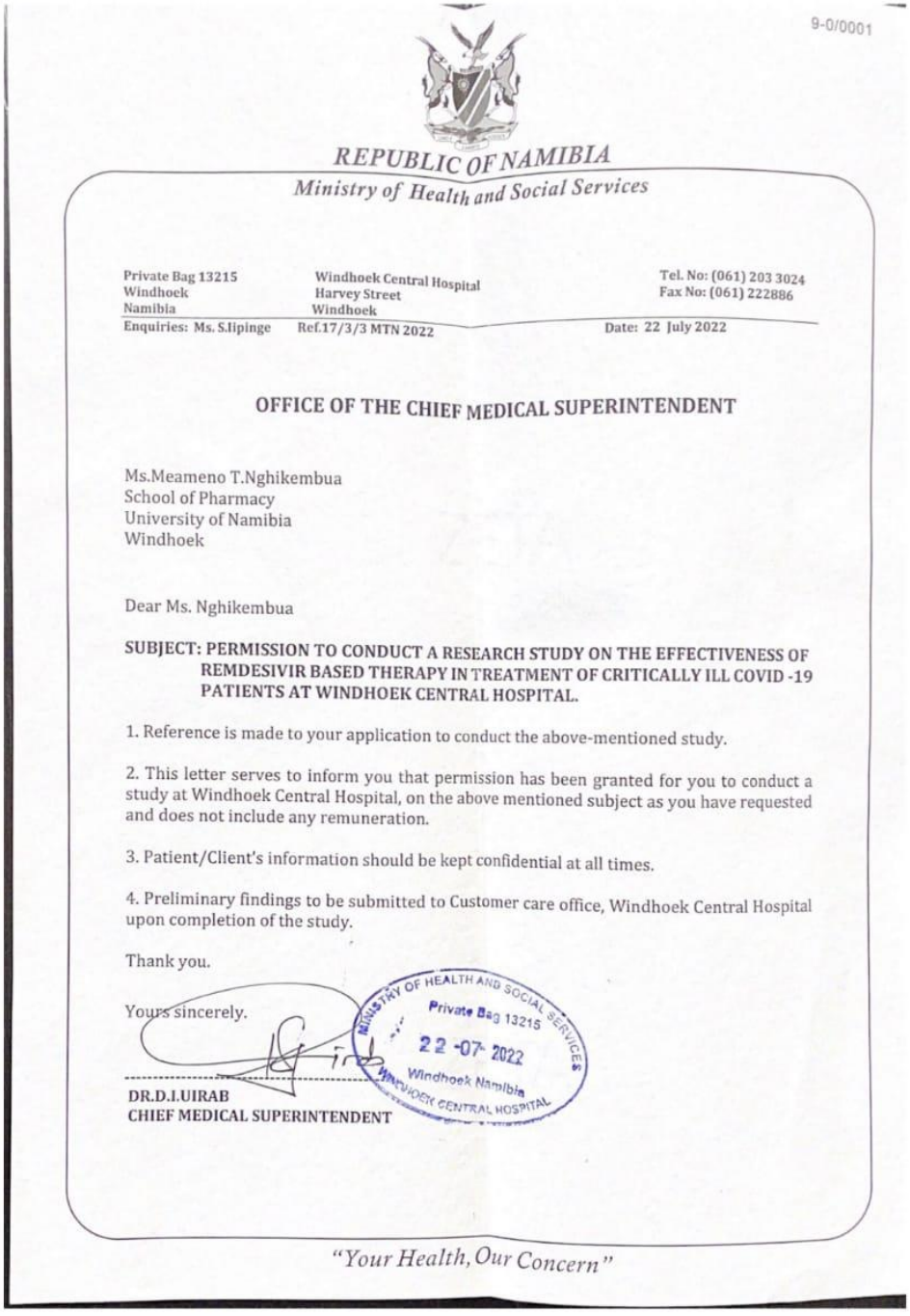
1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
   - 3.1 The data to be collected must only be used for academic purpose;
   - 3.2 No other data should be collected other than the data stated in the proposal;
   - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
   - 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
   - 3.5 Preliminary findings to be submitted upon completion of the study;
   - 3.6 Final report to be submitted upon completion of the study;
   - 3.7 Separate permission should be sought from the Ministry for the publication of the findings.
4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

BEN NANGOMBE
EXECUTIVE DIRECTOR

All official correspondence must be addressed to the Executive Director.

ANNEX 4: Windhoek Central Hospital Waiver of consent



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REPUBLIC OF NAMIBIA
Ministry of Health and Social Services

Private Bag 13215
Windhoek
Namibia

Windhoek Central Hospital
Harvey Street
Windhoek

Tel. No: (061) 203 3024
Fax No: (061) 222886

Enquiries: Ms. S.Iipinge Ref.17/3/3 MTN 2022 Date: 22 July 2022

OFFICE OF THE CHIEF MEDICAL SUPERINTENDENT

Ms.Meameno T.Nghikembua
School of Pharmacy
University of Namibia
Windhoek

Dear Ms. Nghikembua

SUBJECT: PERMISSION TO CONDUCT A RESEARCH STUDY ON THE EFFECTIVENESS OF REMDESIVIR BASED THERAPY IN TREATMENT OF CRITICALLY ILL COVID -19 PATIENTS AT WINDHOEK CENTRAL HOSPITAL.

1. Reference is made to your application to conduct the above-mentioned study.

2. This letter serves to inform you that permission has been granted for you to conduct a study at Windhoek Central Hospital, on the above mentioned subject as you have requested and does not include any remuneration.

3. Patient/Client's information should be kept confidential at all times.

4. Preliminary findings to be submitted to Customer care office, Windhoek Central Hospital upon completion of the study.

Thank you.

Yours sincerely.

MINISTRY OF HEALTH AND SOCIAL SERVICES
Private Bag 13215
22 -07- 2022
Windhoek Namibia
WINDHOEK CENTRAL HOSPITAL

DR.D.I.UIRAB
CHIEF MEDICAL SUPERINTENDENT

"Your Health, Our Concern"

ANNEX 5: Data Abstraction Tool

Section A: Patient-Related Factors

<table>
<tr><td colspan="3">Part A: Socio-demographic information of the patient</td></tr>
<tr><td>101) REG number:</td><td colspan="2">Initials of data collector: _____ Date: _____</td></tr>
<tr><td>Date admitted: _____</td><td colspan="2">Date: Discharged/Died _____</td></tr>
<tr><td>102) Sex of the patient
1. □ Male
2. □ Female</td><td>103) Age (years): _____

104) Vaccination status
□ Not vaccinated □ First dose only □ Fully vaccinated</td><td>105) Type of Covid-19 Case
1. □ New, Direct case
2. □ New, Referred case
3. □ Retreatment case</td></tr>
<tr><td>106) Residence
1. □ Windhoek
2. □ Windhoek suburbs
3. □ Other regions_____</td><td>107) Employment status
1. □ Formal employment
2. □ Informal employment
3. □ Not employed</td><td>108) Marital status
1. □ Married
2. □ Not married
3. □ Divorced/widowed</td></tr>
<tr><td>109) Smokes
1. □ Yes
2. □ No</td><td>110) History of Alcohol
1. □ Yes
2. □ No</td><td>111) Intensive Care Unit
1. □ Yes
2. □ No</td></tr>
<tr><td colspan="3">Part B: Baseline clinical characteristics</td></tr>
<tr><td>112) History of Covid-19
1. □ Yes
2. □ No</td><td>113) Severity of prior infection
1. □ Mild
2. □ Moderate
3. □ Severe</td><td>
4. □ Very Severe
5. □ Not applicable</td></tr>
<tr><td>114) Patient on ventilator*
1. □ Yes
2. □ No</td><td>115) Severity of current infection
6. □ Mild
7. □ Moderate
8. □ Severe</td><td>
9. □ Very Severe
10. □ Not applicable</td></tr>
<tr><td>116) Co-morbidities:
1. □ Yes
2. □ No</td><td colspan="2">117) Co-morbidities:
11. □ HPT 14. □ COPD
12. □ DM 15. □ Obesity
13. □ Cancer 16. □ Other:_____</td></tr>
<tr><td>118) Secondary-infections
3. □ Yes □ Bacterial
4. □ No □Viral

Organism (specify):</td><td>119) Secondary-infections
17. □ Respiratory (LRTI)
18. □ GIT
19. □ Septicaemia</td><td>
20. □ Genitourinary
21. □ Skin
22. □ Other:_____</td></tr>
<tr><td>120) Baseline Vital signs
1. BP _____</td><td>121) Baseline ABGs
1. PH _____</td><td>122) Baseline U&Es
1. Na+ _____</td></tr>
</table>

2. Temp _____ 3. RR* _____ 4. PR _____ 5. SpO2 _____ 6. BMI _____ 7. Pain scale _____	2. PaO2* _____ 3. PCO2 _____ 4. HCO3 _____ 5. PaO2/FiO2* _____	2. K+ _____ 3. HCO3 _____ 4. Cl- _____ 5. BUN _____ 6. Scr _____ 7. CrCl _____
Part C: Baseline Laboratory tests		
123) Absolute WBC 1. Neutrophils _____ 2. Lymphocyte _____ 3. Monocyte _____ 4. Eosinophils _____ 5. Basophil _____	124) RBC 1. HB _____ 2. RBC _____ 3. HCT _____ 4. Ferritin _____ 5. MCV _____	125) PLT 1. D-dimer _____ 2. PLT _____ 3. INR _____
126) Specialist tests 1. CPR _____ 2. LDH _____ 3. Troponin _____ 4. Ferritin _____	127) LFT 1. ALB _____ 2. ALT _____ 3. AST _____	128) RFT 4. Scr _____ 5. BUN _____ 6. AST _____
Liver function during treatment 1. □ Yes 2. □ No	Renal function during treatment 1. □ Yes 2. □ No	If abnormal, treatment continued 1. □ Yes 2. □ No
Part D: Treatment given		
Medication	Duration (days)	Dose
1. □ Remdesivir		
2. □ Dexamethasone		
3. □ Azithromycin		
4. □ Colchicine		
5. □ Other 1:		
6. □ Other 2:		
7. □ Other 3:		
8. □ Other 4:		
9. □ Other 5:		
10. Adverse effects experienced	Yes Specify: _____	No
11. Medication for Co-morbidities Medication	 Dose	 Treatment schedules
Part E: Treatment outcomes		
Treatment successful	Treatment Outcome	Developed complication

1. □ Yes 2. □ No	1. □ Cured/Discharged 2. □ Referred 3. □ Died 4. □ hospitalized, receiving invasive mechanical ventilation 5. □ hospitalized, receiving non-invasive ventilation or high-flow oxygen devices 6. □hospitalized, requiring low-flow supplemental oxygen 7. □ hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19); 8. □ hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration)	1. □ Yes 2. □ No Specify complication: □ Viral pneumonia □ Bacterial pneumonia □ Hyperglycemia □ Acute renal failure □ Anemia □ ARDS □Others (specify): Treatment of complication:
Days of hospitalization	Days in ICU hospitalization (days)	Days in general ward

Section B: Drug administration schedule

Day	Time of admin	Remdesivir	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
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20									
21									
22									
23									
24									
25									
26									
27									
28									
29									
30									

NB: Indicate dose of all drugs administer