CLINICAL, HEMATOLOGICAL, AND BIOCHEMICAL CHARACTERISTICS AS WELL AS TREATMENTS ADMINISTERED AND PREDICTORS OF SURVIVAL IN COVID-19 PATIENTS HOSPITALIZED AT SELECTED CENTRAL HOSPITALS IN MALAWI: A RETROSPECTIVE STUDY

BY

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A Dissertation submitted to the University of Zambia in partial fulfilment of the requirements of the degree of Master of Science in One Health Laboratory Diagnostic Sciences

THE UNIVERSITY OF ZAMBIA

LUSAKA

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DECLARATION

I, Ackim Munthali, declare that the study entitled 'Clinical, Hematological, And Biochemical Characteristics as Well as Treatments Administered and Predictors of Survival in Covid-19 Patients Hospitalized at Selected Central Hospitals in Malawi: A Retrospective Study' is my own original work. To the best of my knowledge, this study has not been presented to any other university for a similar or any other degree award. I also declare that all the sources I have used have been cited and acknowledged by means of complete references.

Signature  ..... Date…16/05/2024…….

CERTIFICATE OF APPROVAL

The University of Zambia approves the dissertation submitted by ACKIM MUNTHALI, as fulfilling the partial requirements for the award of the Master of Science in One Health Laboratory Diagnostic Sciences by the University of Zambia

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ABSTRACT

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). It can present as asymptomatic, mild, or severe pneumonia, with the latter exhibiting signs of multiorgan dysfunction and contributing to millions of deaths. Limited predictive laboratory markers for identifying COVID-19 severity across populations, including Malawi, delays timely intervention. Hence, this study assessed the clinical, hematological and biochemical characteristics, as well as administered treatments, and predictors of survival in COVID-19 patients hospitalized in Malawi. The study employed a retrospective design of 367 COVID-19 patients hospitalized between 2020 and 2022 at Mzuzu, Queen Elizabeth, and Zomba Central Hospitals. The data was analyzed using IBM SPSS version 26. Numerical variables were checked for normality by Kolmogorov-Smirnov test and compared between survivors and non-survivors by Mann–Whitney *U*-test. Categorical variables were compared by either Chi-square test or Fisher's exact test where applicable. Univariate and multivariate regression were conducted to ascertain parameters associated with survival during hospitalization. Statistical significance was defined as $p< 0.05$ for all tests. Of the 367 cases, 59.1% were survivors, with a median age of 44 years, and 40.9% were non-survivors, with a median age of 50.5 years. The majority (51.5%) were males. Overall prevalence of comorbidities was 51.2%, that included HIV (22.9%), hypertension (20.4%), and diabetes mellitus (15.8%). Predominant signs and symptoms were cough (83.1%), dyspnea (78.2%), fever (70.8%), and headache (60.2%). Hematological characteristics displayed elevated leukocytes, neutrophils, and Neutrophil-to-Lymphocyte Ratio in non-survivors. Biochemical characteristics indicated high median levels of γ-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Markedly high levels of aspartate transaminase (AST), alanine transaminase (ALT), γ-GT, ALP, LDH, urea, and creatinine (Cr) were in non-survivors. Treatments administered included antibiotics, glucocorticoids, oxygen therapy, enoxaparin, omeprazole, vitamins, zinc, and nevirapine. Non-survival was associated with old age, low oxygen saturation, increased levels of ALT, Cr, LDH, and low albumin alongside hydroxychloroquine use. Thus, the findings suggest that COVID-19 patients who are elderly and present with high levels of ALT, LDH, and creatinine, as well as low albumin and oxygen saturation at the time of admission, should be prioritized for timely and appropriate intervention.

DEDICATION

Dedicated to my father, Ackim Felix Munthali, and my late mother, Doras Tchuwa.

ACKNOWLEDGEMENTS

With the grace of God in Christ, I am happy to complete this academic endeavor. I extend my heartfelt appreciation to my supervisors, Dr. Ethel M'kandawire, and Dr. Nozyechi N. Chidumayo for their unwavering guidance and support in shaping this study. Special thanks to my sponsors, the Africa Centre of Excellence for Infectious Diseases of Humans and Animals (ACEIDHA).

I am deeply grateful to my family and friends for their constant support and encouragement. My sincere thanks also go to all my classmates and friends at the University of Zambia for their valuable suggestions, encouragement, and cooperation during my studies.

Lastly, my great appreciation extends to the Management and Health Information Systems/Records Departments at Mzuzu Central Hospital, Queen Elizabeth Central Hospital, and Zomba Central Hospital for their assistance and support in organizing patient records and making data collection feasible.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

ACRONYMS AND ABBREVIATIONS

ACE 2	Angiotensin Converting Enzyme 2
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (Alanine Aminotransferase)
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Transaminase (Aspartate Aminotransferase)
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Kinase
CNS	Central Nervous Systems
CoV	Coronaviruses
COVID-19	Coronavirus Disease-2019
Cr	Creatinine
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
CRP	C-Reactive Protein
CT	Computed Tomography
GGT/ γ-GT	Gamma Glutamyl Transaminase
HB	Hemoglobin Concentration
HCT	Hematocrit
HIV	Human Immunodeficiency Virus
hsTnI	High-Sensitivity Troponin I
HCoV	Human Coronaviruses
IATs	Isothermal Amplification Techniques
ICU	Intensive Care Unit
IFN-γ	Interferon-γ
IL	Interleukin
LAMP	Loop-Mediated Isothermal Amplification
LDH	Lactate Dehydrogenase
LYMP	Lymphocyte

MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MLR	Monocyte–Lymphocyte Ratio
MRI	Magnetic Resonance Imaging
MZCH	Mzuzu Central Hospital
NAAT	Nucleic Acid Amplification Testing
NEAR	Nicking Enzyme-Assisted Reaction
NEUT	Neutrophil
NGS	Next Generation Sequencing
NHSRC	National Health Sciences Research Committee
NLR	Neutrophil to Lymphocyte Ratio
NT-proBNP	N-terminal Pro B-type Natriuretic Peptide
PCR	Polymerase Chain Reaction
PCT	Procalcitonin
PLT	Platelet
PPI	Proton Pump Inhibitor
QUECH	Queen Elizabeth Central Hospital
RAAS	Renin-Angiotensin-Aldosterone System
RBC	Red Blood Cell
RBD	Receptor Binding Domain
RdRp	RNA dependent RNA polymerase
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
RPA	Recombinase Polymerase Amplification
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
TBil	Total Bilirubin

TMA	Transcription-Mediated Amplification
TNF-α	Tumor Necrotic Factor - α
TP	Total Serum Protein
Ur	Urea
WBC	White Blood Cell
WHO	World Health Organization
ZMCH	Zomba Central Hospital

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Coronavirus Disease-2019 (COVID-19) is an infectious respiratory disease caused by a virus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This virus belongs to the Betacoronavirus species of Coronaviridae family, which can be found in various animals, such as birds, bats, snakes, and mammals (Borczuk and Yantiss, 2022). Structurally, SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) virus (Kaul, 2020). In December 2019, the outbreak of SARS-CoV-2 infection started in Hubei province, China, among patients who had pneumonia of unknown origin (Deng, *et al.,* 2020a). Researchers later isolated and sequenced the virus and determined that it spreads through respiratory droplets and direct contact (Lu *et al*., 2020). The virus quickly spread across the world, leading the World Health Organization (WHO) to declare it a pandemic (WHO, 2020a). As of 17 December 2023, the pandemic caused more than 772 million cases and close to seven million deaths globally (WHO, 2023a) and in Malawi, the pandemic has caused more than 88,000 cases and over 2,600 deaths (Ministry of Health, Malawi [MOH], 2023).

SARS-CoV-2 infection can occur as an asymptomatic case, mild case, and severe form of pneumonia (Aloisio *et al.*, 2020). The mild case presents with fever, rhinitis, cough, body aches among other non-specific signs and usually do not require hospitalization (Deng *et al.*, 2020a). In others, especially the aged and those with underlying medical comorbidities, COVID-19 develops into a severe form of pneumonia and systemic disease which requires hospitalization, intensive care support and mechanical ventilation (Letelier *et al*., 2021). The severe form of COVID-19 presents with clinical signs of pneumonia including fever, cough, dyspnea, plus respiratory rate of >30 breaths/min, or severe respiratory distress (García de Guadiana-Romualdo *et al*., 2021). When the pneumonic signs and symptoms worsen, patients present with respiratory failure and cardiac failure thus progressing into critical stage which is also evidenced by chest imaging abnormalities such as bilateral opacities and pulmonary infiltrates (WHO, 2022).

The severe form of COVID-19 also shows signs of multi-organ dysfunction including altered mental status, difficult breathing, low oxygen saturation, reduced urinary output, fast heart rate, weak pulse, and low blood pressure (Huang *et al.*, 2020; Bennett *et al.*, 2021). Further, laboratory tests reflect evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, and hyperbilirubinemia (Borczuk and Yantiss, 2022; WHO, 2022). The severe and critical forms of COVID-19 are life threatening, associated with high mortality, morbidity and require immediate intervention. The immediate intervention of severe COVID-19 cases needs accurate predictive methods for early detection of severe forms of disease. However, consensus on the accurate predictive methods has not been reached for clinical applications, given that the disease has recently emerged and the diversity of clinical features as well as laboratory tests (Favaloro and Lippi, 2020). Consequently, clinical data and different laboratory tests have been used to understand the nature of the disease and have been recommended for assessment of prediction of severity (Bastug *et al.*, 2020).

Apart from molecular and serological laboratory specific tests for detecting SARS-CoV-2, there are also other routine tests which are used for further assessment of COVID-19 patients. These tests include routine biochemical and hematological tests that play important roles in assessing diseases' severity, prognosis, following up patients, directing treatment and management (Christensen *et al*., 2020; Deng *et al*., 2020b). The previous studies on clinical and laboratory features of COVID-19 patients suggested that certain changes in laboratory tests can be useful early predictors of severe COVID-19 and can be useful for guiding timely treatment (Favaloro and Lippi, 2020; Kwaan, 2020). Subsequent studies have also indicated that SARS-CoV-2 affects many organs and several laboratory tests are deranged in COVID-19 cases (Asghar *et al*., 2020a; Blomme *et al*., 2022; Sepulchre *et al.*, 2022).

The changes detected in the laboratory profiles of COVID-19 patients, along with their clinical features and administered treatments, have been associated with the severity of SARS-CoV-2 infection (Benenett *et al*., 2021; N'dilimabaka *et al* 2022). For instance, clinical signs and symptoms, including dyspnea, rapid respiratory rate, and oxygen desaturation, have been mentioned as indicators of disease severity in some populations (Benenett *et al*., 2021; Colombo *et al*., 2022).

Moreover, evaluation of hematological and biochemical tests, such as complete blood count (CBC), liver enzymes, markers of renal function, C-reactive protein (CRP), procalcitonin (PCT), interleukin 6 (IL-6), and tests for anticoagulation, has provided insights into disease progression and tissue damage (Sood *et al*., 2020; Satis *et al*., 2021). These clinical and laboratory features have also been linked with poor outcomes during hospitalization (Sadiq *et al.,* 2021). Hence, it is necessary to identify the predictors of COVID-19 outcomes through the evaluation of clinical and laboratory features at the time of admission. This enables the identification of parameters essential for estimating disease severity and prognosis as recommended by Coopersmith *et al*. (2021). To study more on clinical and laboratory parameters along with treatments administered and their roles in prediction of COVID-19 outcomes, this study assessed the clinical, hematological and biochemical characteristics as well as treatments administered in hospitalized patients infected with SARS-CoV-2 among Malawians.

1.2 Statement of the Problem

Severe COVID-19 has caused over 6.8 million deaths globally (WHO, 2023a) and there have been more than 89,500 cases as well as at least 2,680 deaths in Malawi (MOH, 2023). Beyond mortalities and morbidities, COVID-19 has had profound social and economic impacts in Malawi. These include disruptions in labor and production, increased unemployment rates, challenges in crop sales, closure of schools, travel and transport restrictions, reduced tourism, bans on sports and entertainment events, and reduced tobacco exports (MwAPATA Institute, 2020; Magalasi, 2021).

Since COVID-19 is a recent and an emerging viral infection, knowledge on the best parameters to predict the disease severity in different populations prior to life-threatening clinical outcomes is limited (Cobre *et al*., 2021; Karim Shahri *et al*, 2021). Moreover, there is limited knowledge on the roles that biochemical and hematological parameters play in prediction of disease outcomes which deters timely detection of disease severity, hence affecting timely action (Sadiq., *et al*., 2021; Alizad *et al*., 2023). Consequently, COVID-19 that is developing into severe stages continues to cause mortality, and morbidity with increased hospitalization (Keisam *et al.*, 2022), increased pressure on limited health resources and related social and economic impacts in the communities (Chinkhumba *et al.*, 2023). Aside from the limited knowledge on the roles of laboratory parameters in predicting disease outcomes, there is limited to no published literature to show the proportions

of different treatments administered to COVID-19 patients hospitalized in Malawi and their associated outcomes (Bepouka *et al.*, 2022).

1.3 Justification of the Study

SARS-CoV-2 can infect many systems and activate inflammatory reactions, thereby causing severe damage to major body organs such as the lungs, liver, and kidneys (Thakur *et al*., 2021). As a result, clinical features are diverse, and various laboratory parameters like hematological and biochemical tests are altered in COVID-19 patients (Asghar *et al*., 2020a; Alballa and Al, 2021). To improve the outcomes of the severe form of the disease, there is a need of a way to accurately and timely predict the severity of COVID-19 in different populations (coppersmith *et al*., 2021).

One of the approaches in predicting COVID-19 severity is the use clinical and laboratory features of COVID-19 patients (Letelier *et al.,* 2021). This can be done by assessing the clinical, hematological, and biochemical features, as well as treatments administered in hospitalized COVID-19 patients, and identify potential parameters associated with survivors and non-survivors (Letelier *et al.*, 2021; Sadiq *et al.,* 2021). Preliminary assessment can be conducted cost-effectively and time-efficiently using a retrospective design, as hospitals routinely generate clinical, hematological, and biochemical test data as part of patient management processes (Sulejmani *et al.,* 2021). Therefore, a retrospective study on clinical, hematological, and biochemical characteristics, as well as treatments and predictors of survival in hospitalized COVID-19 patients in Malawi, was conducted to identify the predictors associated with survival and non-survival states. The identification of the predictors may provide insights for the timely identification of patients at higher risk of adverse disease outcomes for prompt management. The study may also enhance the understanding of the progression of COVID-19 in relation to routinely generated clinical and laboratory data (Bustag *et al.,* 2020; Letelier *et al.,* 2021). Additionally, establishment of information on the proportions of different treatments administered to COVID-19 patients hospitalized in Malawi and their associated outcomes can assist in adjusting treatment options to improve patient outcomes and in deciding on adequate stocking of the required treatment options.

1.4 Research Questions

1. What are the clinical characteristics of hospitalized COVID-19 patients?
2. What are the hematological characteristics of hospitalized COVID-19 patients?
3. What are the biochemical characteristics of hospitalized COVID-19 Patients?
4. What are the treatments administered to hospitalized COVID-19 patients?
5. What are the predictors of survival in hospitalized COVID-19 patients?

1.5 General Objective

The aim of this study was to assess the clinical, hematological and biochemical characteristics, as well as the treatments administered and predictors of survival, in COVID-19 patients hospitalized at the selected Central Hospitals in Malawi.

1.6 Specific Objectives

The specific objectives were:

1. To determine the clinical characteristics of hospitalized COVID-19 patients.
2. To assess the hematological characteristics of hospitalized COVID-19 patients.
3. To assess the biochemical characteristics of hospitalized COVID-19 Patients.
4. To determine the treatments administered to hospitalized COVID-19 patients
5. To identify the predictors of survival in hospitalized COVID-19 patients

1.7 Scope of the Study

This study analyzed the clinical characteristics, hematological and biochemical test parameters, and treatments administered in COVID-19 patients who were hospitalized in Malawian central hospitals, specifically at Mzuzu, Queen Elizabeth, and Zomba Central Hospitals. The study gathered data from hospital information systems on age, sex, clinical signs and symptoms, comorbidities, hematological and biochemical test results, and treatment instituted in COVID-19 patients who were admitted in the mentioned hospitals between 2020 and 2022. The hematological parameters that were gathered for statistical analysis included total leukocyte/white blood cell count (WBC), neutrophil (NEUT), and lymphocyte (LYMP) counts, total red blood cell count (RBC), hematocrit (HCT), hemoglobin concentration (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood

cell distribution width (RDW), and platelet count (PLT). The individual biochemical test results that were gathered and analyzed statistically included urea (Ur), creatinine (Cr), lactate dehydrogenase (LDH), total serum protein (TP), albumin (Alb), total bilirubin (TBil), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma glutamyl transaminase (GGT).

1.8 Operational Definitions

In the context of this study, the subsequent terms have been defined as follows:

1. **Biochemical characteristics**: Description of changes in measurable biological markers including blood urea nitrogen, creatinine, lactate dehydrogenase, total serum protein, albumin, total bilirubin, aspartate transaminase, and alanine transaminase present in the patients' blood that may provide insights into the disease's progression or severity.
2. **Biomarkers**: Measurable biological indicators that can be detected in a patient's blood, urine, or other bodily fluids to provide information about the disease's progression, severity, or response to treatment.
3. **Central hospitals**: Regional referral hospitals for the District Hospitals that offer comprehensive medical services, including advanced diagnostic and treatment capabilities.
4. **Coronaviruses**: These are enveloped positive sense single stranded RNA viruses, which are named for their crown-like spikes on their surface and can cause illness in both humans and animals. Among the types of coronaviruses that can infect humans are the severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.
5. **COVID-19 Severity:** The degree of illness and the extent of damage caused by the SARS-CoV-2 virus in infected individuals and can vary widely, ranging from asymptomatic, mild symptoms to severe illness that requires hospitalization and can be life-threatening.
6. **Demographic characteristics:** Attributes of a study population, including age and sex.
7. **Hematological characteristics**: Description of changes in the patient's blood cell counts and blood cell related features. This information can assist in determining treatment decisions and monitoring disease progression and the patient's recovery from the disease.
8. **Non-survivors:** Category of hospitalized COVID-19 patients who died during hospitalization.

9. **Survivors:** Category of hospitalized COVID-19 patients who were discharged from the hospitals.
10. **Treatments:** Specific interventions, therapies, and procedures administered to hospitalized COVID-19 patients upon confirmation of SARS-CoV-2 positivity.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 General Overview of Coronaviruses, SARS- CoV-*2* and COVID-19

Coronaviruses (CoVs) are enveloped, positive sense, single stranded RNA viruses. They are classified in the order Nidovirales, suborder Cornidovirineae, and family Coronavirideae (Walker *et al.*, 2020). Further, coronaviruses have been grouped into four genera as Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses, and Deltacoronaviruses. Alphacoronaviruses and Betacoronaviruses have been isolated in mammals while Gammacoronaviruses and Deltacoronaviruses have been associated with birds (Ludwig and Zarbock, 2020). SARS-CoV-2 is a species of coronaviruses in the genus betacoronavirus (Walker *et al.*, 2020).

The first described coronavirus, infectious bronchitis virus (IBV) was isolated from chicken embryos in 1937 (Beaudette and Hudson, 1937). Since then, CoVs have been detected in wild animals, farm animals, pets, and humans. CoVs in animals have been associated with mild to severe intestinal, respiratory, and systemic diseases (Saif, 2004). Investigations show that there are diverse types of CoVs in animals and researchers suggest that some of these CoVs are zoonotic and humans can be infected from animals (Saif, 2004; Drexler *et al*., 2014, Latif and Mukaratirwa, 2020).

Early reports on human coronaviruses (HCoVs) started to be published in 1960s in which HCoV-229E and HCoV-OC43 were isolated and described (McIntosh *et al*., 1967; Hamre and Procknow, 2016). There are four HCoVs (229E, OC43, NL63, and HKU1) that cause endemic mild upper and lower respiratory CoV infections (common cold) (Drexler *et al.*, 2014). CoVs do not only cause mild infections as evidenced by the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002-2003. This changed the perception that CoVs could not cause serious human respiratory diseases. SARS-CoV caused 8000 cases with a case fatality of 9.5% (Drosten *et al.*, 2003). Additional studies on SARS-CoV reported that similar viruses were isolated in bats and civet cats and the authors suggested that the virus might have come from civet cats to humans and spread among humans by human-to-human transmission (Corman *et al.*, 2018).

Another highly pathogenic CoV to mankind emerged in 2012 in Arabian Penisula and it was named Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This virus was isolated from a

patient with acute pneumonia in Saudi Arabia (Moh Zaki *et al.*, 2012). MERS caused an approximate of 2,500 cases with case fatality rate of 30% and its transmission was reported to be of both human to human and by contact with animals especially camels (Mackay and Arden, 2015). In December 2019, a Betacoronavirus was discovered through whole genome sequencing, Polymerase Chain Reaction (PCR) and culture of samples from patients with unusual pneumonia who were epidemiologically linked to seafood and animal wholesale market in Wuhan, China (Zhu *et al.*, 2020). The virus was initially named novel corona virus 19 (2019 nCoV) as it was phylogenetically related to other Betacoronaviruses like SARS-CoV and MERS-CoV, which also cause severe pneumonia in humans (Lu *et al*., 2020). Subsequent findings established that the cases of unusual pneumonia were due to an infection by this 2019 nCoV and the disease was named COVID-19 by WHO (WHO, 2020a). The virus itself was later named SARS-CoV-2 by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (Gorbalenya *et al.*, 2020). Generally, infection by SARS-COV-2 presents with features of viral respiratory illness. The infected individuals can be asymptomatic or symptomatic with complaints of fever, cough, headache, and breathlessness. In some patients, these signs progress into severe state and clinically they present with respiratory failure, shock, acute respiratory distress, and sepsis (Kaul, 2020).

SARS-CoV-2 spread and affected many countries despite several attempts made to contain the disease in China (Sohrabi *et al.*, 2020). On January 30th, 2020, the WHO declared COVID-19 as a public health emergency of international concern (WHO, 2020b). The virus spread globally and in March 2020, COVID-19 was declared a pandemic by WHO (WHO, 2020a). Globally as of December 17, 2023, over 772 million confirmed cases of COVID-19 pandemic, including nearly seven million deaths were reported to WHO (WHO; 2023a). The pandemic has affected many countries including Malawi. Malawi reported its first COVID-19 case on 2nd April 2020. As of 17th December 2023, at least 88,000 confirmed case were reported including 2,600 deaths (MOH; 2023).

Apart from the millions of cases and deaths, COVID-19 also shook up the socio-economic order of the world with interventions to reduce the spread of the pandemic. Importantly, to reduce the effects of COVID-19 there has been a speeding up of scientific research such as understanding the nature of the disease and virus as well as the development of various vaccines (Delardas *et al.*, 2022). After the successful introduction of vaccination programmes, the world experienced some relief

but research on understanding the nature of COVID-19, diagnostics and treatments is still on going as the COVID-19 cases continue being reported.

2.2 Structure and Variants of SARS-CoV-2

SARS-CoV-2 virion structure resembles the structure of other CoV. CoVs have a spherical shape with club-shaped spikes forming a crown-like structure (corona). Each virion is composed of an envelope, structural spike protein (S), membrane (M) protein (membrane glycoprotein), envelope (E) protein, nucleocapsid (N) protein, non-structural proteins and an RNA genome as shown in Figure 2.1 (Kaul, 2020). The envelope is made up of a lipid bilayer derived from the host cell and the viral surface proteins (S, M and E proteins) are embedded in the envelope (Kaul, 2020).

The genome of SARS-CoV-2 is made up of a non-segmented single stranded positive sense RNA. Its size ranges from 26 to 35 kilobases. This RNA genome codes for approximately 29 proteins which include both structural and nonstructural proteins (Yao *et al.*, 2020). The first open reading frame (ORF 1a and ORF 1b) at 5' end of the RNA genome covers 71% and it encodes two polyproteins which are processed by the viral proteases into 15 nonstructural proteins. These non-structural polyproteins function in the processing of other polyproteins, viral RNA replication, and synthesis of messenger RNA (Kim *et al.*, 2020). The other part of the genome transcribes messenger RNAs (mRNAs) for structural and accessory proteins. The structural proteins translated from the mRNAs include envelope protein, membrane protein (matrix protein), nucleocapsid protein, hemagglutinin-esterase (HE) and spike glycoprotein, also shown in Figure 2.1. The envelope and membrane proteins are important for viral assembly, budding and virion morphogenesis. (Kim *et al.*, 2020).

The nucleocapsid proteins complex with the genome to form a nucleocapsid. The S protein forms the major surface glycoprotein, and it is involved in receptor binding and membrane fusion with the host cell receptor (Angiotensin Converting Enzyme 2 [ACE 2]) and this process is necessary for viral replication and pathogenesis (Hamid *et al.*, 2021).

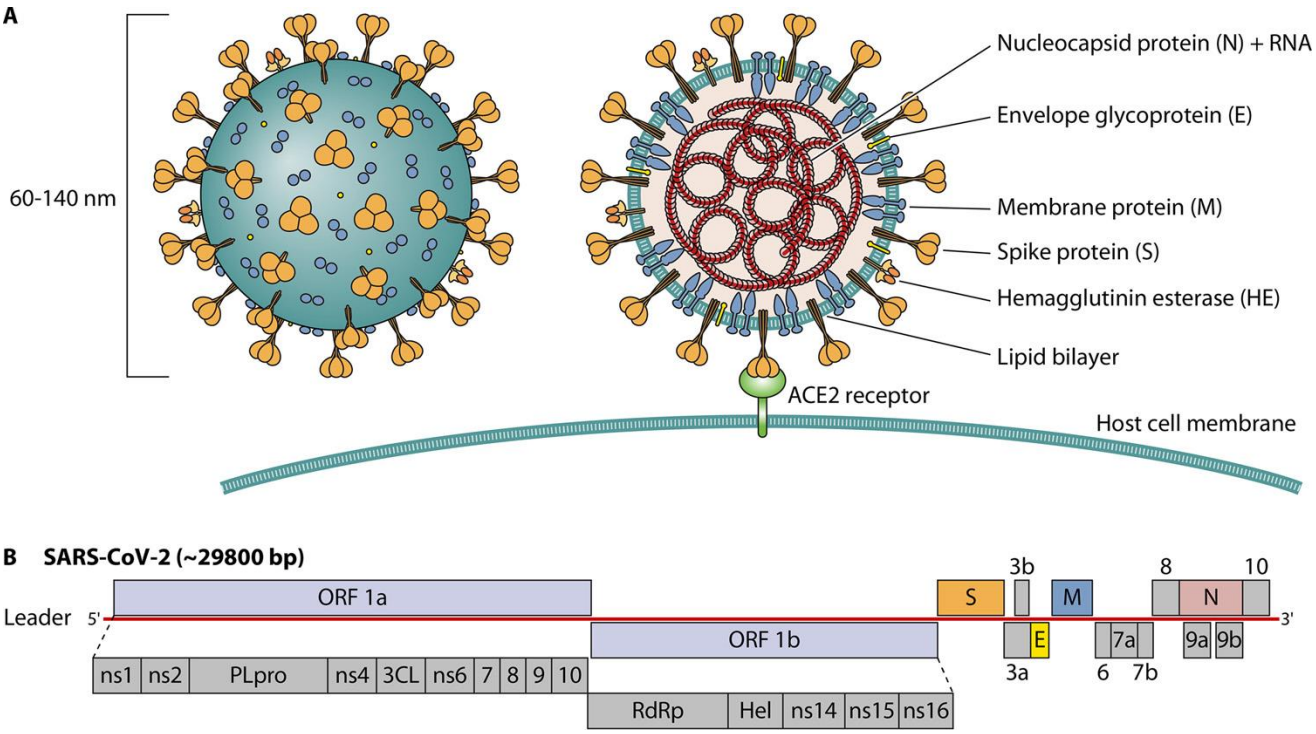

Figure 2.1. Structure of SARS-CoV-2 (A) Diagram of the SARS-CoV-2 virion. (B) RNA Genome organization and proteins (Source: Hamid *et al*., 2021)

Furthermore, CoVs including SARS-CoV-2, have been reported to have high mutation rate due to high homologous recombination rate and error prone activity of RNA dependent RNA polymerase (RdRp), an enzyme responsible for making copies of CoV genome (Sahin, 2020; Cosar *et al*., 2022). These mutations are occurring naturally in the virus RNA genome hence the emergency of new variants of SARS-CoV-2 that may have diverse traits compared to the ancestral strains. Some mutations that occur in SARS-CoV-2 genome have no impact on the virus while other mutations such as the ones that occur in the S-protein coding gene have effects on the virus transmission, virulence, and vaccine development (Cosar *et al.*, 2022).

Some notable SARS-CoV-2 variants due to mutation which have been recorded include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) (Akkız, 2022). These variants have been suspected of having potential effects on viral infectivity, virulence, and ability to evade immune system and detection (Cosar *et al.*, 2022; Guimarães *et al.*, 2022).

2.3 Transmission, Pathogenesis, and Replication of SARS- CoV-2

SARS- CoV-2 is transmitted by spread of droplets through coughing or sneezing and close contact with an infected person. The portals of entry for SARS-CoV-2 are the mucosal membranes such as of nasal and larynx. In the body, the virus targets and replicate in angiotensin-converting enzyme 2 (ACE2) receptor expressing cells found in tissues such as the lungs, heart, kidneys and gastrointestinal tract and the incubation period has been reported to range from 2 to 10 days (Young *et al.*, 2020).

The pathogenicity and replication of SARS-CoV-2 resulting in COVID-19 disease has a life cycle which can be summarized into attachment, penetration, biosynthesis, maturation, and release (Yuki *et al.*, 2020). Thus, the life cycle of SARS-CoV-2 starts with the attachment of the S protein through its receptor binding domain (RBD) to the host cell receptor, ACE2. The attachment determines tissue tropism and mediates the entry of the virus into the host cell (Lan *et al.*, 2020). Once the virus enters the cell and releases its genome, biosynthetic processes start, and the viral RNA genome is used to synthesize proteins and other genomes. The synthesized components are assembled into new viral particles (maturation) and released (Sood *et al.*, 2020). The release of SARS-CoV-2 progeny happens by the process of continuous budding (Park *et al.*, 2020).

The timeline of SARS-CoV-2 replication cycle and the number of viral particles released have been noted to vary significantly due to factors such as the type of cells infected and the immune system (Bar-On *et al.*, 2020, Bartolomeo *et al.*, 2022). While multiplying in the body, the virus exhibits complex pathogenic mechanisms that incite a range of clinical spectrum from asymptomatic forms of COVID-19 to severe respiratory features requiring mechanical ventilation, oxygen therapy and treatment in intensive care units (ICUs) to fatal septic and multiorgan dysfunction syndromes (Borczuk and Yantiss, 2022).

Studies on understanding the full pathogenic mechanisms of SARS-CoV-2 are ongoing. According to the present literature, it is mainly the dysregulated immune response mechanisms that cause tissue injury in SARS-CoV-2 infection (Yuki *et al.*, 2020; Dupont *et al.*, 2021; Borczuk and Yantiss, 2022). These mechanisms have been documented as lymphopenia and cytokine storm (Mina *et al.*, 2020). They cause humoral immunodeficiency with B-cell defects, hyperinflammatory state characterized by loss of T-cell subsets, high cytokine levels driven by interleukin-6 (IL-6), IL-1β,

Tumor Necrotic Factor - α (TNF-α), and complement system (Dupont *et al*., 2021; Jamal *et al*., 2021). Thus, excessive, and dysregulated immune responses cause tissue damage, septic shock, acute respiratory distress syndrome (ARDS) and multiorgan failure that escalate fatality rate of patients with COVID-19 (Jamal *et al.*, 2021). In addition to dysregulated immune response, there are other possible suggested mechanisms that have been outlined on how SARS-CoV-2 leads to multiorgan dysfunction. These suggested mechanisms can be direct action of the SARS-CoV-2 causing viral toxicity, complications arising from ischemic injury due to vasculitis, thrombosis, or thrombo-inflammation, and renin-angiotensin-aldosterone system (RAAS) dysregulation (Coopersmith *et al.*, 2021).

2.4 Clinical Manifestations of SARS- CoV-2 Infection and COVID-19 Severity

In terms of systems that are affected, SARS-CoV-2 has been documented to mainly affect the respiratory system. It causes viral pneumonia as virus attacks and multiply in the lungs and mostly the lower lobes are infected (Ou *et al.*, 2020). Due to this viral pneumonia, the person presents with fever, cough, sore throat, fatigue, headache, and shortness of breath (dyspnea) (Sohrabi *et al.*, 2020; Sood *et al.*, 2020). Notably, it has been observed that the symptoms are exceedingly diverse among individuals ranging from mild symptoms to severe hypoxia with acute respiratory distress syndrome (ARDS) and multiple organ failure (Sood *et al.*, 2020). ARDS has also been documented to associate with pathological findings such as marked desquamation of pneumocytes, development of hyaline membrane, pulmonary edema, epithelial damage, fibrin exudates and infiltration of mononuclear inflammatory cells (Tian *et al*., 2020; Xu, *et al*., 2020c).

Apart from infecting lungs, studies on clinical characteristics of COVID-19 patients have also reported on the clinical features involving other important organ systems like gastrointestinal (GI) tract, hepatobiliary, cardiovascular, renal, and central nervous systems (CNS) (Du *et al*., 2020; Guan *et al*., 2020; Deng *et al*., 2020b). Involvement of other organs in COVID-19 patients has mostly been observed in old-aged patients and those with underlying medical conditions such as cardiovascular diseases, hepatic disorders, renal diseases, obesity, diabetes mellitus, chronic pulmonary or renal disease, immunocompromised states, and malignancies (Du *et al.*, 2020; Jamal *et al.*, 2021).

The effects of SARS-CoV-2 infection in various organs have been supported by observation of clinical and laboratory alterations in relation to the affected organs. GI symptoms that have been observed in COVID-19 patients include diarrhoea (34%), nausea (27%), vomiting (16%), and abdominal pain (11%) (Elmunzer *et al.*, 2021). The damage caused by SARS-CoV-2 infection in GI organs has further been documented to associate with the presence of infiltrating plasma cells and lymphocytes and viral nucleocapsid protein in histopathological samples of gastric, duodenal, and rectal epithelium cytoplasm (Lin *et al.*, 2020). Additional studies have also shown liver dysfunctional characteristics through biochemical analysis in which they reported elevated levels of serum aminotransferases, and bilirubin *(*Guan *et al.*, 2020*;* García de Guadiana-Romualdo *et al*., 2021).

Cardiovascular manifestations and pathological laboratory findings have also been recorded among COVID-19 patients. The remarkable clinical manifestations noted are cardiac failure, cardiac arrhythmia, myocardial infarction, and elevated laboratory cardiac markers such as cardiac troponin (Zeng *et al.*, 2020; Jamal *et al.*, 2021). Other studies have also noted the involvement of the renal and reproductive system in COVID-19 patients. Some renal manifestations reported include proteinuria, hematuria, and increased levels of blood urea nitrogen and creatinine (Huang *et al*., 2020; Li, *et al*., 2020) plus detection of SARS-CoV-2 in urine samples of SARS-CoV-2 infected patients (Huang *et al.*, 2020). COVID-19 patients have also been noted to present with neurological symptoms that indicate the effect of SARS-CoV-2 on the CNS. Some notable symptoms reported include headache, dizziness, nausea and vomiting, and loss of taste and smell *(*Deng *et al.*, 2020a; WHO, 2022).

Studies on the clinical presentation of SARS-CoV-2 infection have reported that infected individuals may range from having no symptoms to experiencing severe and critical illness (Bennett *et al*., 2021; Nishiura *et al*., 2020). An estimation of the asymptomatic ratio of COVID-19 among Japanese nationals found 17.9% to 33.3% of infected individuals remained asymptomatic (Nishiura *et al.*, 2020). An evaluation of 174,568 adults with SARS-CoV-2 infection in United States reported that 20.2% had severe disease with 18.6% requiring hospitalization in 2020 (Bennett *et al.*, 2021). Based on such different presentations and the clinical severity of COVID-19 illness, the WHO, and the National Institutes of Health (NIH) published similar guidelines that classify COVID-19 into asymptomatic, mild disease, moderate disease, severe disease, and critical disease as defined in

Table 2.1. The classification considers the severity of clinical symptoms, laboratory and radiographic findings, hemodynamics, and organ function (Guimarães *et al*., 2022; WHO, 2022).

Table 2.1. COVID-19 disease severity

Class	Definition
Asymptomatic or Pre-symptomatic Infection	Positive SARS-CoV-2 nucleic acid test, without any clinical symptoms and signs and with normal chest imaging.
Mild disease	Presentation of any symptoms of SARS-CoV-2 such as fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing, nausea, vomiting, abdominal pain, and diarrhea but without presentation of shortness of breath or abnormal chest imaging.
Moderate disease	Presentation of pneumonia with signs such as frequent fever and cough, radiologic sign of lower respiratory tract disease but with oxygen saturation (SpO2) ≥ 94% at room air.
Severe disease	Presentation of pneumonia with one of the following: hypoxemia (SpO2< 90%), respiratory rate >30 breaths/min, or severe respiratory distress
Critical disease	Occurrence of ARDS and may present with sepsis, shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction, acute kidney injury and bilateral opacities

2.5 Diagnosis of COVID-19

Symptomatic COVID-19 patients present with non-specific signs and symptoms hence, diagnostic imaging and laboratory tests are used for screening and diagnosis (Guan *et al*., 2020; Hamid *et al*., 2021). Laboratory tests, especially molecular tests, are regarded as the most suitable for accurate diagnosis than diagnostic chest imaging due to ability of molecular tests to detect and identify the specific pathogen. Despite the suitability of laboratory tests, shortage of test kits and probability of false negatives, initiated temporal use of imaging techniques in some hospitals in China (Udugama *et al.*, 2020; Yang, *et al*., 2020a). Diagnostic imaging techniques that have been applied in COVID-19 diagnostics include computed tomography (CT) scan, Chest radiography (chest X ray), ultrasound, magnetic resonance imaging (MRI), and positron emission tomography-CT (PET/CT) (Hamid *et al.*, 2021). CT scans are the most used techniques for COVID-19 diagnosis among other

diagnostic imaging techniques. Diagnostic imaging in COVID-19 has also been applied in patient follow up, and assessment of involvement of disease in the lower respiratory tract and other anatomical parts (Yang *et al*., 2020a).

According to WHO, the reference methods of diagnosis are laboratory tests which detect the specific pathogen (WHO, 2022). These laboratory tests include molecular diagnostic and protein testing methods. The molecular techniques which have been mostly used in SARS-CoV-2 pandemic include nucleic acid amplification testing (NAAT) technologies and Next generation sequencing (NGS) (Sood *et al.*, 2020). The widely used NAAT method is real time Reverse Transcriptase Polymerase Chain Reaction (real-time RT-PCR) technology and currently it is regarded as the primary method (WHO, 2022). The samples of patients for real-time RT-PCR and other tests are collected from upper respiratory tract using nasopharyngeal swab, nasal aspirate, and oral pharyngeal swab. Sometimes lower respiratory tract samples such as sputum and tracheal aspirate are used (WHO, 2021a, Udugama *et al.*, 2020).

In addition to real-time RT-PCR, there are other NAAT methods which have been explored for SARS-CoV-2 testing to meet the need for rapid testing and portability required for community clinics and hospitals (Hamid *et al.*, 2021). These methods are collectively known as isothermal amplification techniques (IATs) as they perform at a constant temperature thereby taking out the use of PCR thermocyclers. Examples of IATs which have been investigated and used in COVID-19 testing include transcription-mediated amplification (TMA), nicking enzyme-assisted reaction (NEAR), loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), and techniques utilizing clustered regularly interspaced short palindromic repeat (CRISPR)–CRISPR-associated (Cas) (CRISPR-Cas) systems (James and Alwneh, 2020; Udugama *et al.*, 2020; Hamid *et al*., 2021).

NGS is another molecular method which has been used in COVID-19 pandemic. NGS has been important for pathogen detection from different clinical samples, identification of COVID-19 pandemic origins, characterization of transmission patterns, understanding pathogenesis and mutations and surveillance of viral mutations overtime (Lu *et al.*, 2020; Udugama *et al*., 2020; John *et al.*, 2021).

Alongside nucleic acid testing, protein testing methods were also developed and introduced in COVID-19 pandemic with main purpose of improving patient screening as they are direct, faster, and less expensive (WHO, 2021b). Protein testing methods in COVID-19 involve the detection of specific viral antigens and antibodies. Antigen based detection assays detect SARS-CoV-2 viral proteins. The two primary targeted proteins in SARS-CoV-2 antigen-based detection assays are S and N proteins (Hamid *et al.*, 2021). The SARS-CoV-2 antigen-based detection assays are conducted in a similar way to the serological detection methods which use enzyme linked immunosorbent assays (ELISAs), chemiluminescence immunoassays (CLIAs) and lateral flow immunochromatographic assays (LFIAs) or lateral flow assays (LFAs) (Mahmoudi *et al.*, 2020).

The other variation of the protein test is the serological method which detects antibodies to SARS-CoV-2. The specific antibodies produced in response to SARS-CoV-2 viral proteins can be indirectly detected in serum, plasma, and whole blood (Udugama *et al.*, 2020). Besides that, antibodies have a longer window period necessary for surveillance of COVID-19 (Sood *et al.*, 2020). The main antibodies in antibody-based detection systems are immunoglobin G and M (IgG and IgM) in human serum (Bastos *et al*., 2020). These antibodies are detected by common systems which include ELISAs and CLIAs (Kai-Wang To *et al.*, 2020).

2.6 COVID-19 Routine Laboratory Investigations and Biomarkers

Aside from detecting SARS-CoV-2 as the causative agent of COVID-19, the laboratory also performs routine blood tests in hospitalized COVID-19 patients. Mainly, these blood tests are hematological and biochemical tests (O'Shea *et al*., 2020). Some of these tests include markers for inflammatory conditions (C-reactive protein [CRP], procalcitonin [PCT], and interleukin 6 [IL-6]), tests for anticoagulation, indicators of tissue damage and complete blood count (CBC) counts (Sood *et al.*, 2020). These routine blood tests are used in assessment of a patient's health and determination of the state of the disease *(*Cai, *et al*., 2020a).

Hematological and biochemical test parameters have been observed as biomarkers to be considered important in the assessment of disease severity, prognostication, and risk factors for death (Mutair *et al*., 2020; Chang *et al*., 2020; Zemlin *et al*., 2022). In this regard, research studies have recommended further exploration on hematological and biochemical biomarkers to determine their potential in evaluating COVID-19 prognosis (Zheng *et al*., 2020; Alizad *et al*.,2023; Zlojutro *et al*.,

2023). To assess such biomarkers, one approach involves studying the biochemical and hematological characteristics of COVID-19 patients in different populations.

2.7 Hematological Characteristics of Hospitalized COVID-19 Patients

The investigation of hematological test parameters garnered attention during the COVID-19 pandemic due to reports of thrombocytopenia, defective oxygen transport, and hypercoagulable states in COVID-19 patients (Jamal *et al.*, 2021). Though lower respiratory tract infection is the primary cause of morbidity and mortality in SARS-CoV-2 infection, there has been evidence that the virus also affects multiple organ systems including the hematopoietic system (Tian *et al.,* 2020; Zayratyants *et al*., 2020; Bennett *et al*., 2021). This has been reflected by routine laboratory hematologic tests, particularly complete blood count (CBC) and coagulation tests, which have revealed some deranged results indicating hematopoietic effects of SARS-CoV-2 (Thompson *et al.*, 2020; Iroungou *et al*., 2023). In addition, several studies have documented hematological manifestations in COVID-19 patients, including lymphopenia, leukocytosis, thrombocytopenia, disseminated intravascular coagulation, and prothrombotic states *(*Arentz *et al., 2020;* Bhatraju *et al., 2020;* Guan *et al.*, 2020; Michael *et al*., 2024).

Moreover, the severity and outcome of COVID-19 disease have been linked to routine hematological parameters in different patient populations. One study conducted at a hospital in Ankara, Turkey, aimed to identify predictors of severe illness in hospitalized COVID-19 patients found that patients in ICU had decreased lymphocytes, percentage of large unstained cell (%LUC), and hemoglobin concentration, but increased leucocytes, neutrophils, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-lymphocytes ratio (PLR), and D-dimer compared to non-critically ill patients. The study also found that low %LUC and high D-dimer had the highest odds ratios of 0.093 and 5.597, respectively, in predicting severe prognosis of COVID-19 (Bastug *et al.*, 2020).

Although Bastug *et al.*'s (2020) study was conducted at a single center but had similar findings to a systematic review and meta-analysis by Asghar *et al.*, (2020a) involving 23 published articles on hematological changes in COVID-19 patients. The systematic review and meta-analysis additionally reported that patients with severe COVID-19 had thrombocytopenia, leukopenia, increased D-dimer, fibrinogen, and prothrombin time. Asghar *et al.*, (2020a), further suggested that

hematological test results could help in early identification of severe infection. However, the findings in the systematic review and meta-analysis were influenced by various factors such as inclusion of mostly retrospective case series, different definitions of severe disease, and varying cut-offs for laboratory values. The studies included in the review were also mostly from China, and the authors recommended future studies from Africa, America, and Europe to better understand the disease (Asghar *et al*., 2020a).

Hematological tests parameters have also been investigated in relation to prediction of mortality in COVID-19 patients. For example, a retrospective and observational study conducted in Pakistan investigated the role of hematological parameters in predicting the prognosis and mortality in COVID-19 patients. The study found significant leukocytosis, neutrophilia, and lymphopenia, as well as increased CRP levels among the patients who had died (Asghar *et al*., 2020b). Similarly, a study conducted at the University Hospital of Leuven in Belgium collected and analyzed routine blood analysis data from 197 confirmed COVID-19 cases. The study observed that deceased COVID-19 patients had decreased platelet count, elevated leukocyte count, neutrophil count, and reduced eosinophil, lymphocyte, and monocyte count compared to patients who recovered (Blomme *et al.*, 2022).

Regarding the reporting of hematological findings in many studies, some parameters are consistent while others vary among different populations. For instance, elevated leukocyte count was reported in Pakistan (Asghar *et al*., 2020b) and Belgium (Blomme *et al.*, 2022) as described above, but low leukocyte count was reported in China (Guan *et al*., 2020) and Spain (García de Guadiana-Romualdo *et al*., 2021). To expound upon that, a study on clinical characteristics of 1099 COVID-19 patients in China, from several hospitals found that most patients had lymphocytopenia, thrombocytopenia, and leukopenia on admission. Severe COVID-19 patients had more marked laboratory abnormalities, particularly lymphocytopenia and leukopenia, than those with non-severe disease (Guan *et al*., 2020). Another large multicenter study conducted in Spain involving 2873 hospitalized COVID-19 patients found altered hematological parameters, including elevated levels of ferritin, D-dimer, and NLR, and decreased lymphocyte count from the early stages of infection. The study also observed that hematological markers were higher in patients who died, and abnormal laboratory findings were a signature of severe COVID-19 (García de Guadiana-Romualdo *et al*., 2021).

2.8 Biochemical Characteristics of Hospitalized COVID-19 Patients

Biochemical test parameters are routinely analyzed to assess the metabolic status and health of organs. In hospitalized COVID- 19 patients, biochemical tests are also necessary to obtain helpful knowledge related to the outcomes of the disease (Mir *et al.*, 2022). Indeed, studies have been conducted in relation to biochemical parameters and COVID-19 outcomes (Guan *et al,*. 2020*;* García de Guadiana-Romualdo *et al.,* 2021; Mir *et al*., 2022; Nyasulu *et al.*, 2022). Some of the biochemical markers of interest evaluated in hospitalized COVID-19 patients in assessment of disease severity and progression include lactate dehydrogenase (LDH), Creatine kinase (CK), blood urea nitrogen (BUN), creatinine (Cr), total serum protein (TP), albumin (Alb), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALT), bilirubin and markers of inflammation such as CRP, PCT, and IL-6 (Hamid *et al.*, 2021; Zlojutro *et al*., 2023).

2.8.1 LDH in Hospitalized COVID-19 Patients

LDH is an enzyme that plays a key role in the interconversion of lactic and pyruvic acids and the interconversion of NADH and NAD^+ as a coenzyme. It is found in various organs including the heart, liver, skeletal muscles, kidney, erythrocytes, and in small amounts in the lungs, smooth muscle, and brain. Elevated levels of LDH can indicate organ injury or multiple organ injury (Bishop *et al*., 2018). Serum LDH has been among the most recurrent biochemical abnormalities in COVID-19 patients on admission. High LDH serum levels in COVID-19 have been found in many clinical and laboratory characteristics' studies of COVID-19 patients in China (Guan *et al*., 2020; Huang *et al*., 2020; Wu *et al*., 2020; Deng *et al.,* 2020b). Likewise, other researchers demonstrated significantly high LDH levels among hospitalized COVID-19 patients in Iran (Mir *et al.*, 2022), Turkey (Bastug *et al.*, 2020), Italy (Aloisio *et al.*, 2020) and South Africa (Zemlin *et al.*, 2022). In addition, analysis on the association of LDH and severity of COVID-19 also found that COVID-19 mortality was associated with increasing levels of LDH (LDH ≥280 U/L) together with elevated levels of other markers such as urea and CK (Aloisio *et al.*, 2020; Bastug *et al.*, 2020; Henry *et al.*, 2020; Mir *et al.*, 2022).

2.8.2 Liver Function Assessment in Hospitalized COVID-19 Patients

Other biochemical parameters that indicate tissue and organ injury include AST, ALT, ALT, GGT, TBil, TP, and Alb. These biochemical parameters are among the test profiles for liver function

assessment. Transaminases (AST and ALT) are enzymes dominantly expressed in the hepatocytes and proteins (TP and Alb) are synthesized by the hepatic cells hence an injury to hepatocytes may result in abnormal levels in the blood (Bishop *et al*., 2018). GGT, ALP and bilirubin are also incorporated to assess the biliary system of the liver and these hepatic markers have been evaluated in COVID-19 patients to understand COVID-19 pathology, prognosis, and patient monitoring (Letelier *et al*., 2021).

Studies on clinical and laboratory characteristics of hospitalized COVID-19 patients in China have reported significant deranged levels of hepatic function markers especially, AST, ALT, TBil, TP and Alb and the alterations varied significantly when the death group was compared with recovered patients (Chen *et al*., 2020a; Huang *et al.*, 2020; Wang *et al.*, 2020a). Cai *et al*., (2020a), specifically assessed the clinical features of COVID-19 in patients with abnormal liver test results in Shenzhen, China. They reported that out of 417 patients with COVID-19, 76.3% had deranged liver tests including AST, ALT, GGT, TP and TBil. It was also noted that abnormal liver test results were more remarkable during hospitalization within two weeks and that liver injury during hospitalization was associated with the use of lopinavir and ritonavir and the odds of developing severe pneumonia was significantly higher in such patients (Cai *et al*., 2020a). In this regard, it is necessary to use commonly tested biomarkers such as liver enzymes that would allow monitoring of the progression of the disease, the impact of treatment and predict which patients would require advanced medical procedures for immediate intervention. This is also in line with studies on use of biochemical markers in understanding of COVID-19 patients conducted in Turkey (Bastug *et al.*, 2020), Spain (García de Guadiana-Romualdo *et al*., 2021), Ireland (O'shea *et al.*, 2020), Nigeria (Jibrin *et al.*, 2020) and South Africa (Nyasulu *et al*., 2022) in which they obtained similar findings to Chinese studies.

2.8.3 Kidney Function Assessment in Hospitalized COVID-19 Patients

BUN is another routine biochemistry analyte that has been assessed in hospitalized COVID-19 patients. Urea is a product of protein catabolism formed in the liver, circulates in blood, and excreted in urine as a waste product. BUN is analyzed in the assessment of renal function together with Cr and electrolytes (Sodium [Na^+], Potassium [K^+] and Chloride [Cl^-]) (Favaloro and Lippi, 2020). Both normal and deranged levels of serum urea and Cr have been reported among COVID-19 patients. Normal ranges of BUN and Cr with no significant differences between severe and mild

COVID-19 patients on admission were reported in China (Cheng *et al.*, 2020b; Huang *et al.*, 2020) and South Africa (Zemlin *et al.*, 2022). Another retrospective study on clinical features of 85 fatal COVID-19 cases in Wuhan demonstrated that 56.6% of the cases had increased levels of BUN and Cr indicating the possibility of renal impairment though the sample size was smaller compared to other studies (Du *et al.*, 2020).

Further reports indicated the involvement of kidneys in COVID-19 patients in which renal disease presented as acute renal injury, hematuria, and proteinuria, thereby increasing the risk of mortality (Angel-Korman *et al*., 2020; Zhou *et al.*, 2022). To concur with Angel-Korman *et al.*, (2020) and Zhou *et al.*, (2022), an alternative study examining the kidney functions of COVID-19 patients and their correlation with mortality among 193 adult patients in China found that, 59% had proteinuria, 44% had hematuria, 14% had high BUN, and 10% had elevated levels of serum Cr. Additionally, the study showed that proteinuria, hematuria, elevated levels of BUN, serum Cr, uric acid, and D-dimer were all significantly associated with the death of COVID-19 patients (Li *et al*., 2020a). In Italy, BUN was also among the significant abnormal parameters in addition to CBC parameters, LDH and AST in severe patients (Sulejmani *et al.*, 2021), suggesting that BUN and Cr can be studied further to assess their capacity in establishing the prognosis of hospitalized COVID-19. Similarly, a study in Zambia found that a greater percentage of kidney abnormalities were detected in individuals who tested positive for COVID-19 compared to those who tested negative, indicating that the kidneys may be affected by the COVID-19 syndrome, even if not directly caused by the virus itself (Mudenda *et al.*, 2021).

2.8.4 Cardiac Biomarkers in Hospitalized COVID-19 Patients

Cardiac biomarkers have also been investigated as significant biochemical tests related to COVID-19 hospitalized patients. These biomarkers include high-sensitivity troponin I markers (hsTnI), N-terminal pro B type natriuretic peptide (NT-proBNP), myoglobin, and creatine kinase-MB (CK-MB) (Favaloro and Lippi, 2020). The presentation of cardiac symptoms in SARS-CoV-2 patients led to hypothesize the involvement of the heart in COVID-19 pathology (López-Ponce de León *et al*., 2020; Molina, *et al*., 2020). Myocardial injury has indeed been reported in COVID-19 patients, as shown in a meta-analysis of 4,189 patients in 28 studies that identified significantly elevated levels of CK-MB, troponin, myoglobin, and NT-proBNP in severe COVID-19 patients. Increased troponin was more common in patients with severe illness than in patients with mild illness. Levels

of hsTnI and NT-proBNP were exclusively elevated during hospitalization in non-survivors (Li *et al*., 2020b). Although the study by Li *et al*. (2020b) focused mainly on the Chinese population, it highlights the need to monitor heart health effectively in patients infected with SARS-CoV-2. A prospective study in South Africa among ICU-admitted COVID-19 patients also demonstrated higher troponin T and NT-proBNP levels in patients who died than in those who survived (Allwood *et al.*, 2022). Other observations and retrospective studies have also reported elevated cardiac biomarkers in Canada (Rutledge *et al*., 2021) and the United States (Churchill *et al.*, 2020).

2.8.5 Inflammatory Biomarkers in Hospitalized COVID-19 Patients

Inflammatory biomarkers also received significant attention in understanding of COVID-19. These biomarkers include CRP, serum ferritin, PCT, IL-6, IL-10, IL-2, and Interferon-γ (IFN-γ) (Thompson *et al.*, 2020). Infection with SARS-CoV-2 cause dysregulated immune responses, known as cytokine storms, that lead to tissue damage (Mehta *et al.*, 2020; Qin *et al.*, 2020). This phenomenon is associated with an unfavorable prognosis among COVID-19 patients and a higher risk of requiring intensive care or experiencing fatal outcomes (Zhang *et al*., 2020; Wolszczak-Biedrzycka, *et al*. 2023). As demonstrated by one longitudinal study at Wuhan Union Hospital in China, levels of IL-6, IL-10, IL-2, and IFN-γ were more elevated in severe COVID-19 cases than in mild cases (Liu *et al.*, 2020). Several other early studies in China, Italy and Canada have reported similar findings of increased levels of proinflammatory cytokines such as IFN-γ, TNF-α, IL-6, and IL-8, as well as PCT, serum ferritin, and CRP in severe cases of COVID-19 compared to non-severe cases (Chang *et al*., 2020; Guan *et al*., 2020; Huang *et al*., 2020; Li *et al*., 2021; Rutledge *et al*., 2021; Satış *et al*., 2021).

2.9 Treatment Administered to COVID-19 Patients

Numerous treatment and intervention options for COVID-19 patients since the beginning of the pandemic have been reported. Some of these include the use of antivirals, antibiotics, micronutrients, plasma therapy, steroids, anticoagulants, immunomodulatory therapy (IL-1 or IL-6 inhibitors), oxygen therapy, mechanical ventilation, and stem cells (Bastug *et al*., 2020; Panahi *et al*., 2023). Others, especially in China and Africa have also been using herbs as remedies for COVID-19 (Nugraha *et al.*, 2020).

2.9.1 Antiviral Treatment

Some studies have evaluated the effectiveness of existing and newly developed antiviral drugs against SARS-CoV-2. These studies have focused on antivirals such as molnupiravir, remdesivir, lopinavir, ritonavir, and favipiravir (Panahi *et al*., 2023). Molnupiravir, an oral antiviral drug, has shown significant benefits in reducing hospital stays and mortality among mild COVID-19 patients (Singh *et al.*, 2021). However, its effectiveness in moderate to severe COVID-19 cases remains uncertain (Khan *et al*., 2022; Panahi *et al*., 2023). For remdesivir, despite presenting mild to moderate side effects, has demonstrated antiviral activity in treating COVID-19 patients when compared to a placebo (Khan *et al.*, 2022). In contrast, some studies have suggested that remdesivir has no substantial effect on the mortality rate of COVID-19 patients (Haddad *et al.*, 2022; Khan *et al.*, 2022). Lopinavir and ritonavir, both oral antiretroviral protease inhibitors, have shown positive effects (Haddad *et al.*, 2022). Favipiravir, an analog of purine nucleoside that inhibits RdRp of the virus, has also been reported to have favorable effects in COVID-19 patients (Cai *et al*., 2020b).

2.9.2 Micronutrient Supplementation

Another reported treatment approach used in COVID-19 patients involves micronutrient supplementation, including vitamins and zinc (Beran *et al.*, 2022). A meta-analysis and systematic review study found that vitamin C could decrease hospital mortality (Olczak-Pruc *et al.*, 2022). Further, vitamin D has been previously noted for its protective effect and reducing the incidence of respiratory infections (Bergman *et al.*, 2013). A systematic review on the effects of vitamin D supplementation in COVID-19 patients indicated that patients benefited from receiving daily or sustained vitamin D doses, regardless of their initial vitamin D serum levels. However, outcomes varied, and larger clinical trials have been recommended (Feiner *et al*., 2022). As for Zinc, it is known for its anti-inflammatory and antioxidant properties (Balboni *et al.*, 2022). It is also under consideration as a prophylactic or adjuvant therapy for COVID-19 patients, with ongoing studies to demonstrate its efficacy (Balboni *et al.*, 2022; Jiménez-Uribe *et al.*, 2022).

2.9.3 Convalescent Plasma Therapy

Convalescent plasma therapy has also been used as a treatment of COVID-19 in some areas (Haddad *et al.*, 2022). Previously it was used in infectious disease treatment (Cheng *et al.*, 2005) and the same has been applied in the search for COVID-19 treatment. A study conducted at Houston Methodist Hospital in 2020 reported that convalescent plasma administration was a safe treatment

option for severe COVID-19 cases, based on the results from a case series of 25 patients (Salazar *et al.,* 2020).

2.9.4 Anticoagulant and Anti-inflammatory Therapy

There have been reported cases of thromboembolic events, coagulopathies, and multi-organ complications in COVID-19 (Klok *et al.*, 2020; Zhang *et al.*, 2020). To address this, one approach has been the use of low molecular weight heparin (LMWH), such as Enoxaparin, to provide anticoagulant therapeutic effects (Rentsch *et al.*, 2021; Vaughn *et al.*, 2021). To mitigate the hyperinflammation caused by SARS-CoV-2 (Zhang *et al.*, 2020), immunomodulators like siltuximab, anakinra, tocilizumab, and corticosteroids have been utilized in the treatment of COVID-19 patients (Zhang *et al*., 2020; Haddad *et al*., 2022; Panahi *et al*., 2023). Other treatment options, including sarilumab, colchicine, canakinumab, thalidomide, tofacitinib, and Mesenchymal Stem Cells, have also demonstrated significant effects on the treatment of COVID-19 patients (Haddad *et al.*, 2022; Islam *et al.*, 2022).

2.9.5 Herbal medicine in treatment of COVID-19

The use of herbal medicine in treatment of COVID-19 as immunomodulators, anti-inflammatory ingredients, antioxidants, and antimicrobials has also been reported (Nugraha *et al.*, 2020; Komariah *et al*., 2023). Examples of such herbs include *Echinacea purpurea, Curcumin, Turmeric, Nigella sativa, Zingiber officinale* (Komariah *et al.*, 2023), Eucalyptus and lemons (Khairiah *et al.*, 2022), and ginger (Jafarzadeh *et al.*, 2021). Despite the use of herbal medicines, there are inconsistencies regarding their safety, mechanisms of action and efficacy (Nugraha *et al*., 2020; Ang *et al*., 2022).

2.9.6 Treatments in Malawi

In the case of Malawi, the treatment interventions that have been followed, especially for hospitalized cases, have mostly been based on the updates of WHO recommendations and the usual management of respiratory signs, symptoms, and complications as described by WHO (MOH, 2022; WHO, 2021; WHO, 2022). For those who were not hospitalized, recommendations included strengthening their immune system through healthy meals, nutritional supplements such as vitamin C, vitamin B, and zinc, adequate fluid intake, sufficient rest, exercise, and controlling underlying medical conditions (MOH, 2020). Additionally, the use of traditional remedies was recommended,

such as black seed, turmeric, ginger, and other natural substances known for their anti-inflammatory properties (MOH, 2020).

2.10 Prevention and Control of COVID-19

The pandemic situation also led to rapid research and approval of various SARS-CoV-2 vaccines for prophylaxis and prevention of spread of the virus. Importantly, vaccination has emerged as one of the primary strategies to combat the COVID-19 pandemic. As of late 2023, there were over 183 vaccines in clinical development and more than 199 in preclinical development (WHO, 2023b). Various platforms, including vector, RNA, protein subunit, inactivated vaccines, and DNA vaccines, have been employed, with some having received approval for human use in different regions (Kudlay and Svistunov, 2022). Regarding vaccination coverage at the global level, over 13.59 billion COVID-19 vaccine doses have been administered, while in the African region, at least 646.35 million COVID-19 vaccine doses have been administered (WHO, 2024).

In Malawi, there are six approved COVID-19 vaccines. These vaccines include Moderna Spikevax and Pfizer/BioNTech Comirnaty (RNA based vaccines), Janssen (Johnson & Johnson) and Oxford/AstraZeneca (non-replicating viral vector vaccines), as well as Sinopharm and Sinovac (Inactivated viruses' vaccine) (MOH, 2023). Mostly, AstraZeneca, Johnson & Johnson, and Pfizer vaccinations are the ones which have been available for vaccination (MOH, 2023). As of late 2023, a total of 8.5 million COVID-19 vaccine doses have been administered (WHO, 2024).

2.11 Knowledge Gaps

Aside from respiratory complications, studies based on epidemiological and case data have demonstrated that COVID-19 mortality is also linked to the involvement of multiple organs (Arentz *et al.*, 2020; Lin *et al.*, 2020; Wang *et al.*, 2020a; Zhou *et al.*, 2022). Indeed, early research in COVID-19 pandemic has documented abnormalities in multiple organs of COVID-19 patients (Mutair *et al*., 2020; Churchill *et al.,* 2020; Li *et al*., 2020a). Additionally, several researchers have conducted studies and reviews on the clinical and laboratory features or biomarkers of COVID-19 patients to gain a better understanding of the nature of the virus infection, predict prognosis and improve patient care (Ciaccio and Agnello, 2020; Kantri *et al*., 2021; Zhang 2023; Michael 2024). However, consensus on the prescribed predictive laboratory markers for clinical applications remains elusive, and some markers such as PCT, IL-6, IL-10, IL-2, D-dimer and IFN-γ are not

commonly available and tested in limited resource country health systems, such as in Malawi (Nayupe *et al*., 2023; Zlojutro *et al*., 2024).

In terms of population diversity, most of the prior studies used population data from China, where the pandemic originated, as well as other developed regions like Europe and America. Few studies have examined the clinical, hematological and biochemical characteristics of COVID-19 in the African population (Mutair *et al*., 2020; Ghayda *et al*., 2020; Nyasulu *et al*., 2022). The available literature on the biochemical and hematological characteristics of hospitalized COVID-19 patients also exhibits significant heterogeneity. This is related to the usage of different definitions of COVID-19 severity, varying reference values for hematological and biochemical tests, and the use of various laboratory analytical methods in multi-centre studies and across studies incorporated in meta-analyses and reviews (Salamanna *et al*., 2020; Deng *et al*., 2020a; García de Guadiana-Romualdo *et al*., 2021). Moreover, most studies were conducted at a single center, which limits the generalizability of their findings. Other notable features observed in COVID-19 pandemic studies include variations in severity and mortality across different populations (Cobre *et al.*, 2021; Karimi Shahri *et al.*, 2021; N'dilimabaka *et al.*, 2022). As such, it is crucial to conduct assessments across different populations to achieve a comprehensive understanding of the disease's characteristics and nature.

Furthermore, there has been little, or no attention given to the Malawian population on assessment of hematological and biochemical features of hospitalized COVID-19 patients. Previous COVID-19 studies in Malawi did not focus on clinical features along with hematological and biochemical characteristics, treatments and prediction of COVID-19 disease outcomes (Chibwana *et al*., 2020; Chibwana *et al.*, 2022; Chisale *et al*., 2022; Anscombe *et al*., 2023). As such, the present study was conducted to analyze hematological and biochemical data, along with clinical and treatment data, of hospitalized COVID-19 cases in Malawi to predict survival and non-survival outcomes. Hence, this study may provide and supplement knowledge on the ideal routine clinical features and laboratory tests for identification of COVID-19 patients at risk of poor outcomes during hospitalization to facilitate timely and appropriate management.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

This study used a retrospective design and quantitative approach. Data from the year 2020 to 2022 of hospitalized COVID-19 patients were extracted from laboratory information systems and patient medical records and analyzed quantitatively.

3.2 Study Area

The study was conducted in Malawi. Malawi is a landlocked country located in southeastern Africa and covers an area of 118,484 km². It shares international borders with Tanzania, Zambia, and Mozambique. It is also a densely populated nation with a population of 17,563,749 in 2018 basing on the 2018 census and the estimated population was 20.9 million in 2023 with an annual growth rate of 2.6% (United Nations Population Fund, 2023).

In this study, data of hospitalized COVID-19 patients were collected from three selected central hospitals. Central/tertiary hospitals are regional referral hospitals for the District Hospitals and they provide comprehensive medical services, including advanced diagnostic and treatment capabilities. There are four central hospitals in Malawi and they are located in the four major geographical regions. These central hospitals include Mzuzu Central Hospital (Mzimba District, Northern Region), Kamuzu Central Hospital (Lilongwe District, Central Region), Queen Elizabeth Central Hospital (Blantyre District, Southern Region), and Zomba Central Hospital (Zomba District, Eastern Region). The individual central hospitals included were Mzuzu Central hospital (MZCH), Queen Elizabeth Central Hospital (QUECH) and Zomba Central Hospital (ZMCH) as shown in the map of Malawi, Figure 3.1. The selection of these hospitals was based on their superior COVID-19 patient data management systems, particularly in terms of patient record data organization and storage. This decision was informed by consultation feedback received from both district and central hospitals during the proposal development stage.

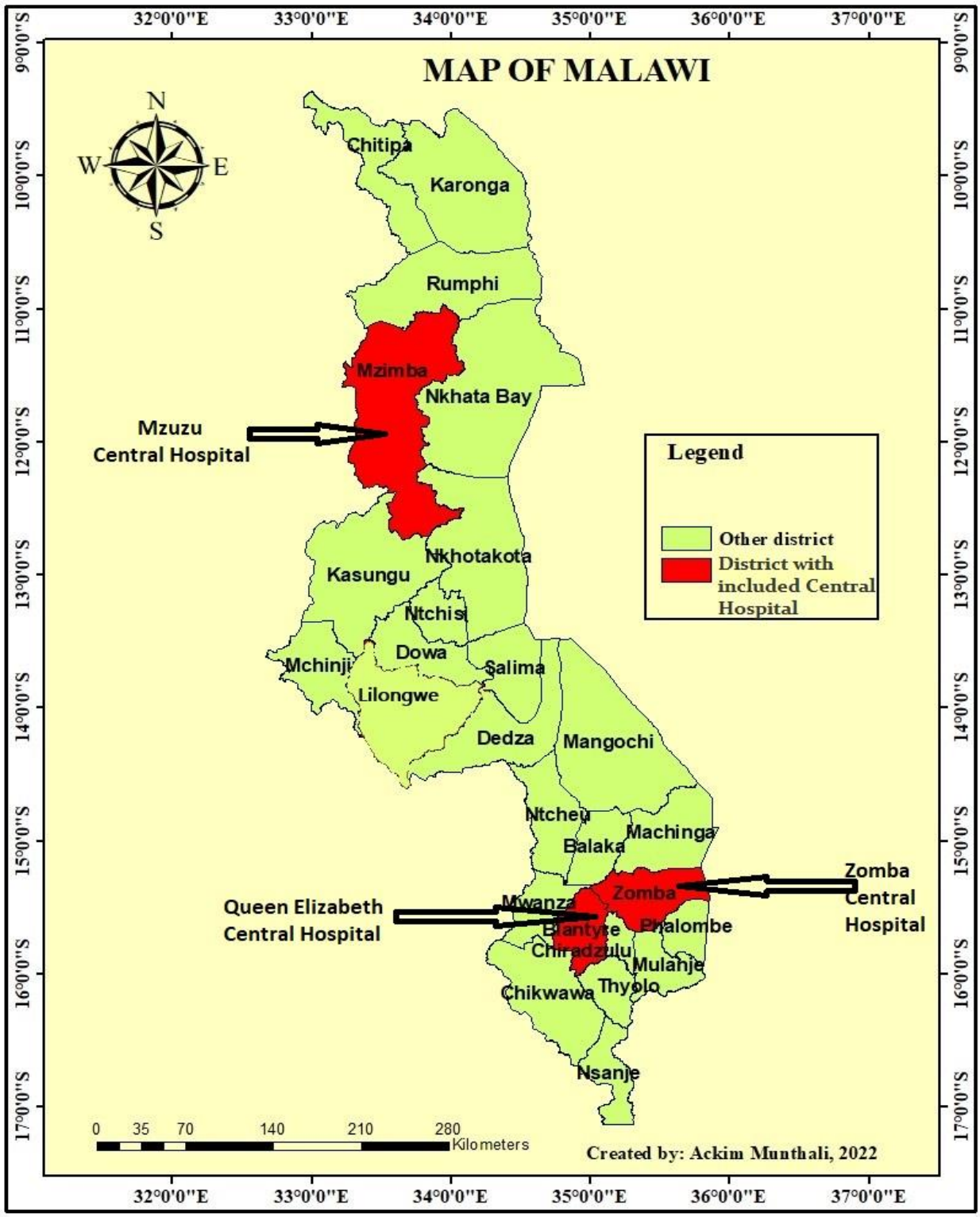

Figure 3.1. Map of Malawi showing study sites**:** (Source: Generated from Arc GIS software by the researcher)

3.3 Study Population

The study population comprised of patient records of individuals who were admitted to the three central hospitals in Malawi (MZCH, QUECH and ZMCH) between 2020 and 2022 with severe and critical forms of COVID-19 and tested positive for SARS-CoV-2 using RT-PCR.

3.4 Sample Size Calculation and Sampling

The formula (equation 1) for minimum sample size in a proportion estimation was utilized to calculate the total sample size, considering the required level of precision, confidence level, and the estimated proportion of COVID-19 cases (Nanjundeswaraswamy and Divakar, 2021). Due to unavailability of published data regarding the proportion of hospitalized COVID-19 cases in each hospital, a proportion of 50 percent was employed.

$$\boldsymbol{n = \frac{Z^2\, P(1-P)}{d^2}}\textbf{: .....}\ \text{Equation 1}$$

Where **n** is the sample size, **Z** = confidence level (95%), **P** = expected proportion in unknown (50%) and **d**= Precision (5%).

Hence, $\boldsymbol{n = \frac{(1.96^2) \times 0.5 \times (1-0.5)}{0.05^2}}$ = 384.16

The minimum sample size was determined to be 384.16. Hence, records of at least 385 hospitalized COVID-19 patients were planned to be collected by stratified sampling technique. Thus, the study population was divided into three strata (MZCH, QUECH, ZMCH), with each hospital representing a stratum. Each stratum was then proportionately and randomly sampled. Since in this study, the exact population sizes of hospitalized COVID-19 cases in each hospital were unknown, a proportional allocation approach was employed. This method considered the occurrence of COVID-19 cases based on preliminary assessment of COVID-19 situational reports and databases in the selected study sites to determine the number of records to be collected in each stratum (Ministry of Health, 2023). Therefore, the hospitals were ranked according to the number of COVID-19 cases reported. Blantyre in which QUECH is located had recorded the highest number of cases (6006) followed by Mzimba North (5134) where MZCH is, and Zomba (ZMCH) with the least cases (4013) (Ministry of Health, 2023).

Allocation of the sample sizes proportionally was done by dividing the population size of each stratum by the sum of all population sizes as follows:

Proportion for each stratum = $\text{population size} / \text{sum of all population sizes}$ ..Equation 2

- Proportion for QUECH = $6006 / 15153 = 0.396$
- Proportion for MZCH = $5134 / 15153 = 0.339$
- Proportion for ZMCH = $4013 / 15153 = 0.265$

Hence QUECH was assigned a proportion of 0.396, MZCH a proportion of 0.339, and ZMCH a proportion of 0.265. Thus, the calculation of sample size in each stratum was as follows:

Sample size for each stratum = $\text{Proportion} \times \text{Total Sample size}$ ….Equation 3

- Sample size for QUECH = $0.396 \times 385 = 152.46$ (rounded to 152)
- Sample size for MZCH = $0.339 \times 385 = 130.51$ (rounded to 131)
- Sample size for ZMCH = $0.265 \times 385 = 102.02$ (rounded to 102)

Therefore, the sample size of 385 hospitalized COVID-19 patient records was distributed as follows: 152 from QUECH, 131 from MZCH, and 102 from ZMCH.

3.5 Inclusion Criteria of the Study Population

The study included medical records from 2020 to 2022 of hospitalized COVID-19 patients that contained complete data on demographics, clinical features, treatment records as well as hematological and biochemical tests conducted within twenty-four hours of admission.

3.6 Exclusion Criteria of the Study Population

Excluded from the study were records of outpatient COVID-19 cases (individuals who tested positive for COVID-19 but were not hospitalized) and records of hospitalized COVID-19 patients that did not have complete data on clinical findings, treatment records and hematological and biochemical tests.

3.7 Data collection instrument

The collection of data was facilitated by a data collection form (Appendix A) that was customized to meet the objectives of the study and aligned with the Malawian context, building on previous research studies (Cheng *et al*., 2020; Guan *et al*., 2020; Bennett *et al*., 2021; Shi *et al*., 2021). The

form was also made in Microsoft Office Excel 2016 sheet which was used for collection and data entry. The data collection form gathered information on various characteristics including demographics, clinical characteristics, hematological and biochemical test results, treatment records, and outcomes categorized as either survivor or non-survivor.

3.8 Data Collection

Demographic, clinical history, biochemical test results, and hematological test results, and treatment records, were extracted from the electronic medical records and files of PCR- confirmed COVID-19 patients admitted at MZCH, QUECH, and ZMCH and directly entered into a Microsoft Office Excel 2016 sheet. The data on the hematological tests results collected were on complete blood count (CBC) parameters. Biochemical test results data collected were on BUN, Cr, TP, Alb, TBil, AST, ALT, ALP, GGT, and LDH. Additionally, the hematological test results used in this study were tested by Sysmex XN 1000 and Sysmex XP-300 hematology analyzers (Sysmex, 2023). Biochemical parameters used in this study were measured using Mindray BS 360E, Mindray BS 420 and Mindray BS 120 chemistry analyzers (Shenzhen Mindray Bio-Medical Electronics Co., L, 2023).

3.9 Statistical Analysis

The collected data was analyzed using IBM SPSS version 26. Firstly, the data was categorized based on hospital and COVID-19 outcomes, specifically survival and non-survival groups. Numerical variables including age, body temperature, and biochemical and hematological test results were checked for normality by Kolmogorov-Smirnov test, and were presented as median with minimum and maximum values. Categorical variables, such as sex, comorbidities, treatments and clinical signs and symptoms, were reported as counts and percentages (%). The categorical variables were compared between survivors and non-survivors using Chi-square (χ^2) test, or Fisher's exact test where appropriate with a significance level set at $p<0.05$. Biochemical and hematological test results measurements outside the normal range were also presented. The Mann–Whitney *U* -test was further used to compare biochemical and hematological test parameters between survivors and non-survivors, with a significance level set at $p<0.05$. Univariate logistic regression analyses, employing the enter method, were also conducted to ascertain parameters associated with survival and non-survival during hospitalization. Variables with $p<0.200$ in

univariate analysis were then included in multivariate backward logistic regression analysis. Variables with $p<0.05$ on multivariate regression were chosen as predictors of survival.

3.10 Ethical Consideration

The study ethical clearance was obtained from the National Health Sciences Research Committee (NHSRC) in Malawi (Protocol #23/04/4076), as well as the research ethics committees of the respective central hospitals in the study sites (Appendix C, D, E and F). Regarding issues of risks, benefits, privacy, and confidentiality, this was a retrospective study that utilized pre-existing data, without involving direct engagement with study participants. As a result, the potential risk of causing harm to them was minimized. While the study did not provide direct benefits to anyone whose data was used, the analysis of hematological and biochemical data aimed to increase healthcare providers' knowledge of COVID-19 thereby refining their capacity to appropriately manage COVID-19 cases in the Malawian population.

The privacy and confidentiality of study patient records was also safeguarded. This was achieved by de-identifying any data used in the study, replacing identifying information with new identification numbers. This process was to prevent the data from being linked back to specific individuals. To further ensure that ethical and legal guidelines were followed, the data was stored in password-protected computers, and access was limited to supervisors and the researcher, who only used it for research purposes. Apart from the standard academic benefits, there were no other expected gains from this study. Therefore, there was no conflict of interest.

CHAPTER FOUR

4.0 RESULTS

4.1 Description of Hospitalized COVID-19 Patients in Central Hospitals and COVID-19 Diagnostic Tests

The required sample sizes of 131 at MZCH and 152 at QUECH were successfully achieved. However, a challenge was encountered at ZMCH, where the targeted sample size of 102 was not achieved due to lack of complete records in some patient files. Hence the study comprised 367 hospitalized COVID-19 patient records, of which 217 (59.1%) were records of survivors and 150 (40.9%) were records of non-survivors, with varying percentages among the three central hospitals as presented in Table 4.1.

Regarding COVID-19 diagnostic tests, all the 367 hospitalized COVID-19 patient records in this study had a confirmed positive test for SARS-CoV-2 using RT-PCR. Additionally, 81 (22.07%) of patients were also tested with SARS-CoV-2 rapid diagnostic tests (RDT) (Table 4.1).

Table 4.1 Hospitalized COVID-19 Patients in Central Hospitals and COVID-19 Tests

Variable	Total (n=367)	Survivors (n= 217)	Non-survivors (n= 150)	*p*-value
Central Hospitals				
- **QECH**	152 (41.4%)	96 (44.2%)	56 (37.3%)	
- **MZCH**	131 (35.7%)	64 (29.5%)	67 (44.7%)	0.0091*
- **ZMCH**	84 (22.9%)	57 (26.3%)	27 (18.0%)	
COVID-19 Tests				
- **RT-PCR**	367 (100%)	217 (100%)	150 (100%)	
- **SARS-CoV-2RDT**	81 (22.07%)	47 (21.7%)	34 (22.7%)	
• **Positive**	75 (20.4%)	43 (19.8%)	32 (21.3%)	0.8813
• **Negative**	6 (1.6%)	4 (1.8%)	2 (1.3%)	

n= number of hospitalized COVID-19 patient records. %= percentage. QUECH= Queen Elizabeth Central Hospital. MZCH= Mzuzu Central Hospital. ZMCH= Zomba Central Hospital. Data are counts, n (%). The *p*-values were calculated by χ^2 test to compare survivors and non-survivors. **p*-value indicates statistical significance at $p<0.05$.

4.2 Demographic Characteristics of Hospitalized COVID-19 Patients on Admission

The demographic characteristics of hospitalized COVID-19 patients assessed in this study were age and sex and the results are shown in table 4.2. The median age of the entire cohort was 45 years. Survivors had a lower median age of 44 years compared to non-survivors (50.5 years), (p=0.0020). In terms of sex, 51.5% were males, and the distribution of survivors between males and females was 46.5% and 53.5% respectively. Among non-survivors, the majority were males (58.7%).

Table 4.2 Demographic Characteristics of Hospitalized COVID-19 Patients

Variable	**Total (n=367)**	**Survivors (n= 217)**	**Non-survivors (n= 150)**	***p*-value**
Age (years)	45 (15-97)	44 (16-96)	50.5 (15-97)	0.0020*
Sex				
- **Male**	189 (51.5%)	101 (46.5%)	88 (58.7%)	0.0223*
- **Female**	178 (48.5%)	116 (53.5%)	62 (41.3%)	

Data are median (minimum value – maximum value) for age and counts, n (%) for sex. *p*-values were calculated by Mann–Whitney *U* -test, and χ^2 test, as appropriate to compare survivors and non-survivors. **p*-values indicate statistical significance at $p<0.05$.

4.3 Comorbidities of Hospitalized COVID-19 Patients on Admission

Table 4.3 illustrates that the prevalence of comorbidities or underlying diseases was 51.2% among hospitalized COVID-19 patients assessed in this study. Human Immunodeficiency Virus (HIV) infection was the most prevalent underlying disease (22.9%). In addition, a category labeled "Others" had a prevalence of 2.5% and these were underlying diseases including malaria, Alzheimer, sickle cell anemia, cardiovascular disease, and endometrial mass.

Table 4.3 Comorbidities of Hospitalized COVID-19 Patients on Admission

Variable	Total (n=367)	Survivors (n= 217)	Non-survivors (n= 150)	*p*-value
Comorbidities	188 (51.2%)	104 (47.9%)	84 (56.0%)	0.1571
- **HIV infection**	84 (22.9%)	47 (21.7%)	37 (24.7%)	0.5838
- **Hypertension**	75 (20.4%)	40 (18.4%)	35 (23.3%)	0.3112
- **Diabetes mellitus**	58 (15.8%)	33 (15.2%)	25 (16.7%)	0.8172
- **Asthma**	13 (3.5%)	9 (4.1%)	4 (2.7%)	0.6403
- **Tuberculosis**	11 (3.0%)	6 (2.8%)	5 (3.3%)	0.9980
- **Carcinoma**	8 (2.2%)	4 (1.8%)	4 (2.7%)	0.7208
- **Chronic lung disease**	4 (1.1%)	1 (0.5%)	3 (2.0%)	0.3090
- **Kidney disease**	4 (1.1%)	0	4 (2.7%)	0.0272*
- **Others**	9 (2.5%)	6 (2.8%)	3 (2.0%)	0.9025

Data are counts, n (%). *p*-values were calculated by χ^2 or Fishers' exact test, as appropriate to compare survivors and non-survivors. HIV= Human Immunodeficiency Virus. **p*-value indicates statistical significance at $p<0.05$

4.4 Clinical Characteristics of Hospitalized COVID-19 Patients on Admission

As portrayed in Table 4.4, the hospitalized COVID-19 patients were presented with diverse clinical signs and symptoms as well as vital signs. The most prevalent clinical characteristics reported were coughing (83.1%), dyspnea (78.2%), fever (70.8%) and headache (60.2%). All the clinical signs and symptoms were present in both survivors and non-survivors. Only dyspnea exhibited a statistically significant difference between survivors and non-survivors ($p=0.0040$).

The measurements of vital signs included respiratory rate, temperature, heart rate, systolic and diastolic blood pressure, as well as oxygen saturation at room air. Among these, statistically significant variations between survivors and non-survivors were noted in respiratory rate, heart rate, and oxygen saturation ($p<0.05$), as highlighted in Table 4.4.

Table 4.4. Clinical Characteristics of Hospitalized COVID-19 Patients on Admission

Clinical Characteristics	Total (n=367)	Survivor (n= 217)	Non-survivor (n= 150)	*p*-value
Signs and Symptoms				
- **Cough**	305 (83.1%)	182 (83.9%)	123 (82.0%)	0.7425
- **Dyspnea**	287 (78.2%)	158 (72.8%)	129 (86.0%)	0.0040*
- **Fever**	260 (70.8%)	149 (68.7%)	111 (74.0%)	0.3227
- **Headache**	221 (60.2%)	135 (62.2%)	86 (57.3%)	0.4064
- **Chest Pain**	141 (38.4%)	75 (34.6%)	66 (44.0%)	0.0858
- **General body pain**	126 (34.3%)	67 (30.9%)	59 (39.3%)	0.1174
- **Myalgia and Fatigue**	116 (31.6%)	69 (31.8%)	47 (31.3%)	0.9839
- **Ageusia**	78 (21.3%)	42 (19.4%)	36 (24.0%)	0.3474
- **Anorexia**	69 (18.8%)	34 (15.7%)	35 (23.3%)	0.0870
- **Anosmia**	68 (18.5%)	42 (19.4%)	26 (17.3%)	0.7238
- **Nausea and Vomiting**	46 (12.5%)	33 (15.2%)	13 (8.7%)	0.0891
- **Diarrhea**	29 (7.9%)	18 (8.3%)	11 (7.3%)	0.8895
- **Abdominal**	29 (7.9%)	19 (8.8%)	10 (6.7%)	0.5944
- **Wheezing**	22 (6.0%)	10 (4.6%)	12 (8.0%)	0.2619
- **Sore throat**	14 (3.8%)	9 (4.1%)	5 (3.3%)	0.9020
- **Confusion**	10 (2.7%)	6 (2.8%)	4 (2.7%)	1.000
- **Runny nose**	9 (2.5%)	6 (2.8%)	3 (2.0%)	0.7428
- **Convulsions**	5 (1.4%)	2 (0.9%)	3 (2.0%)	0.6523
Vital Signs				
- **Respiratory rate, Median (max-min) bpm**	24 (14-54)	23 (14-47)	26 (14-54)	0.0008*
- **Temperature, Median, (min-max) ^{0}C**	36.7 (33.6-39.9)	36.7 (34.2-39.9)	36.8 (33.6-38.6)	0.9664
- **Heart rate, Median, (max-min) beats per minute**	104 (42-209)	102 (49-156)	108 (32-209)	0.0441*
- **Systolic blood pressure, Median (max-min) mmHg**	128 (70-247)	127 (72-209)	128 (70-247)	0.7085
- **Diastolic blood pressure, Median (max-min) mmHg**	76 (34-133)	76 (38-128)	78 (34-133)	0.8495
- **Oxygen Saturation Median (max-min) %**	93 (52-100)	94 (56-100)	90 (52-100)	0.0001*

Data are median (minimum – maximum) and counts, n (%). *p*-values were calculated by Mann–Whitney U -test, χ^2 or Fishers' exact test, as appropriate to compare survivors and non-survivors. bpm= breaths per minute, ^{0}C= degrees Celsius and mmHg= millimeters of mercury. **p*-values indicate statistical significance at $p<0.05$.

4.5 Hematological Characteristics of Hospitalized COVID-19 Patients on Admission

The study also evaluated hematological tests in hospitalized COVID-19 patients, which were based on the complete blood count results as displayed in Table 4.5. In comparison to normal reference ranges, many parameters were within their reference ranges. However, the overall medians of neutrophil count and NLR were higher than their normal intervals, while the median hemoglobin concentration (11.7 g/dL) was lower than the expected interval (13-18 g/dL). On hematological differences between survivors and non-survivors, total leukocyte count, neutrophil count, and NLR displayed statistically significant differences ((p<0.0001). Additionally, both MCH (p=0.0215) and MCHC (p=0.2026) also showed differences between the two groups (Table 4.5).

Table 4.5. Hematological Characteristics of Hospitalized COVID-19 Patients on Admission

Variable	Normal Range	Total (n=367)	Survivor (n=217)	Non-survivor (n=150)	*p*-value
Leucocytes ($x10^3$/µL)	4- 10	8.80 (0.40 -30.20)	7.26 (1.50-28.90)	12.35 (0.40-30.20)	<0.0001*
Neutrophils ($x10^3$ /µL)	0.82-4.1	6.38 (0.10 -25.90)	5.01 (0.61-25.90)	9.90 (0.10-25.80)	<0.0001*
Lymphocytes ($x10^3$/µL)	1.26-3.62	1.30 (0.10-10.10)	1.30 (0.24-10.10)	1.40 (0.10-8.60)	0.7241
NLR	0.78-3.53	5.00 (0.11-68.50)	3.79 (0.36-50.00)	6.74 (0.11-68.58)	<0.0001*
RBC ($x10^6$/ µL)	4-6	4.23 (1.16 – 7.14)	4.30 (1.16-6.56)	4.04 (1.22-7.14)	0.0761
Hemoglobin (g/dl)	13-18	11.7 (2.1- 21.6)	11.6 (2.1-18.8)	11.8 (3.6-21.6)	0.3296
Hematocrit (%)	32-50	34.6 (8.5-58.8)	35.0 (8.5-57.6)	33.75 (11.2-58.8)	0.1959
MCV (fL)	80-100	82.4 (58.5-110.7)	81.8 (58.5-107.1)	83.3 (60.1-110.7)	0.0982
MCH (pg)	23-34	27.9 (16.6-39.2)	27.8 (16.9-38.0)	28.2 (16.6-39.2)	0.0215*
MCHC (g/dl)	33- 36	33.9 (24.7-83.5)	33.5 (24.7-47.8)	34.1 (27.6-83.5)	0.0250*
RDW (%)	11.5-14.5	13.70 (9.30-63.50)	13.80 (9.60-43.90)	13.50 (9.30-63.50)	0.2026
Platelet ($\times10^3$/ µL)	122-330	220 (15-1092)	219 (24-822)	225.5 (15-1092)	0.8617

Data are median (minimum– maximum). *p*-values were calculated by Mann–Whitney *U* -test. NLR= Neutrophil-to-Lymphocyte Ratio, RBC= Red Blood Cells, MCV= Mean corpuscular volume. MCH= Mean corpuscular hemoglobin. MCHC= Mean corpuscular hemoglobin concentration. RDW= Red cell distribution Width. **p*-value indicates statistical significance at $P<0.05$.

4.6 Biochemical Characteristics of Hospitalized COVID-19 Patients on Admission

The other objective of the study was to assess the biochemical characteristics of hospitalized COVID-19 patients and the results are summarized in Table 4.6. The specific biochemical test results evaluated and compared between survivors and non-survivors included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), total bilirubin (TBil), total protein (TP), albumin (Alb), lactate dehydrogenase (LDH), urea (Blood urea Nitrogen [BUN]), and creatinine (Cr).

In comparison to the reference ranges, the overall median values of AST, ALT, ALP, TP, Alb, TBil, BUN, and Cr levels were within their respective normal ranges, while median values of γ-GT, and LDH surpassed their acceptable intervals. The biochemical parameters were also compared between survivors and non-survivors. All the parameters demonstrated statistical differences ($p<0.05$) and most of them were higher in non-survivors than survivors, except for Alb (Table 4.6).

Table 4.6. Biochemical Characteristics of Hospitalized COVID-19 Patients on Admission

Variable	Normal Range	Total (n=367)	Survivor (n=217)	Non-survivor (n=150)	*p*-value
AST (U/L)	9.0-50	43.1 (7.75 -1107.36)	31.45 (7.75-301.00)	87.13 (10.40-1107.36)	<0.0001*
ALT (U/L)	9.0 -50	37.8 (6.7-300.49)	28.5 (6.70-172.19)	77.60 (10.0-300.49)	<0.0001*
γ-GT (U/L)	0.0-41.0	74.4 (12-760.60)	61.76 (13.30-479.00)	118.56 (12.00-760.60)	<0.0001*
ALP (U/L)	53-128	92.34 (38.0-352.52)	83.15 (38.00-352.52)	129.89 (43.20-312.93)	<0.0001*
TP (mg/dL)	6.0-8.3	6.83 (4.24-10.90)	6.87 (4.44-10.90)	6.80 (4.24-8.80)	0.0325*
Alb (mg/dL)	3.5-5.0	3.60 (1.07-6.00)	3.70 (1.07-6.00)	3.50 (1.63-4.86)	0.0036*
TBil (mg/dl)	0.2-1.0	0.63 (0.11-9.13)	0.51 (0.11-5.74)	0.67 (0.13-9.13)	0.0025*
LDH (U/L)	120-250	529.62 (214-2313.89)	452.91 (214-1932.41)	672.45 (225-2313.89)	<0.0001*
Urea (mg/dl)	10-43	36.6 (6.21-391.20)	27.42 (10.40-391.20)	52.19 (6.21-386.10)	<0.0001*
Cr (mg/dL)	0.5-1.2	1.00 (0.12-33.95)	0.85 (0.12-19.50)	1.35 (0.17-33.95)	<0.0001*

Data are median (minimum– maximum). *p*-values were calculated by Mann–Whitney *U* -test to compare survivors and non-survivors. U/L= units per liter (U/L), mg/dL = milligrams per deciliter, AST= Aspartate amino transferase, ALT= Alanine amino transferase, γ-GT= gamma-glutamyl transferase, ALP=Alkaline Phosphatase, TP=Total Protein, Alb = Albumin, TBil = Total Bilirubin, LDH= Lactate dehydrogenase, Cr = Creatinine. **p*-value indicates statistical significance at $p<0.05$.

4.7 Treatments Administered to Hospitalized COVID-19 Patients in Three Central Hospitals

Different types of treatments, including antibiotics, glucocorticoids, oxygen therapy, enoxaparin, zinc, omeprazole, hydroxychloroquine, nevirapine, ferrous sulphate, and antifungals, were administered to hospitalized COVID-19 patients across the three central hospitals. These treatments were given at varying frequencies, as shown in Table 4.7. Predominant among the administered treatments were antibiotics (98.9%), mostly ceftriaxone (63.8%), glucocorticoids (85.3%), mainly dexamethasone (82.3%), oxygen therapy (79.6%), and enoxaparin (71.7%).

Table 4.7. Treatments Administered to Hospitalized COVID-19 Patients in Three Central Hospitals

Treatment	Total (n=367)	QUECH (n=152)	MZCH (n=131)	ZMCH (n=84)
Antibiotics	363 (98.9%)	150 (98.7%)	130 (99.2%)	83 (98.8%)
- **Ceftriaxone**	234 (63.8%)	86 (56.6%)	97 (74%)	51 (60.7%)
- **Azithromycin**	62 (16.9%)	12 (7.9%)	34 (26%)	16 (19%)
- **Metronidazole**	28 (7.6%)	10 (6.6%)	12 (9.2%)	6 (7.1%)
- **Ciprofloxacin**	10 (2.7%)	5 (3.3%)	1 (0.8%)	4 (4.8%)
- **Meropenem**	8 (2.2%)	1 (0.7%)	4 (3.1%)	3 (3.6%)
- **Ampicillin**	6 (1.6%)	2 (1.3%)	0	4 (4.8%)
- **Co-Trimoxazole**	4 (1.1%)	4 (2.6%)	0	0
- **Amoxicillin**	3 (0.8%)	1 (0.7%)	1 (0.8%)	1 (1.2%)
- **Doxycycline**	2 (0.5%)	2 (1.3%)	0	0
- **Nalidixic Acid**	1 (0.3%)	0	0	1 (1.2%)
- **Tazobactam**	1 (0.3%)	0	1 (0.8%)	0
Glucocorticoids	313 (85.3%)	126 (82.9%)	109 (83.2%)	78 (92.9%)
- **Dexamethasone**	302 (82.3%)	126 (82.9%)	100 (76.3%)	76 (90.5%)
- **Prednisolone**	6 (1.6%)	2 (1.3%)	2 (1.5%)	2 (2.4%)
- **Hydrocortisone**	4 (1.1%)	0	4 (3.1%)	0
Oxygen Therapy	292 (79.6%)	112 (73.7%)	111 (84.7%)	69 (82.1%)
Enoxaparin	263 (71.7%)	122 (80.3%)	69 (52.7%)	72 (85.7%)
Vitamins	83 (22.6%)	16 (10.5%)	54 (41.2%)	13 (15.5%)
- **Vitamin C**	59 (16.1%)	9 (5.9%)	41 (31.3%)	9 (10.7%)
- **Vitamin B**	28 (7.6%)	7 (4.6%)	16 (12.2%)	5 (6 %)
- **Vitamin D**	6 (1.6%)	2 (1.3%)	3 (2.3%)	1 (1.2%)
Zinc	73 (19.9%)	2 (1.3%)	60 (45.8%)	11 (13.1%)
Omeprazole	44 (12%)	3 (2 %)	39 (29.8%)	2 (2.4%)
Hydroxychloroquine	18 (4.9%)	8 (5.3%)	9 (6.9%)	1(1.2%)
Nevirapine	14 (3.8%)	3 (2%)	0	11(13.1%)
Ferrous Sulphate	8 (2.2%)	2 (1.3%)	4 (3.1%)	2 (2.4%)
Antifungals	8 (2.2%)	3 (2%)	3 (2.3%)	2 (2.4%)
- **Fluconazole**	5 (1.4%)	3 (2%)	2 (1.5%)	0
- **Nystatin**	2 (0.5%)	0	0	2 (2.4%)
- **Flucytosine**	2 (0.5%)	1 (0.7%)	1 (0.8%)	0

Data are counts, n (%). QUECH= Queen Elizabeth Central Hospital. MZCH= Mzuzu Central Hospital. ZMCH= Zomba Central Hospital.

4.8 Treatment Administered to Hospitalized COVID-19 Patients According to Survivors and Non-survivors.

Table 4.8 presents the comparison of treatments administered to hospitalized COVID-19 patients according the survivors and non-survivors. Most of the treatments were statistically administered without differences between survivors and non-survivors (p >0.05). The treatments that showed a significant difference were ceftriaxone (p=0.0022), oxygen therapy (p=0.0014), omeprazole (p=0.0140), hydroxychloroquine (p=0.0466), and nevirapine (p=0.0101) (Table 4.8).

Table 4.8. Treatment Administered to Hospitalized COVID-19 Patients According to Survivors and Non-survivors.

Treatment	Total (n=367)	Survivor (n=217)	Non-survivor (n=150)	*p*-value
Antibiotics	363 (98.9%)	214 (98.6%)	149 (99.3%)	0.8903
- **Ceftriaxone**	234 (63.8%)	124 (57.1%)	110 (73.3%)	0.0022*
- **Azithromycin**	62 (16.9%)	38 (17.5%)	24 (16%)	0.8117
- **Metronidazole**	28 (7.6%)	12 (5.5%)	16 (10.7%)	0.1047
- **Ciprofloxacin**	10 (2.7%)	4 (1.8%)	6 (4%)	0.3281
- **Meropenem**	8 (2.2%)	4 (1.8%)	4 (2.7%)	0.7208
- **Ampicillin**	6 (1.6%)	6 (2.8%)	0	0.0853
- **Co-Trimoxazole**	4 (1.1%)	2 (0.9%)	2 (1.3%)	1.0000
- **Amoxicillin**	3 (0.8%)	2 (0.9%)	1 (0.7%)	1.0000
- **Doxycycline**	2 (0.5%)	1 (0.5%)	1 (0.7%)	1.0000
- **Nalidixic Acid**	1 (0.3%)	1 (0.5%)	0	1.0000
- **Tazobactam**	1 (0.3%)	1 (0.5%)	0	1.0000
Glucocorticoids	313 (85.3%)	183 (84.3%)	130 (86.7%)	0.6377
- **Dexamethasone**	302 (82.3%)	175 (80.6%)	127 (84.7%)	0.3937
- **Prednisolone**	6 (1.6%)	4 (1.8%)	2 (1.3%)	1.0000
- **Hydrocortisone**	4 (1.1%)	3 (1.4%)	1 (0.7%)	0.6478
Oxygen Therapy	292 (79.6%)	160 (73.7%)	132 (88%)	0.0014*
Enoxaparin	263 (71.7%)	160 (73.7%)	103 (68.7%)	0.3468
Vitamins	83 (22.6%)	52 (24%)	31 (20.7%)	0.5384
- **Vitamin C**	59 (16.1%)	36 (16.6%)	23 (15.3%)	0.8590
- **Vitamin B complex**	28 (7.6%)	18 (8.3%)	10 (6.7%)	0.7057
- **Vitamin D**	6 (1.6%)	3 (1.4%)	3 (2%)	0.6917
Zinc	73 (19.9%)	41 (18.9%)	32 (21.3%)	0.6581
Omeprazole	44 (12%)	18 (8.3%)	26 (17.3%)	0.0140*
Hydroxychloroquine	18 (4.9%)	15 (6.9%)	3 (2%)	0.0466*
Nevirapine	14 (3.8%)	13 (6.0%)	1 (0.7%)	0.0101*
Ferrous Sulphate	8 (2.2%)	7 (3.2%)	1 (0.7%)	0.1485
Antifungals	8 (2.2%)	4 (1.8%)	4 (2.7%)	0.7208
- **Fluconazole**	5 (1.4%)	3 (1.4%)	2 (1.3%)	1.0000
- **Nystatin**	2 (0.5%)	1 (0.5%)	1 (0.7%)	1.0000
- **Flucytosine**	2 (0.5%)	0	2 (1.3%)	0.1664

Data are counts, n (%). *p*-values were calculated by χ^2 or Fishers' exact test, as appropriate to compare survivors and non-survivors. **p*-value indicates statistical significance at $p<0.05$.

4.9 Logistic Regression Analysis for Predictors of Survival in Hospitalized COVID-19 Patients

Univariate and Multivariate logistic regression analysis were also performed to assess factors associated with survival in hospitalized COVID-19 patients. Only significant variables, (p<0.2), after univariate analysis were included in the multivariate analysis. The variables included in multivariate analysis were age, ageusia, ALT, albumin, anosmia, antibiotic, asthma, ciprofloxacin, carcinoma, confusion, convulsion, creatinine, dexamethasone, doxycycline, general body pain, glucocorticoid, headache, HCT, hemoglobin, hydroxychloroquine, LDH, MCH, MCHC, MCV, metronidazole, omeprazole, oxygen saturation, platelet, pulse rate, and total protein. The final stepwise model indicated that age (p=0.0090), ALT levels (p<0.0001), creatinine levels (p=0.0048), use of hydroxychloroquine (p=0.0418) and LDH levels (p<0.0001) had a negative association with survival state. Conversely, albumin levels (p=0.0140), presence of carcinoma (p=0.0201), and higher oxygen saturation levels (p=0.0001) demonstrated positive association with survival state.

CHAPTER FIVE

5.0 Discussion

This study assessed the clinical, hematological and biochemical characteristics, as well as the treatments administered and predictors of survival, in COVID-19 patients hospitalized at QUECH, MZCH, and ZMCH in Malawi. The results are based on records of 367 hospitalized COVID-19 patients with positive test for SARS-CoV-2 using RT-PCR.

In reference to demographic characteristics, survivors had a lower median age than non-survivors, indicating to potential association between age and survival outcomes. Similar findings were previously reported among the hospitalized COVID-19 cases in Turkey, (Bastug *et al.*, 2020), China (Guan *et al*., 2020) and other countries (Lin *et al*., 2023). Poor outcomes in infectious diseases among elderly individuals have long been attributed to changes that occur with aging, which involve significant alterations in both the immune and endocrine systems, rendering individuals more susceptible to infections (Müller *et al*., 2019; Santoro *et al.*, 2021). Some of the changes associated with aging, such as increased cellular senescence in the lungs, epigenetic dysregulation, mitochondrial dysfunction, inflammaging, and immunosenescence, compromise the functions of both adaptive and innate immunity (Schneider *et al*., 2021; Santoro *et al.*, 2021). Thus, the poor outcomes and severity of COVID-19 in adults might be due to the effects of factors associated with aging (Santoro *et al.*, 2021).

The other demographic factor was sex. Non-survivors had a higher proportion of males, while survivors had higher proportion females. These differences were statistically significant and are consistent with a study on factors affecting the survival rate in patients with COVID-19 in Iran, where men showed elevated risk of mortality compared to women (Eshrati *et al.*, 2020). Being male was also reported to have significant hazard ratio for in hospital mortality in a multicenter study in Spain (García de Guadiana-Romualdo *et al*., 2021). Elsewhere, it has been explained that men have more risk of deaths than women due to poor immune response, unhealthy lifestyles (Klein and Flanagan, 2016; Eshrati *et al*., 2020), genetic factors, estrogen, and testosterone levels (Hussain *et al*, 2020; Raimondi *et al.*, 2021). In this context, it is important to promote the significance of comprehending demographic and gender-related factors when managing COVID-19 cases in Malawi.

Overall prevalence of comorbidities or underlying diseases in this study was 51.2%. Specific comorbidities were HIV infection, hypertension, diabetes mellitus, asthma, tuberculosis, carcinoma, chronic lung disease, and kidney disease, and they are comparable to the previous findings obtained in Malawi (Anscombe *et al.*, 2023), and other countries (Wan *et al*., 2020; Nagy *et al*., 2023; Djorwé *et al.,* 2024). More evidence from previous studies also indicated that COVID-19 patients with pre-existing conditions like hypertension, cardiovascular diseases, diabetes, HIV infection, immune and metabolic disorders, respiratory diseases, cerebrovascular diseases, various cancers, renal, and liver diseases have an increased likelihood of death and severity (Khan *et al.*, 2020; Manickum, 2021; Nagy *et al.*, 2023). Individuals with comorbidities such as diabetes mellitus, malignancy, pulmonary diseases, chronic kidney disease, and HIV infection are severely affected by SARS-CoV-2 infection due to impaired immunity associated with these conditions (Rao *et al*., 2020; Spinelli *et al* 2022; Zsichla and Müller, 2023). Additionally, ACE2 receptor expression has been noted to be increased in diabetes mellitus, pulmonary diseases, and chronic kidney disease, thereby facilitating SARS-CoV-2 entry (Rao *et al*., 2020; Zsichla and Müller, 2023).

Various clinical signs and symptoms among hospitalized COVID-19 patients were presented in this study. The clinical features were diverse, observed in both survivors and non-survivors and they are similar to those reported in other studies (Stokes *et al*., 2020; Wu and McGoogan, 2020; Elmunzer *et al*., 2021; Chibwana *et al*., 2022). In this study, dyspnea exhibited a statistically significant difference, being more prevalent in non-survivors compared to survivors. Clinically, dyspnea has been used as a significant indicator of severe disease and associated with poor prognosis in COVID-19 cases (Guimarães *et al*., 2022; WHO, 2022). In COVID-19 patients, SARS-CoV-2 primarily affects the respiratory system, causing alveoli and lung tissue inflammation, which compromise gas diffusion (Gattinoni *et al*., 2020; Hentsch *et al*., 2021). Consequently, individuals display respiratory clinical signs such as dyspnea (Nishiura *et al.,* 2020; Sood *et al.,* 2020).

This study also identified clinical features involving other body systems, including the gastrointestinal tract, cardiovascular, musculoskeletal, and central nervous systems, aligning with reports on multi-organ involvement in COVID-19 patients (Sood *et al.,* 2020; Borczuk and Yantiss, 2022; WHO, 2022). In SARS-CoV-2 infection, ACE2 receptors have been observed to be the primary targets bound by SARS-CoV-2 (Jamal *et al*., 2021) and ACE2 is expressed in many cell

types and tissues (Borczuk and Yantiss, 2022). This allows SARS-CoV-2 to invade various cells and tissues, which explains the presence of clinical features involving other body systems apart from the respiratory system (Duloquin *et al*., 2024).

On vital signs, this study found statistically significant deranged vital signs' median readings among non-survivors pertaining to respiratory rate, heart rate, and oxygen saturation. These signs indicated respiratory distress among COVID-19 patients (Agarwal *et al*., 2021). Similar findings were also reported in the past studies (Deng *et al*., 2020b; Zhou *et al*., 2020; Nachega *et al.*, 2020) and in the subsequent studies (Hasani *et al*., 2023; Hormozi Jangi, 2023). In COVID-19, vital characteristics of a typical COVID-19 patient, such as low oxygen saturation, a high respiratory rate, and a high heart rate, are crucial for identifying those who require early mechanical ventilation, continuous positive airway pressure (CPAP) and they associated with a higher viral load (Colombo *et al.*, 2022; Dergaa *et al.*, 2022).

Alterations in hematological parameters like white blood cell counts and differential counts have been reported among hospitalized COVID-19 patients (Słomka *et al*., 2020; Asghar *et al*., 2020a). In this study, the overall median leukocyte count was within the reference interval. However, in the non-survival group, the leukocyte count exceeded the reference interval and was significantly higher compared to the survival group. The overall median neutrophil count was elevated compared to the reference range, with a more increase in non-survivors. Further, in some studies, lymphocytopenia has been described as one of the main characteristics of COVID-19 patients (Chen, *et al*., 2020b; Chen *et al*., 2020b). In contrast, a normal overall median lymphocyte count was found in this study, with no significant differences between survivors and non-survivors. The NLR, which serves as an indicator of systemic inflammation (Forget *et al.*, 2017), was significantly high in non-survivors. This means the high leukocyte count was due to neutrophilia as also observed by Gujar *et al*. (2021). Neutrophils are known to increase and play main roles in bacterial infections and may slightly increase in patients with other viral infections (Lamichhane and Samarasinghe, 2019; McKenna *et al*., 2022). SARS-CoV-2 causes a dysfunctional innate and adaptive immune response (Jamal *et al*., 2021). In this dysfunctional immune response, there is an increased activation of neutrophils and inflammatory cytokines, which are associated with lymphopenia, inflammation, and tissue damage (Jamal *et al*., 2021; McKenna *et al*., 2022). Similar prior studies indicated that elevated leukocyte count, neutrophil count, and NLR, as well as lymphocytopenia,

are effective in discriminating between severe and mild COVID-19 cases (Bastug *et al.*, 2020) or survival from non-survival states (Tjendra *et al*., 2020; Shi *et al.*, 2021).

Other hematological parameters, including RBC count, hematocrit, and RDW were found to be within normal ranges in this study as earlier reported (Xu *et al*., 2020a; Guan *et al*., 2020). Only hemoglobin was found to be slightly lower than the reference range, but no significant differences were observed between survivors and non-survivors. Consistent with the decreased hemoglobin levels observed among COVID-19 patients, previous studies have reported associations between low hemoglobin levels and severe COVID-19, as well as anemia in such patients (Fan *et al*., 2020; Taneri *et al*., 2020; Dhinata, 2021). Some previous research indicated that SARS-CoV-2 infection can lead to substantial alterations in RBC size and rigidity, along with a decrease in hematocrit levels and an increase in RDW (Anai *et al.,* 2020; Thomas *et al.,* 2020; Russo *et al.,* 2022). As such, clinical management should still consider RBC-related parameters, and further research is needed to enhance our understanding in this area.

As for platelets, the median count in this study remained within the normal range. While some earlier reports linked COVID-19 to thrombocytopenia, particularly in severe cases (Xu *et al.*, 2020b; Gavriilaki *et al*., 2021). Others also found no significant differences between patients with severe and mild disease (Guan *et al*., 2020; Satış *et al*., 2021). More prior research on platelets and COVID-19, indicated an association between thrombocytopenia due to increased destruction or decreased platelet production and the severity of COVID-19 (Buioni *et al.*, 2020; Lippi *et al.*, 2020b). Despite variations in different study observations including this study, it is advisable to monitor platelet count and its changes in each patient, as suggested by (Lippi *et al*., 2020b).

This study also identified increase in the levels of routine biochemical test parameters. Increased levels of γ-GT, ALP, and LDH in relation to the reference ranges were found among hospitalized COVID-19 patients. Markedly elevated levels in the biochemical tests were observed, among non-survivors. These results are consistent with results reported in other populations (Lippi and Plebani, 2020; Yang *et al*., 2020b; Rutledge *et al*., 2021; Nyasulu *et al*., 2022). Elevated levels of biochemistry analytes in COVID-19 patients are due to SARS-CoV-2 infection which exhibits multiorgan dissemination and extensive disease tissue damage (Jamal *et al.*, 2021; Thakur *et al.*, 2021). SARS-CoV-2 infection has been reported to cause dermatological complications,

myocardial dysfunction, gastrointestinal symptoms, neurological disorders, hepatic, and renal injury (Thakur *et al.*, 2021). In this study, the routine biochemistry analytes that showed significant alterations in non-survivors primarily pertain to liver injury (AST, ALT, γ-GT, and ALP), renal system injury (BUN and Cr), and the indication of organ injury or multiple organ injury (LDH). This aligns with the notion that organs such as the liver, urinary system, and other vital organs may be affected by SARS-CoV-2(Letelier *et al*., 2021). Moreover, in related studies, high levels of biochemical parameters such as LDH, AST, ALT, TBil, LDH, BUN, and Cr were reported to significantly associate with severe disease states, ICU admission and death among COVID-19 patients (Ciaccio and Agnello, 2020; Henry *et al*., 2020; Alizad *et al* 2023; Michael et al., 2024).

In this study majority of hospitalized COVID-19 patients received treatments, including antibiotics, glucocorticoids, oxygen therapy, and enoxaparin. These treatments were similar to those administered in other studies (Haddad *et al.*, 2022; Panahi *et al.*, 2023) and were also listed and explained in WHO recommendations (WHO, 2021c). Antibiotics were widely used, with ceftriaxone being the most commonly used antibiotic especially in non-survivors. WHO recommended the administration of antibiotics to be based on the local prevalence of bacterial coinfections/secondary infections (WHO, 2020d). In this study, many records did not indicate evidence of bacterial coinfections or secondary infections, as also reported by Beovic *et al*. (2020) and Chedid *et al*. (2021). Equally, WHO reported on the widespread overuse of antibiotics in hospitalized COVID-19 patients with the highest usage observed in the African Region (WHO 2024). As previously published, the increased in the use of antibiotics in Malawi could be explained by the already present irrational and high prevalence of antibiotic use among hospitals in the sub-Saharan Africa (Balala *et al*., 2020; Siachalinga *et al*., 2023).

Apart from antibiotics, the other most frequently administered treatment was glucocorticoids. Glucocorticoids have been used in COVID-19 to manage hyper inflammation and minimize tissue injury by suppressing the immune response (Haddad *et al*., 2022). However, there is conflicting evidence regarding whether corticosteroids decrease or increase fatality rates in COVID-19 patients (Panahi *et al*., 2023). In this study, glucocorticoids were administered with no significant differences in rates between survivors and non-survivors.

Other treatments administered in significantly different proportions between survivors and non-survivors included oxygen therapy, omeprazole, and hydroxychloroquine. Oxygen therapy was given to a greater number of non-survivors than survivors, likely due to a higher percentage of non-survivors presenting with dyspnea, low oxygen saturation, and increased respiratory rate at the time of admission, as explained in a study by Colombo *et al.* (2021). Omeprazole, a proton pump inhibitor (PPI), was administered to a higher number of non-survivors than survivors. COVID-19 patients have been treated with PPIs previously to prevent stress ulcers (Yao *et al*., 2022). These PPIs have further been linked to worse clinical outcomes in COVID-19 patients due to inhibition of gastric acid secretion, leading to increasing the risk of SARS-CoV-2 infection, and their adverse effects (Yao *et al*., 2022; Luxenburger *et al*., 2021). Hydroxychloroquine, an immunomodulatory drug, was administered to a small proportion (4.9%) of individuals, mostly survivors. Initially, hydroxychloroquine showed *in vitro* antiviral activity against SARS-COV-2 (Wang *et al*., 2020b), prompting to suggestions of its effectiveness in COVID-19 patients. However, clinical efficacy has not been demonstrated in COVID-19 patients (Deng *et al*., 2022; Haddad *et al*., 2022).

Multivariate logistic regression analysis of factors associated with survival and non-survival in COVID-19 patients revealed that younger age and low levels of LDH, ALT, and creatinine, plus use of hydroxychloroquine were significantly associated with survival during hospitalization. Other studies also demonstrated elevated levels of enzymes such as ALT, ALP, and LDH as well as old age as predictors of COVID-19 severity and linked to death in various countries, including Turkey (Ketenci *et al.*, 2022), Botswana (N'dilimabaka *et al.*, 2022), China (Shi *et al*., 2021) and Morocco (Kantri *et al.*, 2021). As age increases, the immunity weakens due to age-related changes, resulting in a poorer response to infections, leading to increased severity and worse prognosis (Sadiq *et al.*, 2021; Santoro *et al*., 2021).

Severe form of COVID-19 is known to induce systemic inflammation and multiorgan injuries resulting in elevated levels of LDH, particularly in those who do not survive (Thakur *et al* 2021). Organ damage, such as to the liver and kidneys, is indicated by high levels of biomarkers like ALT and creatinine, respectively, which correlate with a higher risk of mortality (Letelier *et al* 2021; Thakur *et al* 2021). Despite the fact that hydroxychloroquine inhibited viral replication *in vitro* (Wang, *et al*., 2020b), the use of hydroxychloroquine indicated statistically negative association with survival in this study and other clinical trials (Khan *et al.*, 2022). Although the safety profile

of hydroxychloroquine has already been established, there are still reported side effects, such as cardiomyopathy and arrhythmic problems in COVID-19 patients. These side effects could, in turn, contribute to non-survival outcomes (Pathak. *et al*., 2020; Sadiq *et al*., 2021).

Albumin level, higher oxygen saturation as well as the presence of carcinoma, showed positive association with survival state. Low serum albumin has been noted in severe cases of COVID-19 and strongly correlated with mortality (Xu *et al.,* 2021). The decrease in serum albumin in severe COVID-19 has been attributed to essential amino acid consumption during viral replication, transcriptional inhibition, and impaired liver protein synthesis due to SARS-CoV-2 infection (Ambade, 2021; Turcato *et al* 2022). Therefore, normal serum albumin levels may indicate good health and can serve as a biomarker to predict the progression of COVID-19 (Xu *et al.,* 2021, Turcato *et al* 2022).

Low oxygen saturation in this study, in agreement with a study by Mejia *et al* (2020), was significant in non-survivors. Symptomatic COVID-19 patients with low oxygen saturation levels indicate hypoxemia, caused by lung inflammation and impaired gas exchange (Mejía *et al*. 2020; Hentsch *et al*., 2021). As for carcinoma, it has been documented as a risk factor for adverse outcomes related to COVID-19 in many studies (Jani *et al*., 2023; Nagy *et al*., 2023). However, in this study, the presence of carcinoma statistically had a positive association with survival. The results of this study might be different from other studies due to the small number of COVID-19 patients with carcinoma, (eight), that were reviewed, which could have affected the statistical association. In addition, some reports documented that active immunotherapy, targeted therapy, or chemoimmunotherapy are not linked to adverse COVID-19 outcomes (Park *et al*., 2021; Jani *et al*., 2023).

CHAPTER SIX

6.0 Conclusion and Recommendations

6.1 Conclusion

This study evaluated clinical, hematological and biochemical features, as well as treatments and predictors of survival in 367 hospitalized COVID-19 patients in Malawi. The clinical features were diverse, with common ones including cough (83.1%), dyspnea (78.2%), fever (70.8%), and headache (60.2%). Vital signs showed significant variations in respiratory rate, heart rate, and oxygen saturation between survivors and non-survivors. Hematological characteristics displayed increased median leukocyte count, neutrophil count and NLR in non-survivors compared to survivors. Biochemical characteristics indicated that AST, ALT, γ-GT, ALP, LDH, urea and creatinine were more elevated in non-survivors than survivors. Predominant types of treatments that were administered included antibiotics, glucocorticoids, oxygen therapy, and enoxaparin. Regarding predictors of survival, multivariate logistic regression analysis revealed that age, ALT, LDH and creatinine, and use of hydroxychloroquine had a negative association with survival state. Conversely, albumin, presence of carcinoma, and higher oxygen saturation levels demonstrated positive association with survival state. Therefore, the findings of this study suggest that COVID-19 patients who are old and have high ALT, LDH, and creatinine, as well as low albumin and low oxygen saturation at the time of admission should be prioritized for timely appropriate intervention.

6.2 Recommendations

This study primarily recommends identifying high-risk patients based on age and oxygen saturation, in conjunction with biochemical markers such as ALT, LDH, albumin, and creatinine, for timely intervention. Continuously monitoring respiratory rate, heart rate, and oxygen saturation is also important, as these indicators showed statistically significant differences between survivors and non-survivors upon admission. Monitoring hematological parameters, especially leukocyte count, neutrophil count, and NLR, is recommended, as these also demonstrated marked increases in the non-survival group. It is further encouraged to conduct biochemical assessments of liver, urinary system, and other vital organs in the management and assessment of COVID-19 cases, as alterations in these parameters, particularly AST, ALT, γ-GT, ALP, LDH, urea, and creatinine, were more pronounced in the non-survival category of hospitalized COVID-19 patients. Appropriate laboratory testing to assess indications for antibiotic use in COVID-19 patients is also suggested for proper antimicrobial stewardship in Malawian settings. Further research is needed on

indicators of heart injury, inflammation, and coagulation tests in relation to SARS-CoV-2 infection among Malawians, for better comparisons and enhanced clinical management.

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APPENDICES

Appendix A: Data Collection Form

Central Hospital Name: _____

ID	COVID-19 Tests		Age	Sex	Comorbidities					Clinical signs and Symptoms					Hematological Test Results and their reference values									
															WBC 4-10 $x10^3/\mu l$	NEUT 0.82-4.1 $x10^3/\mu l$	LYMP 1.3-3.6 $x10^3/\mu l$	RBC 4-6x $10^6/\mu l$	HB 13-18 g/dl	MCV 80-100fL	MCH 23-34 pg	MCHC 33-36 g/dl	RDW 11.5-14.5 %	PLT 122-330 $x10^9/L$

Central Hospital Name: _____

Biochemical Test Results and their reference values									Administered Treatments												Survivor/ Non-survivor
AST 9-50 U/L	ALT 9-50 U/L	TP 6- 8.3 g/dl	TBil 0.2– 1 mg/dl	GGT 0-41 U/L	Alb 3.5-5 g/dl	Ur 10-43 mg/dl	Cr 0.5-1.2 mg/dl	LDH 120-250 U/L													

Appendix B: Institutional Approval

THE UNIVERSITY OF ZAMBIA
SCHOOL OF VETERINARY MEDICINE
OFFICE OF THE DEAN (POSTGRADUATE)

Telephone: 293727
Telegrams: UNZA LUSAKA
Telex: UNZALU ZA 44370
Fax: 293727/253952
School Fax: 293727
Vet. Clinic Telephone: 291515

P.O. Box 32379
Lusaka, Zambia

Your Ref:

Our Ref:

13th December 2022

Mr. Ackim Muntali
Department of Disease Control
School of Veterinary Medicine
University of Zambia
P. O. Box 32379
LUSAKA

Dear Mr. Muntali

SUBJECT: APPROVAL OF RESEARCH PROPOSAL

At the meeting of the School Board of Graduate Studies held on 7th December, 2022, your research proposal entitled: ***"Assessment of Biochemical and Hematological Characteristics of Hospitalized COVID-19 patients in Malawian Central Hospitals: A Retrospective Study"*** was tabled and discussed. I am therefore, pleased to inform you that the research proposal was subsequently approved by the Board.

On behalf of the Board, I wish you success as you apply for ethical approval and carry on with your research activities.

Yours sincerely,

Dr. Chisoni Mumba
ASSISTANT DEAN (PG), SCHOOL OF VETERINARY MEDICINE

Cc *Director, DRGS*
Dean, School of Veterinary Medicine
Head, Disease Control
File

Appendix C: Ethical Approval

Telephone: + 265 1 789 400
Facsimile: + 265 1 789 431
E-mail:
research@health.gov.mw
All Communications should be addressed to: The Secretary for Health

In reply please quote No. MED/4/36c
Ministry of Health
P.O. Box 30377
Lilongwe 3
Malawi

23rd June 2023

Ackim Munthali
University of Zambia

Dear Sir/Madam

Re: Protocol # 23/06/4076: Assessment of Biochemical and Hematological Characteristics of Hospitalized Covid-19 Patients at Mzuzu, Queen Elizabeth and Zomba Central Hospitals in Malawi: A Retrospective Study

Thank you for the above titled proposal that researcher submitted to the National Health Sciences Research Committee (NHSRC) for review. Please be advised that the NHSRC has **reviewed** and **approved** the above named study.

- **APPROVAL NUMBER :4076**
- The above details should be used on all correspondences, consent forms and documents as appropriate.
- **APPROVAL DATE :23/06/2023**
- **EXPIRATION DATE :22/06/2024**
  This approval expires on **22/06/2024**. After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the NHSRC Secretariat should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING:** All serious problems having to do with subject safety must be reported to the NHSRC within 10 working days using standard forms obtainable from the NHSRC Secretariat.
- **MODIFICATIONS**: Prior NHSRC approval using forms obtainable from the NHSRC Secretariat is required before implementing any changes in the protocol (including changes in the consent documents). You may not use any other consent documents besides those approved by the NHSRC.
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the NHSRC using standard forms obtainable from the NHSRC Secretariat.
- **QUESTIONS**: Please contact the NHSRC on phone number *+265 999397913* or by email on mohdoccentre@gmail.com.
- **OTHER**: Please be reminded to send in copies of your final research results for our records (Health Research Database).

Kind regards from the NHSRC Secretariat.

National Health Sciences Research Committee
2023 -06- 23
APPROVED

.....
CHAIRPERSON, NATIONAL HEALTH SCIENCES RESEARCH COMMITTEE
Promoting Ethical Conduct of Research [1]

[1] Executive Committee: Dr M. Joshua (Chairperson), Dr F. Sinyiza (Vice-Chairperson)
Registered with the USA Office for Human Research Protections (OHRP) as an International IRBIRB Number IRB00003905 FWA00005976

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the National Health Science Research Committee has reviewed and approved the study titled:

Study Title: **Protocol # 23/04/4076: Assessment of Biochemical and Hematological Characteristics of Hospitalized COVID-19 Patients at Mzuzu, Queen Elizabeth and Zomba Central Hospitals in Malawi: A Retrospective Study**

Investigator: Ackim Munthali

StartDate: 23/06/2023

End Date:22/06/2024

Date of issue: 23/06/2023

Dr. Collins Mitambo
For: Chairperson-NHSRC

National Health Sciences Research Committee
2023 -06- 23
APPROVED

Mr. Billy Nyambalo
NHSRC -Administrator

Appendix D: Letter of Support to Conduct a study at Queen Elizabeth Central Hospital

Telephone: (265)874 333/877 333
Facsimile: (265)874 603
Email: queenshospital@malawi.net

All *Communications should be addressed to:*
The Hospital Director

In reply please quote No. .....
QUEEN ELIZABETH CENTRAL HOSPITAL
MINISTRY OF HEALTH
P. O. BOX 95
BLANTYRE
MALAWI

Ref. QE/Research/11/05/2023- 0114

11th May, 2023

The Chairperson
National Research Council
P. O. Box 30745
Lilongwe

Dear Sir/ Madam

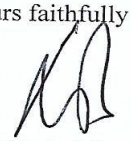
Assessment of Biochemical and Haematological Characteristics of Hospitalized COVID-19 patients in Malawian Central Hospital: A Retrospective Study

I write to support the conduct of the above research activity in this hospital by Munthali Ackim and his study team. The study will determine the biochemical and haematological characteristics of Covid-19 patients admitted to Queen Elizabeth Central hospital.

We request that the findings of the study be made available to our Hospital Research Committee and the relevant department in this hospital.

We wish the study team success.

Yours faithfully



Dr Kelvin Mponda
Acting Hospital Director

Appendix E: Letter of Support to Conduct a study at Mzuzu Central Hospital

Telephone: 01320916/878
Fax: 320223/320973/878
Email:
mzuzucentraldirector@gmail.com

In reply please quote No. ....
The Hospital Director
Mzuzu Central Hospital
P/Bag 209
Luwinga
Mzuzu 2

25th April, 2023

Ackim Munthali, MSc. Student
University of Zambia,
Department of laboratory diagnostic sciences
P. O. Box
Zambia

Cell: +265882992457
Email:

Dear Ackim Munthali,

PERMISSION TO CONDUCT A RESEARCH STUDY AT MZUZU CENTRAL HOSPITAL

Reference is made to your email received on Wednesday 5 April, 2023 in which you are seeking permission to conduct a research study titled ***"Assessment of Biochemical and Haematological Characteristics of Hospitalized Covid-10 Patients in Malawian Central Hospitals: A Retrospective Study"*** at Mzuzu Central Hospital (MCH). MCH Research Committee has now reviewed your study protocol and I am pleased to inform you that permission has been granted. You can use this letter as evidence of support from an institution (MCH) when seeking ethical clearance from COMREC/NHSRC/NCST or any other recognized Institutional Review Board (IRB).

Note: Please take note that MCH policy requires that you pay a financial contribution to the institution which is pegged at 5% of your total research budget before you can start implementing your study at the facility. If the study will be implemented in multiple sites an appropriate amount shall be determined taking into account the number of sites in which the study is to be implemented. Payment is strictly through National Bank of Malawi, Mzuzu Central Hospital Research and Partnership Account, Current account number **1004797902.**

When you are ready for data collection at MCH you will be required to present this letter, ethical approval letter from a recognized ethical review body and evidence of payment of the stipulated fees to the Chairperson of MCH Research Committee before you can begin data collection. We trust that you shall strictly adhere to study procedures as outlined in your study protocol.

Dr. Ted Bandawe
HOSPITAL DIRECTOR

THE DIRECTOR
MZUZU CENTRAL HOSPITAL
25 AOD
PRIVATE BAG 209

Appendix F: Letter of Support to Conduct a study at Zomba Central Hospital

Telephone No.:**01 526266/01525195**
TelefaxNo.: **(265) 1 524538**
Telex No.:
E-Mail:medzch@malawi.net

All correspondences should be addressed to:
The Hospital Director

ZOMBA CENTRAL HOSPITAL
P.O. BOX 21
ZOMBA
MALAWI

1st March 2023

The Chairperson
NHSRC
Ministry of Health and Population
P.O. Box 30377,
Lilongwe 3
Malawi.

LETTER OF NO OBJECTION

On behalf of Zomba Central Hospital management, I am pleased to inform you that **Ackim Munthali** would like to conduct a study using Zomba Central Hospital as one of the study sites and no objection has been granted.

The study title **'ASSESSMENT OF BIOCHEMICAL AND HEMATOLOGICAL CHARACTERISTICS OF HOSPITALIZED COVID-19 PATIENTS IN MALAWIAN CENTRAL HOSPITALS: A RETROSPECTIVE STUDY.'**

Yours faithfully,

DIRECTOR
ZOMBA CENTRAL HOSPITAL
2023 -05- 04
P.O. BOX 21, ZOMBA

Saulos Nyirenda (Dr)
ACTING HOSPITAL DIRECTOR